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Physical Activity in Women With Hypothyroidism on Thyroid Hormone Therapy: Associated Factors and Perceived Barriers and Benefits

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Background: The purpose of this study was to analyze factors associated with physical activity (PA) and to identify perceived barriers and benefits of PA among patients with hypothyroidism on thyroid hormone therapy. **Methods**: This survey-based cross-sectional study was conducted among members of the Dutch thyroid patient organization. Self-reported data on respondents' PA levels and demographic, clinical, and physical health variables were collected. Moreover, perceived barriers and benefits to PA were identified. Respondents were categorized as physically active when meeting the recommended Dutch PA guidelines and physically inactive otherwise. To compare physically active and inactive respondents, potential confounders were entered into univariate analyses. Factors showing significant correlations ($P < .20$) were added to a multivariate model to determine the associated factors of PA. **Results**: About 1724 female respondents (mean age 53.0 [11.6] y) were included; 16.1% reported meeting the PA recommendations. Multivariate analysis showed that factors associated with PA included levothyroxine/liothyronine therapy, comorbidities, self-perceived physical fitness, and diminished physical endurance. Overall, physically related barriers to PA were rated highest. **Conclusions**: The vast majority of treated hypothyroid respondents are physically inactive and experience long-term exercise intolerance. Considering the health implications of physical inactivity, promotion of regular PA is of key importance in this population.

Keywords: comorbidity, exercise intolerance, health promotion

Hypothyroidism is a common condition of thyroid hormone deficiency that affects up to 5% of people worldwide,[1] with autoimmune thyroiditis (AIT) accounting for the vast majority of hypothyroidism cases in iodine-sufficient areas.[2] Hypothyroidism can be treated effectively with optimal thyroid hormone therapy (THT), reflecting a normal thyroid-stimulating hormone (TSH) level to minimize thyroid-related complaints. The standard treatment of hypothyroidism consists of daily administration of levothyroxine monotherapy.[3]

Generally, it is presumed that hypothyroidism and biochemically adequate THT will improve quality of life and reverse impairments of cardiovascular, respiratory, and muscle functions at rest and during exercise. However, despite adequate treatment, approximately 10% to 15% of patients with hypothyroidism on levothyroxine monotherapy continue to experience impaired quality of life,[4–6] including persistent fatigue, physical constraints, and exercise intolerance.[7,8] These persistent constraints can lead to a vicious circle of deconditioning, resulting in a further loss of functional capacity and to the ability to perform physical activity (PA).[9,10]

Physical inactivity, defined as "PA levels less than those required for optimal health and prevention of premature death,"[11] has been identified as the fourth leading risk factor for global mortality. The promotion of PA has increasingly been recognized as a priority for public health action, and many countries have responded through the development of global recommendations on PA for health.[12,13] In this, PA is defined as any body movement produced by skeletal muscles that requires energy, with both moderate- and vigorous-intensity PA (MVPA) improving health.[12] According to the Dutch PA guidelines,[13] adults must engage in MVPA for at least 150 minutes every week, spread over several different days, and must practice physical activities that strengthen muscles and bones at least twice a week. The promotion of PA is especially relevant for patients with chronic conditions and multimorbidity, who in general are less physically active than the general population.[14–16] According to a study using data from the US National Health and Nutrition Examination Survey, lower PA levels are also found among treated patients with hypothyroidism compared with the general population.[5,17]

A better understanding of the correlates of PA and the variation in PA patterns of treated patients with hypothyroidism can help identify meaningful strategies for PA interventions. One way of increasing such understanding is to identify individual factors associated with PA levels in treated patients with hypothyroidism. Individual factors can be defined as person-specific attributes, such as demographic variables (eg, gender, education); clinical variables (eg, type of THT, thyroid hormone blood levels); and physical health variables (eg, subjective health and physical fitness, number of health conditions, long-term PA limitations). Moreover, additional insight can be obtained by analyzing the perceived barriers and benefits to PA in the hypothyroid population, including physical, psychological, social, and environmental factors.[18] Chronic health conditions have been identified both as a barrier and as benefit to PA, because individuals may exercise to prevent further physical decline, while their ability to participate in PA

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could be limited by the same conditions.[19] However, to our knowledge, no studies have investigated these correlates of PA focusing specifically on treated patients with hypothyroidism.

A better picture of how individual factors of treated patients with hypothyroidism interfere with participation in PA may serve as a basis for the development and implementation of an effective intervention strategy adapted to the needs of this patient population. Thus, this study anlayzes the factors associated with PA, and identifies the perceived barriers and benefits of PA among treated patients with hypothyroidism.

Methods

Respondents

In 2014, a survey-based cross-sectional study was conducted among members of the Dutch thyroid patient organization (Schildklier Organisatie Nederland). The study was approved by the medical ethics review committee of the University Medical Center Utrecht, The Netherlands (number 13-684/C). As the study concerned an anonymous survey, an informed consent was not needed. For this study, all members of the Dutch thyroid patient organization with a registered e-mail address received an e-mail invitation to participate in the survey. As a unique reference URL was generated and subsequently validated for each individual e-mail address, duplicates in this anonymous survey were precluded. Inclusion criteria for the respondents were: (1) primary hypothyroidism, (2) treatment with THT, (3) aged ≥ 18 years, and (4) ability to understand the Dutch language.

Measures

In this study, a self-constructed survey was applied regarding PA patterns, specifically focusing on treated patients with hypothyroidism. The survey consisted of 3 parts. First, survey questions related to PA-level assessment, demographic characteristics, and self-perceived general health and physical fitness were selected from the national survey on "Injuries and Physical Activity in the Netherlands." This is a continuous national questionnaire and database on injuries, PA, and sports participation, as operated by the Dutch Consumer Safety Institute (VeiligheidNL).[20] Second, survey questions related to clinical characteristics and long-term PA limitations were included. Finally, survey questions related to barriers and benefits of PA were adopted for our patient population.

Ascertainment of PA Level. Respondents were categorized as physically active if they met the recommended Dutch PA guidelines[13] and physically inactive otherwise. According to these guidelines, adults must engage in MVPA for at least 150 minutes every week spread over several different days, and must practice physical activities that strengthen muscles and bones at least twice a week. The proportion of respondents meeting the Dutch PA recommendations was estimated based on responses to 2 questions from the Injuries and Physical Activity in the Netherlands survey. MVPA was assessed by asking respondents how many days a week they engaged in MVPA for a minimum of 30 minutes. Examples of MVPA include activities with intensities that are at least equal to walking at a firm pace or cycling.[21] Muscle strengthening activity was assessed by asking respondents how many days a week they performed muscle strengthening activity using the major muscles of the body in order to maintain or increase muscular strength and endurance.[22] For our analysis, participating in MVPA for a minimum of 30 minutes on at least 5 days a week and engaging in muscle strengthening activity at least twice a week meant respondents were categorized as physically active. Respondents were classified physically inactive otherwise.

Demographic Characteristics. Respondents reported their gender (male or female), age (in years), height (in centimeters), and weight (in kilograms). Reported education level was categorized into lower (no school graduation and lower general secondary education), middle (higher general secondary education, preuniversity education, and vocational school), and higher education (university degree). Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. The BMI was categorized as underweight (<18.5 kg/m^2), normal weight (18.5–24.9 kg/m^2), overweight (25–29.9 kg/m^2), obese (30.0–39.9 kg/m^2), and morbidly obese (≥40 kg/m^2).

Clinical Characteristics. Self-reported clinical characteristics included type(s) of THT that were used as treatment of hypothyroidism, with the following options (combinations of multiple therapies were possible): levothyroxine (in micrograms per day), liothyronine (in micrograms per day), desiccated thyroid extract from animal origin (in milligrams per day), and unknown. The results of the most recent thyroid function blood test were requested as well, (ie, TSH [in milli-international units per liter], free thyroxine [in picomoles per liter], and free triiodothyronine [in picomoles per liter]). Because treatment goals of hypothyroidism include normalization of TSH concentrations and resolution of physical or psychological complaints while avoiding undertreatment or overtreatment, levels of TSH were divided into 3 categories according to the Dutch Guidelines of General Practitioners, that is, values were considered normal between 0.4 and 4.0 mIU/L, reflecting undertreatment when >4.0 mIU/L, and overtreatment when <0.4 mIU/L.[3] Respondents were also asked to report the etiology of primary hypothyroidism. The outcome of this survey question would be categorized into 3 groups: (1) AIT group consisting of respondents with primary hypothyroidism caused by Hashimoto's thyroiditis; (2) non-AIT group consisting of respondents 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) or De Quervain's thyroiditis; and (3) unknown group consisting of respondents with primary hypothyroidism in which the etiology of hypothyroidism was unknown to the patient.

Physical Health Characteristics. Respondents could indicate which other chronic health conditions were restricting their PA performance currently besides hypothyroidism, such as asthma, depression, diabetes mellitus, or heart disease. Moreover, 2 survey questions from the Injuries and Physical Activity in the Netherlands survey on self-perceived general health and physical fitness were included. Data concerning self-perceived general health were obtained by the question: "How do you rate your own health in general?" A similar question was used to obtain data concerning self-perceived physical fitness: "How do you rate your own physical fitness in general?" Respondents were asked to rate their own general health and physical fitness as "good," "moderate," "bad," or "do not know." Besides, they were asked about the most common long-term PA limitations reported in patients with hypothyroidism,[8] for example, fatigue, muscle pain, arthralgia, and diminished physical endurance. Respondents were asked to

indicate the self-reported limitations in the categories "none," "some," "much," and "extreme" as experienced during the past 12 months. Finally, respondents reported whether they felt hypothyroidism limited their PA performance, and the answer could be "yes" or "no."

Perceived Barriers and Benefits. To gain insight into potential barriers and benefits of PA in this population, self-questionnaires were used to evaluate and rank barriers and benefits of regular PA. As no validated survey specifically addressing perceived barriers and benefits of PA exists for treated patients with hypothyroidism, items from related questionnaires were adopted for our patient population.[23–30] On the questionnaires, respondents indicated on a 5-point Likert-type scale how often 23 items interfered with or limited them from being physically active (1 = never, 2 = rarely, 3 = sometimes, 4 = often, and 5 = very often). Next, respondents ranked, on a 4-point Likert-type scale, whether they agreed or disagreed with 11 statements based on their personal experiences on benefits of PA (1 = strongly disagree, 2 = disagree, 3 = agree, and 4 = strongly agree). Lower scores indicated negative belief, while higher scores indicated positive belief.

Statistical Analyses

Descriptive statistics were used to describe the demographic, clinical, and physical health characteristics of respondents. Continuous variables were presented as mean with SD or as median with interquartile range in case of highly skewed variables. Percentages were determined for categorical variables. Independent sample *t* tests (for continuous variables, *F* value is presented), chi-square tests (for categorical variables, χ^2 and degrees of freedom are presented), and Mann–Whitney *U* tests were used to compare differences in physically active and inactive respondents. To investigate significant factors associated with PA, adjusted for possible confounders among respondents, univariate logistic regression analyses were used. Possible confounders were age, education level, weight status (BMI), THT, TSH level, etiology of hypothyroidism, number of comorbidities in addition to hypothyroidism, self-perceived general health and physical fitness, and long-term PA limitations. Factors from the univariate logistic regression analyses with $P < .20$ were included in the multivariate logistic regression analysis to determine the independent associated factors of PA while adjusting for confounding effects. Differences were considered statistically significant at $P < .05$. Odds ratios (ORs) were presented with 95% confidence interval (CI). The Nagelkerke R^2 estimates the amount of variation in the dependent variable explained by the model (from a minimum value of 0 to a maximum value of approximately 1). Data were analyzed using SPSS (version 25.0; IBM Corp, Armonk, NY) .

Results

Study Population

Members of the Dutch thyroid patient organization (n = 5363) received an invitation by e-mail to participate in the online survey, and 2119 respondents completed the survey (39.5%). As only 175 (8.3%) were male, 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 (1) surveys with missing values on the outcome measures (n = 80), (2) no treatment with THT (n = 101), (3) no primary hypothyroidism (ie, Graves' disease [n = 24] or secondary hypothyroidism [n = 4]), and (4) aged <18 years (n = 11). After excluding these cases, 1724 female respondents remained for analyses, subsequently divided into 2 groups based on their compliance with the recommended Dutch PA guidelines: physically active (16.1%) and physically inactive (83.9%).

Demographic, Clinical, and Physical Health Characteristics

As shown in Table 1, the mean (SD) age of respondents was 53.0 (11.6) years, almost half of the respondents had a higher education level (49.0%), and the majority was represented in the BMI category "normal" and "overweight" (respectively 41.1% and 36.7%). Respondents predominantly used levothyroxine monotherapy as treatment (98.4%), and 60.7% had a TSH level between 0.4 and 4.0 mIU/L (normal treatment). The most prevalent cause of hypothyroidism was AIT (46.3%), and more than half (54.2%) of the respondents identified one or more coexisting chronic health conditions in addition to hypothyroidism. Over half (55.3%) perceived their own general health as "good," whereas 39.9% perceived their own physical fitness as "good." Their main reported long-term PA limitations (calculated as the total of categories "much" and "extreme") were muscle pain (75.1%), fatigue after exercise (43.3%), and arthralgia (36.9%). Two-thirds (66.9%) of the respondents indicated that their current condition of hypothyroidism limited their PA performance.

Univariate and Multivariate Regression Analysis

Univariate logistic regression analysis (Table 2) showed that several factors were significantly associated with PA. First of all, age resulted in a higher OR for PA (OR 1.015; 95% CI, 1.003–1.026). Moreover, the BMI category "overweight" resulted in a higher OR for PA compared with the BMI category "normal weight" (OR 1.108; 95% CI, 0.770–1.347). Also, levothyroxine/liothyronine combination therapy resulted in higher OR for PA (OR 1.375; 95% CI, 0.916–2.064). In addition, number of comorbidities was associated with a higher OR for PA (OR 1.503; 95% CI, 1.091–2.069). Finally, univariate logistic regression analysis indicated a lower OR for self-perceived physical fitness and PA (OR 0.343; 95% CI, 0.196–0.600), fatigue after exercise and PA (OR 0.819; 95% CI, 0.716–0.936), diminished physical endurance and PA (OR 0.677; 95% CI, 0.577–0.794), and general fatigue and PA (OR 0.850; 95% CI, 0.728–0.991). As education level, TSH level, etiology of hypothyroidism, and self-perceived health showed no statistically significant association with PA, these variables were excluded from the multiple regression analysis.

To determine the independent associated factors with PA (Table 2), age, BMI, levothyroxine/liothyronine combination therapy, number of comorbidity, self-perceived physical fitness, and long-term PA limitations were all included in the multivariate logistic regression analysis. Multivariate logistic regression analysis indicated an association between levothyroxine/liothyronine combination therapy and PA (OR 1.656; 95% CI, 1.086–2.524), comorbidities and PA (OR 2.171; 95% CI, 1.503–3.135), self-perceived physical fitness and PA (OR 0.451; 95% CI, 0.235–0.864), and diminished physical endurance and PA (OR 0.744; 95% CI, 0.609–0.908). In the model, Nagelkerke $R^2 = 7.1\%$.

Table 1 Demographic, Clinical, and Physical Health Characteristics of Respondents, Overall and Stratified in Physically Inactive and Active Respondents

Characteristic	Total	Inactive	Active	Effect size and *P* value
N, %	1724 (100.0)	1446 (83.9)	278 (16.1)	
Age, mean (SD), y	53.0 (11.6)	52.7 (11.6)	54.6 (11.6)	$F = 0.794$, ***P* = .012**
Education level, %				$\chi^2 = 0.561$, df = 2, $P = .755$
Lower	16.3	16.5	15.1	
Middle	34.7	34.4	36.3	
Higher	49.0	49.1	48.6	
Body mass index, kg/m^2 (%)				$\chi^2 = 14.578$[c], df = 4, ***P* = .006**
Underweight (<18.5 kg/m^2)	1.0	1.1	0.4	
Normal weight (18.5–24.9 kg/m^2)	41.1	40.3	45.3	
Overweight (25–29.9 kg/m^2)	36.7	35.8	41.0	
Obese (30–39.9 kg/m^2)	19.4	20.7	12.6	
Morbid obese (≥40 kg/m^2)	1.8	2.0	0.7	
THT[a], %				
Levothyroxine	98.4	98.5	97.8	$\chi^2 = 0.592$, df = 1, $P = .442$[d]
Liothyronine	9.4	8.9	11.9	$\chi^2 = 2.382$, df = 1, $P = .123$
Desiccated thyroid extract from animal origin	2.7	2.7	2.9	$\chi^2 = 0.029$, df = 1, $P = .866$
Unknown	0.4	0.4	0.4	$\chi^2 = 0.018$, df = 1, $P = .895$[e]
Thyroid hormone levels[b]				
TSH, mIU/L, median (IQR)	0.9 (1.82)	0.9 (1.82)	0.9 (1.92)	.919
Free thyroxine, pmol/L, median (IQR)	17.9 (4.6)	17.7 (6.63)	18.0 (5.33)	.156
Free triidothyronine, pmol/L, median (IQR)	1.7 (0.90)	1,7 (0.83)	1.9 (2.34)	.541
TSH level, %				$\chi^2 = 0.990$[c], df = 2, $P = .610$
Overtreatment (<0.4 mIU/L)	30.3	30.2	30.9	
Normal treatment (0.4–4.0 mIU/L)	60.7	61.1	58.3	
Undertreatment (>4.0 mIU/L)	9.0	8.7	10.9	
Etiology of hypothyroidism, %				$\chi^2 = 2.104$, df = 2, $P = .349$
Autoimmune thyroiditis	46.3	46.1	47.8	
Nonautoimmune thyroiditis	28.3	27.9	30.2	
Unknown	25.3	26.0	21.9	
Number of additional comorbidities, %				$\chi^2 = 6.304$, df = 2, ***P* = .043**
n = 0	45.8	46.9	39.9	
n = 1	31.6	31.5	32.4	
n ≥ 2	22.6	21.6	27.7	
Self-perceived general health, %				$\chi^2 = 2.099$, df = 2, $P = .350$
Good	55.5	55.1	57.4	
Moderate	40.0	40.1	39.7	
Bad	4.5	4.8	2.9	
Self-perceived physical fitness, %				$\chi^2 = 28.527$, df = 2, ***P* < .001**
Good	39.9	37.3	53.6	
Moderate	50.0	51.8	40.8	
Bad	10.1	10.9	5.4	
Long-term physical activity limitations (top 7), %				
Muscle pain	75.1	75.3	73.7	$\chi^2 = 0.307$, df = 1, $P = .579$
Fatigue after exercise	43.3	44.8	35.3	$\chi^2 = 8.684$, df = 1, ***P* = .003**
Arthralgia	36.9	37.3	34.9	$\chi^2 = 0.602$, df = 1, $P = .438$
Precarious level of exercise performance	34.0	33.9	34.9	$\chi^2 = 0.105$, df = 1, $P = .746$
Diminished physical endurance	31.6	34.0	19.1	$\chi^2 = 23.940$, df = 1, ***P* < .001**

(continued)

Table 1 *(continued)*

Characteristic	Total	Inactive	Active	Effect size and *P* value
General fatigue	26.6	27.6	21.6	$\chi^2 = 4.312$, df = 1, ***P* = .038**
Prolonged recovery after physical activity	24.2	24.1	25.2	$\chi^2 = 0.157$, df = 1, $P = .692$
Hypothyroidism is limiting physical activity, %				
Yes	66.9	67.6	63.7	$\chi^2 = 1.600$, df = 1, $P = .206$

Abbreviations: IQR, interquartile range; FT3, free triiodothyronine; FT4, free thyroxine; THT, thyroid hormone therapy; TSH, thyroid-stimulating hormone. Note: Bold values are significant, $P < .05$.

[a]Patients use multiple therapies at the same time, making the total more than 100. [b]Number of patients differ per category "total," "inactive," and "active"; TSH, respectively, 1154, 979, and 175; FT4, respectively, 996, 846, and 150; and FT3, respectively, 108, 90, and 18. [c]Two cells (20.0%) have expected count <5. The minimum expected count is 2.74. [d]One cells (25.0%) have expected count <5. The minimum expected count is 4.52. [e]One cells (25.0%) have expected count <5. The minimum expected count is 1.13.

Perceived Barriers and Benefits

The presence and importance of physical, psychological, social, and environmental barriers are listed in Table 3. Physically inactive and active respondents largely agreed which barriers were the most restrictive, with physical barriers being the most frequently reported. Two main physical barriers in both groups were similar: "too fatigued to exercise" and "lack of energy." Moreover, physically inactive respondents rated 20 of the 23 potential barriers as more restrictive ($P < .05$) than did physically active respondents.

The presence and importance of physical, psychological, and social benefits are shown in Table 4. Although respondents considered "lack of energy" as one of the main barriers, "exercise gives me more energy" was also perceived as an important benefit of PA. Moreover, physically inactive respondents rated 10 of the 11 potential benefits as less beneficial ($P < .05$) than did physically active respondents.

Discussion

Patients with treated hypothyroidism experience long-term exercise intolerance and are less physically active compared with the general population. Despite the importance of regular PA for the prevention and management of many chronic health conditions, no studies have investigated the factors related to low compliance to PA in treated patients with hypothyroidism. The present study represents the first attempt to identify a variety of individual factors that may be associated with PA in this patient population, such as demographic, clinical, and physical health variables, and to analyze perceived barriers and benefits of PA.

Meeting Recommended Levels of PA

This cross-sectional study demonstrated that only 16.1% of treated patients with hypothyroidism are meeting the recommendations of the Dutch PA guidelines for adults. This is considerably lower than to the self-report-based analyses by the Dutch National Institute for Public Health and the Environment, which indicate that 52% of Dutch adults met these PA guidelines.[31]

Demographic Characteristics

Multivariate analysis revealed that age, education level, and BMI were not associated with PA, suggesting that these factors do not significantly affect adherence to PA recommendations among respondents in our study population. This is not in agreement with the literature. However, comparison of results is difficult, because other studies have included different target groups, such as the general population[32–34] or populations with other chronic health diseases.[15,35] Therefore, further large-scale studies including patients with hypothyroidism are needed.

Clinical Characteristics

The TSH level and etiology of hypothyroidism were not associated with PA, whereas levothyroxine/liothyronine combination therapy was positively associated with PA. In general, treatment goals for hypothyroidism include normalization of TSH levels and resolution of physical or psychological complaints by administering levothyroxine monotherapy, without the patient experiencing the adverse effects and negative health consequences of undertreatment or overtreatment.[3] Although there is a general consensus that the majority of patients with hypothyroidism respond well to the standard treatment of levothyroxine monotherapy, a substantial subset of patients continue to experience persistent complaints and express dissatisfaction with levothyroxine monotherapy.[5,36]

We recognize that 39.3% of the respondents in our study reported TSH levels outside the normal reference range, and it is worth noting that this is similar to the rate of 39.9% in the Colorado thyroid disease prevalence study.[37] However, when focusing on the 30.3% of the respondents with decreased TSH levels reflecting overtreatment, half had only mildly diminished TSH levels between 0.1 and 0.4 mIU/L. When focusing on the 9.0% of respondents with increased TSH levels reflecting under treatment, more than half had only mildly elevated TSH levels between 4.0 and 7.0 mIU/L. Moreover, with no internationally agreed and evidence-based reference range for adequate TSH levels, it can be argued whether any reference range can be considered normal, not only because of the differences in determination of TSH between different laboratories worldwide, but also due to different preferences in optimum TSH levels within individual patients.

Although our observations might be limited by the cross-sectional nature of this study, persistent complaints can have other possible explanations. Explanations include the patient's awareness of a chronic illness requiring lifelong dependency on medication,[6,17] inadequacy of levothyroxine monotherapy to restore physiological thyroid hormone concentrations of thyroxine and triiodothyronine at tissue level, as well as the presence of associated autoimmune diseases[6] and recognized or unrecognized comorbidities.[17] Besides, the mere presence of thyroid peroxidase antibody in serum in patients with AIT has been linked to a decreased quality of life.[6,38]

Though our study indicated a positive association between the use of the levothyroxine/liothyronine combination therapy and PA, whether addition of liothyronine to levothyroxine will reduce persistent symptoms is a long-standing debate in the literature.[4] There is universal consensus among all clinical guidelines that

Table 2 Univariate and Multivariate Logistic Regression Analysis for Factors Associated With Physical Activity

	Univariate (n = 1724)		Multivariate	
Variable	**Odds (95% CI)**	***P* value**	**Odds (95% CI)**	***P* value**
Age, y	1.015 (1.003–1.026)	**.012**	1.004 (0.992–1.017)	.473
Education level		.756		
Lower	Reference category			
Middle	1.156 (0.782–1.711)			
High	1.082 (0.743–1.576)			
Body mass index, kg/m^2		**.007**		.051
Underweight (<18.5 kg/m^2)	0.289 (0.038–2.201)		0.384 (0.050–2.978)	
Normal weight (18.5–24.9 kg/m^2)	Reference category		Reference category	
Overweight (25–29.9 kg/m^2)	1.108 (0.770–1.347)		1.070 (0.799–1.433)	
Obese (30–39.9 kg/m^2)	0.540 (0.362–0.805)		0.608 (0.399–0.925)	
Morbid obese (≥40 kg/m^2)	0.319 (0.075–1.355)		0.383 (0.087–1.678)	
THT				
Levothyroxine	0.700 (0.281–1.743)	.444		
Liothyronine	1.375 (0.916–2.064)	**.124**	1.656 (1.086–2.524)	**.019**
Desiccated thyroid extract from animal origin	1.069 (0.494–2.313)	.866		
Unknown	0.866 (0.104–7.225)	.895		
TSH level		.611		
Overtreatment (<0.4 mIU/L)	1.070 (0.748–1.530)			
Normal treatment (0.4–4.0 mIU/L)	Reference category			
Undertreatment (>4.0 mIU/L)	1.310 (0.764–2.249)			
Etiology of hypothyroidism		.350		
Autoimmune thyroiditis	Reference category			
Nonautoimmune thyroiditis	1.041 (0.771–1.405)			
Unknown	0.812 (0.585–1.128)			
Number of comorbidity besides hypothyroidism		**.044**		**<.001**
n = 0	Reference category		Reference category	
n = 1	1.208 (0.893–1.635)		1.443 (1.051–1.981)	
n ≥ 2	1.503 (1.091–2.069)		2.171 (1.503–3.135)	
Self-perceived general health		.358		
Good	Reference category			
Moderate	0.952 (0.730–1.242)			
Bad	0.579 (0.273–1.228)			
Self-perceived physical fitness		**<.001**		**.01**
Good	Reference category		Reference category	
Moderate	0.546 (0.418–0.714)		0.575 (0.421–0.784)	
Bad	0.343 (0.196–0.600)		0.451 (0.235–0.864)	
Long-term physical activity limitations (top 7)				
Muscle pain	0.921 (0.687–1.234)	.581		
Fatigue after exercise	0.819 (0.716–0.936)	**.003**	0.974 (0.827–1.147)	.752
Arthralgia	0.948 (0.829–1.085)	.438		
Precarious level of exercise performance	1.023 (0.984–1.170)	.746		
Diminished physical endurance	0.677 (0.577–0.794)	**<.001**	0.744 (0.609–0.908)	**.004**
General fatigue	0.850 (0.728–0.991)	**.038**		.673
Prolonged recovery after physical activity	1.030 (0.888–1.195)	.692	1.041 (0.865–1.252)	

Abbreviations: CI, confidence interval; THT, thyroid hormone therapy; TSH, thyroid-stimulating hormone. Note: Bold values for univariate logistic regression analysis are significant: $P < .20$. Bold values for multivariate logistic regression analysis are significant: $P < .05$. Nagelkerke $R^2 = 7.1\%$.

Table 3 Comparison of the Medians (IQR) of Perceived Barriers Between Physically Inactive and Active Respondents on the 5-Point Likert-Type Scale

Perceived barrier	Inactive (n = 1446)	Active (n = 278)	*P* value
Physical barriers (internal)			
Too tired/fatigue[a,d,e,f]	3 (2)	3 (1)[g]	**<.001**
Lack of energy[a,c,e]	3 (1)	3 (2)[g]	**<.001**
Exercise is hard work[b,d,e]	3 (1)	2 (2)[g]	**<.001**
Limiting health problem[b,c,e,f]	2 (2)	2 (2)[g]	**.006**
Psychological barriers (internal)			
Not interested[b]	2 (2)	2 (2)[g]	**<.001**
No willpower[e]	2 (2)	2 (2)[g]	**<.001**
Not enjoying[c]	2 (2)	2 (1)[g]	**<.001**
Exercise is boring[d,e]	2 (2)	1 (1)[g]	**<.001**
Too overweight[c,d,e]	1 (2)	1 (2)[g]	**.002**
Not sporty[c]	1 (2)	1 (1)[g]	**<.001**
Insecure about appearance[a,c,e,f]	1 (2)	1 (1)[g]	.070
Do not know how to exercise[e,f]	1 (1)	1 (1)[g]	**<.001**
Fear of injury[b,c]	1 (1)	1 (1)[g]	.513
Afraid to fail[d]	1 (0)	1 (0)[g]	**.001**
Social barriers (external)			
Family-related responsibilities[a,c,e,f]	2 (2)	2 (2)[g]	**<.001**
Work-related responsibilities[f]	2 (2)	2 (2)[g]	**<.001**
Social-related responsibilities[e,f]	2 (2)	2 (2)[g]	**<.001**
Not enough time[a,b,c,d,e,f]	2 (1)	2 (2)[g]	**<.001**
No one to exercise with[c,d,e,f]	1 (1)	1 (1)[g]	**<.001**
Environmental barriers (external)			
Weather conditions[b,d,e]	2 (2)	1 (1)[g]	**<.001**
Too expensive[a,c,d,e,f]	1 (2)	1 (1)[g]	**.024**
Lack of facilities nearby[a,c,d,e,f]	1 (0)	1 (0)[g]	**.006**
No sports equipment[c]	1 (0)	1 (0)[g]	.112

Abbreviation: IQR, interquartile range; PA, physical activity. Note: Data are expressed as median (IQR). Bold values are significant, $P < .05$.
[a]Sechrist et al,[23] [b]Melillo et al,[24] [c]Booth et al,[25] [d]NISB,[26] [e]Korkiakangas et al,[27] [f]Justine et al.[28] [g]The group that experiences the least PA barriers and where the difference found is in their favor.

Table 4 Comparison of the Medians (IQR) of Perceived Benefits Between Physically Inactive and Active Respondents on the 4-Point Likert-Type Scale

Perceived benefit	Inactive (n = 1446)	Active (n = 278)	*P* value
Physical benefits (internal)			
Gives more energy[a,b]	3 (1)	3 (1)[e]	**.006**
Control my weight[c]	3 (1)	3 (1)[e]	**.001**
Improves cardiovascular system[b,c,d]	3 (1)	3 (1)[e]	**.009**
Body will look better[a,c]	3 (1)	3 (1)[e]	.163
Stay physically healthy[c]	3 (0)	3 (1)[e]	**.032**
Psychological benefits (internal)			
Feelings of well-being[b,d]	3 (1)	3 (1)[e]	**<.001**
Improves mental alertness[a,b]	3 (1)	3 (1)[e]	**<.001**
Good for my mental state[a,d]	3 (1)	3 (1)[e]	**<.001**
Lowers stress[a,c]	3 (0)	3 (1)[e]	**<.001**
Sense of personal accomplishment[a,b]	3 (0)	3 (1)[e]	**.005**
Social benefits (external)			
Meeting other people[a]	3 (0)	3 (1)[e]	**.040**

Abbreviations: IQR, interquartile range; PA, physical activity. Note: Data are expressed as median (IQR). Bold values are significant, $P < .05$.
[a]Sechrist et al,[23] [b]Melillo et al,[24] [c]Meriwether et al,[29] [d]Malone et al.[30] [e]The group that experiences increased PA effects and where the difference found is in their favor.

newly diagnosed patients with hypothyroidism should be treated with levothyroxine monotherapy.[39] However, after excluding other explanations, physicians should consider levothyroxine/liothyronine combination therapy for those patients with hypothyroidism who have persistent symptoms or metabolic abnormalities despite normalization of serum TSH level and are unambiguously not benefiting from levothyroxine monotherapy.[39,40]

Physical Health Factors

The consideration of physical health factors is important as it can limit people's ability to be physical active, but it can also necessitate participation in PA aimed at prevention or rehabilitation.[34] In this study, physical health factors included number of self-reported chronic health conditions, subjective general health and physical fitness, and long-term PA limitations. After multivariate analysis, all variables were associated with PA with the exception of self-reported general health.

Comorbidity was inversely associated with PA with respondents with one or more comorbidities being more likely than respondents with no comorbidity to meet the PA recommendations. This seems surprising, but studies examining the association between multi-morbidity and PA have demonstrated conflicting results with some studies finding an association[14,41,42] while others show no association between PA and multi-morbidity.[43,44] The results of our study might therefore indicate that respondents with one or more comorbidities are more aware of the importance of regular PA as a preventative and managing their general health more carefully, therefore engaging in more regular PA.

Whereas our study did not indicate an association between self-perceived general health and PA, it did show that respondents with a lower self-perceived physical fitness were less likely to meet PA recommendations compared with respondents with a good self-perceived physical fitness. Self-perceived health and physical fitness are both considered epidemiological predictors of subsequent mortality and/or functional limitation.[45] Lower self-perceived physical fitness may also have a negative psychological influence on PA engagement, as it may be more important how people are feeling subjectively than whether they have one or more comorbidities. Treated thyroid patients with a lower self-perception of physical fitness must therefore receive better explanations of the benefits of regular PA, as awareness of the positive health effects of regular PA may be crucial to motivating them to be more physically active.

Frequently reported long-term PA limitations by respondents in this study were fatigue, prolonged recovery after PA, and diminished physical endurance, with only the latter being significantly associated with PA. In particular, patients reported persistent fatigue and fatigue-related symptoms, both hallmarks of hypothyroidism despite adequate THT.[46] In general, patients often describe fatigue as a lack of energy, mental or physical tiredness, diminished physical endurance, and prolonged recovery after PA.[47] Interestingly, they could benefit from PA, which can combat feelings of fatigue and low energy: Several studies suggest a strong, consistent, temporally appropriate dose–response relationship between PA and feelings of fatigue and low energy.[48] These patients could benefit from treatment of fatigue, such as structured and tailored intervention strategies for regular PA to improve quality of life.

Perceived Barriers and Benefits

One of the aims of this study was to identify the perceived barriers and benefits to PA among women with treated hypothyroidism and to establish whether differences existed between physically inactive and active respondents. The results show that both physically inactive and active respondents identified similar barriers and benefits to PA. At the same time, physically inactive respondents experienced barriers as more restrictive and perceived benefits as less beneficial compared with physically active respondents. This tendency for less physically active individuals to consider each barrier to be more difficult than do physically active individuals is also reported in healthy subjects.[49] One explanation is that physically inactive respondents are inactive, in part, because they face objectively higher barriers. It is also possible that barriers are objectively similar (eg, similar fatigue, not enough time, and weather conditions), but physically inactive respondents perceive these barriers as more problematic. In contrast, physically active women may have more confidence in their ability to overcome barriers.[49] In our study, a frequently mentioned barrier for all respondents was lack of energy, whereas improvements in this outcome were perceived as an important benefit of PA. Similarities between disease-specific barriers and benefits of PA have also been observed in other studies.[50] A final observation is that lack of time is often considered one of the most common barriers to PA among the general population.[25] However, our respondents did not report this as a major barrier. In contrast, barriers related to physicality were rated strongest by our patient population.

Strengths, Limitations, and Recommendations

The strengths of this study include the large sample size and their stratification based on their compliance with recommended PA guidelines: physically active and physically inactive.

We recognize that all respondents' data from the online survey are based on self-report, which can introduce potential bias, as the data are not objectively measured or medically validated and can therefore be subjective due to underreporting or overreporting. Moreover, inviting members of the Dutch thyroid patient organization to participate in an online survey focused on PA is theoretically biased toward patients with PA limitations for the reason that they may be most likely to respond to the online survey. Therefore, our study participants may not be representative of the hypothyroid population, which limits the study's generalizability. They are, however, representative of the reasonable target population for PA promotion. In addition, although our study provided an extensive number of potential influencing factors associated with PA and perceived barriers and benefits of PA, the low Nagelkerke R^2 of the model indicates under fitting, meaning that other important, unexplored factors in determining differences in PA between the physically inactive and active respondents are missing from the model. Furthermore, although the cross-sectional data does not show cause–effect relationships, it does identify associations. On a final note, it has not been the focus of this paper to examine PA and associated factors that may vary with gender. For instance, studies on self-reported assessment of PA have consistently found that women are less physically active than men.[51] As the inclusion in our study was limited to women, the results cannot simply be transferred to men.

Conclusions

This study provided information on factors associated with PA and identified perceived barriers and benefits of PA among patients with hypothyroidism on THT. The vast majority of treated hypothyroid respondents were physically inactive and experienced

long-term exercise intolerance. In addition, levothyroxine/liothyronine combination therapy, number of comorbidities, self-perceived physical fitness, and diminished physical endurance were independently associated with PA, while physical barriers in particular were most problematic. This variety of individual factors associated with PA may indicate that this patient population experienced additional barriers to perform regular PA, which can jeopardize recommended PA levels for health. Considering the health implications of physical inactivity, increasing the awareness of PA-related health benefits is of key importance in the promotion of regular PA in this patient population. Finally, multidisciplinary collaboration between sports physicians, physiotherapists, general practitioners, and endocrinologists is recommended for an integrated health approach in this heterogeneous population.

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References

1. Duntas LH, Jonklaas J. Levothyroxine dose adjustment to optimise therapy throughout a patient's lifetime. *Adv Ther*. 2019;36(suppl 2):30–46. doi:10.1007/s12325-019-01078-2
2. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. *Lancet*. 2017;390(10101):1550–1562. doi:10.1016/S0140-6736(17)30703-1
3. Flinterman LE, Kuiper JG, Korevaar JC, et al. Impact of a forced dose-equivalent levothyroxine brand switch on plasma TSH: a cohort study. *Thyroid*. 2020;30(6):821–828. doi:10.1089/thy.2019.0414
4. Hennessey JV, Espaillat R. Current evidence for the treatment of hypothyroidism with levothyroxine/levotriiodothyronine combination therapy versus levothyroxine monotherapy. *Int J Clin Pract Suppl*. 2018;72(2):e13062. doi:10.1111/ijcp.13062
5. Peterson SJ, Cappola AR, Castro MR, et al. An online survey of hypothyroid patients demonstrates prominent dissatisfaction. *Thyroid*. 2018;28(6):707–721. doi:10.1089/thy.2017.0681
6. Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. *Eur Thyroid J*. 2012;1(2):55–71. doi:10.1159/000339444
7. McAllister RM, Delp MD, Laughlin MH. Thyroid status and exercise tolerance. Cardiovascular and metabolic considerations. *Sports Med*. 1995;20(3):189–198. doi:10.2165/00007256-199520030-00005
8. Lankhaar JAC, de Vries WR, Jansen JACG, Zelissen PMJ, Backx FJG. Impact of overt and subclinical hypothyroidism on exercise tolerance; a systematic review. *Res Q Exerc Sport*. 2014;85(3):365–389. doi:10.1080/02701367.2014.930405
9. Verbunt JA, Seelen HA, Vlaeyen JW, et al. Disuse and deconditioning in chronic low back pain: concepts and hypotheses on contributing mechanisms. *Eur J Pain*. 2003;7(1):9–21. doi:10.1016/S1090-3801(02)00071-X
10. Lankhaar JAC, Kemler E, Hofstetter H, et al. Physical activity, sports participation and exercise-related constraints in adult women with primary hypothyroidism treated with thyroid hormone replacement therapy. *J Sports Sci*. 2021:1–10. doi:10.1080/02640414.2021.1940696
11. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol*. 2012;2:1143–1211.
12. World Health Organization. *Global Recommendations on Physical Activity for Health*. Geneva, Switzerland: WHO; 2020. https://www.who.int/news-room/fact-sheets/detail/physical-activity. Accessed October 15, 2020.
13. Weggemans RM, Backx FJG, Borghouts L, et al. The 2017 Dutch physical activity guidelines. *Int J Behav Nutr Phys Act*. 2018;15(1):58–69. doi:10.1186/s12966-018-0661-9
14. Vancampfort D, Koyanagi A, Ward PB, et al. Chronic physical conditions, multimorbidity and physical activity across 46 low- and middle-income countries. *Int J Behav Nutr Phys Act*. 2017;14(1):6–19. doi:10.1186/s12966-017-0463-5
15. Forechi L, Mill JG, Griep RH, Santos I, Pitanga F, Molina MDCB. Adherence to physical activity in adults with chronic diseases: ELSA-Brasil. *Rev Saude Publica*. 2018;52(52):31–42. doi:10.11606/S1518-8787.2018052000215
16. Sharif K, Watad A, Bragazzi NL, Lichtbroun M, Amital H, Shoenfeld Y. Physical activity and autoimmune diseases: get moving and manage the disease. *Autoimmun Rev*. 2018;17(1):53–72. doi:10.1016/j.autrev.2017.11.010
17. Peterson SJ, McAninch EA, Bianco AC. Is a normal TSH synonymous with "euthyroidism" in levothyroxine monotherapy? *J Clin Endocrinol Metab*. 2016;101(12):4964–4973. doi:10.1210/jc.2016-2660
18. Wilcox S, Der Ananian C, Abbott J, et al. Perceived exercise barriers, enablers, and benefits among exercising and nonexercising adults with arthritis: results from a qualitative study. *Arthritis Rheum*. 2006;55(4):616–627. doi:10.1002/art.22098
19. Costello E, Kafchinski M, Vrazel J, Sullivan P. Motivators, barriers, and beliefs regarding physical activity in an older adult population. *J Geriatr Phys Ther*. 2011;34(3):138–147. doi:10.1519/JPT.0b013e31820e0e71
20. Kemler E, Blokland D, Backx F, Huisstede B. Differences in injury risk and characteristics of injuries between novice and experienced runners over a 4-year period. *Phys Sportsmed*. 2018;46(4):485–491. doi:10.1080/00913847.2018.1507410
21. Bernaards CM, Hildebrandt VH, Hendriksen IJM. Correlates of sedentary time in different age groups: results from a large cross sectional Dutch survey. *BMC Public Health*. 2016;16(1):1121. doi:10.1186/s12889-016-3769-3
22. Nelson ME, Rejeski WJ, Blair SN, et al. Physical activity and public health in older adults: recommendation from the American College of Sports Medicine and the American Heart Association. *Med Sci Sports Exerc*. 2007;39(8):1435–1445. doi:10.1249/mss.0b013e3180616aa2
23. Sechrist KR, Walker SN, Pender NJ. Development and psychometric evaluation of the exercise benefits/barriers scale. *Res Nurs Health*. 1987;10(6):357–365. doi:10.1002/nur.4770100603
24. Melillo KM, Williams E, Futrell M, Chamberlain C. A self-assessment tool to measure older adults' perceptions regarding physical fitness and exercise activity. *J Adv Nurs*. 1997;25(6):1220–1226. doi:10.1046/j.1365-2648.1997.19970251220.x
25. Booth ML, Bauman A, Owen N, Gore CJ. Physical activity preferences, preferred sources of assistance, and perceived barriers to increased activity among physically inactive Australians. *Prev Med*. 1997;26(1):131–137. doi:10.1006/pmed.1996.9982
26. Netherlands Institute for Sports and Physical Activity (NISB). Pace questionnaire 'Physician-based assessment and counseling for

exercise' (in Dutch). 2019. https://meetinstrumentenzorg.nl/wp-content/uploads/instrumenten/PACE-overige.pdf. Accessed December 19, 2020.
27. Korkiakangas EE, Alahuhta MA, Laitinen JH. Barriers to regular exercise among adults at high risk or diagnosed with type 2 diabetes: a systematic review. *Health Promot Int*. 2009;24(4):416–427. doi:10.1093/heapro/dap031
28. Justine M, Azizan A, Hassan V, Salleh Z, Manaf H. Barriers to participation in physical activity and exercise among middle-aged and elderly individuals. *Singapore Med J*. 2013;54(10):581–586. doi:10.11622/smedj.2013203
29. Meriwether RA, Lee JA, Lafleur AS, Wiseman P. Physical activity counseling. *Am Fam Physician*. 2008;77(8):1129–1136.
30. Malone LA, Barfield JP, Brasher JD. Perceived benefits and barriers to exercise among persons with physical disabilities or chronic health conditions within action or maintenance stages of exercise. *Disabil Health J*. 2012;5(4):254–260. doi:10.1016/j.dhjo.2012.05.004
31. Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Sport Kernindicatoren (in Dutch). 2019. www.sportenbewegenincijfers.nl/kernindicatoren/beweegrichtlijnen. Accessed December 6, 2020.
32. Droomers M, Schrijvers CT, Van de Mheen H, Mackenbach JP. Educational differences in leisure-time physical inactivity: a descriptive and explanatory study. *Soc Sci Med*. 1998;47(11):1665–1676. doi:10.1016/S0277-9536(98)00272-X
33. Piirtola M, Kaprio J, Kujala UM, et al. Association between education and future leisure-time physical inactivity: a study of Finnish twins over a 35-year follow-up. *BMC Public Health*. 2016;16(720):1–11.
34. Notthoff N, Reisch P, Gerstorf D. Individual characteristics and physical activity in older adults: a systematic review. *Gerontology*. 2017;63(5):443–459. doi:10.1159/000475558
35. Dontje ML, Krijnen WP, de Greef MH, et al. Effect of diagnosis with a chronic disease on physical activity behavior in middle-aged women. *Prev Med*. 2016;83:56–62. doi:10.1016/j.ypmed.2015.11.030
36. Madan R, Celi FS. Combination therapy for hypothyroidism: rationale, therapeutic goals, and design. *Front Endocrinol*. 2020;11(371):1–11.
37. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. *Arch Intern Med*. 2000;160(4):526–534. doi:10.1001/archinte.160.4.526
38. Ott J, Promberger R, Kober F, et al. Hashimoto's thyroiditis affects symptom load and quality of life unrelated to hypothyroidism: a prospective case-control study in women undergoing thyroidectomy for benign goiter. *Thyroid*. 2011;21(2):161–167. doi:10.1089/thy.2010.0191
39. Idrees T, Palmer S, Maciel RMB, Bianco AC. Liothyronine and desiccated thyroid extract in the treatment of hypothyroidism. *Thyroid*. 2020;30(10):1399–1413. doi:10.1089/thy.2020.0153
40. Ettleson MD, Bianco AC. Individualized therapy for hypothyroidism: Is T4 enough for everyone? *J Clin Endocrinol Metab*. 2020;105(9):e3090. doi:10.1210/clinem/dgaa430
41. Autenrieth CS, Kirchberger I, Heier M, et al. Physical activity is inversely associated with multimorbidity in elderly men: results from the KORA-Age Augsburg study. *Prev Med*. 2013;57(1):17–19. doi:10.1016/j.ypmed.2013.02.014
42. Cimarras-Otal C, Calderón-Larrañaga A, Poblador-Plou B, et al. Association between physical activity, multimorbidity, self-rated health and functional limitation in the Spanish population. *BMC Public Health*. 2014;14(1):1170–1179. doi:10.1186/1471-2458-14-1170
43. Fortin M, Haggerty J, Almirall J, Bouhali T, Sasseville M, Lemieux M. Lifestyle factors and multimorbidity: a cross sectional study. *BMC Public Health*. 2014;14(1):686–693. doi:10.1186/1471-2458-14-686
44. Hudon C, Soubhi H, Fortin M. Relationship between multimorbidity and physical activity: secondary analysis from the Quebec health survey. *BMC Public Health*. 2008;8(1):304–311. doi:10.1186/1471-2458-8-304
45. Okano G, Miyake H, Mori M. Leisure time physical activity as a determinant of self-perceived health and fitness in middle-aged male employees. *J Occup Health Psychol*. 2003;45(5):286–292. doi:10.1539/joh.45.286
46. Louwerens M, Appelhof BC, Verloop H, et al. Fatigue and fatigue-related symptoms in patients treated for different causes of hypothyroidism. *Eur J Endocrinol*. 2012;167(6):809–815. doi:10.1530/EJE-12-0501
47. Filler K, Lyon D, Bennett J, et al. Association of mitochondrial dysfunction and fatigue: a review of the literature. *BBA Clinical*. 2014;1(1):12–23. doi:10.1016/j.bbacli.2014.04.001
48. Puetz TW. Physical activity and feelings of energy and fatigue: epidemiological evidence. *Sports Med*. 2016;36(9):767–780. doi:10.2165/00007256-200636090-00004
49. Cadmus-Bertram LA, Gorzelitz JS, Dorn DC, Malecki KMC. Understanding the physical activity needs and interests of inactive and active rural women: a cross-sectional study of barriers, opportunities, and intervention preferences. *J Behav Med*. 2019;43(4):638–647. doi:10.1007/s10865-019-00070-z
50. Veldhuijzen van Zanten JJ, Rouse PC, Hale ED, et al. Perceived barriers, facilitators and benefits for regular physical activity and exercise in patients with rheumatoid arthritis: a review of the literature. *Sports Med*. 2015;45(10):1401–1412. doi:10.1007/s40279-015-0363-2
51. Slootmaker SM, Schuit AJ, Chinapaw MJ, Seidell JC, van Mechelen W. Disagreement in physical activity assessed by accelerometer and self-report in subgroups of age, gender, education and weight status. *Int J Behav Nutr Phys Act*. 2009;25:6–17.