Thyroid

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THYROID FUNCTION AND PHYSICAL ACTIVITY: A POPULATION-BASED COHORT STUDY[1]

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ABSTRACT

BACKGROUND: Thyroid hormones are important metabolic regulators exerting effects in multiple systemic functions including muscular and cardiorespiratory. Thyroid hormones may influence physical activity levels. However, there are currently no studies evaluating the association between thyroid function and physical activity levels in the general population.

METHODS: In a population-based cohort-study between 2006 and 2013, we assessed the cross-sectional and longitudinal (with a mean follow-up time of 5 years) association of serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) with physical activity (Metabolic equivalent task (MET)-hours per week). Information on physical activity was collected using a validated questionnaire (LASA, median 22.50 METh/wk). The association of TSH and FT4 with physical activity was examined using linear regression models in the cross-sectional and longitudinal analyses, adjusted for age, sex, lifestyle factors and cardiovascular disease. In sensitivity analyses, we examined the association between thyroid function and physical activity including only participants within the reference range of thyroid function. We additionally examined moderate and vigorous physical activity separately as outcomes.

RESULTS: We included 2,470 participants for the cross-sectional analysis (mean age 57.3 years, 58% women) and 1,907 participants for the longitudinal analysis (mean age 56.9 years). There was no association between TSH (mIU/L) or FT4 (ng/dL) and physical activity (ß = 0.65, 95% confidence interval (CI), -1.67; 2.98 and ß = 2.76, CI, -7.15; 12.66, respectively) on cross-sectional analysis,. Similarly, in the longitudinal analyses, we observed no association of TSH (ß = 1.16, CI, -1.31; 3.63) or FT4 (ß = -6.63, CI, -17.06; 3.80) with physical activity.

CONCLUSIONS: We did not observe an association between the endogenous thyroid hormone level and total physical activity. Further studies need to be performed to evaluate whether thyroid hormone replacement therapy is associated with physical activity.

INTRODUCTION

Thyroid hormones are important regulators of the metabolic system (1). During exercise as well as rest, the thyroid hormones affect the muscular and cardiorespiratory function (2). Patients with hypothyroidism can present with profound musculoskeletal weakness and severe thyroid hormone excess is related to myopathy (3, 4). Hypothyroidism, in the clinical and subclinical range, is characterized by chronotropic dysfunction, including low heart rate and conduction abnormalities (5, 6). Upon treatment with levothyroxine, hypothyroid patients show improved cardiovascular parameters such as heart rate and cardiac output (7). When thyroid hormones increase, the muscle responds vigorously (5). Previous studies have reported thyroid hormone abuse by professional athletes and strength-training individuals with the aim of enhancing their physical performance (8-10). Potential benefits are unclear but may be related to cardiac stimulation, muscle performance and/or fat reducing effects (11).

Thyroid function affects several systems that can change the physical activity and the physical capacity (5). Physical capacity includes factors like strength, balance and range of movement (12). These are closely related with the skeletal muscle system (5). Thyroid hormone stimulates the Na/K-ATPase in the skeletal muscle increasing the transmembrane resting potential (13), and also promotes the expression of heavy chain myosin, a protein characteristic of fast-twitch fibers, the number of mitochondria and the frequency of contraction and relaxation (14). Thyroid hormone may therefore very well affect physical capacity via skeletal muscles. Physical activity is related to the movement of skeletal muscles and the resulting energy expenditure (15). Thyroid hormones have a well-known effect on energy metabolism as well (16), generating changes in the demand and synthesis of ATP (16). This may explain a possible link between thyroid function and physical activity.

On the other hand, thyroid function can also negatively impact physical activity through diseases that may hamper a person’s general physical performance. For example, thyroid function variations, even within the reference range, have been related to cardiovascular disease (CVD), stroke and frailty in middle-aged and elderly populations (17-19). Vice versa, physical activity can also affect thyroid function. For example, physically active people generally have a beneficial cardio-metabolic profile including a favorable fat distribution (20). Higher body mass index (BMI) and obesity are known factors influencing thyroid function through production of leptin, which influences the hypothalamic-pituitary-thyroid axis (21).

Altogether, this suggests that thyroid function may be related to physical activity in the general population. The aim of the current study was to investigate the association of thyroid function, defined by serum thyroid-stimulating hormone (TSH) and free thyroxine (FT4) and physical activity in a large population-based cohort study.

MATERIALS AND METHODS

Study population

The analyses were performed using data from the Rotterdam Study, a large prospective population-based cohort study. The rationale, design and aims have been previously described (22). The Rotterdam Study was initiated in 1989 in the city of Rotterdam, The Netherlands and included 7,983 participants 55 years or older. In 2000, a second cohort of 3,011 participants age 55 years old were added. In 2006, the study was extended with a third cohort of 3,932 participants 45 years or older that were not invited before. For the current study, we included participants from the Rotterdam Study that had information on thyroid function parameters and measurement on physical activity for the cross-sectional analyses and repeated measurements of physical activity for the longitudinal analyses, as measured by the LASA questionnaire (Figure 1). Baseline data were collected from 2006 to 2008 and repeated measures were conducted from 2008 to 2013.

The Rotterdam Study was approved by the Erasmus University Medical Ethics Committee and the Ministry of Health, Welfare and Sport of the Netherlands, according to the Population Studies Act: Rotterdam Study. In accordance with the Declaration of Helsinki, all participants in this analysis provided written informed consent.

Assessment of thyroid function

TSH, FT4, and thyroid peroxidase antibodies (TPOAb) were measured in serum samples stored at -80°C (electrochemiluminescence immunoassay "ECLIA", Roche). The normal range values were defined for TSH as 0.40-4.0 mIU/L and FT4 as 0.85-1.95 ng/dL, consistent with guidelines and previous studies (17, 23). TPOAb levels with a value higher than 35kU/mL were regarded as positive according to the recommendations of the manufacturer.

Physical activity assessment

Physical activity was evaluated through an adapted version of the LASA Physical Activity Questionnaire (LAPAQ) (24). This questionnaire was validated in the Longitudinal Aging Study Amsterdam (LASA), in which 439 participants aged 69 to 92 years used a pedometer for 7 days and completed the LAPAQ twice and a 7-day activity diary (24). The LAPAQ had a reasonably good repeatability (0.65–0.75) and the correlations between this questionnaire with the pedometer and the diary were 0.56 and 0.68, respectively (24). LAPAQ has questions concerning the physical activity duration expressed in hours per week and frequency of walking, cycling, sports, gardening, and housework during the previous two weeks (25). Also, the questionnaire has two extra questions to get information about sports that were not asked in previous questions (25).

The intensity of each physical activity was assessed with the metabolic equivalent of task (MET). One MET is defined as 1 kcal/kg/hour (26). The MET-hours per week for each participant were calculated by multiplying the MET-value by time (in hours) spent on the specific activity for each activity and summing all activities per week (26). MET values were assigned to all activities based on the Compendium of Physical Activity of 2011 (27). Sports that were not in this compendium were not included in the analyses (28).

Covariates

We adjusted for potential confounders based on previous research, data availability and biological plausibility (29, 30). Alcohol consumption was assessed with a questionnaire and addressed as number of glasses of alcohol per day. Smoking was assessed with a questionnaire and categorized as never, past and current smoking. Cardiovascular disease (CVD) was defined as the presence of heart failure, stroke, atrial fibrillation or coronary heart disease. The prevalence of CVD was assessed through interview and verified in medical records (22, 31). Diet was assessed by a food-frequency questionnaire, and a diet quality score was calculated as described previously (32). Height and weight were measured at the research center and BMI was defined as weight/height^2, with weight in kilograms and height in meters.

Statistical analyses

We studied the association of TSH or FT4 with physical activity expressed as MET*hours/week by cross-sectional analysis. Also, we prospectively investigated the association between thyroid function and physical activity as the outcome variable in the longitudinal analyses adjusting for physical activity at baseline. The first model was adjusted for sex and age. The second model additionally included smoking, alcohol and diet and was regarded as our main model. In a third model, we additionally adjusted for BMI and prevalent CVD, which can be confounders a well as mediators. Furthermore, to explore if thyroid autoimmunity has a role on physical activity levels we studied the cross-sectional and prospective association between TPOAb and physical activity, additionally adjusting for TSH or FT4. TSH was logarithmically transformed to approach a normal distribution.

We also performed several sensitivity analyses: a) In participants with TSH within the reference range (between 0.4 and 4 mIU/L), b) additionally by restricting the analysis to participants with FT4 within the reference range, and c) we cross-sectionally and longitudinally performed our analyses in moderate (defined as 3 to 6 METS) and vigorous (defined as higher than 6 METS) physical activity, measured with LASA questionnaire and expressed in MET*hours/week. Additionally, we checked for non-linearity, but we did not find evidence for that. We checked for interaction between several variables (sex, age, BMI, prevalent CVD and diet) and thyroid function and planned a stratified analysis if the p-value for interaction was <0.1.

Multiple imputation was performed for covariates with missing data (the rate of missingness for all variables was <1%, except for CVD, BMI and diet, which were missing in 8%, 9% and 31%, respectively) (33). Statistical analyses were performed using R statistical software (rms package, R version 3.2.2 (34)).

RESULTS

We included a total of 2,470 subjects and their baseline characteristics are summarized in Table 1. Of those, 1,907 also had repeated measurement of physical activity. The mean age was 57.3 years and 58% were women. The median TSH was 2.04 mIU/L, with an interquartile range of 1.4-2.79. The mean FT4 was 1.21 ng/dL with a standard deviation (SD) of 0.17. The median physical activity was 22.50 MET with an interquartile range of 11.56 to 40.67 (Table 1). The median TSH and mean FT4 concentrations at baseline were very similar between participants in the cross-sectional analyses and longitudinal analyses (Table 1) with an average follow-up time of 5 years, range 2 to 8 years.

Thyroid function and physical activity

In the cross-sectional analyses there was no association in TSH (adjusted mean difference (ß) = 0.65, 95% confidence interval [CI], -1.67; 2.98) and FT4 (ß = 2.76, CI, -7.15; 12.66) levels with the baseline LASA physical activity score in model 2 (Table 2). Similarly, there was no association between TPOAb and physical activity (ß = -1.51, CI, -6.49; 3.47) in model 2 (Supplementary Table 1). Furthermore, our results in the longitudinal analyses also showed no association of thyroid function with physical activity (TSH ß =1.16, CI, -1.31; 3.63; and FT4 ß = -6.63, CI, -17.06; 3.80) in model 2 (Table 3). Also, there was no association between TPOAb and physical activity (ß = 2.63, CI, -2.58; 7.84) in model 2 (Supplementary Table 2). We did not perform stratification analyses as all p-values for interaction terms for sex, age, BMI, prevalent CVD and diet were > 0.1.

Sensitivity analyses

After performing our analyses restricting to participants with TSH and FT4 in the reference range, the lack of association of thyroid function with physical activity persisted in both the cross-sectional and longitudinal analyses (Supplementary Tables 3 and 4). After repeating our analyses in participants with hypo- and hyperthyroidism defined by TSH, the lack of association remained (Supplementary Table 5). Also, there was no association of TSH, FT4 or TPOAb with moderate or vigorous physical activity on cross-sectional or longitudinal analysis after adjusting for multiple testing (data not shown).

DISCUSSION

In this large population-based cohort study, there was no association between thyroid function and physical activity levels as assessed by the LAPAQ questionnaire on physical activity.

Most of the studies so far have focused on the relationship between physical activity and thyroid hormones in athletes and military personal (35),while only very few articles have studied the association of thyroid function and physical performance (defined as the disability or satisfactorly performing activities of daily living) in the general population (36). The studies that have investigated this association were conducted primarily in men (35-37) with very few data in women or with a low sample size (n = < 50) (38-40). Finally, there are no studies that have acquired longitudinal data studying this association. The latter is especially important to disentangle the effect of thyroid hormone on physical activity as opposed to vice versa (i.e. reverse causation). Nevertheless, our results in a large population-based cohort clearly suggest no relation between thyroid function and physical activity levels in cross-sectional or longitudinal analyses.

One of the explanations for our negative findings could be that while thyroid hormones have clear effects on several components of physical capacity, physical activity entails other factors that are not captured by physical capacity. Physical capacity involves different bodily functions, such as skeleton-muscular and cardiovascular system (41). Thyroid hormones have profound effects on these systems (5). However, the link between physical capacity and physical activity is not completely clear (41). Therefore, better or worse physical capacity may not necessarily translate into differences in levels of physical activity (42).

To date, the association between thyroid autoimmunity and physical activity has not been investigated in a population-based setting. Autoimmune thyroid disease (AITD) is not an uncommon finding in patients with other autoimmune disorders (43, 44) such as rheumatoid arthritis (44). In addition, a systematic review suggested that AITD may be associated with osteoarthritis and chronic widespread pain, implicating AITD as an important risk factor for these conditions (45), independent of thyroid function. Despite these possible mechanisms that could change physical activity patterns, our results showed that thyroid autoimmunity itself is not associated with physical activity levels either.

The major strengths of this study are the large number of participants from a population-based cohort. All data were collected irrespective of the baseline thyroid function of participants (i.e. collection was performed blinded). Furthermore, we had a reliable method of outcome ascertainment and were able to adjust for several factors, reducing the possibility of confounding factors.

There are some limitations to our study. The information on physical activity was collected through a self-report questionnaire, where misclassification could be caused by socially desirable answers (24). Furthermore, although the questionnaire showed reasonably good ranking in a previous validation study (24), the LAPAQ was developed and validated for older individuals (69-to-92 year olds) than our study population (45.5 - 89.4 years) and patterns of physical activity might differ across ages. Additionally, we only had information on duration of physical activity. Unfortunately, we did not have information on the intensity of the physical activities. This might lead to non-differential misclassification of physical activity in our population with higher or lower values than the ones that were assigned. This could contribute to our estimates being biased towards the null. Furthermore, since our study is observational, one could argue that reverse causation may have affected the results. However, this is unlikely as we have similar findings in the cross-sectional and longitudinal analyses. In addition, although we adjusted extensively for several confounders, residual confounding cannot be completely ruled out. Finally, the Rotterdam Study population is primarily Caucasian, which limits extrapolation to other ethnicities.

In conclusion, our large population-based study suggests that there is no detectable impact of thyroid function on physical activity levels in a sample of predominantly middle-age-individuals (45.5 - 89.4 years) from the general population. We hypothesize that similar results pertain to exogenously determined thyroid function (i.e. in patients that received LT4 therapy). This is relevant in case thyroid hormone therapy is given with the intention to improve daily physical activity levels in adults, especially in individuals with subclinical hypothyroidism. Further studies are required to replicate our results, including other populations (i.e. ethnicity and age group) and with patients on LT4 therapy specifically.

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Authors Contributions Statement

OHRD performed the analyses and drafted the manuscript. OHF, RPP and LC conceived the study and RPP and LC supervised the analyses and drafting of the manuscript. All authors and co-authors have taken part in writing the manuscript, reviewing it, and revising its intellectual and technical content.

Authors Disclosure Statement

The authors declare they have nothing to disclose.

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Data Availability Statement

Data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (secretariat.epi@erasmusmc.nl), which has a protocol for approving data requests.

REFERENCES

1. Silva J 2003 THe thermogenic effect of thyroid hormone and its clinical implications. Annals of Internal Medicine **139**:205-213.

2. Mainenti MRM, Vigario PS, Teixeira PFS, Maia MDL, Oliveira FP, Vaisman M 2009 Effect of levothyroxine replacement on exercise performance in subclinical hypothyroidism. Journal of endocrinological investigation **32**:470-473.

3. Roberts CGP, Ladenson PW 2004 Hypothyroidism. The Lancet **363**:793-803.

4. Rhee EP, Scott JA, Dighe AS 2012 Case 4-2012. New England Journal of Medicine **366**:553-560.

5. Hall JE, Ac G 2015 Guyton and Hall textbook of medical physiology. 13th Editi. Saunders.

6. Paul MY 2001 Physiological and Molecular Basis of Thyroid Hormone Action. Physiological Reviews **81**:1097-1142.

7. Udovcic M, Pena RH, Patham B, Tabatabai L, Kansara A 2017 Hypothyroidism and the Heart. Methodist Debakey Cardiovasc J **13**:55-59.

8. Ip EJ, Barnett MJ, Tenerowicz MJ, Perry PJ 2011 The Anabolic 500 Survey: Characteristics of Male Users versus Nonusers of Anabolic-Androgenic Steroids for Strength Training. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy **31**:757-766.

9. Thompson H 2012 Performance enhancement: Superhuman athletes. Nature **487**:287.

10. Albertson TE, Chenoweth JA, Colby DK, Sutter ME 2016 The Changing Drug Culture: Use and Misuse of Appearance- and Performance-Enhancing Drugs. FP Essent **441**:30-43.

11. Hausmann R, Hammer S, Betz P 1998 Performance enhancing drugs (doping agents) and sudden death – a case report and review of the literature. International Journal of Legal Medicine **111**:261-264.

12. Kasper JD, Chan KS, Freedman VA 2017 Measuring Physical Capacity. J Aging Health **29**:289-309.

13. Bannett RR, Sampson SR, Shainberg A 1984 Influence of thyroid hormone on some electrophysiological properties of developing rat skeletal muscle cells in culture. Brain Res **294**:75-82.

14. Flavia FB, Aline C, Tania Maria O-C 2018 Role of thyroid hormone in skeletal muscle physiology. **236**:R57.

15. Caspersen CJ, Powell KE, Christenson GM 1985 Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep **100**:126-131.

16. Harper ME, Seifert EL 2008 Thyroid hormone effects on mitochondrial energetics. Thyroid **18**:145-156.

17. Chaker L, van den Berg ME, Niemeijer MN, Franco OH, Dehghan A, Hofman A, Rijnbeek PR, Deckers JW, Eijgelsheim M, Stricker BH, Peeters RP 2016 Thyroid Function and Sudden Cardiac Death: A Prospective Population-Based Cohort Study. Circulation **134**:713-722.

18. Chaker L, Heeringa J, Dehghan A, Medici M, Visser WE, Baumgartner C, Hofman A, Rodondi N, Peeters RP, Franco OH 2015 Normal Thyroid Function and the Risk of Atrial Fibrillation: the Rotterdam Study. The Journal of Clinical Endocrinology & Metabolism **100**:3718-3724.

19. Chaker L, Baumgartner C, Ikram MA, Dehghan A, Medici M, Visser WE, Hofman A, Rodondi N, Peeters RP, Franco OH 2014 Subclinical thyroid dysfunction and the risk of stroke: a systematic review and meta-analysis. Eur J Epidemiol **29**:791-800.

20. Koolhaas CM, Dhana K, Schoufour JD, Ikram MA, Kavousi M, Franco OH 2017 Impact of physical activity on the association of overweight and obesity with cardiovascular disease: The Rotterdam Study. Eur J Prev Cardiol **24**:934-941.

21. Zimmermann-Belsing T, Brabant G, Holst JJ, Feldt-Rasmussen U 2003 Circulating leptin and thyroid dysfunction. European Journal of Endocrinology **149**:257-271.

22. Ikram MA, Brusselle G, Ghanbari M, Goedegebure A, Ikram MK, Kavousi M, Kieboom BCT, Klaver CCW, de Knegt RJ, Luik AI, Nijsten TEC, Peeters RP, van Rooij FJA, Stricker BH, Uitterlinden AG, Vernooij MW, Voortman T 2020 Objectives, design and main findings until 2020 from the Rotterdam Study. European Journal of Epidemiology **35**:483-517.

23. Chaker L, Heeringa J, Dehghan A, Medici M, Visser WE, Baumgartner C, Hofman A, Rodondi N, Peeters RP, Franco OH 2015 Normal Thyroid Function and the Risk of Atrial Fibrillation: the Rotterdam Study. J Clin Endocrinol Metab **100**:3718-3724.

24. Stel VS, Smit JH, Pluijm SM, Visser M, Deeg DJ, Lips P 2004 Comparison of the LASA Physical Activity Questionnaire with a 7-day diary and pedometer. J Clin Epidemiol **57**:252-258.

25. Koolhaas CM, Dhana K, Van Rooij FJA, Schoufour JD, Hofman A, Franco OH 2018 Physical activity types and health-related quality of life among middle-aged and elderly adults: the Rotterdam study. The journal of nutrition, health & aging **22**:246-253.

26. de Bruijn RFAG, Schrijvers EMC, de Groot KA, Witteman JCM, Hofman A, Franco OH, Koudstaal PJ, Ikram MA 2013 The association between physical activity and dementia in an elderly population: the Rotterdam Study. European Journal of Epidemiology **28**:277-283.

27. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, Greer JL, Vezina J, Whitt-Glover MC, Leon AS 2011 2011 Compendium of Physical Activities: a second update of codes and MET values. Medicine & science in sports & exercise **43**:1575-1581.

28. Koolhaas CM, Dhana K, Schoufour JD, Lahousse L, van Rooij FJA, Ikram MA, Brusselle G, Tiemeier H, Franco OH 2018 Physical activity and cause-specific mortality: the Rotterdam Study. Int J Epidemiol **47**:1705-1713.

29. King AC, Blair SN, Bild DE, Dishman RK, Dubbert PM, Marcus BH, Oldridge NB, Paffenbarger RS, Jr., Powell KE, Yeager KK 1992 Determinants of physical activity and interventions in adults. Med Sci Sports Exerc **24**:S221-236.

30. Chaker L, Korevaar TI, Medici M, Uitterlinden AG, Hofman A, Dehghan A, Franco OH, Peeters RP 2016 Thyroid Function Characteristics and Determinants: The Rotterdam Study. Thyroid **26**:1195-1204.

31. Leening MJ, Kavousi M, Heeringa J, van Rooij FJ, Verkroost-van Heemst J, Deckers JW, Mattace-Raso FU, Ziere G, Hofman A, Stricker BH, Witteman JC 2012 Methods of data collection and definitions of cardiac outcomes in the Rotterdam Study. Eur J Epidemiol **27**:173-185.

32. Voortman T, Kiefte-de Jong JC, Ikram MA, Stricker BH, van Rooij FJA, Lahousse L, Tiemeier H, Brusselle GG, Franco OH, Schoufour JD 2017 Adherence to the 2015 Dutch dietary guidelines and risk of non-communicable diseases and mortality in the Rotterdam Study. Eur J Epidemiol **32**:993-1005.

33. van Buuren S, Groothuis-Oudshoorn K, Robitzsch A, Vink G, Doove L, Jolani S 2015 Package 'mice'. Vienna: Comprehensive R Archive Network.

34. R Core Team 2020 R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria.

35. Opstad PK, Falch D, Öktedalen O, Fonnum F, Wergeland R 1984 The thyroid function in young men during prolonged exercise and the effect of energy and sleep deprivation. Clinical endocrinology **20**:657-669.

36. Van den Beld AW, Visser TJ, Feelders RA, Grobbee DE, Lamberts SWJ 2005 Thyroid hormone concentrations, disease, physical function, and mortality in elderly men. The Journal of Clinical Endocrinology & Metabolism **90**:6403-6409.

37. Huang W-S, Yu M-D, Lee M-S, Cheng C-Y, Yang S-P, Chin H-ML, Wu S-Y 2004 Effect of treadmill exercise on circulating thyroid hormone measurements. Medical Principles and Practice **13**:15-19.

38. Baylor LS, Hackney AC 2003 Resting thyroid and leptin hormone changes in women following intense, prolonged exercise training. Eur J Appl Physiol **88**:480-484.

39. Loucks AB, Callister R 1993 Induction and prevention of low-T3 syndrome in exercising women. Am J Physiol **264**:R924-930.

40. Krotkiewski M, SjÖStrÖM L, Sullivan L, Lundberg PA, Lindstedt G, Wetterqvist H, BjÖRntorp P 1984 The Effect of Acute and Chronic Exercise on Thyroid Hormones in Obesity. Acta Medica Scandinavica **216**:269-275.

41. Martínez-Vizcaíno V, Sánchez-López M 2008 Relationship between physical activity and physical fitness in children and adolescents. Revista Española de Cardiología (English Edition) **61**:108-111.

42. Dencker M, Thorsson O, Karlsson MK, Lindén C, Svensson J, Wollmer P, Andersen LB 2006 Daily physical activity and its relation to aerobic fitness in children aged 8–11 years. European Journal of Applied Physiology **96**:587-592.

43. Frohlich E, Wahl R 2017 Thyroid Autoimmunity: Role of Anti-thyroid Antibodies in Thyroid and Extra-Thyroidal Diseases. Front Immunol **8**:521.

44. Cardenas Roldan J, Amaya-Amaya J, Castellanos-de la Hoz J, Giraldo-Villamil J, Montoya-Ortiz G, Cruz-Tapias P, Rojas-Villarraga A, Mantilla RD, Anaya JM 2012 Autoimmune thyroid disease in rheumatoid arthritis: a global perspective. Arthritis **2012**:864907.

45. Tagoe CE, Sheth T, Golub E, Sorensen K 2019 Rheumatic associations of autoimmune thyroid disease: a systematic review. Clinical rheumatology:1-9.

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Tables

Table 1. Baseline characteristics

	Cross-sectional analyses N = 2470	**Longitudinal analyses N = 1907**
Characteristics	Mean (SD)	Mean (SD)
Women, N (%)	1429 (58%)	1125 (59 %)
Age (years)	57.3 (6.5)	56.8 (5.7)
Glasses alcohol/day	1.1 (2.3)	1.0 (2.1)
Smoking, N (%)		
Never	782 (31.6%)	628 (32.9%)
Former	1103 (44.7%)	877 (46%)
Current	585 (23.7%)	402 (21.1%)
BMI (kg/m2)	27.4 (4.49)	27.3 (4.34)
TSH (mU/l), median (IQR)	2.04 (1.4-2.79)	2.05 (1.4-2.8)
FT4 (ng/dL)	1.21 (0.17)	1.20 (0.17)
TPOAb positive, N (%)	316 (12.82%)	257 (13.50%)
Physical activity level METh/week, median (IQR)	22.50 (11.56-40.67)	24 (12.24-44.21)
CVD, N (%)	204 (8.3%)	131 (6.9%)

Values are in mean and standard deviation unless otherwise specified.

Abbreviations: SD, standard deviation; BMI, body mass index; TSH, thyroid stimulating hormone; IQR, interquartile range; FT4, free thyroxin; TPOAb, thyroid peroxidase antibodies; CVD, cardiovascular disease; HDL, high density lipoprotein; The cutoff for TPOAb positivity was 35 KU/ml, METh/week; Metabolic Equivalent Task*hours/week

Table 2. Cross-sectional associations between thyroid function and physical activity (Metabolic Equivalent Task*hours/week).

	N = 2470	
	FT4 (ng/dL)	**TSH (mIU/L)**
	Beta (95% CI)	**Beta (95% CI)**
Model I	3.93 (-5.97; 13.84)	0.79 (-1.53; 3.11)
Model II	2.76 (-7.15; 12.66)	0.65 (-1.67; 2.98)
Model III	2.40 (-7.54; 12.34)	0.66 (-1.67; 2.98)

Abbreviations: N, number; CI, confidence interval; FT4, free thyroxin; TSH, log-transformed thyroid stimulating hormone.

Beta: Adjusted mean difference per unit increase

Model I: Adjusted for sex and age.

Model II: Model I + smoking, alcohol consumption and diet.

Model III: Model II + BMI and CVD.

Table 3. Longitudinal associations between thyroid function and physical activity (Metabolic Equivalent Task*hours/week).

	N = 1907	
	FT4 (ng/dL)	**TSH (mIU/L)**
	Beta (95% CI)	**Beta (95% CI)**
Model I	-5.54 (-15.93; 4.84)	1.09 (-1.37; 3.55)
Model II	-6.63 (-17.06; 3.80)	1.16 (-1.31; 3.63)
Model III	-7.56 (-17.99; 2.88)	1.10 (-1.36; 3.57)

Abbreviations: N, number; CI, confidence interval; FT4, free thyroxin; TSH, log-transformed thyroid stimulating hormone.

Beta: Adjusted mean difference per unit increase

Mean (range) of follow-up was 5 (2 to 8) years.

Model I: Adjusted for baseline physical activity, sex and age.

Model II: Model I + smoking, alcohol consumption and diet.

Model III: Model II + BMI and CVD.

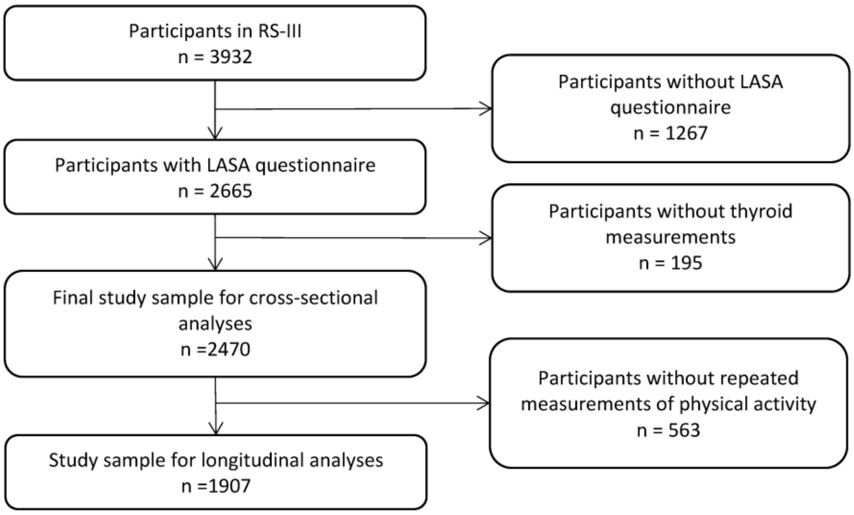

Figure 1. Flowchart of the study sample.

Abbreviation RS- III, Rotterdam Study third cohort.