STUDY PROTOCOL

Study protocol: A profile of physical performance variables in an outpatient adult population with narcolepsy [version 1; peer review: 2 approved with reservations]

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Abstract

Background: Narcolepsy is a sleep disorder characterised by excessive daytime sleepiness and significantly impacts quality of life. People with narcolepsy demonstrate many potential barriers to being physically fit and active, such as sleepiness and social isolation. Very little is known about how physical performance variables may be affected in people with narcolepsy. This study aims to profile the physical fitness of adults with narcolepsy and to explore the relationship between physical fitness and quality of life, symptom severity and disease duration in this cohort.

Methods and Analysis: In this cross-sectional observational study, participants will undergo a comprehensive physical performance test battery that will investigate cardiopulmonary fitness, objective measures of physical activity, muscle strength and endurance. Furthermore, quality of life, symptom severity and physical activity will be ascertained through self-report questionnaires. The study population will consist of adults with narcolepsy aged 18-65 years attending the National Narcolepsy Centre located in St. James's Hospital as an outpatient.

Ethics and Dissemination: Ethical approval has been obtained from the St. James’s Hospital and Tallaght University Hospital Research Ethics Committee, and this study is presently underway. The results obtained from this study will be used to help tailor exercise and possible rehabilitation strategies for this population. Dissemination will be sought through peer-reviewed journals, national and international conferences, and through engagement with service user groups.

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Keywords
Exercise, Physical Activity, Narcolepsy, Sleep Disorders, Quality of Life.

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Introduction

Narcolepsy is a sleep disorder that is characterised by excessive daytime sleepiness and is regularly associated with episodic muscular weakness, known as cataplexy, following intense emotions such as laughter or anger. Disrupted night-time sleep (DNS) is a common complaint in people with narcolepsy and can be accompanied by hallucinations and sleep paralysis (Roth et al., 2013). With an estimated incidence of 25–50 per 100,000 in western populations (Overeem et al., 2008), approximately 1200–2415 people live with narcolepsy in Ireland. Furthermore, Ireland, similar to other European countries (Heier et al., 2013; Nohynek et al., 2012; Partinen et al., 2012; Szakacs et al., 2013), has experienced an increased number of cases of narcolepsy following the 2009–2010 Swine Flu epidemic, with crude associations identified in pandemic-vaccination recipients (O’Flanagan et al., 2014).

People with narcolepsy have a strong likelihood of experiencing occupational and social difficulties (Morse & Sanjeev, 2018) with strong links identified between narcolepsy, health care usage and unemployment (Jennum et al., 2009). Narcolepsy can be disabling from a young age as over half will develop symptoms before 16 years of age (Thorpy & Krieger, 2014). Symptom onset is commonly associated with an increase in body mass, often resulting in obesity (Ponziani et al., 2016). Additionally, higher incidences of chronic conditions including diabetes mellitus, sleep apnoea, chronic obstructive pulmonary disease, back pain, and arthritis have been observed in people with narcolepsy when compared to the general population (Jennum et al., 2013). Furthermore, quality of life in people with narcolepsy is significantly lower than the general population, with physical role limitations and vitality commonly being the most affected quality of life domains (Becker et al., 2004; Campbell et al., 2011; Dodel et al., 2007; Vignatelli et al., 2004).

Correlations between physical fitness and symptom severity in narcolepsy are not fully understood and likely complex. A study conducted by Matoulek et al. (2017) identified that cardiopulmonary endurance was inversely correlated with sleepiness severity and the monthly frequency of cataplexy attacks in people with narcolepsy. However, people with narcolepsy typically have decreased opportunities to exercise and engage in leisurely pastimes due to sleepiness and social isolation, and less spontaneous activity has been noted in this population (Bruck et al., 2005). A vicious cycle can develop with sedentary behaviour increasing sleepiness severity (Golden & Lipford, 2018), and the worsening of narcolepsy-related symptoms reducing activity levels and quality of life (Matoulek et al., 2017). Additionally, this functional decline can lead to the secondary development of mental health problems, which can exacerbate the reduction in function and quality of life (Morse & Sanjeev, 2018).

This study aims to profile the physical performance of people with narcolepsy attending an outpatient clinic at St. James’s Hospital, to ascertain the perception of unmet physical health needs, exercise habits and preferences. Secondary objectives of this study will be to explore the relationship between physical performance indices and sleep quality, functional ability, depression and quality of life in this population.

Methods

Study design

This study will be a cross-sectional study which will comprehensively profile the physical performance of adults attending a dedicated narcolepsy outpatient clinic at St. James’s Hospital, Dublin.

Study population

Participants will be required to meet the following eligibility criteria: aged 18 to 65 years, diagnosis of type 1 or type 2 narcolepsy based on the International Classification of Sleep Disorders third edition criteria (American Academy of Sleep, 2014) for at least six months, eligibility screened by their treating clinician, and able to understand English and follow simple instruction to enable completion of assessments. Additionally, participants will be required to provide signed and informed consent to participate in the study, and for processing of their data to be eligible for participation. Individuals with sleep disorders other than narcolepsy, contraindications to moderate-intensity exercise, confirmed pregnancy or significant psychiatric illness or cognitive impairment will be excluded from participating in the study.

Recruitment

Potential participants will be screened by their treating clinicians in advance of their scheduled clinic visit, and sent an information leaflet at least 5–7 days before their appointment if deemed eligible to participate. A follow-up call from the specialist nurse will be made to answer any study-related questions. During their clinic visit, the primary study assessor (a research physiotherapist, R.T.) will approach potential participants and provide additional information regarding the study.

Assessment

The assessment will be divided into three components, described below.

1. Physical variables

Participants will be asked to undergo an expanded physiotherapy assessment which consists of measures of cardiovascular fitness and physical activity. The primary study assessor will conduct the following test battery:

Cardiopulmonary fitness will be assessed by the YMCA submaximal bike test to estimate \( \text{VO}_2 \) max (Golding et al., 1989). The YMCA submaximal bike test is reported to have a moderately high correlation coefficient of \( r = 0.79 \), and when used to assess cardiopulmonary fitness in a heterogeneous population, Beeley et al. (2004) found no statistical difference between the predicted \( \text{VO}_2 \) max and the criterion measure (mean difference \( = 1.3 \text{ ml/kg/min} \)). The YMCA protocol uses two to four 3-minute stages of continuous exercise. The test is designed to raise the steady-state heart rate of the subject to between 110 beats per minute and 85% of the age-predicted...
maximal heart rate for at least two consecutive stages (American College of Sports Medicine, 2013).

Actigraphy. Physical activity and sedentary behaviour will be measured objectively through the use of actigraphy. Actigraphy is based on miniaturised acceleration sensors that translate physical motion to numeric representations (Sadeh et al., 1995). Actigraphy utilises a portable device to collect movement information over prolonged periods of time (Berry, 2012). Actigraphy is based on the concept that movement is increased during waking hours and reduced during sleep (Littner et al., 2003). The GTX3 model actigraph has strong relationships between counts per minute and VO2 (r=0.810, p<0.001), and can reliably quantify physical activity when compared to oxygen consumption (Kelly et al., 2013). Participants will be asked to wear the Actigraph around their waist for seven consecutive days, excluding swimming or bathing, and log the duration worn. Participants will be asked to post the Actigraph and wear time log to the study assessor in stamped addressed envelopes previously provided to them. Actigraph data will be downloaded and analysed using the ActiLife Software (ActiGraph Manufacturing Technology Inc., FL).

Lower body assessments. Vertical jump height and power will be measured through the countermovement jump test. The countermovement jump test correlates with sprint performance, maximal strength, and explosive-strength tests (Nuzzo et al., 2008). When compared to other jump tests, the countermovement jump test is the most reliable measure of lower-body power (Markovic et al., 2004). Furthermore, the countermovement jump test demonstrates great factorial validity through its relationship with explosive power (r = 0.87), low within-subject variation of 2.8% and high reliability with a Cronbach’s alpha of 0.98 (Markovic et al., 2004). Subjects are instructed to place chalk on their dominant hand. Participants will stand with their dominant shoulder about 6 inches (15 cm) from the wall and, with both feet flat on the floor, reach as high as possible with the dominant hand and make a chalk mark on the wall. They then lower their dominant hand and perform a countermovement by quickly flexing the knees and hips, moving the trunk forward and downward, and swinging their arms backwards. During the jump, the dominant arm reaches upward, and at the highest point in the jump, the participant places a second chalk mark on the wall with the fingers of the dominant hand using a swiping motion of the fingers. The score is the vertical distance between the two chalk marks. The best of three trials will be recorded to the nearest 0.5 inches or 1.0 cm (Haff & Triplett, 2015).

The isometric wall sit test is commonly used for evaluating endurance because it can be administered almost anywhere and is not complex (Tomchuk, 2011). Little equipment is necessary for the wall squat test, making it both cost-effective and accessible (Goldring et al., 2014). The intra-class correlation coefficient for the wall squat test ranges from 0.69 to 0.88 (Lubans et al., 2011). Participants will be instructed to place their back flat against the wall, with their toes pointed straight out and away from the wall. When instructed to go, the participant slides their back down the wall until their knees are at a 90-degree angle. This position is maintained until exhaustion, and only one trial is performed. The participants will be timed from the moment they obtain the proper test position until they can no longer maintain this position (Tomchuk, 2011).

Upper body assessment. Grip strength will be assessed using a handheld calibrated dynamometer (JAMAR, Hatfield, PA, USA). Although the relationship is not causative, grip strength has been reported to correlate with chronic health conditions (Bohannon, 2008; Massy-Westropp et al., 2011). Low grip strength has been associated with low spinal and pelvic bone mineral density and increased risk of vertebral fractures in women (Dixon et al., 2005). Additionally, longitudinal studies have identified strong inverse relationships between grip strength and all-cause mortality, mortality from cardiovascular disease, respiratory disease, and cancer (Celis-Morales et al., 2018). The American Society of Hand Therapists recommends that the Jamar dynamometer is used as the gold standard for the assessment of grip strength (Fess et al., 1992). The Jamar dynamometer has excellent test-retest reliability (ICC = 0.822), and interrater reliability (ICC = 0.996-0.998) as reported by Mathiowetz et al. (1984), and Lindstrom-Hazel et al. (2009), respectively. Furthermore, Jamar dynamometry has excellent concurrent validity between participant’s dominant hand (ICC = 0.99) and non-dominant hand (ICC = 0.98) as reported by Belllace et al. (2000) Measurements will be obtained in standardised conditions and following testing conditions as outlined by the American Society of Hand Therapists (MacDermid et al., 2015). The participants will be instructed to squeeze as hard as they can for 3 to 5 seconds. The procedure will be performed three times with each hand alternately, with an interval of one minute between each measurement (MacDermid et al., 2015).

The American College of Sports Medicine (ACSM) Push-Up test will be used to assess the strength and endurance of the upper limb. The Push-up test is a simple, cost-effective measure that can provide an approximation of functional status (Yang et al., 2019). Muscle strength and endurance have been shown to provide an independent protective effect for all-cause mortality and hypertension in healthy males (Artero et al., 2011). Furthermore, longitudinal studies suggest that push up capacity is inversely related to the risk of cardiovascular disease, with individuals capable of performing 11 or more push-ups having significantly reduced risk of subsequent cardiovascular events (Yang et al., 2019). The Push-Up test is highly reliable (r = 0.95 and 0.91) for predicting upper limb muscular endurance in collegiate students (Baumgartner et al., 2002). The Push-Up test has a test-retest interclass correlation coefficient of 0.95, with a 95% confidence interval of 0.85-0.99 (Ryman Augustsson et al., 2009). The maximal number of push-ups performed consecutively without rest is counted. The test is stopped when the participant strains forcibly or is unable to maintain the appropriate technique within two repetitions (ACSM, 2013).
II. Questionnaires:
Participants will be asked to complete several questionnaires which will subjectively explore participant’s perception of their physical activity levels, quality of life and symptom severity.

Health-related quality of life. Health-related quality of life (HRQoL) will be evaluated using the Medical Outcomes Short-Form 36 (SF36) and the functional outcomes of daytime sleepiness questionnaire (FOSQ). The SF36 is one of the most widely used scales for measuring HRQoL, and it has been used in various populations and different health conditions (Ware, 2000). The SF36 includes one multi-item scale that assesses eight health domains: Physical Functioning, Physical Role Limitations, Bodily Pain, General Health, Vitality, Social Function, Emotional Role Limitations and Mental Health. A higher score implies better health status. Eight domains can be combined into a physical component score (PCS) and mental component score (MCS) to provide a general overview of health (Ware & Sherbourne, 1992). The FOSQ takes approximately 15 minutes to complete and measures how the sleepiness affects a person’s actual daily ability to function, which is conceptually defined as those everyday behaviours encompassing the areas of physical, mental, and social functioning in daily life (Weaver et al., 1997).

Symptom severity. Symptom severity will be assessed through condition-specific questionnaires such as the Epworth Sleepiness Scale (ESS) and the Narcolepsy Severity Scale (NSS). The ESS is a simple method for measuring the general level of daytime sleepiness in adults. The ESS is an eight-item measure of daytime sleepiness. Respondents report their likelihood of falling asleep in particular situations using a 4-point Likert scale. Subjects are asked to distinguish dozing behaviour from feelings of tiredness. The ESS score is the sum of eight item-scores and can range from 0 to 2, and higher scores indicate greater sleepiness; scores more than 10 suggest excessive daytime sleepiness (Johns, 1991). The NSS is a 15-item scale that assesses all clinical symptoms of narcolepsy (EDS, cataplexy, hallucinations, sleep paralysis and disturbed night-time sleep) with a good balance of items on these key symptoms that were selected and validated by sleep experts who took into account the patients’ feedback (Dauvilliers et al., 2017).

Physical activity. Physical activity will be subjectively assessed through the Physical Activity Vital Sign and Sedentary Behaviour Questionnaire. The Physical Activity Vital Sign is a clinical assessment tool designed to gauge adult moderate to vigorous physical activity levels. The Physical Activity Vital Sign ascertains how many days during the past week participants performed physical activity for at least 30 minutes where their heart beats faster and their breathing is heavier than normal (Greenwood et al., 2010). The Sedentary Behaviour Questionnaire was designed to assess the amount of time spent doing the following sedentary activities: watching television, playing computer games, listening to music, talking on the phone, doing paperwork or office work, reading, playing an instrument, doing arts and crafts, sitting and driving/riding in a car, bus, or train. These items will be completed separately for weekdays and weekend days and summed to provide an estimate of weekly sedentary behaviour (Rosenberg et al., 2010).

III. Qualitative interview
A qualitative interview to explore perceptions of unmet physical health needs will be carried out by the research physiotherapist (R.T) in the Physiotherapy Department in St James’s Hospital. Interviews will last approximately ten minutes, and participants will be asked several open-ended questions that will be audio-recorded and transcribed verbatim by the study assessor. The following questions will be asked: What matters most to you at the moment? Do you have any concerns with your physical health (your strength, how fit you feel) at the moment? Is there anything you could do/offe to address these concerns? What do you feel are your main barriers to being more physically active/exercising? Have you any suggestions for us based on the tests you have just completed or anything else to add?

Statistical analysis
The data obtained from the study will be analysed using SPSS V26 software. Data will be entered into Excel, checked and coded. Data will be analysed using SPSS; normality will be assessed using the Kolmogorov-Smirnov test to determine the appropriate statistical test that will be used to compare between-group variables. A p-value of <0.05 will be considered statistically significant. Physical performance variables of participants within this study will be descriptively quantified. Regression analyses will be used to explore relationships between the following data:

I. Physical performance variables and sleep quality as well as narcolepsy severity,
II. Physical performance variables and quality of life.

Straight forward thematic analysis (Braun & Clarke, 2006) will identify patterns/themes in data generated from open-ended questions and will be analysed using NVivo (NVivo, 2012).

Sample size calculation
As this is an exploratory cross-sectional study in a predominantly unresearched area, sample size calculation is challenging. This study will recruit participants via a process of consecutive clinic attendances. Between a 9-month period (September 2019–May 2020), all attendees of the Narcolepsy outpatient clinic will be eligibility screened. Approximately 15–20 outpatients attend the Narcolepsy outpatient clinic in St James’s Hospital each month. Over a 9-month period, taking the lower threshold of 15 per month, this would be approximately 135 outpatients which will be eligibility screened. Allowing for those not meeting the inclusion criteria, repeat visit attenders, and a 10–20% refusal rate, a conservative estimate is that 70 people will participate in this study.
Data management
In compliance with GDPR, data will only be shared with those in the project team. Data will be archived for seven years as per the institutional ethical obligations, in a password protected data drive for purposes including subsequent dissemination in peer-reviewed journals or at national and international conferences. A Data Protection Impact Assessment form has been completed and submitted to the Data Impact Officer in Trinity College Dublin. This ensures that the risks associated with processing personal data and the impact on individuals are minimised throughout the proposed research. In order to prevent unauthorised consultation, alteration, disclosure or erasure of the collected data, the following strategies will be employed:

I. Hard copies of the data collected during the study will be filed and stored in a locked cabinet within the Physiotherapy Department in St James’s Hospital for the minimal time period possible in compliance with GDPR.

II. The electronic data will be stored on a networked computer, with hard disk encryption provided by St James’s Hospital.

III. Strong encryption software and passwords will be used to protect collected data, and will only be accessible to authorised data processors. The most secure versions of all software packages will be run and will be protected by anti-virus software.

IV. Every available step will be taken to ensure GDPR compliance by ensuring computing devices used for this study are safe and secure.

Discussion
Very little is known about physical performance variables of people with narcolepsy. This article presents a study protocol to comprehensively profile physical performance of people with narcolepsy and explore the relationship between physical variables, quality of life, symptom severity and disease duration. Conduction of a comprehensive physical performance test battery will facilitate the establishment of population-specific normative values and enable comparison to the general population. Furthermore, through establishing the normative values for the cardiovascular fitness, physical activity, strength and power of this population, considerable insight will be provided to help tailor exercise and possible physical rehabilitation strategies for this population. Strengths of this protocol include a broad and representative sample, as this study will be undertaken in the National Narcolepsy Centre for Ireland, located in St. James’s Hospital and the robust physical performance measures employed in this study. Limitations of this proposed protocol include that this is a novel research area, and as such, it is difficult to do a formal sample size calculation.

Data availability
No data are associated with this article.

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Narcolepsy is a rare neurological disorder characterized by excessive daytime sleepiness with irresistible sleep attacks and cataplexy (sudden loss of muscle tone triggered by emotions), associated sometimes with other abnormal rapid eye movement manifestations such as hypnagogic hallucinations, sleep paralysis, REM sleep behavior disorder and disturbed nocturnal sleep. The frequent comorbidities of NC include obesity with its metabolic and OSAS complications, restless legs syndrome, periodic limb movement syndrome, depressive mood and symptoms of attention-deficit/hyperactivity disorder. These patients have low quality of life.

WHO recommends regular physical activity. Its positive effects have been demonstrated in anxiety-depressive disorders, in the prevention of obesity, for sleep, cognitive function and quality of life. Cardiorespiratory performance were lower in NT1 than in controls. In addition, a low level of physical activity was associated with more severe depressive symptoms in narcoleptic adolescents. However, it is not clear if this low physical performance is due to the hypocretin deficit (narcolepsy type 1) or to the comorbidities such as obesity, depression, or both of them.

This work is original and could give new unmet strategies to improve the life of these patients.

The first objective of this study will be to evaluate the physical needs and the physical activities in adult narcoleptic patients. The physical needs are evaluated with a series of questions and the physical activities with two questionnaires (physical activity vital sign and sedentary behaviour questionnaire). These data will be related to the duration of disease, the symptom severity and the health related quality of life of the patients.

The second objective will be to evaluate the physical performances indices of these patients with different exercises and their relationships with depressive feelings and the quality of life of these patients.
I have several major concerns about the methodology:

- Patients: I am afraid that there will be numerous variables in this population that could influence physical activities and performances indices: Narcolepsy type 1 or 2, age (18 to 65 years), gender, presence of cataplexy, of comorbidities (obesity, OSAS, depression), disease onset, duration of the disease and treatments (with cardiovascular secondary effects).

- Statistics: How the authors will integrate these variables in their statistical models?

- In the same way, the statistical model has to be more detailed. There will be a lot of data. What is the principal criteria?

- Minor: It will be more accurate to organize the article in this way: subjective questionnaires and after the objective measurements.

**Is the rationale for, and objectives of, the study clearly described?**
Yes

**Is the study design appropriate for the research question?**
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Partly

**Are the datasets clearly presented in a useable and accessible format?**
Partly

**Competing Interests:** No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 27 January 2021

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This is a nice study about a still quite neglected aspect of narcolepsy: the physical profile, performance and activity limitations. I really appreciated that the authors included in the protocol a qualitative part.
I have a few questions and suggestions.

First, I did not find how the authors will evaluate sleep quality, that is one of the main variables of the study.

Second, I did not understand the relationship between this study and the population-specific normative values. The author mentioned this issue only within the discussion. Also, only in discussion they reported the disease duration as a variable, but in methods they did not report collection of data about the disease onset. Maybe, the authors may add a paragraph describing the socio-demographic and narcolepsy (e.g., age at onset, treatment, etc...) variables that they plan to collect. With this regard, did they plan to collect height and weight and other anthropometric measures?

Minor aspects:
- In the first paragraph of Introduction, the authors describe NT1. It would be useful to introduce here both NT1 and NT2, since they will recruit both populations.
- Few lines below, I suggest to replace “incidence” with “prevalence”.
- Among previous studies, I do not see the study by Filardi ¹ that is one of the few addressing this topic.
- At page 5, the range of the ESS is 0-3 (not 0-2).
- Since the NSS was developed for patients with NT1, I wonder how the authors will interpret its results when the patient suffers from NT2.

I do not have expertise in physiotherapy, and therefore I was not able to evaluate the specialist part of the protocol.

References
1. Filardi M, Pizza F, Antelmi E, Pillastrini P, et al.: Physical Activity and Sleep/Wake Behavior, Anthropometric, and Metabolic Profile in Pediatric Narcolepsy Type 1. Front Neurol. 2018; 9: 707 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?
Partly

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Partly

Are the datasets clearly presented in a useable and accessible format?
Not applicable
**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Sleep medicine, legal medicine, bioethics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.