Is climacterium by the mid-40s associated with thyroid dysfunction or autoimmunity? A population-based study

Running title: Climacteric status and thyroid at mid-40s

Susanna M. Savukoski, MD[1,2], Maarit J. Niinimäki, MD[1,2], Paula RO. Pesonen, MSc[3,] Juha P. Auvinen, MD[2,4], Tuija Männistö, MD[2,5,6], Katri S. Puukka, PhD[2,5,6], Tapani Ebeling, MD[2,7], Eila TJ. Suvanto, MD[1,2]

[1]Department of Obstetrics and Gynaecology, PEDEGO Research Unit, Oulu University Hospital and University of Oulu, 90029 OYS, Finland [2]Medical Research Centre Oulu, Oulu University Hospital and University of Oulu, 90014 Oulu, Finland [3]Infrastructure for Population Studies, Faculty of Medicine, University of Oulu, 90014 Oulu, Finland [4]Centre for Life Course Health Research, University of Oulu, 90014 Oulu, Finland [5]NordLab Oulu, Oulu University Hospital, 90029 Oulu, Finland [6]Department of Clinical Chemistry, University of Oulu, 90014 Oulu, Finland [7]Department of Internal Medicine, Oulu University Hospital and University of Oulu, 90029 OYS, Finland

Sources of funding: Juha Auvinen, Paula Pesonen, Tuija Männistö, Katri Puukka, Tapani Ebeling and Eila Suvanto received no financial support for the research, authorship, and/or publication of this article. Maarit Niinimäki received a research grant from the University of Oulu. Susanna Savukoski received a research grant from the Finnish Menopause Society, Juho Vainio Foundation and Finnish Medical Foundation.

Financial disclosures/conflicts of interest: Tuija Männistö has received speaker fees from Labquality, Inc. The other authors have nothing to disclose.

Corresponding author: Susanna Savukoski (susanna.savukoski@oulu.fi). Address Kajaanintie 50, 90220 Oulu, Finland, phone +358408341559.
Reprint request: to Susanna Savukoski (susanna.savukoski@oulu.fi).

Abstract

Objective: We investigated whether more advanced climacteric stage in the mid-40s is associated with thyroid autoimmunity and dysfunction.

Methods: This cross-sectional cohort study included 2569 46-year-old women. Thyroid hormone, thyroid peroxidase antibodies, and follicle stimulating hormone levels were determined. Using menstrual history and follicle stimulating hormone levels, the participants were divided into climacteric (n = 340) and preclimacteric (n = 2229) groups. Women diagnosed with premature ovarian insufficiency (menopause by 40 years of age) were excluded. The use of thyroid medication was evaluated from the medication reimbursement register. The prevalence of thyroid medication use, laboratory-based thyroid dysfunction, and thyroid peroxidase antibody positivity was compared between the two groups. The association between climacteric status and thyroid disorders was investigated using a logistic regression model including smoking and thyroid antibody status.

Results: At 46 years old, climacteric women used thyroid medication more often than preclimacteric women (9.1% vs. 6.1%; $P = 0.04$). There was no difference in the prevalence of subclinical or clinical hypothyroidism and hyperthyroidism in non-medicated participants (5.5% vs. 5.0%; $P = 0.7$) or thyroid peroxidase antibody positivity (14.0% vs. 15.0%, $P = 0.7$). In the regression model, being climacteric (OR = 1.6; 95% CI 1.1 to 2.3; $P = 0.02$) and antibody positivity (OR 4.9; 95% CI 3.6 to 6.6; $P < 0.001$) were associated with a higher prevalence of thyroid dysfunction.

Conclusions: More advanced climacteric stage in the mid-40s was slightly associated with thyroid dysfunction but not thyroid autoimmunity.

Keywords: menopause / early menopause / thyroid dysfunction / thyroid autoimmune disorders / anti-thyroid peroxidase antibodies

Introduction

Women in Western countries experience menopause at the 50–51 years of age on average [1,2]. Early menopause (EM) is defined as menopause at 40–44 years of age [1], and the prevalence of EM is reported to be up to 12% [3]. Premature ovarian insufficiency (POI), menopause before 40 years old, affects approximately 1% of women [4]. Several genetic variants are associated with variations in the age of menopause [5,6], and the age at menopause is known to be strongly hereditary [7,8].

POI has been shown to be a comorbidity with autoimmune disorders [9,10]. Genetic, iatrogenic, and autoimmune factors can cause POI, even though the etiology for two-thirds of cases remains unknown [11]. Approximately 4–30% of POI cases have been reported to be of autoimmune origin [12]. These disorders include hypo/hyperthyroidism, Addison's disease, hypoparathyroidism, hypophysitis, diabetes mellitus type 1, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune hemolytic anemia, pernicious anemia, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome, primary biliary cirrhosis, chronic active hepatitis, and celiac disease [13]. Among women diagnosed with POI, 25–30% have thyroid peroxidase antibodies (TPOAbs) [14,15], whereas the general prevalence of thyroid antibodies among young women is 5–20% [16].

Only a few studies have evaluated the health risks in women who are facing menopause earlier than average but do not fulfill the criteria for POI. In our earlier studies, we found that women facing the onset of the climacteric phase by the mid-40s are at risk of adverse changes in their lipid profile, liver enzymes, and body composition [17], as well as decreased insulin sensitivity [18].

POI has been associated with an increased prevalence of thyroid autoimmune disorders [14,15]. However, to the best of our knowledge, no studies have evaluated thyroid function among women who experience the onset of the climacteric phase by their mid-40s. In this

population-based study, our aims were to investigate the prevalence of thyroid disorders and thyroid autoimmunity in relation to climacteric status at 46 years of age in female participants of the Northern Finland Birth Cohort 1966 (NFBC1966). We compared thyroid medication use, laboratory-based thyroid dysfunction, and TPOAb positivity between climacteric and non-climacteric women.

Materials and Methods

Study population and data collection

The participants were members of NFBC1966, which originally included 96.3% of all live-born children born in Oulu and Lapland provinces from late 1965 to early 1967 (6169 boys and 5889 girls). All mothers with an estimated date of delivery during 1966 who were living in the area were originally recruited. The cohort members were prospectively followed since the antenatal period by comprehensive questionnaires and clinical examinations [19]. This study was based on a 46-year follow-up survey performed in the year 2012. This follow-up study included a broad postal questionnaire, clinical examinations, and laboratory samples at 46 years old. The questionnaires included a multitude of questions concerning the participants' health, lifestyle, and life situations. Their current menstrual cycle situation was also evaluated by asking whether they had menstrual cycles a) regularly, b) irregularly, c) not anymore, d) no, because of hormonal medication, or e) no, because the uterus was removed. The participants were also asked to report the date of their last menstrual period. Questionnaires also requested information on current and past smoking habits, marital status, and level of education. The 46-year follow-up study also included a clinical examination comprising physical tests, laboratory samples, and imaging studies, to which every study participant was invited to attend. In the clinical examination, weight and height were measured and body mass index (BMI) calculated.

Laboratory analysis and thyroid function classification

Serum samples were taken from the participants at 46 years old and analyzed for follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), free thyroxine (FT4), and TPOAbs. These biomarkers were determined by immunochemiluminometric methods (Advia Centaur XP, Siemens Healthcare Diagnostics, Tarrytown, NY, USA). The samples were analyzed at NordLab Oulu, a testing laboratory (T113) accredited by the Finnish Accreditation Service (FINAS) (EN ISO 15189).

Reference values for TSH and FT4 were 0.5–3.8 mU/L and 10.2–21 pmol/L, respectively [20]. TPOAbs < 60 IU/mL was defined as negative and ≥ 60 IU/mL as positive. Serum FSH ≥ 25 IU/L was classified as diagnostic for late perimenopausal stage [21].

Registry data

NFBC1966 data collection has been linked to the nationwide registry data for study participants who gave their permission for register data use. The National Institute for Health and Welfare's Care Register for Health Care includes all diagnoses from hospital health care in Finland. The diagnoses are restored with a personal identifier using the International Statistical Classification of Diseases and Related Health Problems (ICD) coding system. In this registry, women with previous POI diagnosis (ICD-10 codes E28.3, E89.4, E89.8, and Q96) were identified. In addition, women with iatrogenic hypothyroidism (post-surgical or post-radioiodine, ICD-10 codes E89.00, E89.01, and E89.09) were identified from the Care Register for Health Care.

The Social Insurance Institution of Finland's statistics on reimbursements for prescription medicines were used to identify study participants who purchased thyroid disorder medications [Anatomical Therapeutic Chemical Classification (ATC) codes starting with H03], as well as women currently using systemic hormone therapy with estrogen (HT) (ATC codes starting with G03C and G03F) in the 6 months prior to the 46-year clinical examination. In Finland, it is possible to buy prescription medicines for 3 months at a time,

and the time period was chosen based on this. Medicine reimbursement information for the NFBC1966 participants was available until the end of 2016, so we also evaluated the study participants who started thyroid medication within 4 years after the clinical examination.

Study groups

The women taking part in the 46-year follow-up study were divided into two groups, climacteric and preclimacteric, based on their menstrual history and FSH values. This division has been described in detail in our earlier studies [17,18]. As there are no general criteria for climacterium, the European Society of Human Reproduction and Embryology (ESHRE) criteria for POI and Stages of Reproductive Aging Workshop (STRAW +109) criteria for menopausal transition were applied [4,21]. The group of climacteric women included women in the late perimenopausal and postmenopausal stages with FSH ≥ 25 IU/L and amenorrhea ≥ 4 months. Women using HT were automatically included in the climacteric group. The group of preclimacteric women included women in the premenopausal and early perimenopausal stages with FSH < 25 IU/L and regular/irregular menstrual cycles.

Women with a discrepancy between the FSH value and menstrual anamnesis were excluded. Combined contraceptive pill or ring users were excluded because these may interfere with both the menstrual cycle and FSH value. As progestin-only treatments and progestin intrauterine devices affect menstrual bleeding, women using these were classified according to their FSH values. Tamoxifen users were excluded. Data on the current use of contraceptive preparations was based on self-reported data in the questionnaire, as these are not recorded in the medicine reimbursement statistics.

Ethical issues

The study design was approved by the Ethical Committee of the Northern Ostrobothnia Hospital District (94/2011, 12/2003) and rigorously followed the principles of the Declaration of Helsinki and national guidelines. Permission to use the Care Register for Health Care was

sought from the National Institute for Health and Welfare. A license to use statistics on reimbursements for prescription medicines was sought from the Social Insurance Institution of Finland. All study participants signed written, informed consent to use their cohort data collectively and their registry data separately for scientific purposes.

Statistical analyses

The distributions of background variables in study groups were compared using an independent sample *t*-test or Pearson's chi-squared test. Because of the nature of the distributions, the Mann-Whitney *u*-test was used to compare thyroid hormone values between climacteric and preclimacteric women. To compare the prevalence of TPOAb positivity, abnormal thyroid function in laboratory tests, use of thyroid medications, and prevalence of overall mediated or laboratory value-based thyroid dysfunction between climacteric and preclimacteric women, we used Pearson's chi-squared or Fisher's exact test.

The association of climacteric status with thyroid dysfunction was investigated in a binary logistic regression model. In this model, present/evolving thyroid disorder was a dependent variable and climacteric status, TPOAb status, and current smoking habits were independent variables. The effects of interaction terms were checked. The model was formed based on earlier findings that TPOAb positivity significantly increases the risk of thyroid dysfunction [22], and there is also evidence that smoking is associated with an increased risk of thyroid disease [23]. The Hosmer-Lemenshow test was performed to ensure the goodness of fit of the model.

All tests were two-sided, with significance set at $p < 0.05$. Statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 26 (IBM Corp., Armonk, NY, USA). Figure 1 was created using CorelDRAW Graphics Suite 2019, Version 21.0.0.593 (Corel Corporation, Ottawa, Canada) and Figure 2 with GraphPad Prism Version 8.0.1.244 (GraphPad Software, San Diego, California, USA).

Results

The flow chart of the study population is shown in Fig. 1. 5118 female cohort members were invited to attend the 46-year follow-up study; 3102 (60.6%) answered the questionnaire and attended the clinical examination. According to medicine reimbursement statistics, 18 women had received a higher special rate of medicine reimbursement for HT, as they were diagnosed with POI or their ovaries were removed before 45 years old. These women were excluded from the study population. In addition, there were four women who had not received a higher special rate of medicine reimbursement for HT but were diagnosed with POI (ICD10 codes: E28.3, E89.4, E89.8, or Q96); these women were also excluded. The final study population included 340 climacteric women and 2229 preclimacteric women with laboratory tests of thyroid function, questionnaire data, and who gave permission to use their medicine reimbursement registry data.

The baseline characteristics of these women are given in Table 1. Study groups did not differ by BMI, or marital status, whereas climacteric women were more often smokers and less educated than preclimacteric women. In two-thirds of the climacteric women who were able to report the exact time of their last menstrual period, the duration of amenorrhea was less than 2 years [17].

Thyroid dysfunction and autoimmunity

The thyroid hormone distribution in climacteric and preclimacteric women is shown in Table 2. FT4 and TSH values did not differ between study groups. The TPOAb levels were available for 1874 study participants. The proportion of TPOAb-positive participants was also very similar in climacteric and preclimacteric women (14.0% vs. 15.0%, $P = 0.7$). Thyroid medication purchases based on Social Insurance Institution of Finland's statistics are shown in Table 3. A significantly higher proportion of climacteric women purchased thyroid medication during the 6 months prior to the 46-year follow-up ($P = 0.04$). As medication

purchases for hypothyroidism and hyperthyroidism were compared separately, there were no significant differences between the study groups in medication purchases for hypothyroidism. A slightly higher proportion of climacteric women than preclimacteric women had bought medicine for hyperthyroidism (P = 0.05), but the number of participants who purchased hyperthyroid medication was very small [n=2 (0.6%) and n=1 (0.0%)]. Of all study participants with no thyroid medication purchases before the 46-year follow-up, 3.5% evolved thyroid disease between the study visit in 2012 and the end of 2016 according to their thyroid medication purchases. The prevalence of evolving medicated thyroid disorders did not differ between the study groups (P = 0.8). In addition, the prevalence of post-surgical or post-radioiodine hypothyroidism [n=1 (0.2%) climacteric women and n=5 (0.3%) preclimacteric women] did not significantly differ between the study groups (P = 0.8). All participants with iatrogenic hypothyroidism received medication for hypothyroidism.

According to the laboratory values, the majority of study participants who had not bought thyroid medication prior to the 46-year follow-up [n=289 (93.5%) climacteric women and 1950 (93.2%) preclimacteric women] had both TSH and FT4 levels within the reference range. Based on laboratory values for climacteric and preclimacteric women, 1 (0.3%) vs. 5 (0.2%) had hypothyroidism, 7 (2.3%) vs. 54 (2.6%) had subclinical hypothyroidism, 9 (2.9%) vs. 42 (2.0%) had subclinical hyperthyroidism, and 0 (0.0%) vs. 3 (0.1%) had hyperthyroidism, respectively. Distribution into classes by thyroid function did not differ between the study groups (P = 0.9). 57 (16.8%) climacteric women and 310 (13.9%) preclimacteric women purchased thyroid medication or had laboratory-based subclinical or clinical thyroid dysfunction (P = 0.2).

Of the study participants with thyroid medication before and/or after the 46-year follow-up, 43.4% were TPOAb-positive. In the study participants who did not use thyroid medication, the prevalence of TPOAb positivity was 60% in those with laboratory-based hypothyroidism,

44.8% in those with subclinical hypothyroidism, 23.7% in those with subclinical hyperthyroidism, and 40% in those with hyperthyroidism. Among euthyroid women, the prevalence was 12.9%.

The results of the binary logistic regression model are presented in Fig. 2, showing that both TPOAb positivity and being climacteric at 46 years old were significantly associated with thyroid dysfunction. However, the association of TPOAb positivity was much stronger.

We performed a subanalysis excluding participants with post-surgical or post-radioiodine hypothyroidism. The results of the analysis comparing the prevalence of medicated thyroid dysfunction before and/or after the 46-year follow-up, the prevalence of overall medicated or laboratory-based thyroid dysfunction, and the prevalence of TPOAb positivity, and the results of the binary logistic regression model did not change significantly in the subanalysis.

Discussion

In this population-based cohort study, climacteric status in the mid-40s was not associated with the prevalence of TPOAb positivity, as women diagnosed with POI were excluded. Untreated, laboratory value-based thyroid dysfunction was rare, and the prevalence did not differ between climacteric and preclimacteric women. TSH and FT4 levels among study participants who did not use thyroid medications did not differ between the study groups. However, a minor but significant association between thyroid dysfunction and earlier onset of the climacteric phase was found in the logistic regression model. Climacteric women were also more often thyroid medicine users. The association between thyroid autoimmunity and POI has been documented in many studies [10,13]. However, to the best of our knowledge, no previous studies investigated thyroid function and autoimmunity in women facing the menopausal transition in their 40s.

TPOAb positivity substantially increases the risk of hypothyroidism and hyperthyroidism [22]. The prevalence of untreated laboratory value-based subclinical and overt hypothyroidism in

our study participants was smaller than that reported by earlier studies; the prevalence of undiagnosed subclinical and overt hypothyroidism was reported to be 5.86% and 0.8% in European women [24]. The literature has generally reported hypothyroidism in 2–4% of women of reproductive age [25]. Different kinds of thyroid hormone abnormalities have been described to be more common in women with POI in their 30s compared to menstruating women of the same age [15]. The prevalence of hypothyroidism in women with POI is substantially higher than in the general population; Conway *et al.* reported that the prevalence was 7.4% in a study population consisting of 135 women aged 17-39 years who were diagnosed with POI [26]. In a study by Kim *et al*., 27% of 119 women with POI who were aged 15–39 years had either previously diagnosed or laboratory value-based hypothyroidism [27]. A large population-based study reported that 1.7% of European women had undiagnosed subclinical and overt hyperthyroidism [24]. In our study population, the prevalence was a little higher: 2.9% in climacteric women and 2.1% in preclimacteric women.

Our study has several strengths. The study population was based on a large birth cohort, which is representative of the whole population. The study participants had a narrow age range, as they were all born within 1 year. We were able to determine their objective climacteric status, as both FSH values and menstrual history were available at the 46-year follow-up. The evaluation of thyroid dysfunction was based on reliable sources, as thyroid function was determined based on laboratory sampling, and the current use of thyroid medication and diagnosis with iatrogenic hypothyroidism were derived from the high-quality nationwide registry data. We were able to reliably identify the participants with post-surgical or post-radioiodine hypothyroidism, finding that their proportion was small but did not differ between the study groups. We were also able to perform a subanalysis excluding the participants with iatrogenic hypothyroidism, but the results did not change significantly.

This study also had some limitations. The aim of the study was to describe the prevalence of thyroid dysfunction in an unselected, middle-aged female population in relation to their climacteric status. For more detailed analysis, a clinical case-control study would be needed to describe the effect of climacterium on thyroid function. NFBC1966 participants' thyroid hormone levels had not been determined in earlier follow-up studies, so longitudinal analysis of thyroid function at different ages was not possible. However, in the literature, that FT4 and TSH values have been reported to remain stable from youth to middle age [28], whereas the TPOAb levels increase with age [20,29]. We could not specify the indications and background for thyroid medication use. In the Care Register for Health Care, only thyroid dysfunction diagnoses made in special health care are recorded reliably; therefore, we could not identify the diagnosis for participants diagnosed with thyroid dysfunction in primary health care. The climacteric women more often used thyroid medications, even though the rate of TPOAb positivity did not differ between the groups. It is possible that climacteric women had utilized health care more often than preclimacteric women because of their climacteric symptoms and other health issues, and that the threshold for prescribing thyroid medication was lower among them. Some members of the original cohort were lost to follow-up and were not included in this study. It is possible that the threshold for using health care services and to obtain a thyroid medication prescription has been different in cohort members participating in the follow-up study compared to those who did not.

In our previous studies, we found that earlier onset of the climacteric phase increases the risk of adverse metabolic changes [17,18]. Women who were climacteric at 46 years old also had lifestyle related risk factors, as they gained more weight from 31 to 46 years of age and were more often current smokers [18]. As women with POI have various etiological reasons for their condition, including autoimmune disorders and chromosomal disturbances [4], women facing climacterium 40 to 46 years seem to present with different entities. It is likely that heredity

plays an important role in the etiology of their earlier menopausal transition. Smoking is a significant, dose-dependent risk factor preponing menopause [30]. Thus, despite the other metabolic risks, the present study suggests that the risk of thyroid dysfunction is only slightly elevated among women with earlier onset climacteric phase when excluding women diagnosed with POI.

Conclusions

We found a minor but significant association between thyroid disorders and more advanced climacteric stage in women in their mid-40s. However, as the prevalence of TPOAb positivity and thyroid disorders was very similar between the study groups, our study findings suggest that the risk of thyroid disorders in women reaching the late perimenopausal stage in their 40s is substantially smaller than in women with POI. In this population, genetic and lifestyle factors may play more important roles in the etiology of menopausal age than autoimmunity. The findings of this study do not support routine screening for thyroid dysfunction among women with early-onset climacteric phase who do not fulfill the criteria for POI.

Acknowledgements: This work was supported by the Northern Ostrobothnia Hospital District, Oulu University Hospital, the University of Oulu, the Finnish Menopause Society, Juho Vainio Foundation, and the Finnish Medical Foundation. We thank the late professor Paula Rantakallio, the NFBC1966 participants in the 46-year follow-up study, and the Northern Finland Birth Cohort (NFBC) Project Centre.

References

1. Mishra GD, Pandeya N, Dobson AJ, et al. Early menarche, nulliparity and the risk for premature and early natural menopause. *Hum Reprod* 2017;32(3):679–686.
2. Bjelland EK, Hofvind S, Byberg L, Eskild A**.** The relation of age at menarche with age at natural menopause : a population study of 336 788 women in Norway. *Hum Reprod* 2018;33(6):1149–1157.
3. Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z**.** The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. *Climacteric* 2019;22(4):403–411.

4. Webber L, Davies M, Anderson R, et al. ESHRE Guideline: management of women with premature ovarian insufficiency. *Hum Reprod* 2016;31(5):926–937.
5. Perry JRB, Corre T, Esko T, et al. A genome-wide association study of early menopause and the combined impact of identified variants. *Hum Mol Genet.* 2013;22(7):1465–1472.
6. Murray A, Bennett CE, Perry JRB, et al. Common genetic variants are significant risk factors for early menopause: Results from the breakthrough generations study. *Hum Mol Genet.* 2011;20(1):186–192.
7. Morris DH, Jones ME, Schoemaker MJ, Ashworth A, Swerdlow AJ**.** Familial concordance for age at natural menopause: results from the Breakthrough Generations Study. *Menopause* 2011;18(9):956–961.
8. Murabito JM, Yang Q, Fox C, Wilson PWF, Cupples LA**.** Heritability of age at natural menopause in the framingham heart study. *J Clin Endocrinol Metab* 2005;90(6):3427–3430.
9. Ayesha J V., Jha V, Goswami D**.** Premature ovarian failure: An association with autoimmune diseases. *J Clin Diagn Res* . 2016;10(10):QC10–QC12.
10. Pogačnik RK, Vrtovec HM, Vizjak A, Levičnik AU, Slabe N, Ihan A**.** Possible role of autoimmunity in patients with premature ovarian insufficiency. *Int J Fertil Steril.* 2014;7(4):281–290.
11. Jiao X, Zhang H, Ke H, et al. Premature ovarian insufficiency: Phenotypic characterization within different etiologies. *J Clin Endocrinol Metab* 2017;102(7):2281–2290.
12. Kirshenbaum M, Orvieto R**.** Premature ovarian insufficiency (POI) and autoimmunity-an update appraisal. *J Assist Reprod Genet* 2019;36(11):2207–2215.
13. Domniz N, Meirow D**.** Premature ovarian insufficiency and autoimmune diseases. *Best Pract Res Clin Obstet Gynaecol.* 2019;60:42–55.
14. Ashrafi M, Fallahian M, Eshrati B, Salman Yazdi R**.** The presence of anti thyroid and anti ovarian auto-antibodies in familial premature ovarian failure. *Int J Fertil Steril.* 2008;1(4):171–174.
15. Goswami R, Marwaha RK, Goswami D, et al. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type 1 diabetes and premature ovarian failure. *J Clin Endocrinol Metab* . 2006;91(11):4256–4259.
16. Poppe K, Velkeniers B, Glinoer D**.** The role of thyroid autoimmunity in fertility and pregnancy. *Nat Clin Pract Endocrinol Metab.* 2008;4(7):394–405.
17. Savukoski S, Makela H, Auvinen J, et al. Climacteric Status at the Age of 46: Impact on Metabolic Outcomes in Population-Based Study. *J Clin Endocrinol Metab* 2019;104(7):2701–2711.
18. Savukoski SM, Suvanto ETJ, Auvinen JP, et al. Onset of the climacteric phase by the mid-forties associated with impaired insulin sensitivity. *Menopause* 2020;28(1):70–79.
19. Rantakallio P**.** Groups at risk in low birth weight infants and perinatal mortality. *Acta Paediatr Scand* 1969;193:1–71.
20. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 2002;87(2):489–499.
21. Harlow SD, Gass M, Hall JE, et al. Executive summary of the stages of reproductive aging workshop + 10: Addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab* 2012;97(4):1159–1168.
22. Strieder TGA, Prummel MF, Tijssen JGP, Endert E, Wiersinga WM**.** Risk factors for and prevalence of thyroid disorders in a cross-sectional study among healthy

female relatives of patients with autoimmune thyroid disease. *Clin Endocrinol (Oxf)* . 2003;59(3):396 – 401.
23. Brix TH, Hansen PS, Kyvik KO, Hegedüs L**.** Cigarette smoking and risk of clinically overt thyroid disease: A population-based twin case-control study. *Arch Intern Med* 2000;160(5):661–666.
24. Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F, Galofré JC**.** The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. *J Clin Endocrinol Metab* 2014;99(3):923–931.
25. Verma I, Sood R, Juneja S, Kaur S**.** Prevalence of hypothyroidism in infertile women and evaluation of response of treatment for hypothyroidism on infertility. *Int J Appl Basic Med Res* 2012;2(1):17–19.
26. Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS**.** Characterization of idiopathic premature ovarian failure. *Fertil Steril* . 1996;65(2):337–341.
27. Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM**.** Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. *Obstet Gynecol* 1997;89(5 Pt 1):777–779.
28. Fisher DA**.** Physiological variations in thyroid hormones: physiological and pathophysiological considerations. *Clin Chem* 1996;42(1):135–139.
29. Amouzegar A, Gharibzadeh S, Kazemian E, Mehran L, Tohidi M, Azizi F**.** The prevalence, incidence and natural course of positive antithyroperoxidase antibodies in a population-based study: Tehran thyroid study. *PLoS ONE* 2017;12(1):e0169283.
30. Zhu D, Chung H-F, Pandeya N, et al. Relationships between intensity, duration, cumulative dose, and timing of smoking with age at menopause: A pooled analysis of individual data from 17 observational studies. *PLoS medicine* 2018;15(11):e1002704.

Figure and table legends

FIG 1: Flow chart of the study population.

The study population consisted of female participants of the Northern Finland Birth Cohort 1966 (NFBC1966) taking part in the 46-year follow-up study in 2012.
FSH, follicle stimulating hormone; HT, hormone therapy; TSH, thyroid stimulating hormone; FT4, free thyroxine; POI, premature ovarian insufficiency

TABLE 1: Baseline characteristics of the study population

[a] Independent samples t-test, [b] chi-squared test.

TABLE 2: Thyroid hormone levels in participants not using thyroid medication

[a] Mann-Whitney *u*-test.
FT4, free thyroxine; TSH, thyroid stimulating hormone; IQR, interquartile range

TABLE 3: Thyroid medication purchases

Data are given as n (%). [a] Pearson's chi-squared test, [b] Fisher's exact test. [c] By the end of the year 2016.

FIG 2: Climacteric status and the risk of thyroid dysfunction

Forest plot showing odds ratios (ORs) of predictive factors for having thyroid dysfunction at 46 years old. Analysis was performed using a logistic regression model. The Hosmer-Lemenshow test was performed to test the goodness of fit of the model (P = 1.0). TPOAbs, thyroid peroxidase antibodies; CI, confidence interval.

Table1

Table 1: Baseline characteristics of the study population

Variable	**Climacteric (n=340)**	**Preclimacteric (n=2229)**	***P*-value**
Body mass index, mean (SD)	26.5 (5.2)	26.5 (5.3)	0.9[a]
Current smoker, n (%)			0.03[b]
No	255 (77.5)	1823 (82.6)	
Yes	74 (22.5)	384 (17.4)	
Marital status, n (%)			0.4[b]
Unmarried	36 (10.7)	219 (9.9)	
Married/domestic partnership	266 (79.4)	1733 (78.0)	
Divorced	30 (9.0)	258 (11.6)	
Widow	3 (0.9)	11 (0.5)	
Education, n (%)			0.03[b]
Basic	8 (2.2)	46 (2.1)	
Secondary	213 (62.6)	1236 (55.5)	
Tertiary	119 (35.0)	947 (42.5)	

Table 2: Thyroid hormone levels in participants not using thyroid medication

		n	**Median**	**IQR**	***P*-value[a]**
FT4 (pmol/L)	Climacteric	309	13.81	2.46	0.07
	Preclimacteric	2092	13.62	2.29	
TSH (mU/L)	Climacteric	309	1.40	0.87	0.2
	Preclimacteric	2092	1.41	0.92	

Table 3: Thyroid medication purchases

	Climacteric women	**Preclimacteric women**	***P*-value**
Medication purchased in the 6 months prior to the 46-year study (in 2012)	31 (9.1)	137 (6.1)	0.04[a]
Medication purchased for hypothyroidism	30 (8.8)	137 (6.1)	0.06[a]
Medication purchased for hyperthyroidism	2 (0.6)	1 (0.0)	0.05[b]
Medication purchased after the 46-year study (if no purchase was made before the study)[c]	11 (3.6)	81 (3.9)	0.8[a]
Medication purchased for hypothyroidism	11 (3.6)	74 (3.5)	1.0[a]
Medication purchased for hyperthyroidism	0 (0.0)	7 (0.3)	0.6[b]

Figure1

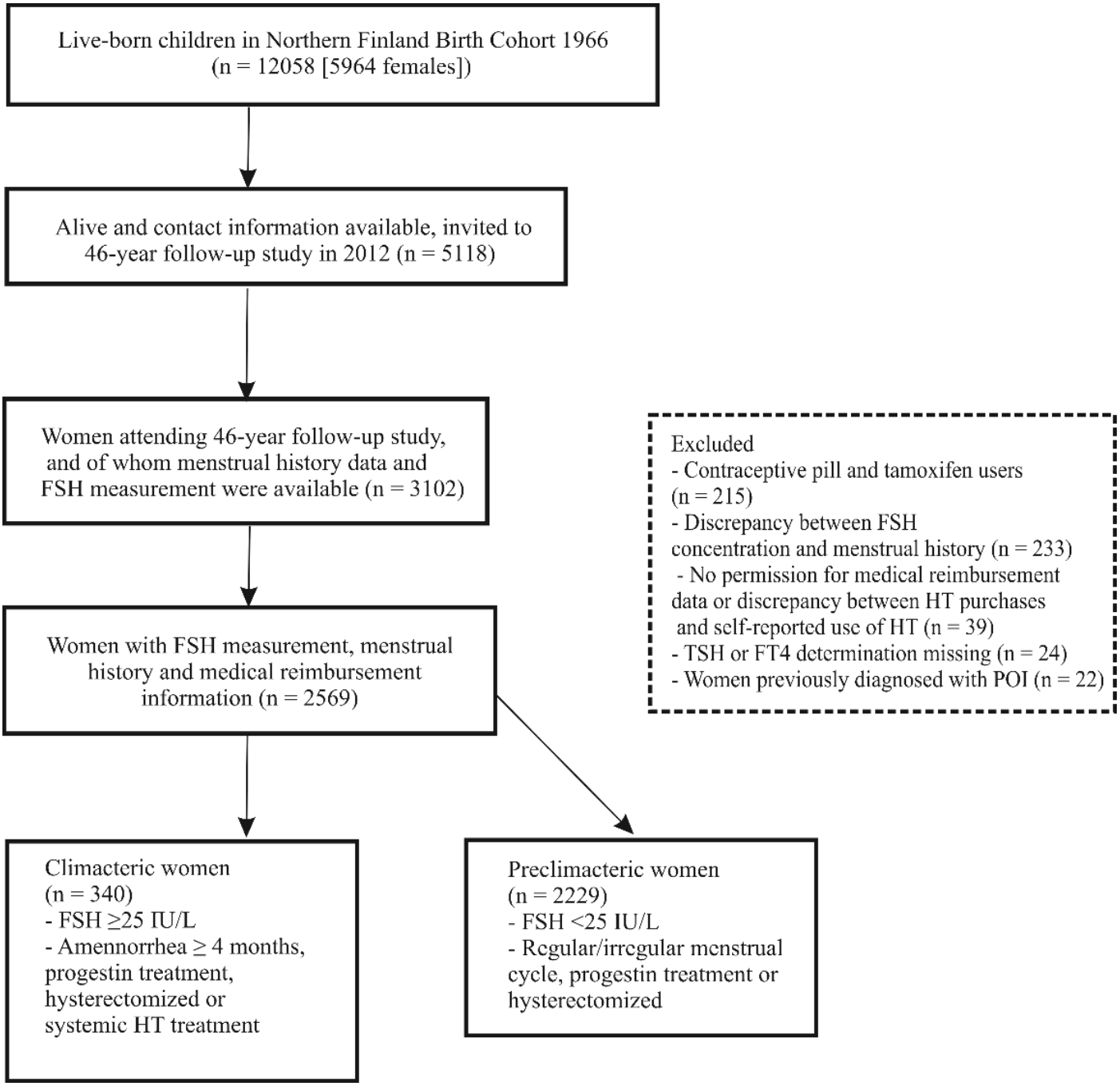
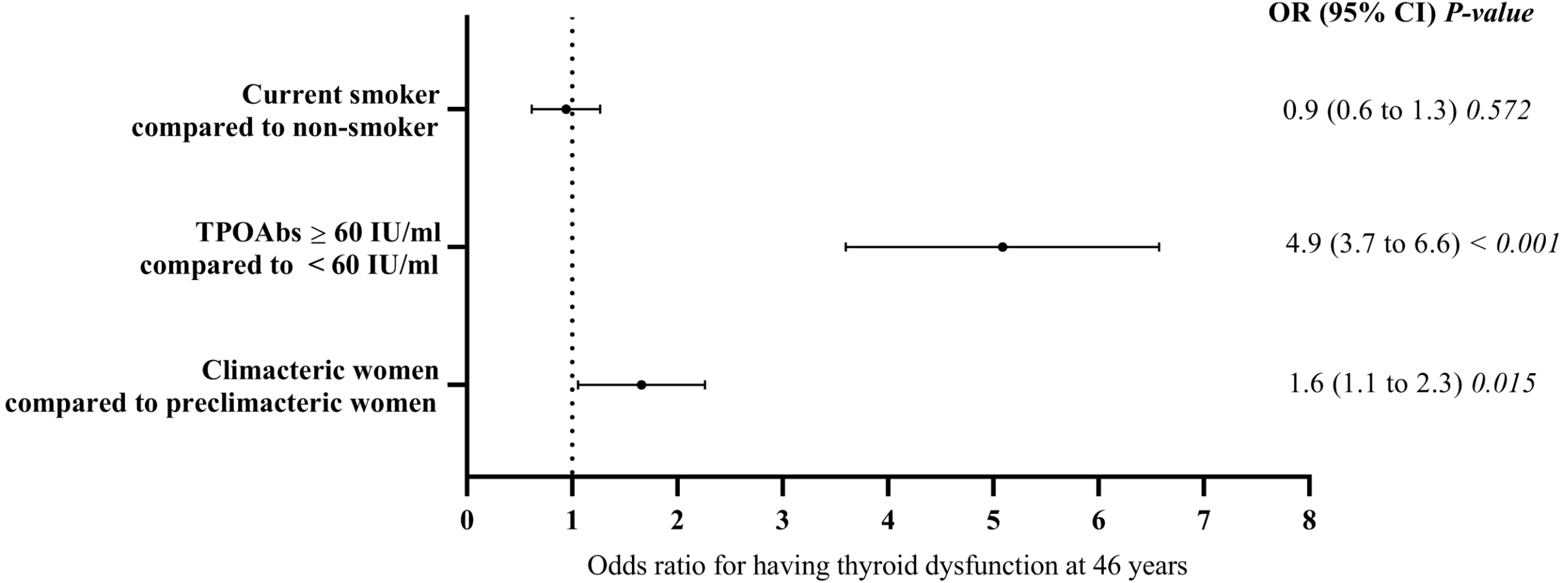

Live-born children in Northern Finland Birth Cohort 1966
(n = 12058 [5964 females])
Alive and contact information available, invited to
46-year follow-up study in 2012 (n = 5118)
Women attending 46-year follow-up study,
and of whom menstrual history data and
FSH measurement were available (n = 3102)
Excluded
- Contraceptive pill and tamoxifen users
(n = 215)
- Discrepancy between FSH
concentration and menstrual history (n = 233)
- No permission for medical reimbursement
data or discrepancy between HT purchases
and self-reported use of HT (n = 39)
- TSH or FT4 determination missing (n = 24)
- Women previously diagnosed with POI (n = 22)
Women with FSH measurement, menstrual
history and medical reimbursement
information (n = 2569)
Climacteric women
(n = 340)
- FSH ≥25 IU/L
- Amennorrhea ≥ 4 months,
progestin treatment,
hysterectomized or
systemic HT treatment
Preclimacteric women
(n = 2229)
- FSH <25 IU/L
- Regular/irregular menstrual
cycle, progestin treatment or
hysterectomized

Figure2


OR (95% CI) P-value
Current smoker compared to non-smoker
0.9 (0.6 to 1.3) 0.572
TPOAbs ≥ 60 IU/ml compared to < 60 IU/ml
4.9 (3.7 to 6.6) < 0.001
Climacteric women compared to preclimacteric women
1.6 (1.1 to 2.3) 0.015
0
1
2
3
4
5
6
7
8
Odds ratio for having thyroid dysfunction at 46 years