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PHYSICAL ACTIVITY, HEALTH AND EXERCISE

Physical activity, sports participation and exercise-related constraints in adult women with primary hypothyroidism treated with thyroid hormone replacement therapy

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ABSTRACT

Awareness of physical activity (PA) constraints in patients with primary hypothyroidism on thyroid hormone replacement therapy (THR) is important. Hence, this cross-sectional matched case-control study aimed to determine PA and sports participation (SP) in patients with hypothyroidism on THR in comparison to control subjects. Accordingly, survey questions were selected from the National Survey on Injuries and Physical Activity in the Netherlands (IPAN), supplemented with questions related to self-reported clinical characteristics and exercise-related constraints (ERC) of patients. In total, 1,724 female patients (mean age 53.0 years ±11.6) and 1,802 controls (mean age 52.6 ± 13.2) were included. Compared to controls, patients were less likely to comply with the moderate-intensity PA guideline (OR 0.70; 95% CI: 0.611–0.803), although patients were more actively participating in sports (OR 1.40; 95% CI: 1.156–1.706). Two-thirds of patients reported that hypothyroidism was limiting their PA performance. These limitations were more pronounced in patients with autoimmune thyroiditis (AIT) than in patients with hypothyroidism from other aetiology (OR 1.93; 95% CI: 1.518–2.457), representing disease-specific exercise intolerance. In order to establish effective intervention programmes to encourage regular PA in hypothyroid patients on THR with exercise intolerance, further research is warranted to better understand PA barriers.

ARTICLE HISTORY
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KEYWORDS
Autoimmune thyroiditis; comorbid conditions; exercise tolerance; Hashimoto disease; physical fitness

1. Introduction

Primary hypothyroidism is the second most common endocrine disease worldwide after diabetes mellitus and is caused by thyroid hormone deficiency. Hypothyroidism can be categorised based on its time of onset (congenital or acquired) and its severity, as in overt (clinical), subclinical, and mild diseases (Biondi & Wartofsky, 2014). The prevalence of overt hypothyroidism in the general population varies between 0.3% and 3.7% in the USA and between 0.2% and 5.3% in Europe (Åsvold et al., 2013; Aoki et al., 2007; Canaris et al., 2000; Garmendia Madariaga et al., 2014; Hollowell et al., 2002), depending on the definition used (Chaker et al., 2017). Hypothyroidism affects women 10 times more frequently than men, and its rate increases with age (Vanderpump, 2011). Hashimoto's thyroiditis, which is also referred to as autoimmune thyroiditis (AIT), is characterised by the presence of thyroid peroxidase antibody (TPO-Ab) in serum and is the most common cause of hypothyroidism (Caturegli et al., 2014; Chaker et al., 2017; Vanderpump, 2011). The standard treatment of hypothyroidism is thyroid hormone replacement therapy (THR) with levothyroxine (Chaker et al., 2017), which is one of the main prescribed drugs worldwide (Korevaar et al., 2018).

Hypothyroidism can have a considerable negative impact on the quality of life (McMillan et al., 2004), including persistent fatigue and exercise intolerance (Lankhaar et al., 2014; McAllister et al., 1995). In general, it is presumed that adequate THR in hypothyroidism will improve quality of life and reverse impairments of cardiovascular, respiratory, and muscle functions at rest and during exercise. However, approximately 10–15% of patients on THR with levothyroxine continue to experience impaired quality of life (Hennessey & Espaillat, 2018; Peterson et al., 2018; Watt et al., 2006; Wiersinga, 2019), including physical constraints and exercise intolerance (Lankhaar et al., 2014). Moreover, the mere presence of TPO-Ab in AIT patients has been linked to a decreased quality of life (Ott et al., 2011; Wiersinga, 2019). As a result, continual physical constraints can lead to a negative spiral of deconditioning, resulting in a further loss of functional capacity and the ability to perform physical activity (PA) and exercise (Verbunt et al., 2003).

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Hedwig Hofstetter has changed jobs, whereas Pierre M.J. Zelissen has retired.

Physical inactivity has been identified as the fourth leading risk factor for global mortality. Therefore, the promotion of PA has increasingly been recognised as a priority for public health action and many countries have responded through the development of global recommendations on PA for health (World Health Organization, 2010). Studies have shown that patients with chronic diseases (including autoimmune diseases) are more physically inactive as compared to the general population (Hildebrandt et al., 2015; Sharif et al., 2018). According to a study using data from the US National Health and Nutrition Examination Survey (NHANES), this also applies to patients with hypothyroidism, as the reported PA levels of hypothyroid patients on THR were lower compared to the general population (Peterson et al., 2018, 2016). However, little is known about the nature and extent of PA, sports participation (SP) and exercise-related constraints (ERC) among the population with hypothyroidism on THR.

The aim of this survey was to investigate PA and SP in patients with primary hypothyroidism on THR and to compare the outcomes with those of the control population by means of a cross-sectional matched case–control survey. In order to meet the recommendations on PA for health, it is of vital importance to know if there are exercise-related barriers for this target group. Therefore, we investigated the ERC in the patients group as well.

2. Methods

2.1. Study population

We performed a cross-sectional matched case–control study in which patients with primary hypothyroidism on THR were compared with a control population. The study was approved by the Medical Ethics Review Committee of the University Medical Center Utrecht, the Netherlands (METC number 13–684/C). Since the study concerned an anonymous survey, an informed consent was not needed. For our study, all members of the Dutch thyroid patient organisation (Schildklier Organisatie Nederland, SON) with a registered email address received an invitation by email with a request to participate in a survey. As a unique reference URL was generated and subsequently validated for each individual email address, duplicates in this anonymous survey were precluded. During the period of 13 March until 14 April 2014, members of SON could complete the survey. Within this period, reminders were sent twice by email to members who did not respond. Inclusion criteria for the patients group were: (a) primary hypothyroidism, (b) treatment with THR, (c) aged ≥18 years, and (d) ability to understand the Dutch language. To investigate PA and SP in patients and to compare the outcomes with those of the control population, survey questions were selected from a large existing population-based study, called "Injuries and Physical Activity in the Netherlands" (IPAN). IPAN is a national continuous survey and database on injuries, PA and SP, operated by the Dutch Consumer Safety Institute (VeiligheidNL). Each year a representative sample of about 11,000 members are questioned for IPAN, either by telephone or online (Kemler et al., 2018). For our study, control subjects were selected from the IPAN database and matched for age and sex. In order to have sufficient matched control subjects, the survey period of the control subjects was taken at a wider range (1 July 2013 and 31 December 2014). Control subjects were matched into non-overlapping subgroups, in order to assure that patients and control subjects would have the same distributions (defined by age group: 18–30 years, 31–50 years, 51–70 years, and >70 years). Specific exclusion criteria for control subjects were having missing values on the outcome measures. Control data were provided by the Netherlands Organisation for Applied Scientific Research (TNO: www.tno.nl) and Mulier Institute (www.mulierinstituut.nl), two independent Dutch research organisations in social sciences.

2.2. Primary hypothyroidism

Patients were asked to self-report the cause of primary hypothyroidism. The outcome of this survey question would be the basis for dividing the patients group into three subgroups: 1) AIT group consisting of patients with primary hypothyroidism caused by Hashimoto's thyroiditis, 2) Non-AIT group consisting of patients with primary hypothyroidism caused by thyroidectomy, radioiodine I-131 therapy, neck irradiation for conditions other than thyroid diseases, congenital hypothyroidism, medication (such as lithium, amiodarone) and De Quervain's thyroiditis, and 3) Unknown group consisting of patients with primary hypothyroidism in which the cause of hypothyroidism is unknown to the patient.

2.3. Clinical characteristics

For the patients group, self-reported clinical characteristic involved the results of the most recent thyroid function blood test, i.e. thyroid-stimulating hormone (TSH in mU/L), free thyroxine (FT_4 in pmol/L), free 3,5,5′-triiodothyronine (FT_3 in pmol/L), or unknown. Respondents were also asked what type(s) of THR were used as primary treatment of hypothyroidism, with the following options (combinations were possible): levothyroxine (mcg per day), liothyronine (mcg per day), desiccated thyroid extract from animal origin (mg per day), and unknown. Finally, respondents were asked which comorbid conditions were restricting PA performance currently besides hypothyroidism, e.g., asthma, depression, diabetes mellitus, etc.

2.4. General characteristics

Gender (male or female), age (years), height (cm) and weight (kg) of the respondents were self-reported. BMI was defined as weight in kilograms divided by height in metres squared (kg per m^2). BMI was categorised as underweight (<18.5 kg per m^2), normal weight (18.5–24.9 kg per m^2), overweight (25–29.9 kg per m^2), obesity (30.0–39.9 kg per m^2) and morbid obese (≥40 kg per m^2). To limit the asking time for respondents in the IPAN sample, only one-fourth was questioned about height and weight, i.e. a random subsample of 436 control subjects was included in the analysis. Self-reported education level was categorized into lower (no school graduation, lower general secondary education), middle (higher general secondary education, pre-university education, vocational school) and high education (Bachelor degree, Master degree).

2.5. Perceived health and physical fitness

Two survey questions from the IPAN survey on self-reported perceived health and physical fitness were included. Data concerning self-reported health was obtained by the question: "How do you rate your own health in general?" Participants were asked to rate their own physical fitness as "good", "moderate", "bad" or "do not know". A similar question was used to obtain data concerning self-reported physical fitness: "How do you rate your own physical fitness in general?", and respondents were asked to rate their own physical fitness as "good", "moderate", "bad" or "do not know". To limit the asking time for respondents in the IPAN sample, only one-fourth was questioned about their own perception on health and physical fitness, i.e. a random subsample of 462 control subjects was included in the analysis.

2.6. Physical activity

PA evaluation was based on two Dutch guidelines, i.e. the moderate-intensity aerobic physical activity (MPA) and the vigorous-intensity aerobic physical activity (VPA) guideline. Adults meet the MPA guideline if they engage in MPA during at least 30 minutes a day at minimally five days a week, during summer- and wintertime. Examples of MPA are activities with intensities that are at least equal to walking at a firm pace or cycling. Adults meet the VPA guideline if they engage in VPA during at least 20 min for at least three times a week, during summer- and wintertime. VPA is defined as strenuous physical/sport activity during leisure time that makes you sweat (Bernaards et al., 2016).

2.7. Sports participation

To determine sports behaviour, we asked the participants whether they engaged in sports activities during the past 12 months and if they did so, how many weeks or how many times during this period. In our study, respondents were considered sports participants if they engaged in sports activities at least once a week or at least 40 times a year, regardless of the type of sports (Bernaards et al., 2016).

2.8. Exercise-related constraints

The most common ERC reported in hypothyroid patients were selected for the survey (Lankhaar et al., 2014). Examples of these complaints are fatigue, prolonged recovery post-exercise, precarious level of exercise performance and muscle complaints. Patients were asked to indicate the self-reported complaints in the categories "none", "some", "much" and "extreme" as experienced during the past 12 months. Beside, patients were asked whether their current condition of hypothyroidism was limiting their PA performance, and the answer could be "yes" or "no".

2.9. Statistical analyses

In the IPAN database, 61.7% of the healthy adults meet the recommendations on PA for health, compared to 54.9% of adults with a chronic disease (unpublished data). A group sample size of 825 in the group patients and 825 in the group with healthy Dutch adults was needed to detect a difference in adherence to the norm of PA between the group proportions of 0.068 ($\alpha < .05$) with a power of 80%. Sample size calculation was based on unadjusted analysis and did not account for any anticipated alteration in power resulting from controlling for confounding factors (because matching on confounders typically leads to an increase in power). Continuous variables were reported as mean, standard deviation (SD) or as median with interquartile range (IQR) in case of highly skewed variables. Percentages were determined for categorical variables. Chi-square tests (for categorical variables, X^2 and degrees of freedom (df) are presented) were used to test for differences in characteristics between the patient and control groups. Univariate logistic regression analysis was used to determine the association between physical activity and sports participation of adult female patients with primary hypothyroidism on THR compared to a cross-section of the Dutch population. In addition, univariate logistic regression analysis was also used to determine the association between the aetiology of hypothyroidism and ERC. In this cross-sectional study, controls were matched for age and sex. As education level has shown to be strongly associated with time spent in PA (Droomers et al., 1998; Piirtola et al., 2016), education level was considered as a potential confounding factor in the univariate logistic regression analysis. As for BMI, it may be argued that this variable qualifies as a mediator between primary hypothyroidism and PA/SP or be a consequence of low PA/SP. Therefore, BMI was not considered as a potential confounding factor in the univariate logistic regression analysis. The odds ratios (OR) were presented with 95% confidence intervals (CI). Statistical analysis were performed using SPSS Statistics for Windows version 23.0. Values of $p < .05$ were considered statistically significant for all tests.

3. Results

3.1. Study population

A total of 5,363 patients, being a member of SON, received an invitation by email to participate in the online survey. Subsequently, 2,119 patients completed the survey (response rate 39.5%). Only 175 male respondents (8.3%) completed the survey. As the percentage of male respondents was low for statistical analysis, it was decided to exclude this subgroup due to lack of representativeness and instead focus on the group of female respondents. Other exclusion criteria were: (a) surveys with missing values on the outcome measures (n = 80), (b) no treatment with THR (n = 101), (c) no primary hypothyroidism (i.e. Graves' disease (n = 24) and secondary hypothyroidism (n = 4)), and (d) aged < 18 years (n = 11). After excluding these cases, 1,724 female patients were included in the analyses (see Figure 1). In addition, 1,802 female controls were included in the study. The patients and controls were comparable in terms of age group.

3.2. Clinical characteristics of patients

Table 1 shows the self-reported clinical characteristics of the included patients. AIT was the main cause of primary hypothyroidism (46.3%), whereas 25.4% of the patients reported that they were unsure of hypothyroidism aetiology. The vast majority of patients used levothyroxine as primary treatment (98.4%).

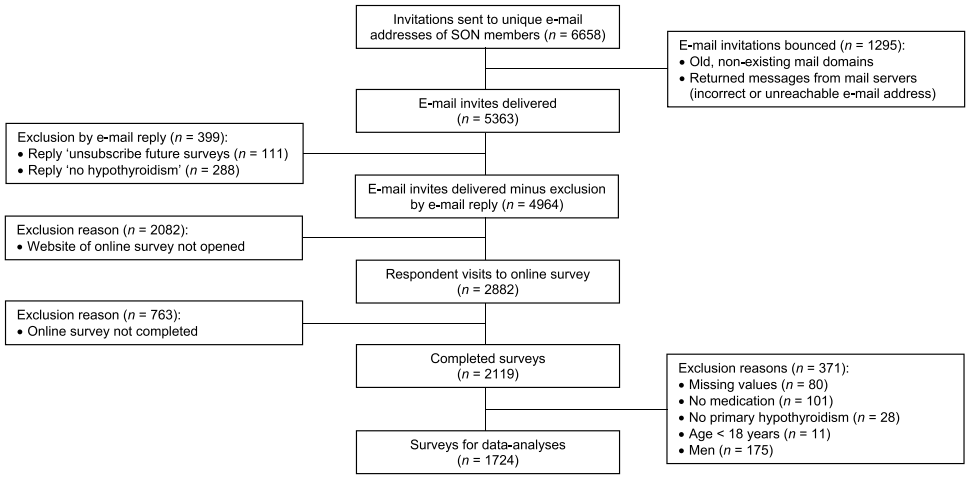

Figure 1. Flow diagram of a survey among adult female patients with primary hypothyroidism on thyroid hormone replacement therapy. *Abbreviation*: SON, the Dutch thyroid patient organisation "Schildklier Organisation Nederland".

Regarding self-reported comorbid conditions restricting PA besides hypothyroidism, osteoarthritis (22.3%) was scored highest by patients, followed by vitamin B12 deficiency (9.2%) and asthma (7.5%). In total, 54.2% of the patients reported one or more comorbid conditions restricting PA.

3.3. General characteristics

As Table 2 shows, more than half of the patients were within the age range of 51–70 years (57.4%). Almost half of the patients had completed a high education level compared to 35.6% of the controls ($p < .001$). The mean BMI of patients (26.7 kg per m^2 (±5.2)) and controls (26.3 kg/m2 (±5.7)) was not significantly different ($p = .109$). Both the own perception on health as the own perception on physical fitness was significantly lower in patients (55.3% and 39.8%) compared to controls (69.9% and 50.2%) in the category "good" (own perception on health: $p < .001$; own perception on physical fitness: $p < .001$).

3.4. Physical activity and sports participation

As summarised in Table 3, patients were less likely to comply with the MPA guideline compared to controls (OR 0.70; 95% CI: 0.611–0.803). In contrast, no significant association was found with compliance to the VPA guidelines (OR 1.03; 95% CI: 0.873–1.220). Compared to controls, patients were more actively engaged in sports activities (OR 1.40; 95% CI: 1.156–1.706) and participated more often in two or more types of sports (OR 2.45; 95% CI: 1.974–3.047). The most popular types of PA performed by patients were brisk walking (54.5%), aerobics/fitness (48.5%) and swimming (31.1%). Compared to controls, patients were more actively participating in brisk walking (OR 1.92; 95% CI: 1.590–2.323), cycling (OR 1.73; 95% CI: 1.376–2.181) and yoga (OR 2.28; 95% CI: 1.716–3.034). When comparing controls with the hypothyroid subgroups, AIT patients were more actively participating in all sports except for aerobics/fitness, whereas non-AIT patients were more actively engaging in all sports except for swimming.

3.5. Exercise-related constraints of patients

As Table 4 shows, the main self-reported ERC (as calculated by the total of categories "much" and "extreme") in the total patients group were muscle pain (75.1%), fatigue after exercise (43.3%) and arthralgia (36.9%). Moreover, general fatigue (OR 0.77; 95% CI: 0.598–0.999), fatigue after exercise (OR 0.76; 95% CI: 0.606–0.960) and prolonged recovery post-exercise (OR 0.75; 95% CI: 0.576–0.980) were less often perceived by non-AIT patients than AIT patients. As shown in Tables 3, 66.9% of all patients indicated that the current condition of hypothyroidism was limiting their PA performance. Additional analysis showed that these PA limitations were more pronounced in AIT patients than in non-AIT patients (73.7 vs 58.8%, OR 1.93; 95% CI: 1.518–2.457). In a supplementary univariate logistic regression analysis, which was corrected for the number of comorbid conditions and education level, a significant higher odds ratio was demonstrated for the association between AIT patients and PA limitations compared to non-AIT patients (OR 1.99; 95% CI: 1.562–2.546).

4. Discussion

The present study reports the results on PA, SP and ERC in patients with hypothyroidism on THR, uncovering several novel factors that are associated with exercise intolerance. Limited PA and SP data in the literature exists regarding the hypothyroid population, but as a general trend, patients with chronic diseases (including autoimmune diseases) tend to be less physically active as compared to the general population (Hildebrandt et al., 2015; Peterson et al., 2016; Sharif et al., 2018). Although our study suggests that MPA was lower in patients compared to controls, patients were more engaged in sports activities and participated more often in more than one type of sports compared to controls. This might indicate that the patient group is aware of the importance and positive effects of exercise on their general

Table 1. Clinical characteristics of adult female patients with primary hypothyroidism on thyroid hormone replacement therapy (*N = 1724*).

	Total patient group (*N* = 1724)
Thyroid function parameters	
TSH in mU/l (median (IQR))	0.9 (0.3–2.1)
FT_4 in pmol/l (median (IQR))	17.9 (15.4–20.0)
FT_3 in pmol/l (median (IQR))	4.7 (3.9–5.4)
Primary treatment [a]	
Levothyroxine (%)	98.4
Liothyronine (%)	9.3
Desiccated thyroid extract from animal origin (%)	2.7
Unknown (%)	0.4
Cause of primary hypothyroidism	
Hashimoto's thyroiditis (%)	46.3
Radioiodine I-131 therapy (%)	15.0
Thyroidectomy (%)	9.0
Congenital hypothyroidism (%)	3.5
De Quervain's thyroiditis (%)	0.6
After neck irradiation for non-thyroid condition (%)	0.1
Medication (e.g., lithium, amiodarone) (%)	0.1
Unknown (%)	25.4
Top 10 of comorbid conditions restricting physical activity others than hypothyroidism	
Osteoarthritis (%)	22.3
Vitamin B12 deficiency (%)	9.2
Asthma (%)	7.5
Fibromyalgia (%)	6.6
Depression (%)	5.7
Heart disease (%)	5.3
Diabetes mellitus (%)	3.6
Rheumatoid arthritis (%)	3.0
Malignant tumour (%)	2.9
Anaemia (%)	1.7
Number of comorbid conditions restricting physical activity others than hypothyroidism	
n = 0 (%)	45.8
n = 1 (%)	31.6
n = 2 or more (%)	22.6

Note: Data are expressed as median (IQR) or proportion of patients (%).
Abbreviations: TSH = Thyroid-stimulating hormone, FT_4 = Free thyroxine, FT_3= Free 3,5,5′-triidothyronine, IQR = Interquartile range indicating the extent to which the central 50% of values within the dataset are dispersed (it is based upon, and related to, the median).
[a]Patients use multiple therapies at the same time, making the total more than 100.

health. Also, when recruiting members of SON, we may have approached an active group by using the research title "Sports and exercise with hypothyroidism". Another possible explanation is educational attainment, i.e. physical inactivity is more prevalent in the lower educational groups (Droomers et al., 1998; Piirtola et al., 2016). In our study, the educational level of the patient group was higher compared to the control group. Consequently, we adjusted the univariate logistic regression analysis for education level, revealing that the impact of education level was only significantly different in three separate analyses. This seems to contradict the literature. However, comparison of results is difficult, because other studies have included different target groups, such as the general population (Droomers et al., 1998; Notthoff et al., 2017; Piirtola et al., 2016) or populations with other chronic health diseases (Dontje et al., 2016; Forechi et al., 2018). It could therefore be an indication that education level does not outweigh the negative impact of ERC and disease characteristics in this patient group. Hence, further large-scale studies including hypothyroid patients on THR are needed.

The most frequently reported ERC limiting the PA performance of patients were muscle pain, fatigue, arthralgia, precarious level of exercise performance and diminished physical endurance. Although these aspects are general ERC, it is well known that exercise intolerance in untreated hypothyroidism is multifactorial due to limitations in different functional systems, with cardiovascular, cardiopulmonary, pulmonary, musculoskeletal, neuromuscular and cellular metabolic systems acting in concert. Furthermore, exercise intolerance is not always reversible during biochemically adequate THR, resulting in persistent ERC and chronic limitations in daily activities (Lankhaar et al., 2014). Suggested explanations for persistent constraints include patients' awareness of a chronic disease and lifelong dependency of medication, inadequacy of levothyroxine monotherapy to restore physiological thyroid hormone concentrations of thyroxine and triiodothyronine in serum and tissue, as well as the presence of associated autoimmune diseases besides hypothyroidism (Wiersinga, 2019). ERC can lead to an unwanted inactive lifestyle with similar physiological consequences as observed with physical deconditioning (Painter, 2008; Valkenet et al., 2011), resulting in a further loss of functional capacity and the ability to be engaged in regular PA and sports (Verbunt et al., 2003).

Noteworthy, ERC were more pronounced in AIT patients compared to non-AIT patients as regards general fatigue, fatigue after exercise and prolonged recovery post-exercise. Although no data on TPO-Ab in serum is available from our patient population, it has been reported that the mere

Table 2. General characteristics of adult female patients with primary hypothyroidism on thyroid hormone replacement therapy (N = 1724) versus a cross-section of the Dutch population (N = 1802).

	Patient group								
	Total	AIT	Non-AIT	Unknown	Control group	Comparison between total versus control	Comparison between AIT versus control	Comparison between non-AIT versus control	Comparison between unknown versus control
N	1724	799	488	437	1802				
Age									
18–30 years (%)	3.6	3.3	4.3	3.4	3.5	X^2 = 0.100, df = *3*	X^2 = 10.438, df = *3*	X^2 = 2.879, df = *3*	X^2 = 10.728, df = *3*
31–50 years (%)	34.4	39.0	34.0	26.3	34.2	p = .992	**p = .015**	p = .441	**p = .013**
31–50 years (%)	57.4	55.1	55.3	64.1	57.5				
>70 years (%)	4.6	2.6	6.4	6.2	4.8				
Education level									
Lower (%)	16.3	12.3	18.8	20.8	36.3	X^2 = 171.089, df = *2*	X^2 = 152.560, df = *2*	X^2 = 50.817, df = *2*	X^2 = 37.377, df = *2*
Middel (%)	34.7	34.0	32.8	38.0	28.0	**p < .001**[a]	**p < .001**[a]	**p < .001**[a]	**p < .001**[a]
High (%)	49.0	53.7	48.4	41.2	35.6				
Unknown (%)	0.0	0.0	0.0	0.0	0.1				
BMI									
Underweight (<18.5 kg/m^2) (%)	1.0	1.6	0.6	0.2	2.1	X^2 = 16.053, df = *4*	X^2 = 8.688, df = *4*	X^2 = 10.773, df = *4*	X^2 = 18.835, df = *4*
Normal weight (18.5–24.9 kg/m^2) (%)	41.1	41.6	42.6	38.7	47.9	**p = .003**	p = .069	**p = .029**	**p = .001**
Overweight (25–29.9 kg/m^2) (%)	36.7	36.4	35.5	38.4	30.7				
Obese (30–39.9 kg/m^2) (%)	19.4	18.5	19.7	20.8	16.1				
Morbid obese (≥40 kg/m^2) (%)	1.8	1.9	1.6	1.9	3.2				
Own perception on health									
Good (%)	55.3	52.9	57.0	57.7	69.9	X^2 = 42.228, df = *2*	X^2 = 42.411, df = *2*	X^2 = 20.565, df = *2*	X^2 = 33.034, df = *2*
Moderate (%)	39.8	41.7	37.1	39.6	23.6	**p < .001**[b]	**p < .001**[b]	**p < .001**[b]	**p < .001**[b]
Bad (%)	4.5	5.0	5.7	2.1	6.3				
Do not know (%)	0.4	0.4	0.2	0.7	0.2				
Own perception on physical fitness									
Good (%)	39.8	37.7	42.4	41.0	50.2	X^2 = 17.621, df = *2*	X^2 = 19.462, df = *2*	X^2 = 6.894, df = *2*	X^2 = 11.988, df = *2*
Moderate (%)	49.9	50.2	48.0	51.5	39.6	**p < .001**[b]	**p < .001**[b]	**p = .032**[b]	**p < .002**[b]
Bad (%)	10.0	11.6	9.6	7.6	9.3				
Do not know (%)	0.2	0.5	0.0	0.0	0.9				

Note: Data are expressed proportion of patients and controls (%).

Abbreviations: AIT = Patients with primary hypothyroidism caused by autoimmune thyroiditis, Non-AIT = Patients with primary hypothyroidism caused by thyroidectomy, radioiodine I-131 therapy, neck irradiation for conditions other than thyroid diseases, congenital hypothyroidism, medication and De Quervain's thyroiditis, BMI = Body Mass Index, Df = Degrees of freedom, X^2 = Value Chi square test.

[a]The answer category "Unknown" has been left out for calculation of the p value.

[b]The answer category "Do not know" has been left out for calculation of the p value.

Bold values are significant, $p < .05$.

Table 3. Physical activity and sports participation of adult female patients with primary hypothyroidism on thyroid hormone replacement therapy (*N* = 1724) versus a cross-section of the Dutch population (*N* = 1802).

	Patient group					Effect size OR (95% CI)			
PA and SP variables	Total (n = 1724)	AIT (n = 799)	Non-AIT (n = 488)	Unknown (n = 437)	Control group (n = 1802)	Total vs control	AIT vs control	Non-AIT vs control	Unknown vs control
% hypothyroidism is limiting PA [c]	66.9	73.7	58.8	63.6	-	-	-	-	-
% meeting MPA guidelines	39.8	40.3	41.0	37.8	48.6	**0.70 (0.613–0.800)** [a]	**0.71 (0.603–0.845)** [a]	**0.73 (0.599–0.899)** [a]	**0.64 (0.518–0.795)** [a]
						0.70 (0.611–0.803) [b]	**0.73 (0.610–0.865)** [b]	**0.73 (0.595–0.897)** [b]	**0.64 (0.519–0.800)** [b]
% meeting VPA guidelines	20.6	20.5	22.7	18.3	20.8	0.99 (0.838–1.161) [a]	0.98 (0.800–1.208) [a]	1.12 (0.881–1.425) [a]	0.85 (0.652–1.115) [a]
						1.03 (0.873–1.220) [b]	1.07 (0.863–1.322) [b]	1.17 (0.914–1.487) [b]	0.90 (0.685–1.176) [b]
% participating in sports	80.2	79.5	81.1	80.3	74.8	**1.36 (1.131–1.639)** [a]	**1.31 (1.039–1.647)** [a]	**1.45 (1.084–1.933)** [a]	**1.38 (1.030–1.840)** [a]
						1.40 (1.156–1.706) [b]	**1.38 (1.082–1.758)** [b]	**1.53 (1.138–2.063)** [b]	**1.43 (1.065–1.922)** [b]
% number of types of sports									
One type of sports	18.2	17.3	18.4	19.7	34.4	**2.35 (1.917–2.889)** [a]	**2.50 (1.919–3.264)** [a]	**2.33 (1.690–3.210)** [a]	**2.14 (1.554–2.950)** [a]
More than one type of sports	81.8	82.7	81.6	80.3	65.6	**2.45 (1.974–3.047)** [b]	**2.76 (2.083–3.650)** [b]	**2.64 (1.897–3.684)** [b]	**2.33 (1.675–3.229)** [b]
% most popular types of sports									
Brisk walking	54.5	52.5	55.7	56.9	38.8	**1.89 (1.581–2.289)** [a]	**1.74 (1.400–2.167)** [a]	**1.96 (1.526–2.581)** [a]	**2.08 (1.591–2.720)** [a]
						1.92 (1.590–2.323) [b]	**1.73 (1.369–2.184)** [b]	**2.02 (1.538–2.658)** [b]	**2.08 (1.576–2.731)** [b]
Aerobics/fitness	48.5	48.5	49.5	47.6	44.6	1.17(0.981–1.396) [a]	1.17 (0.940–1.450) [a]	1.22 (0.939–1.580) [a]	1.13 (0.865–1.470) [a]
						1.20 (0.994–1.445) [b]	1.24 (0.983–1.562) [b]	**1.37 (1.045–1.799)** [b]	1.24 (0.940–1.622) [b]
Swimming	31.1	33.8	28.5	29.0	27.7	1.18 (0.972–1.431) [a]	**1.34 (1.058–1.686)** [a]	1.04 (0.781–1.390) [a]	1.06 (0.794–1.427) [a]
						1.20 (0.980–1.479) [b]	**1.35 (1.055–1.739)** [b]	1.11 (0.825–1.504) [b]	1.09 (0.810–1.477) [b]
Cycling	26.5	25.6	27.5	27.2	17.7	**1.68 (1.354–2.089)** [a]	**1.60 (1.232–2.077)** [a]	**1.77 (1.305–2.398)** [a]	**1.74 (1.278–2.376)** [a]
						1.73 (1.376–2.181) [b]	**1.59 (1.201–2.106)** [b]	**1.81 (1.314–2.481)** [b]	**1.77 (1.287–2.436)** [b]
Yoga	19.6	23.5	17.4	14.8	9.2	**2.39 (1.824–3.130)** [a]	**3.01 (2.225–4.082)** [a]	**2.07 (1.425–3.001)** [a]	**1.71 (1.153–2.540)** [a]
						2.28 (1.716–3.034) [b]	**3.22 (2.303–4.490)** [b]	**2.18 1.466–3.235)** [b]	**1.75 (1.165–2.631)** [b]
Running	17.4	18.7	18.0	14.5	15.0	1.19 (0.938–1.515) [a]	1.30 (0.974–1.729) [a]	1.25 (0.882–1.757) [a]	0.96 (0.659–1.394) [a]
						1.25 (0.970–1.618) [b]	**1.64 (1.198–2.254)** [b]	**1.50 (1.042–2.160)** [b]	1.13 (0.766–1.662) [b]

Note: Data are expressed as proportion of patients and controls (%).

Abbreviations: AIT = Patients with primary hypothyroidism caused by autoimmune thyroiditis, Non-AIT = Patients with primary hypothyroidism caused by thyroidectomy, radioiodine I-131 therapy, after neck irradiation for conditions other than thyroid diseases, congenital hypothyroidism, medication and De Quervain's thyroiditis, MPA = Moderate-intensity aerobic physical activity guideline, VPA = Vigorous-intensity aerobic physical activity guideline.

[a]Unadjusted OR (95% CI) values.

[b]Adjusted OR (95% CI) values.

[c]Additional analysis of the differences in being limited in physical activity between AIT and non-AIT patients: 73.7 vs 58.8%, OR 1.93; 95%CI: 1.518–2.457.

Values in bold indicate a statistically significant difference, $p < .05$.

Table 4. Exercise-related constraints in the categories much and extreme of adult female patients with primary hypothyroidism on thyroid hormone replacement therapy (*N = 1724*).

	Total (n = 1724)	AIT (n = 799)	Non-AIT (n = 488)	Unknown (n = 437)	Effect size OR (95% CI) AIT versus Non-AIT
General fatigue (%)	26.6	30.2	24.6	22.4	**0.76 (0.585–0.975) [a]** **0.77 (0.598–0.999) [b]**
Fatigue after exercise (%)	43.3	45.9	39.1	43.0	**0.76 (0.602–0.952) [a]** **0.76 (0.606–0.960) [b]**
Dyspnoea during exercise (%)	21.5	21.2	22.1	21.5	1.06 (0.806–1.392) [a] 1.03 (0.785–1.362) [b]
Prolonged recovery post-exercise (%)	24.2	27.9	22.1	19.9	**0.73 (0.564–0.956) [a]** **0.75 (0.576–0.980) [b]**
General feeling unwell after exercise (%) (duration is several days)	9.9	11.6	9.2	7.6	0.77 (0.530–1.122) [a] 0.79 (0.543–1.154) [b]
Precarious level of exercise performance (%)	34.0	37.4	32.8	29.3	0.82 (0.643–1.034) [a] 0.83 (0.654–1.053) [b]
Diminished physical endurance (%)	31.6	33.5	29.3	30.4	0.82 (0.643–1.048) [a] 0.83 (0.647–1.056) [b]
Muscle (%)					
Muscle pain	75.1	73.2	76.6	76.7	1.20 (0.924–1.559) [a] 1.20 (0.924–1.564) [b]
Weakness	23.3	26.4	21.9	19.2	0.78 (0.600–1.021) [a] 0.80 (0.615–1.049) [b]
Cramps	18.4	20.5	16.6	16.7	0.77 (0.574–1.034) [a] 0.78 (0.579–1.044) [b]
Joints (%)					
General arthralgia complaints	36.9	36.4	39.1	35.5	1.12 (0.890–1.416) [a] 1.11 (0.877–1.398) [b]
Stiffness	34.9	35.5	35.9	32.7	1.01 (0.802–1.282) [a] 1.00 (0.785–1.261) [b]
Inflammation	8.4	8.5	10.2	5.9	1.23 (0.836–1.801) [a] 1.18 (0.803–1.740) [b]

Notes: Self-reported exercise-related constraints in the categories "much" and "extreme", indicated to the extent of these symptoms as experienced during the past 12 months (the four used categories "none", "some", "much" and "extreme" make 100%); Data are expressed as proportion of patients (%).

Abbreviations: AIT = Patients with primary hypothyroidism caused by autoimmune thyroiditis, Non-AIT = Patients with primary hypothyroidism caused by thyroidectomy, radioiodine I-131 therapy, after neck irradiation for conditions other than thyroid diseases, congenital hypothyroidism, medication and De Quervain's thyroiditis.

[a]Unadjusted OR (95% CI) values.

[b]Adjusted OR (95% CI) values.

Values in bold indicate a statistically significant difference, $p < .05$.

presence of TPO-Ab in serum of AIT patients has been linked to a decreased quality of life (Ott et al., 2011; Promberger et al., 2014; Wiersinga, 2019), and fatigue-related symptoms appear to be more present in patients with hypothyroidism caused by AIT than in patients with hypothyroidism after total thyroidectomy (Louwerens et al., 2012). These complaints in AIT patients with elevated anti-TPO levels seems to be related to autoimmunity rather than thyroid function (Ott et al., 2011).

In our study, 54.2% of the patients reported one or more comorbid conditions besides hypothyroidism. A comparable survey study among Dutch patients with diabetes mellitus (type 1 and 2) showed that 71% of patients reported multimorbidity (Stuij et al., 2014). Certain comorbid conditions could be age-related (e.g., osteoarthritis), but some are autoimmune diseases (e.g., diabetes mellitus and rheumatoid arthritis) and it is known that the prevalence and relative risk of coexisting autoimmune diseases in patients with autoimmune thyroid disease is significantly increased (Boelaert et al., 2010; Ness-Abramof et al., 2006; Ruggeri et al., 2017). Based on the self-reported comorbid conditions besides hypothyroidism, the origin of the PA limitations could be of a heterogeneous nature. Nevertheless, a supplementary univariate logistic regression analysis, which was corrected for the number of comorbid conditions besides hypothyroidism, revealed a statistically significant stronger association between AIT patients and PA limitations compared to non-AIT patients.

The strengths of this study can be attributed to the large sample size and the division in aetiology of the patients group into AIT and non-AIT subgroups. Furthermore, the response rate of members of SON to the online survey was 39.5%. As studies on survey administration show that online surveys are likely to achieve response rates as high as 33% (Nulty, 2008), the good response rate to our online survey could suggest that the patients group was motivated and that the results obtained are enough representative of the whole group (patient population).

We recognise that all respondents' data from the online survey are based on self-report, which can introduce potential bias, as the data is not medically validated and can be subjective due to under- or over-reporting. Moreover, inviting members of the Dutch thyroid patient organisation SON to participate in an online survey focused on physical activity is theoretically biased towards patients with exercise-related constraint for the reason that they may be most likely to respond to the online survey. With respect to the median level of TSH in included patients (0.9 mU/l), this seems to be within the reference range for adequate THR, indicating a state of euthyroidism at the hypothalamus-pituitary axis level (Celi et al., 2011). However, it is not possible to state that all patients were medicated within the optimal reference range for TSH, because

there is no international agreed and evidence-based reference range for adequate THR. Not only because of the differences in TSH determination between different laboratories worldwide, but also due to different preferences in optimum TSH values within individual patients. In addition, in order to have sufficient matched control subjects, the survey period of the control subjects have been taken at a wider range (1 July 2013 and 31 December 2014), causing a possible seasonal effect on PA and SP. Moreover, PA, SP, ERC and associated characteristics may vary with gender. For instance, studies on self-reported assessment of PA have consistently found that women are less physically active than men (Slootmaker et al., 2009). As the inclusion was limited to women, the results cannot simply be transferred to men. Finally, the online survey in this cross-sectional matched case–control study was conducted in 2014, but the results could not be processed sooner due to lack of manpower. Since then, a slightly positive trend has been reported in adherence to PA guidelines among adults (RIVM, 2020; RIVM, 2021; Duijvestijn et al., 2020). Although this implies the actual rate of meeting PA guidelines may have slightly increased, the data of this study remains relevant as so little is known about the nature and extent of PA, SP and ERC among patients with hypothyroidism on THR. In this specific patient population, the results will contribute to a better scientific understanding of exercise intolerance.

5. Conclusion

This study has uncovered several novel factors that are associated with exercise intolerance in patients with hypothyroidism on THR. As expected, MPA was lower in patients, but surprisingly more patients engaged in sports activities compared to the general population. Two-thirds of the patients indicated that the current condition of hypothyroidism was limiting their PA performance due to ERC. Remarkably, these limitations were more pronounced in AIT patients compared to non-AIT patients, representing disease-specific exercise intolerance. The perceived ERC could indicate that patients may experience additional barriers to perform regular PA, which could jeopardise recommended PA levels for health. In order to establish effective intervention programmes that encourage regular PA in patients on THR with exercise intolerance, further research is needed to better understand the motivators and barriers to PA, including physical, psychological, social and environmental factors. Consequently, because of the prevalence of multimorbidity in our patient group, we advise individual PA coaching of patients and a multidisciplinary collaboration between sports physicians, general practitioners, and endocrinologists for an integral health approach of this particular group of patients.

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Authors' contribution

JL conceived and designed the study, contributed to the data collection and analyses, interpreted the results, and drafted the manuscript; EK performed the overall statistical analyses and revised the manuscript; HH performed statistical analyses and revised the manuscript, DC performed statistical analyses and revised the manuscript; PZ revised the manuscript; JS conceived and designed the study, and revised the manuscript; and FB conceived and designed the study, and revised the manuscript. All authors have approved the final version of the manuscript, and agree with the order of presentation of the authors.

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