Daily-life training and monitoring methodologies for chronic obstructive pulmonary disease patients
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Daily-life training and monitoring methodologies for chronic obstructive pulmonary disease patients

PROEFSCHRIFT

ter verkrijging van de graad van doctor aan de Technische Universiteit Eindhoven, op gezag van de rector magnificus prof.dr.ir. C.J. van Duijn, voor een commissie aangewezen door het College voor Promoties, in het openbaar te verdedigen op donderdag 2 juni 2016 om 16:00 uur

door

Gabriele Spina

geboren te Palermo, Italië
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Gabriele Spina
Daily-life training and monitoring methodologies for chronic obstructive pulmonary disease patients
Eindhoven University of Technology

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<td>WASO</td>
<td>Wake After Sleep Onset,</td>
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They can't bury you while you're still moving [1].
1 Introduction

1.1 Background

For the first time in history, our generation and future generations will live in a world populated by people that are dominantly old. It is estimated that human life expectancy in the Stone Age was around 20-34 years [2]. We can consider this as the natural life expectancy at birth for our species. However, nowadays, those born in Japan can expect to live 84 years [3]. This implies there has been roughly a tripling of life expectancy for humans in the last few thousand years, which has dramatically altered the way societies and communities including healthcare systems work. Before the 20th century, medical care was delivered at home, through visits from mobile family physicians who packed the necessary medical technology into a doctor's bag. In the 20th century rare and expensive resources, such as heavy technology and specialist providers, had to be centralized in hospitals to make their utilization effective [4]. Nowadays, driven by a massive increase of age-related illnesses, high healthcare costs and the need for long-term care and assistance [5], the healthcare systems need to change radically from healthcare professional-centric systems to distributed networked healthcare systems in which the individual becomes an active partner in the care process [6]. In this transformation, pervasive technologies and data analysis techniques are playing a major role enabling new care services such as long term monitoring and supportive systems [7]. Research on pervasive computing technologies for healthcare does not aim to replace traditional healthcare but is rather directed towards paving the way for a pervasive, user-centred and preventive healthcare model in which, for example, patients will be managed in their own environment under the remote assistance of the caregiver. This model particularly applies to the management of chronic disease conditions that exert a big pressure on the healthcare systems due to their high costs and increasing death rates. While deaths due to major diseases decrease, the worldwide prevalence and related deaths of chronic diseases are continually increasing. As shown in Figure 1, between 1970 and 2002, out of the six leading causes of death the largest drops occurred in the death rates due to heart disease (52%), cerebrovascular disease or stroke (63%), and accidents (41%) [8]. In contrast, death rates increased by 45% for diabetes mellitus since 1987 (3% net increase from 1970 to 2002) and they even doubled for chronic obstructive pulmonary disease (COPD) since 1970 [8].
COPD is a global health problem because of its high prevalence, increasing incidence, and associated socio-economic costs [9]. COPD is currently the third leading cause of death worldwide [10] and it is estimated that 210 million people have COPD worldwide and 10% of the population older than 40 years have moderate to severe COPD [11]. COPD is caused, among others, by smoking and air pollution and it is characterized by chronic inflammation of the lung airways, and degradation of lung tissue which result in airflow limitation [12], significant extra pulmonary effects (e.g. muscle weakness and osteoporosis) and comorbidities, which are associated with physical inactivity [9]. Patients suffering from COPD have difficulty breathing and develop “air hunger.” Breathlessness is a common occurrence forcing patients to avoid physical activities and enter into a vicious cycle of deconditioning (Figure 2). The pulmonary and skeletal muscle abnormalities limit the pulmonary ventilation and enhance the ventilatory requirements during exercise resulting in exercise-associated symptoms such as dyspnoea and fatigue. These symptoms make exercise an unpleasant experience, which many patients try to avoid, and along with a depressive mood status (in up to 30% of patients), further accelerates the process, leading to an inactive life-style. Muscle deconditioning, associated with reduced physical activity, contributes to further inactivity and as a result patients get trapped in a vicious cycle of declining physical activity levels and increasing symptoms with exercise [13].
1.2 Problem statement

There are several treatment strategies to improve physical activity and break the vicious cycle of deconditioning that affects patients with COPD such as pharmacological therapy, ambulatory oxygen therapy, and pulmonary rehabilitation programs. Pulmonary rehabilitation is recognized as a core component of the management of individuals with chronic respiratory disease and it has taken a lead in implementing strategies for health behaviour change and to optimize and maintain patient’s outcomes [14]. However, with the growth in healthcare staffing shortages and healthcare costs, patients should also be empowered to take a more active role in their personal health management and being able to perform, for example, physical training on their own, in addition to the supervised training with a therapist. It is therefore essential to develop new technologies and service concepts that permit COPD management at home, complementary to the interventions in healthcare centres. User feedback or even personal coaching might help a patient to adjust his lifestyle to the requirement of his health [15]. While systems for health monitoring and patient support are of great interest to both care providers and patients alike, suitable frameworks to achieve the envisioned paradigm shift from managing COPD patients in the hospital towards the home environment are currently lacking and require, among other challenges, the development of systems and metrics to assess patient training, behaviour, and disease stage.

Moreover, although the scientific foundation regarding the clinical importance of assessing and improving physical activity in patients with COPD has grown considerably in the past decade, the effects of the actual treatment strategies to increase and maintain physical activity have yielded inconsistent results [16]. The factors associated with patient’s capability to engage in daily physical activity are currently not well established, which may limit the impact of physical activity enhancement interventions [17]. Despite the widespread acknowledgement of this problem, further understanding is needed regarding the concepts for optimizing the impact of interventions that aim to maintain or increase physical activity levels in patients with COPD. This
has triggered the investigation of specific groups of patients to which tailor effective interventions, and to research the factors related to the spontaneous participation in daily physical activity.

New technologies such as wearable sensorized systems, deployed on a large scale, and data analysis techniques offer new opportunities beyond the traditional way of collecting and interpreting clinical data and may play a major role in understanding and generating new insights into this complex disease. With the availability of large sets of health data, medical doctors and other healthcare professionals may benefit from new diagnostic and therapeutic opportunities far beyond what is possible with today’s occasional examinations. They will have access to long-term recordings of physiological data measured in natural environments including patient’s activity and the situations to which he has been exposed to. An important component in this ecosystem is data analytics, giving value and meaning to the collected data and enabling the personalized healthcare decisions in the full circle of care around an individual. Specifically, the collected data should be the input for analysis and generation of features that can represent the condition (status and trend) of the patient, at multiple levels. It is therefore essential to investigate new techniques to analyse these data in order to fully exploit their potentials, allow the permeation of these new technologies, and in turn enable new care services such as automatic coaching systems and diagnostic supportive systems.

1.3 Aim of the thesis

The thesis aims at developing training, monitoring and decision making systems for patients suffering from chronic diseases with the goal to meet the healthcare challenges by paving the way for a pervasive, user-centred and preventive healthcare model. The overall project objective aims at finding new insights into the disease in order to increase the efficacy of pulmonary interventions and to lay the foundations for the new generation of healthcare services, whilst increasing efficiency to cope with shortage of healthcare staff.

1.4 Scope of the thesis

This thesis concerns the following main areas: i) ubiquitous patient monitoring and training, ii) mining of data from a large cohort of patients, iii) machine learning approaches for physical activity pattern identification and patient classification. In particular, the thesis contains the following contributions:

- Two smartphone-based frameworks have been implemented for the rapid prototyping of healthcare applications able to 1) interconnect external devices and therefore enabling multiple sensing modalities especially suitable for patient monitoring; 2) utilize only the smartphone internal sensors for convenient patient training.
- New insights that may increase the efficacy of tailored physical activity enhancement interventions in patients with COPD were derived analysing a large cohort of patients. In particular, 1) using clustering analysis groups of patients were identified with different physical activity patterns and characteristics; 2) it has been shown that patients having had a better night of sleep as assessed by objective measures spontaneously engaged in more physical activity the following day.
• Clinical relevant holistic metrics that integrate physiological parameters were derived using non-standard algorithms in order to permit a comprehensive and automatic assessment of the patient health status, which is currently non-existent, as a basis for new preventive and treatment approaches. Algorithms employing clinically relevant metrics are the key elements for early home-based monitoring systems assessing patient routine behaviour and sleep modalities. In all likelihood these metrics will also be relevant for other chronic diseases.

1.5 Outline of the thesis

This thesis presents recent methodological approaches in three areas: i) design and evaluation of methods for ubiquitous, patient-centric technologies (chapters 2 and chapter 3); ii) analysis of continuous and real life patients’ data to generate new insights into the disease (chapters 4 and 5); and iii) algorithms for patient behavioural pattern understanding and disease severity classification (chapters 6 and 7). Finally, conclusions are presented in chapter 8.

1.6 Own contributions

Different ubiquitous frameworks and data analytics methodologies have been proposed during this research activity to improve patient’s management and will be extensively explained throughout this manuscript. The author’s main contributions are summarized in this section.

Two smartphone based frameworks are presented for data recording and patient training, respectively. In particular, in chapter 2 a framework for sensors data acquisition, signal processing, pattern analysis, interaction and feedback is introduced and formally evaluated. The framework provides components to read smartphone and external sensor data, supporting annotations, and various output components. It proved to be well-suited for prototyping health applications in real-life, where online sensor data recording and recognition is needed. A new smartphone-based training system that integrates in clinical routines and serves as a tool for therapist and patient is illustrated in chapter 3. Only the smartphone’s build-in inertial sensors were used to monitor exercise execution and providing acoustic feedback on exercise performance and exercise errors. A Teach-mode was used to personalize the system by training under the guidance of a therapist and deriving exercise model parameters. Subsequently, in a Train-mode, the system provides exercise feedback. System performance, trainee performance, and feedback efficacy were analysed and viability of the training system demonstrated.

New insights and understanding were generated related to daily physical activity and sleep of patients with COPD. As described in chapter 4 daily physical activity measures and hourly patterns were analysed based on data from a multi-sensor armband. Principal component analysis and cluster analysis were applied to physical activity measures to identify clusters of patients with COPD. These clusters may be useful to develop interventions aiming to promote physical activity in COPD. Chapter 5 describes how relations between sleep and daytime physical activity data were analysed. The main factors associated with sleep impairment were identified. Moreover, the association of nocturnal sleep impairment with patients’ subsequent physical activity, and daytime sleep, was investigated showing a clear relationship between COPD patients’ sleep and the amount of activity they undertake during the next waking day.
Novel metrics, that can be used for patient’s assessment and monitoring, and the development of classification algorithms to process multiple input parameters were developed. Chapter 6 discusses a methodology able to integrate and analyse physical activity measures, thereby creating a set of probabilistic features that could be valid constructs to quantify physical activity behaviour change. The methodology discovers the main physical activity routines that are active in the assessed days of the subjects under study and these prove to be substantially different between healthy subjects and COPD patients regarding their composition and moments in time at which transitions occur. Furthermore, these routines show consistent trends relating to disease severity as measured by standard clinical practice. In chapter 7 a technique for predicting the pathological condition in patients with COPD is introduced based on features extracted from multimodal sensor data during night-time only. The usefulness of the proposed approach has been demonstrated by applying it to a real-world COPD patient cohort. The results showed that it is possible to differentiate between healthy and patients with COPD with 94% accuracy and between disease severity and dyspnoea severity with an accuracy of 94% and 93%, respectively.
2 CRNTC+: A smartphone-based sensor processing framework for prototyping personal healthcare applications

While smartphone apps for health monitoring and patient support are of great interest to care providers and patients alike, suitable development and evaluation frameworks are currently lacking. We present and evaluate an Android open-source smartphone framework CRNTC+ for sensors data acquisition, signal processing, pattern analysis, interaction and feedback, based on the Context Recognition Network Toolbox (CRNT). CRNTC+ extends the original CRNT by providing components to read smartphone and external sensor data, supporting annotations, and various output components. Here, we formally evaluate CRNTC+ regarding extensibility, scalability, and energy consumption. We present study results where CRNTC+ was deployed in an application to detect epileptic seizures. Results showed that CRNTC+ is well-suited for prototyping health applications in real-life, where online sensor data recording and recognition is needed.
2.1 Introduction

When utilizing the various internal sensors and interconnection to external devices, modern smartphones can become on-body hubs for sensor data acquisition, processing, and feedback in personal health applications. The potential of smartphones has been widely recognized for medical training, monitoring, and assistance [18]. Evaluating smartphone-based solutions with patients often requires developing applications and re-implementing functionality. Smartphone-based software frameworks could reduce this implementation burden and enable developers to quickly prototype solutions. However, many existing smartphone frameworks lack essential features, including algorithms for sensor pattern recognition, signal processing, or software interfaces with different external sensors (see related work in the next section). Thus patients cannot choose and interoperate sensors. Since frameworks such as the Context Recognition Network Toolbox (CRNT) have been widely used with PC-based computer architectures [19], an integrating approach could leverage from existing algorithm implementations on smartphones. In this work, we present an open-source Android-based sensing and processing framework that integrates multiple sensing modalities especially suitable for patient monitoring. Our extended CRNTC+ framework integrates the complete CRNT functionality and provides additional input/output components to utilize smartphone-internal sensors and services as well as external devices attachable via wireless protocols, e.g. Bluetooth, ANT. The smartphone-specific framework and the CRNT were partitioned through dedicated interfaces and thus can be extended independently. Nevertheless, our partitioned design does not affect framework users during configuration and use. In particular, the research makes the following contributions: 1) we introduce our CRNTC+ framework design and present its application-independent implementation. 2) We formally evaluate our framework and consider extensibility, scalability, and energy consumption. 3) In an exemplary prototype design, we evaluate CRNTC+ for detecting epileptic seizure events. We chose epilepsy to evaluate CRNTC+, since patients suffering from epileptic seizures face various difficulties in daily life. In particular, major seizures may render patients unconscious and thus in potentially threatening situations. Thus, seizure detection could support patients and caregivers by alarming when a patient needs external help. Most sensor based seizure monitoring approaches used single modalities focusing on limb acceleration or heart activity during seizures [20, 21]. Our results show that CRNTC+ can be used as a flexible solution for recording and detecting epileptic seizures during daytime using smartphones.

2.2 Related works

Several frameworks have been proposed to facilitate smartphone application prototyping. A number of smartphone data processing frameworks addressed specific applications, e.g. Pocket-Sphinx [22]. Pocket-Sphinx is a continuous speech recognition tool ported to Android. Other approaches include the Dandelion framework that uses remote procedure call (RPC) for message passing [23]. More recently, some general purpose sensor processing frameworks have been proposed. While a full review is beyond the scope of this work, some examples are highlighted. The FUNF framework [24] and the SENSE Observation System platform\textsuperscript{1} are able to acquire data

\textsuperscript{1} The SENSE Observation System, http://www.sense-os.nl/home
over third-party sensors, supporting Bluetooth and ANT protocol transmissions. However, data analysis is primarily done through cloud processing and native processing algorithms have to be implemented with a proprietary API. The Open Service Architecture for Sensors (OSAS) framework\(^2\) is an event-based programming system for sensor networks. It facilitates sensor nodes programming in a sensor network. To implement solutions, functionality needs to be implemented using regular coding. Another software framework designed for rapid prototyping of activity recognition applications is CRNT [19]. CRNT uses a component-oriented architecture, where complete data processing chains can be configured by instantiating, parameterizing, and interlinking components. Users of CRNT can thus develop an application without in-depth knowledge in programming. CRNT has been ported to many different PC-based platforms. The potential for utilizing this framework in a smartphone environment has not been investigated so far.

### 2.3 Processing framework approach

Our CRNTC+ architecture design follows a component oriented approach, including Readers, Writers, Filters, Classifiers, and others. The parameterisable components are incorporated through a run-time engine that can flexibly handle communication links between components in order to customize functionality. The architecture is partitioned into smartphone-specific and generic data processing layers to separate platform API-dependent components and those for general data handling. Besides smartphone-specific components, including many Readers and Writers, CRNTC+ incorporates all generic data processing components of CRNT [19] for signal handling and pattern processing. Moreover, several CRNT Writers, such as for file logging and WLAN communication, are directly usable. Figure 3 illustrates the layered design in a functional example. The basic architectural principles of component instantiation and data handling established for CRNT have been retained in the CRNTC+ framework. Component communication links can be routed within a layer and between layers. The architecture can be expanded by adding further components to both smartphone-specific and generic data processing layers. All components and communication links between them are configured and parameterized jointly through a JavaScript Object Notation\(^3\) (JSON) based description. Hence, to design an application, components just need to be selected, parameterised, and interlinked only.


\(^3\) http://www.json.org/
2. CRNTC+: A smartphone-based sensor processing framework for prototyping personal healthcare applications

2.4 Implementation

In our framework design and implementation we targeted extensibility, and scalability through convenient interfaces to add and customise components. Moreover, design efficiency is fundamental to minimise energy consumption. Here, we detail the implementation of key component classes: Readers and Writers. Moreover, general implementation considerations for CRNTC+ on the Android platform are described. Readers: To interface with sensors and devices via different communication standards Readers are used. Through Readers, various smartphone-integrated sensors can be recorded. Examples for external device interfaces include BluetoothReader and ANTReader components. Readers connect to devices specified in the component configuration. Depending on the sensor device protocol, data streaming is subsequently started and readings are decoded for further processing in the framework. E.g., ANTReader uses the ANT+ protocol to connect to sports or custom devices, such as BodyANT, ETHOS, and Vpatch. The BluetoothReader can be used, e.g., to interface to a heart rate belt or to Bluetooth accelerometers. Due to the phone APIs, Readers reside in the smartphone-specific layer of CRNTC+. Writers: Writers encode data streams from CRNTC+ for further analysis and feedback. E.g., the Graph component provides a time series view on the phone’s screen for reviewing sensor or feature data. Writers reside in smartphone-specific and generic data processing layers. E.g., data file logging to an SD card can be performed through the LogWriter component using generic POSIX calls, whereas the Graph component requires platform-dependent features. Component instantiation: In CRNTC+ a JSON-based configuration is used to describe component instances, their parameters, and communication links. A JSON configuration is instantiated at runtime by matching a class definition of the component. The GSON\(^4\) library

\(^4\) https://github.com/google/gson
was used to convert JSON representation into Java Objects using string mapping. When a JSON configuration file is loaded, the type field representing the module is checked and, if it matches to a map key, this module is instantiated by using the class definition that is coupled to the key. Reader for user annotations: To enable smartphone users annotating sensor data, CRNTC+ integrates an ACTLog component, which works as a reader for user input. ACTLog provides a configurable user interface (UI) within CRNTC+ to capture annotations in pre-configured categories. To annotate data, the phone user needs to tap and hold a category label and then select a sub-category label instance from a configured list displayed. Annotations can be directly processed in CRNTC+ or stored to a labels file for subsequent analysis. ACTLog resides in the smartphone-specific layer. Between-layer communication: Besides direct within layer communication, DirectInput and DirectOutput components are used as internal gateways to transfer data between framework layers. This design is needed to bridge between the different implementations of both layers: while the smartphone-specific layer uses native code of the Android platform, the generic processing is integrated as a library in the CRNTC+ application. A direct data communication between the layers is essential to minimise overhead and processing load compared to other communication forms between layers, such as RPC or TCP/UDP.

2.5 Framework characterization

To evaluate the CRNTC+ framework performance, we assessed extensibility, scalability, and energy consumption. Extensibility: We evaluated the ease of adding a new component and measured the steps necessary to create new Readers and Writers. Table I summarizes the extensibility evaluation results. Four steps were needed to add a new sensor Reader component and Writer, with 18 code lines and 22 code lines, respectively. Adding a new UI element requires five steps and 34 code lines. While the actual complexity of adding components depends on the required functionality, the evaluation indicates the basic framework-specific requirements for an extension. It can be observed that UI elements require the largest effort, since an icon is needed and the Android framework requires to handle life cycles of “Activities”. Overall, the result indicates that the framework does not imply complex steps for functionality extension. Scalability: We evaluated scalability by incrementally adding, recording, and visualizing calibrated accelerometer data from Shimmer sensors. To assess performance we measured CPU usage and measurement jitter. Up to three sensors could be simultaneously recorded without losing samples at a sampling rate of 200 Hz. When using four sensors, responsiveness of the UI reduced and CPU time for updating the UI decreased. This result suggests that three sensors could be safely recorded without losing samples. Energy consumption: For the Epilepsy case study described in paragraph 2.5, two applications have been created for gathering sensors data and for seizure event detection. During the execution of both applications, energy consumption of the smartphone was monitored. With the full sensor configuration, battery level discharged by 80% during 6 hours of sensor recording. This result can be explained by the continuous data writing onto the SD card, decoding of data sent via Bluetooth, and continuous screen use for annotating data. It can be expected that reducing sensors will reduce energy needs. Similarly, online processing without storing to the SD card could increase battery life.
2. CRNTC+: A smartphone-based sensor processing framework for prototyping personal healthcare applications

Table I Extensibility assessing CRNT+ for adding components.

<table>
<thead>
<tr>
<th>Add Readers components</th>
<th>Minimum lines of code</th>
<th>Other complexities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Extend Module class</td>
<td>3</td>
<td>Further subclassing</td>
</tr>
<tr>
<td>2. Extend ReaderClass class</td>
<td>13</td>
<td>Depending on sensor</td>
</tr>
<tr>
<td>3. Add Module class definition</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>4. Add ReaderClass class definition</td>
<td>1</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Add Writers components</th>
<th>Minimum lines of code</th>
<th>Other complexities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Extend OutputModule class</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>2. Extend OutputClass class</td>
<td>13</td>
<td>None</td>
</tr>
<tr>
<td>3. Add Module class definition</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>4. Add OutputClass class definition</td>
<td>1</td>
<td>None</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Add User Interface components</th>
<th>Minimum lines of code</th>
<th>Other complexities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Extend GUIModule class</td>
<td>12</td>
<td>None</td>
</tr>
<tr>
<td>2. Extend MyTabActivity class</td>
<td>13</td>
<td>Retrieve GUIModule</td>
</tr>
<tr>
<td>3. Create icons</td>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>4. Create layout xml file</td>
<td>3</td>
<td>Depends on GUI structure</td>
</tr>
<tr>
<td>5. Create drawable xml file</td>
<td>6</td>
<td>None</td>
</tr>
</tbody>
</table>

Estimations indicate the smallest effort. For functional components, actual effort can be larger.

2.6 Experimental evaluation

2.6.1 Epilepsy evaluation study

We evaluated the CRNTC+ framework in a case study to investigate data acquisition from multi-modal on-body sensors and recognising seizures. Since epileptic seizures often occur only sporadically in patients during daytime, two expert actors were asked to simulate five different seizures types (myoclonic, tonic, tonic-clonic, clonic, myoclonic tonic-clonic) during ten everyday activities, including lying in bed, getting dressed, scratching, drinking from a glass, brushing teeth, sit-ups, shaking hands, using mouse, typing on a keyboard, folding towels. Heart rate data were acquired using a Shimmer\(^5\) electrocardiogram (ECG) module, placed at the left upper arm. The module featured a 3D accelerometer too. Disposable electrodes were connected to the ECG module and attached to the participant’s chest. Respiratory data were acquired using a Braebon\(^6\), strap, placed around participants’ thorax and connected to a second Shimmer ECG module. Another 3D accelerometer was placed at the right upper arm. Two full inertial motion units (one ETHOS and one Shimmer 9DOF) were placed at participants’ left and right wrists. Data was acquired at two different sampling rates: for the Shimmer units 100 Hz, and for the ETHOS sensor 128 Hz. All the sensing modules were held in place using adjustable velcro straps. Data from all sensors was recorded via Bluetooth (Shimmer) and ANT (ETHOS) using a Sony Ericsson Xperia active smartphone. A study observer was carrying the phone and used ACTLog to


\(^6\) The Braebon Respiratory Effort Sensor, http://www.braebon.com
annotate the activities during recordings. Since expert actors were recorded instead of epilepsy patients, heart rate and breathing pattern reacted with a delay and caused by the physical activity related to simulated seizures, rather than an actual seizure. Thus, ECG and respiratory data was considered to assess the CRNTC+ framework scalability, but excluded from further analysis. Experimental set up is shown in Figure 4.

2.6.2 Epilepsy study results

Approximately 40 min of continuous recording were acquired per participant. Data was segmented using a window size of 100 sa. Variance of the 3D accelerometers unit placed on both the upper arms and on the dominant wrist was analysed and used in a two-class classification (seizure against non-seizure). All analyses were performed using the CRNTC+ and a frame-based evaluation. First, to train an offline kNN classifier (k=3), 500 samples per class were randomly selected from data from both actors. Remaining samples were used for testing. Subsequently, to test the feasibility of real-time seizure detection, the configuration was tested online. For practical application we considered that the system should alarm within one second from the start of a seizure. To satisfy the real-time constraint of the online evaluation, the training set needed reduction to 100 samples and only one sensor was used. The performance limiting factors for the real-time analysis were the Shimmer sensor data transmission and the classifier processing. The offline detection test using 3 accelerometers, showed a class specific accuracy of 74% for seizure event and 64% for non-seizure. For the one-sensor configurations, 72% and 59% was obtained for the upper left arm, 76% and 63% for the upper right arm, and 81% and 62% at the wrist, for seizure events and non-seizure times respectively. Subsequently, the right wrist sensor was chosen to test online recognition performances. Figure 5 summarizes the performance results. For the online recognition, the reduced training set resulted in a deteriorated performance, with 78% for seizure events and 55% for non-seizure times. After
revising the training set to the core seizure phase with high motion intensity only, performance improved to 86% for seizure events and 78% for non-seizure times.

Figure 5 Epilepsy seizure detection performance using the CRNTC+ framework. (a): offline, using three 3D acc. units placed on the upper arms and dominant wrist. (b): online, using one 3D acc. unit at wrist. (c): online, using one 3D acc. unit at wrist with revised training data (see main text for details). (d): Annotation example for a Tonic-clonic seizure. The red square marking indicates the seizure part used as training data for the results in panel (c).

2.7 Conclusion and future work

We proposed and evaluated a new framework for smartphone-based sensor data recording and processing, which emphasizes extensibility and leverages the widely used CRN toolbox for generic data processing algorithms. The new CRNTC+ was implemented in a layered framework design. Our formal evaluation and study results showed that CRNTC+ is versatile to handle various multi-modal sensors and recognition solutions, which are essential to prototype patient care solutions with phones. While the present investigation focused on assessing feasibility of CRNTC+ for epilepsy detection in daily life, further work is needed to optimize the detection by evaluating additional algorithms and evaluation in larger studies.
3 COPDTrainer: A smartphone-based motion rehabilitation training system with real-time acoustic feedback

Patient motion training requires adaptive, personalized exercise models and systems that are easy to handle. In this work, we evaluate a training system based on a smartphone that integrates in clinical routines and serves as a tool for therapist and patient. Only the smartphone’s build-in inertial sensors were used to monitor exercise execution and providing acoustic feedback on exercise performance and exercise errors. We used a sinusoidal motion model to exploit the typical repetitive structure of motion exercises. A Teach-mode was used to personalize the system by training under the guidance of a therapist and deriving exercise model parameters. Subsequently, in a Train-mode, the system provides exercise feedback. We validate our approach in a validation with healthy volunteers and in an intervention study with COPD patients. System performance, trainee performance, and feedback efficacy were analysed. We further compare the therapist and training system performances and demonstrate that our approach is viable.
3.1 Introduction

Cardiopulmonary fitness is a well-known condition for our long-term health and wellness [25]. In particular, patients suffering from the widespread cardiovascular diseases (CVD) and chronic pulmonary obstructive disease (COPD) can benefit from physical training. Nevertheless, CVD and COPD patients have special requirements regarding fitness training, related to their physical ability, determining type and intensity of exercises, and practical systems to support them. For example, generally healthy people could regularly jog and run, and even over-train without immediate health consequences. In chronic patients, both over-training and undertraining could lead to quick and detrimental worsening of the health condition, resulting in exacerbations and hospitalisation, or death [26]. In addition, chronic patients often fear to exercise wrongly [27], if not under therapist supervision. While therapists can recommend exercises for the patient’s independent training, both therapist and patient have no means to assess the exercise performance during independent training. Ubiquitous and on-body systems could enable patients to perform additional physical training on their own, in addition to the supervised training with a therapist. Fitness and sports studies revealed a series of challenges for monitoring and coaching, when using ubiquitous and on-body sensing systems. In a recent survey, Kranz et al. [28] identified usability improvement, instruction quality, and long-term motivation as core design aspects of fitness training systems. Usability improvement refers to reduced labour in maintaining log-books or other manual records during training. Instruction quality refers to the guidance a trainee is provided with, to adequately execute an exercise. We believe that system feedback could prevent injuries, or worsening conditions in patients. During rehabilitation exercise training, for example, different errors can co-occur and should be identified accordingly. Moreover, it is essential that an error estimation algorithm can handle different exercises with minimal adjustments to support training variety. Adequate feedback depends on individual skills and fitness level, which is particularly varying in chronic patients corresponding to their rehabilitation progress. Thus, error estimation algorithms should be adjustable to a patient’s individual capability level. Until now, many error monitoring approaches focused on individual exercises or specific multisensory training devices that helped to stratify error conditions. However, attaching multiple devices is often too difficult for patients to train individually. While on-body sensors could be comfortable during exercise training, their cost and handling is challenging for patients. The widespread adoption of smartphones provides a platform for healthcare applications that is directly available to patients. In this work, we introduce a smartphone-based motion rehabilitation training system, intended for individual exercising of chronic patients. The system processes motion sensor data online on the phone and provides real-time acoustic feedback regarding the exercise performance and quality. We investigate whether exercise model parameters describing typical rehabilitation exercises can be derived from a smartphone’s internal sensors to reliably support patient training and provide real-time feedback. In particular, this work provides the following contributions: 1. we introduce a training approach, where the trainee has to attach a holster carrying the smartphone only. After an initial rehabilitation exercising session with the therapist (Teach-mode), individual training (Train-mode) can be performed. 2. We validated our system with healthy individuals performing six limb movement exercises as they are commonly prescribed for COPD patients. We model errors using motion parameters and classify nine performance classes (including “correct” and eight error conditions). Subsequently, we evaluate our system in an intervention.
study with seven COPD patients. We assess system recognition performance regarding exercise and performance classes. 3. In further analyses of the COPD patient study data, we determine patients’ training performance, error trends, and feedback efficacy. Furthermore, we compare the therapist training error assessment against the sensor-based measurements. We confirm that the smartphone-based training system can achieve similar performance than when assessed by a therapist. Our approach integrates into this clinical rehabilitation routine by incorporating a Teach-mode, where training is performed under therapist supervision. During Teach-mode, our system derives motion parameters that are subsequently used during the Train-mode to estimate training performance and quality. Hence, the system could serve as a novel tool for therapists and their chronic patients to improve training options, both in the rehab centre and at home. The smartphone serves as a single training device, thus reducing starting barriers for rehabilitation training, including cost, availability, and handling of devices.

3.2 Related works

A few works assess the quality of exercise activities being performed, especially for clinical applications. Analysing exercises performance is usually done by means of cameras [29], depth cameras [30] or optical motion capture systems in combination with passive markers (Vicon, OptiTrack). In general vision-based systems allow users to easily extract a human skeleton automatically, but require constrained environments to install and calibrate cameras. Various ambient and on-body device developments identified opportunities for continuous training and coaching in fitness and sports outside the lab, such as the Ubifit Garden [31], MOPET system [32], and Triple-Beat [33]. Smartphones are being widely deployed and provide several integrated sensors to analyse data in real-time and provide training performance feedback. Thus, smartphones could be used as stand-alone systems to minimize costs hurdles in applications. For example smartphones were used as a mobile exercise skill assessment tool (GymSkill) to support personal health and fitness [34]. GymSkill monitors exercise quality performed on a balance board and provides feedback according to various parameters including regularity of movements. Muehlbauer et al. [35] exploited arm worn smartphones to recognize and count upper body resistance training exercises from acceleration sensors. In [36] the authors introduced an algorithm based on dynamic time warping, which uses acceleration data to evaluate the number and duration of correctly recognized repetitions. The application provided real-time feedback on the duration of repetitions and was studied in healthy individuals. Further parameters, including the range of motion and efficacy of the feedback were not considered. Wearable distributed sensors and other dedicated devices were used in several exercise and sports studies. Strohrmann et al. [37] assessed performance level, training assistance and fatigue monitoring of runners. Tseng et al. [38] used accelerometers and compass sensors in a rehabilitation game to increase motivation. The system provided scores on movement quality. A fixed rule-set was used to recognise activities. Chang et al. in [39] proposed a system to recognize motion patterns and count repetitions of a limited set of free-weight exercises using acceleration data from a glove and a chest belt. The system did not provide feedback on execution quality since start and end of a repetition were not detected. Although their counting algorithm showed good results, it needed re-training to obtain accurate results for different exercise speeds. Moreover, training data was required to obtain pattern models off-line. Velloso et al. [40] used five Xsens sensors and a Kinect camera to derive pattern models during an
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exercise demonstration performed by an expert. The system then detected mistakes and guided users on improving their performance. Three weight training exercises were studied, however system recognition performance to detect training errors were not analysed. The deployment of the Kinect camera constrained the field of view to a 2m distance from the system. Limbs should not be pointed directly at the camera or be occluded by the body, which limits the exercises that could be monitored. The related works discussed above focused mainly on gym monitoring applications for healthy subjects. Often these approaches relied on multi-sensor information and pattern recognition methods, requiring individual learning of motion pattern models. Our work aims at describing different training exercises with the same exercise quality parameters and a sinusoidal model. In our approach, a smartphone serves as single measurement, estimation, and feedback device for assessing patient exercise performances. We evaluate our method's recognition performance for classifying execution errors, which is necessary to deploy the system in practice and especially in a clinical application. To the best of our knowledge, no existing commercial or academic work exploits smartphones to assess training quality in chronic patients. Likewise, recognition performance for classifying execution errors was not evaluated in similar systems for a clinical application.

3.3 Smartphone-based training approach

The ability to perform particular motion exercises differs between trainees, due to individual motion constraints. Chronic patients often suffer from limiting pathologies and muscle weakness, thus may not be able to perform exercises at the same speed or range of motion of another trainee. To use the smartphone as an exercise monitoring and feedback device in this user group, it was attached in a holster to a body part or limb involved in the exercise. The phone’s integrated inertial sensors could thus capture the motion performance. After performing one exercise, the holster could be moved to a position designated for the next exercise. Illustrations on the phone’s screen guided the trainee during attachments. Here, we describe our training approach that includes Teach-mode and Train-mode operation as illustrated in Figure 6 and our motion exercise modelling approach.
3.3 Smartphone-based training approach

3.3.1 Teach-mode operation

The Teach-mode allows therapists to personalise the system for a trainee under direct supervision, e.g. during the regular physiotherapy practicing times. Any selectable exercise can be performed and the trainee learns from the therapist how to attach the phone and perform a particular exercise. Illustrations are shown on the screen after selecting an exercise to remind the patient about the exercise execution independently of the operation mode. In Teach-mode, the therapist initially guides the patient during the first trials to perform the exercise accurately. Subsequently, the Teach-mode recording is started by pressing a large button on the phone’s screen. A pre-set number of exercise repetitions (ten in the current implementation) will then be acquired from the phone’s inertial sensors. From the recorded data, all necessary exercise model parameters, i.e. mean and variance of the duration and of the range of motion of the limb during the ten repetitions) are estimated and stored for further use in the Train-mode. The derived parameters are shown on the smartphone, such that the therapist and trainee can review them. If the therapist judges that the trainee did not perform the exercise with sufficient quality, the session could be repeated. Moreover, the system checks consistency of the exercise repetitions...
and can thus reject a Teach-mode session that shows extensive execution variability. These choices consider the clinical routines, where therapists have only 30 to 45 min per patient for assessment, therapy, and exercise training. Thus, complex interactions with the device were avoided.

### 3.3.2 Train-mode operation

During Train-mode, the derived exercise models are arranged in a to-do list for the trainee to complete. This mode is intended to be used by the trainee to exercise without therapist supervision, i.e. at the rehab centre or at home. After selecting an exercise to be performed and starting the Train-mode, inertial motion data is recorded from the phone’s sensors and processed in real-time to count the exercise repetitions and detect errors. While training, the smartphone system will provide acoustic feedback on the counted repetitions and notify when errors occur. E.g., if the trainee had practised an exercise with the therapist before, but starts to perform repetitions faster than during the Teach-mode, the system will provide the feedback “move slower”. This feedback could prevent injuries from repetitive erroneous movements. Finally, after that the configured number of repetitions were detected, the system will ask the trainee to stop and displays a summary of the execution performance.

### 3.3.3 Motion exercise modelling

Based on the observation that many fitness exercises have a repetitive structure, from training with free weights to cardio fitness motion, we consider a sinusoidal motion model. For each exercise, a representative motion feature could be chosen that represents a sinusoidal pattern. The feature can be based on a single raw sensor axis or fused from several sensors, such as orientation estimates. For example, in a lateral arm abduction exercise, where the phone is attached to the wrist, the anterior-posterior orientation angle could be used as motion feature. Figure 7 shows an example waveform for several repetitions of an exercise. Advised by three therapists and after consulting COPD guidelines, we derived speed of motion (corresponding to the period frequency) and range of motion (corresponding to the feature amplitude) from the sinusoidal pattern of each exercise repetition. In Kinesiology speed and range of motion, together with their relative tolerances and the number of repetitions, are considered standard measures for exercise monitoring [41]. Estimating movement speed during exercises is useful to educate patients in breathing techniques (i.e. by exercising the patient can learn how to breathe with a correct timing). Based on these exercise quality parameters, we derived performance classes, such that the classes are applicable to various exercises that are performed by repetitive movements. During the Teach-mode, exercise repetitions are used to represent repetition range and duration parameters using two normal distributions. In the Train-mode, these model parameters are used to identify nine performance classes. The classification approach is further described in the following section.
3.4 Algorithm implementation

Here, we describe the algorithm implementation for segmenting and evaluating exercise performances in a stand-alone Android smartphone application.

3.4.1 Teach-mode implementation

For any exercise to be monitored, the smartphone body attachment and the motion feature representing the sinusoidal pattern need to be chosen. Subsequently, during the Teachmode, the application records inertial sensor data from accelerometers, magnetometers, and the orientation API, and stores the data for the later analysis. Since the Teach-mode is performed under therapist supervision, no real-time feedback will be provided. Once the trainee completes an exercise session with a pre-set number of repetitions, the application loads the stored data and extracts the exercise model parameters. The following processing steps were applied to derive the model parameters.

**Filtering.** The selected motion feature was filtered using a moving average to remove tremor-induced noise and sensor noise. The window size was set proportional to the amount of data acquired (i.e. \( \text{WindowSize} = \text{DataSize} \times \text{ScalingFactor} \), with \( \text{ScalingFactor} \) determined empirically and set to 80). We observed that this approach provided consistent results across the different exercises. Since the number of repetitions is preconfigured, we assume that the total data amount recorded is proportional to the movement speed during the exercise execution: the faster a trainee performs the exercise, the lower muscular tremor would be, and thus, data averaging can be reduced. Bounds were applied to the averaging window size, to prevent ineffective averaging for very fast/slow repetitions (\( 15 \leq \text{WindowSize} \leq 31 \text{ sa.} \)).

**Period estimation.** By estimating the position of positive and negative peaks in the filtered motion feature, exercise repetitions were counted. For the Arm abduction exercise, Oy will be maximal when the arm is raised to shoulder height. It reaches its minimum value when the arm returns to the neutral position (arm aligned to the trunk). We used an adaptive hill climbing algorithm to detect positive and negative peaks (denoted in Figure 7 by pp and np, respectively), given a peak threshold \( \theta \). The hill-climbing algorithm is a popular first choice among optimisation algorithms. While there are many alternatives, such as simulated annealing or tabu search, hill-climbing can achieve sufficient or better results if runtime is constrained, such as in the real-time system targeted here. Figure 7 illustrates an example motion waveform with the exercise parameters. In particular a maximum (minimum) was selected, if both sides (uphill \( h_u \) and downhill \( h_d \)) are greater than the peak threshold \( \theta \). In this work, we estimate \( \theta \) during the Teach-mode. Starting from an initial setting \( \theta = \theta_{\text{in}} \), \( \theta \) was adjusted in steps of 1.2 until the pre-set repetition number was obtained. We set the number of exercise repetitions to ten. The fitted \( \theta = \theta_{\text{opt}} \) was subsequently applied during Trainmode operation.

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3. COPDTrainer: A smartphone-based motion rehabilitation training system with real-time acoustic feedback

![Figure 7 Example waveform of the Pitch motion feature (O) selected for the Arm abduction exercise. The hill-climbing parameter θ is fitted during system runtime (Teach-mode) for each exercise. The horizontal dotted line indicates the estimated duration \( \frac{d}{2} \), the vertical line indicates the estimated range of motion \( r \). Online feedback is provided in the indicated region.]

**Peak correction.** While the hill-climbing algorithm has low runtime complexity, the detection of local maxima and minima remains susceptible to detecting additional peaks (insertion), e.g. during vibrations, or to missing peaks (deletion) if the signal amplitude decreases. In situations where there is one insertion or deletion error in sequence, the alternating order of positive and negative peaks is interrupted. If two consecutive positive or negative peaks were derived a peak correction algorithm was applied. This peak correction works by first removing redundant peaks and then inserting missing peaks that were missed during the first iteration of the hill-climbing algorithm. If two consecutive positive (negative) peaks were detected, the algorithm compare them and removes the one having a smaller (greater) amplitude, thus restoring the alternating of maxima and minima. Subsequently, time intervals \( \Delta t \) between two consecutive peaks were used to determine if there could be peaks missing. If an interval was larger than \( m_{\Delta t} \sigma_{\Delta t} \), where \( m_{\Delta t} \) and \( \sigma_{\Delta t} \) are mean and standard deviation of the intervals, it was assumed that peaks might be missing. Missing peaks were searched by applying hill-climbing within the section delimited by the consecutive peaks. A smaller threshold \( \theta \) (reduced by 20% of its initial value) was then used. The hill-climbing was iterated while adjusting \( \theta \) until a peak was found, or a lower limit of \( \theta < \theta_{opt}/2 \) was reached.

**Exercise model parameter estimation.** The following five parameters were derived: number of repetitions \( (n) \), mean and standard deviation of repetition duration \( (m_d, \sigma_d) \), and mean and standard deviation of the range of motion \( (m_r, \sigma_r) \). The repetition duration was derived from the time interval \( \Delta t \) between two adjacent minima. The range of motion was derived from the magnitude difference between adjacent negative and positive peaks. The number of repetitions
could be obtained by counting the number of maxima. Since capabilities between trainees vary a small initial peak threshold $\theta_i$ was fixed per exercise to detect small motion, while avoiding capturing vibration and noise. Table II provides an overview on the exercises and parameters.

### Table II

<table>
<thead>
<tr>
<th>Exercise</th>
<th>Motion feature</th>
<th>$\theta_i$ [degree]</th>
<th>$[\theta_{mn} - \theta_{med}]$ [degree]</th>
<th>$[d_{mn} - d_{med}]$ [samples]</th>
<th>$[r_{mn} - r_{med}]$ [degree]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ex1: Arm abductions</td>
<td>Pitch $O_y$</td>
<td>25</td>
<td>[22.5-22.5]</td>
<td>[3.1-4.6]</td>
<td>[70.4-82.8]</td>
</tr>
<tr>
<td>Ex2: Elbow circle</td>
<td>Pitch $O_y$</td>
<td>15</td>
<td>[13.5-18.9]</td>
<td>[1.5-2.6]</td>
<td>[24.0-42.6]</td>
</tr>
<tr>
<td>Ex3: Elbow breathing</td>
<td>Azimuth $O_x$</td>
<td>15</td>
<td>[13.5-13.5]</td>
<td>[2.5-3.2]</td>
<td>[40.1-68.1]</td>
</tr>
<tr>
<td>Ex4: Knee extensions</td>
<td>Pitch $O_y$</td>
<td>15</td>
<td>[13.5-13.5]</td>
<td>[2.6-3.5]</td>
<td>[58.3-87.0]</td>
</tr>
<tr>
<td>Ex5: Leg lifts</td>
<td>Pitch $O_y$</td>
<td>10</td>
<td>[3.1-9.0]</td>
<td>[2.5-3.3]</td>
<td>[7.6-21.9]</td>
</tr>
<tr>
<td>Ex6: Steps up</td>
<td>Pitch $O_y$</td>
<td>6</td>
<td>[3.1-9.0]</td>
<td>[3.5-4.9]</td>
<td>[13.0-36.4]</td>
</tr>
</tbody>
</table>

### 3.4.2 Train-mode implementation

#### Data segmentation.
In contrast to the Teach-mode, Trainmode operation requires online period estimation and subsequent performance analysis. A sliding window was used to segment the incoming data stream. The sliding window size was set to cover two average repetitions based on the parameters estimated in the Teach-mode ($2m_d$) with an overlap of 75% between consecutive windows. The overlap ensures timely feedback during a newly detected repetition.

#### Period estimation.
The hill-climbing algorithm was applied in the sliding window, configured according to the Teachmode. Due to the overlap in sliding windows, duplicate peak detections had to be corrected by matching the peak locations across the sliding windows.

### 3.4.3 Exercise performance class estimation

Based on the peak detection, repetitions could be counted. To provide timely feedback, i.e. before the trainee starts a subsequent repetition, the first half of a repetition was evaluated to estimate duration and range of motion estimates. In preliminary tests, we observed that the error incurred by considering only half of a repetition was negligible. The derived duration $d_i$ and range of motion $r_i$ estimates were used to compare with the parameters estimated in the Teachmode, i.e. $m_d$, $\sigma_d$, $m_r$ and $\sigma_r$. For duration and range of motion, each repetition performance is estimated based on a Gaussian distribution $N(m_i; \sigma_i)$ and $N(m_r; \sigma_r)$. The performance of each exercise is classified into 3 class types: in-between, under and above the ranges: $[m_d - 2\sigma_d, m_d + 2\sigma_d]$ and $[m_r - 2\sigma_r, m_r + 2\sigma_r]$. In total, there are then nine different classes to which each performed exercise repetition could be associated. While we aimed here at a generic system that can deal with various exercises, some of them may not benefit from all performance classes. For the exercise Steps up, only three performance classes (Correct, Too fast, Too slow) were expected, since step height was fixed by the stairs used, thus range of motion was not relevant for this exercise. After the performance class corresponding to the ongoing repetition was evaluated, an audio feedback was provided to the trainee, to notify if a repetition was erroneously performed. The nine performance classes and feedback are listed in Table III.
3. COPDTrainer: A smartphone-based motion rehabilitation training system with real-time acoustic feedback

<table>
<thead>
<tr>
<th>#</th>
<th>Performance class (feedback)</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Correct (-)</td>
<td>$d_i \in [m_d - 2\sigma_d, m_d + 2\sigma_d]$, $r_i \in [m_r - 2\sigma_r, m_r + 2\sigma_r]$</td>
</tr>
<tr>
<td>2</td>
<td>Too fast (move slower)</td>
<td>$d_i &lt; m_d - 2\sigma_d$, $r_i \in [m_r - 2\sigma_r, m_r + 2\sigma_r]$</td>
</tr>
<tr>
<td>3</td>
<td>Too slow (move faster)</td>
<td>$d_i &gt; m_d + 2\sigma_d$, $r_i \in [m_r - 2\sigma_r, m_r + 2\sigma_r]$</td>
</tr>
<tr>
<td>4</td>
<td>Too large (move lower)</td>
<td>$d_i \in [m_d - 2\sigma_d, m_d + 2\sigma_d]$, $r_i &gt; m_r + 2\sigma_r$</td>
</tr>
<tr>
<td>5</td>
<td>Too small (move higher)</td>
<td>$d_i \in [m_d - 2\sigma_d, m_d + 2\sigma_d]$, $r_i &lt; m_r - 2\sigma_r$</td>
</tr>
<tr>
<td>6</td>
<td>Too fast and too large (move slower and lower)</td>
<td>$d_i &lt; m_d - 2\sigma_d$, $r_i &lt; m_r + 2\sigma_r$</td>
</tr>
<tr>
<td>7</td>
<td>Too fast and too small (move slower and higher)</td>
<td>$d_i &lt; m_d - 2\sigma_d$, $r_i &lt; m_r - 2\sigma_r$</td>
</tr>
<tr>
<td>8</td>
<td>Too slow and too large (move faster and lower)</td>
<td>$d_i &gt; m_d + 2\sigma_d$, $r_i &gt; m_r + 2\sigma_r$</td>
</tr>
<tr>
<td>9</td>
<td>Too slow and too small (move faster and higher)</td>
<td>$d_i &gt; m_d + 2\sigma_d$, $r_i &lt; m_r - 2\sigma_r$</td>
</tr>
</tbody>
</table>

3.5 Evaluation study

To test and evaluate our training system, two sets of experiments were conducted. Initially, the system was validated with healthy participants using a scripted protocol where all performance classes have been equally represented. Subsequently, the training system was evaluated in an intervention study with COPD patients. The study was performed during normal therapy training sessions to evaluate the overall system performances and the feedback efficacy. Here we summarise the considered exercises and present the study protocols used with healthy participants and COPD patients.

3.5.1 Training exercises

Six exercises were chosen according to the COPD guidelines and in consultation with therapists. The exercises selected (as illustrated in Figure 8) do not require additional equipment to be performed, thus can be used also outside of the rehab centre. Due to their utility in exercising the breathing, the therapists considered these exercises suitable for daily training at home. The exercise set consist of three upper body exercises and three lower body exercises. The upper body exercises, arm abductions (AA), elbow circles (EC) and elbow breathing (EB), increase strength in arm and shoulder muscles, while the lower body exercises, knee extensions (KE), leg lifts (LL) and step-ups (SU), train lower body muscles.
3.5.2 Data collection and exercise features

Both healthy participants and COPD patients were asked to wear the smartphone in a holster during the exercises. The holster was attached to the right wrist during the upper body exercises and to the right ankle during the leg exercises using Velcro straps. Three acceleration signals ($A_x$, $A_y$, $A_z$) and three Euler orientation angles (Azimuth $O_x$, Pitch $O_y$ and Roll $O_z$) were recorded from the 3D accelerometer and magnetometer sensors embedded in a Samsung Galaxy SIII phone. Data was acquired at the sampling frequency of ~50Hz using the Android Software Development Kit (SDK). From the available motion signals, we chose orientation estimates as features to describe the sinusoidal exercise pattern. According to the phone orientation at the body, Azimuth orientation angle ($O_x$) was used for elbow breathing and Pitch ($O_y$) for all other exercises. Orientation estimates can be efficiently derived on smartphones, thus the approach can be used even on entry-level phones.
3.5.3 Validation with healthy participants

In this validation, we quantified the accuracy of the system in detecting the nine performance classes listed in Table III. Four healthy participants (all male, 26±2.5 years old) were individually asked to perform nine exercise sessions of at least ten repetitions in the university sport centre. An expert personal trainer instructed the participants to perform the exercises as required according to the protocol and supervised the whole data collection. After a first set of repetitions to familiarize with the exercise, ten continuous repetitions were recorded for the evaluation. The data gathering started with the acquisition of one correct session of ten repetitions during the Teach-mode. Afterwards participants were asked to perform the repetitions using the Train-mode.

3.5.4 Evaluation with COPD patients

Subsequently to the validation, we tested the training system in a pilot intervention study with COPD patients. For this evaluation, seven COPD patients (age 60 ± 10 years) were recruited while they were following a rehabilitation program in a specialized centre for pulmonary diseases. The patients ranked a COPD GOLD score between II and III, FEV1 was between 37% and 69% and FEV1/FVC was between 27% and 69%. After being instructed on the exercise execution, one Teach-mode session for each exercise was performed with one therapist guiding the patient in order to perform correct movements and rejecting sessions that were not performed correctly. After completing the Teach-mode for all the exercises the therapist did not interact anymore with the patients to simulate individual training exercise executions. The patients started the Train-mode session by touching the start button on the smartphone’s screen and then began with the training. During the exercise execution, the application gave audio feedback if an erroneous repetition was detected and asked the patients to terminate the session when ten repetitions were counted. While the patients were performing the exercises, one therapist judged each repetition, according to the movement errors defined before and annotated the performance for each repetition in a table. After the recordings, the annotations were digitized. Furthermore, a ground truth was derived after the recordings by reviewing the raw sensor data time series and labelling error classes for each exercise repetition based on the data. The ground truth labels were aligned according to the peaks and valleys in the sinusoidal exercise pattern. Speed and range of motion of each repetition were then calculated according to Table III. In total each patient was asked to perform three sessions of ten repetitions of each of the six exercises. Patients could take a break in between if they wished to do so. Data was acquired in two sessions at separate days. During the first session four patients (P1, P2, P3, P4, 1 male and 3 female) were examined and during the second session the remaining 3 patients (P5, P6, P7, 2 male and 1 female). In the first session, patients (P1-P4) were specifically asked to alternate their training such that at least one other exercise was done in between Teach-mode and Train-mode performance of an exercise. With this protocol, we intended to avoid excessive effects of exercise memorisation. In the second session, patients (P5-P7) were not asked for alternating exercises. In our subsequent analysis we did not observe performance differences between the two sessions.
3.6 Results

This section describes the results of our system validation with healthy participants and the evaluation with COPD patients. Performance of the system to detect execution errors is detailed for both investigations. For the patient study, we furthermore analysed feedback efficacy. Finally, we compared the therapist’s performance in detecting erroneous exercise repetitions with the ones of our system.

3.6.1 Validation with healthy participants

We formally evaluated our system with a dataset acquired from healthy participants, using a scripted exercise and performance protocol. According to the protocol, participants were asked to perform all exercise movement errors, besides the correct execution of each exercise. Thus, the script and supervising trainer provided reference information for the ground truth used. Here we detail the recognition accuracy for all nine performance classes and six exercise classes.

Recognition confusion among performance classes. The average performance classification accuracy of the system was 96.2%, confirming that applicable feedback would have been provided for almost every exercise repetition. The confusion matrix for providing matching feedback (i.e. classify too slow when the recorded motion was slower than in the Teach-mode) for all performance classes is shown in Figure 9. The matrix illustrates very good accuracies for all performance classes, above 90%. Lowest accuracy (92%) was observed for performance class 9 (Too slow & too small), where thirteen repetitions were misclassified. A further analysis attributed these classification errors to challenges in performing Leg lifts (Ex. 5).

Recognition accuracy for exercise classes. To further analyse correctness of the feedback, Figure 10 shows the accuracy distribution across exercises and performance classes. It can be observed that most of the erroneous feedback in performance class 9 was given during exercise Leg lifts (Ex. 5), where the system showed lowest accuracy (77.5%).
3.6 Results

3.6.2 Evaluation with COPD patient in intervention study

We evaluated system performance for counting exercise repetitions and recognizing the trainee errors performed in a group of seven COPD patients. During the intervention study recordings, we observed that the therapist could not accurately assess all exercise repetitions, because it was difficult to observe the patient's movements and annotate the exercise performances simultaneously. A ground truth labelling was derived in a post-recording step according to the raw sensor measurements, as explained in Section Evaluation with COPD patients. We needed to exclude two sessions of Step-ups performed by Patient 1, three sessions of Leg lifts, by Patient 3, and one session of Knee extensions by Patient 7, due to data recording issues. Patient 6 could only complete the first session of Elbow circles due to shoulder pain. In total, 1176 exercise repetitions were acquired and analysed.
Results

Figure 10 Recognition accuracies for exercises and performance classes in all validation study participants (healthy individuals). For exercise Step up (Ex. 6), no instances for performance classes 4-9 were recorded.

Accuracy in counting repetitions. Redundant feedback (insertions due to noise or vibration) and missing feedback (deletions due to missing peaks) were further considered in this analysis. Figure 11 shows examples of the two error types. Both insertion and deletion errors were considered for determining repetition counting performances. We denoted \( n_p \) as the number of repetitions performed and \( n_c \) the number of repetitions counted by the application. The repetition counting error incurred by our system for each exercise session is represented by \( e_c = |n_c - n_p| \). The error ratio for each exercise and patient are shown in Figure 12. Even though the average counting error across all exercises for Patient 1 was acceptable (\( e_c = 9\% \)), repetitions of P1 were challenging to identify, in particular during Elbow circle (\( e_c = 20\% \)) and Leg lift (\( e_c = 31\% \)) exercises. By grouping the patients, the two exercises challenging for repetition counting were instead Leg lift (\( e_c = 9.6\% \)) and Step-up (\( e_c = 6.3\% \)). For all other exercises, the error incurred by our training system was below 3%. The overall counting accuracy (\( acc_c \)) across all patients and exercises was set to \( acc_c = 100\% - error_{tot}\% \), with \( acc_c = 96.7\% \).
3.6 Results

Figure 11 Time series plots from Leg lift (top) and Elbow circle (bottom) exercises illustrating insertion and deletion errors. Crosses indicate the local maxima and minima identified. Arrows indicate insertion (top) and deletion errors (bottom).

Figure 12 Exercise repetition counting error distribution in the patient intervention study.
### 3.6 Results

**Accuracy of system feedback.** Feedback caused by insertion errors represented repetitions that were actually not performed by the user (no ground truth reference available). Insertions were not further considered for the feedback analysis. Deletion errors were handled and taken into account when computing feedback accuracy, however deletions are not visible in the confusion matrix. The confusion matrix illustrating the system accuracy for providing matching feedback is shown in Figure 13. Overall, an accuracy of 87.5% was achieved. Correctly performed repetitions (performance class 1) were recognized at 90%. For Too large (class 4) and Too fast and too small (class 9) a lower accuracy (63% and 64%, respectively) with regard to the healthy participants validation, was obtained. Furthermore, the distribution of the error across exercise repetitions was investigated and is shown in Figure 14. It can be observed that errors occurred mostly during first and last repetition of each exercise session (17% and 21% of the total errors, respectively). We assume that these repetitions may have been influenced by interactions of trainee and smartphone to start and stop recordings. Figure 15 further analyses the system's feedback with regard to individual exercises and patient. As the result shows, for Patient 3, lowest accuracy (84%) was obtained. Leg lifts (Ex. 5) were the most challenging to recognise, resulting in an accuracy of 85%.

![Confusion matrix](image-url)
3. COPDTrainer: A smartphone-based motion rehabilitation training system with real-time acoustic feedback

3.6 Results

**Efficacy of the smartphone-based intervention.** We evaluated the efficacy of feedback provided during the exercise sessions. Figure 16 shows how patients reacted to feedback during the training. After an audio feedback, a total of 297 repetitions were performed correctly. Feedback for 57 repetitions was ignored, with subsequent repetitions performed erroneously too. By analysing changes in exercise performances, we observed that in 119 cases feedback caused a change in the following movement (both, correct and other erroneous performance). In 71 cases the feedback was ignored, not causing any change in behaviour. In only 8 cases might the feedback have led to performing errors in the following repetition.
Figure 16 Feedback efficacy of the training system during the patient intervention study.

**Comparison of therapist and training system.** From literature it is known that therapists may disagree amongst them or could make errors when assessing training performance [42]. We analysed the therapist’s assessment in comparison to our ground truth. With this analysis, we could estimate an adequate performance level for our training system. Our analysis showed that the therapist performs better than our training system for the performance class Correct (96% vs. 90%). For all error performance classes, the training system shows better performance. Overall, performances match each other closely suggesting that the training system is suitable for providing exercise feedback.

### 3.7 Discussion

Our training error classification technique is based on a sinusoidal motion model, which showed good results in detecting movement errors for both, healthy adults and chronic patients. We chose this method over others for two reasons: (1) using machine learning techniques requires a training set to obtain the classifier model. In particular, a sufficient number of exercise error instances would be required. For our application, it was not feasible to let patients perform exercise errors due to the risk of injuries. (2) With machine learning techniques, it is difficult to differentiate variations in performance of the same exercise from execution errors. Hence, we formalized error classes by considering deviations from the correct execution using our sinusoidal model. We consider that other exercises can be integrated in our training system by selecting a suitable motion feature that reflects the sinusoidal pattern and estimating the initial hill-climbing parameter threshold. Subsequently, speed and range of motion can be considered to determine the performance classes. The relevance of a Teach-mode was confirmed by the parameter ranges obtained after estimating exercise model parameters for every patient. Hence, we expect that our exercise analysis approach is scalable to other patient groups requiring
Exercise training feedback systems. Figure 9 shows excellent system accuracies in the validation with healthy subjects for all performance classes. The remaining classification errors could be explained by the fact that participants could not always maintain speed and range of motion, while performing all repetitions of an exercise. Lowest accuracy for the error combination Too slow & too small (performance class 9) could be attributed to the challenge in performing individual exercises, e.g. Leg lift (Ex. 5). With regard to the clinical analysis, errors in counting Steps up occurred for all patients (Figure 12). This can be explained by the fact that patients often toed the step before completing it. For Patient 1, the lowest counting accuracy was obtained. Patient 1 was the oldest and most severely affected participant in the study and for this patient the exercises were more difficult to perform fluently. From literature it is known that tremor is larger for slow and small movements [43], which may have resulted in peak detection errors and lower counting accuracies for Elbow circles and Leg lift exercises. When analysing exercises within a small range of motion, the algorithm was more sensitive to noise and resulted in wrong peak detection. The lowered recognition accuracies (Figure 13) of our intervention study compared to healthy participant validation could indicate the effect of vibrations due to muscle tremor. Teaching and training were performed very close in time. The variation of how patients would perform the exercises at home may be higher and exercise memorisation may have diminished. Nevertheless, we think that patients could benefit from the COPDTrainer app when training at home: it is probable that patients will perform more errors at home and thus the system’s guidance feedback on movement errors will be more effective compared to the clinical setting. For this study, the therapist’s presence during all study sessions was required to ensure patient safety. During the train-mode, the therapist did not aim at influencing the exercise performance of patients in any way. Moreover, the therapist was a well-known person to the patients. Still, patients may have been affected in their behaviour in subtle form since they were watched by another person. This would differ from the setting at home. We also considered video recording the exercise repetitions, but apart from the unmet safety requirements, cameras may imply even stronger physiological stress to patients. They were used to train in presence of a therapist while not in presence of a camera. Subsequent clinical studies should aim at a step-wise reduction of supervision through therapists or other means, in order to accustom patients with the new technology. This work focuses on evaluating performance and feedback efficacy of a patient training system using a smartphone only. Our primary goal was to derive an easily reusable modelling approach. We did not investigate in long-term usability, motivational aspects, and user acceptance. Nevertheless, we have taken these aspects into account by choosing the smartphone as sensing and feedback platform. While in our study, patients did not express issues in handling the phone, it is clear that further app design refinement could support patients. We believe that smartphone apps can be optimised for wide user acceptance. A wearable device would incur less weight to carry and be more comfortable during training. In contrast, patients are already familiar with smartphones. Patients could immediately use them remotely, even in developing countries where distances may not allow them to attend a rehab centre regularly. Our training and modelling approach can be used as well with wearable sensor bracelets or smartwatches that integrate audio or vibration feedback.
3.8 Conclusion and future work

In this work, we investigated a novel smartphone-based exercise training and feedback system for chronic patients using smartphone-integrated sensors only. Our approach integrates into therapy routines, where an initial training session with a therapist is used to derive exercise quality parameters. In subsequent patient training sessions, the system can provide instant acoustic feedback on the detected exercise performance. Our validation with healthy participants showed an overall accuracy of 96.2%. We implemented an intervention study with seven COPD patients in their regular rehabilitation environment to assess the viability of our approach. Repetitions were counted at 96.7% accuracy and trainee performance classification rate was 87.5%. Based on our result, we concluded that a smartphone-based training system can be used to assess the performance and execution quality of a rehabilitation exercises in COPD patients. Based on the system performance and feedback efficacy, we believe that our approach and developed methods will be a vital basis for future investigations on training systems for different patient groups. Additional steps are needed to confirm the clinical relevance and integration into clinical practice. In this regard, we consider our work as a pilot study, providing the basis for validating COPDTrainer in a clinically supervised intervention at the patient’s home.
Physical activity levels in chronic obstructive pulmonary disease (COPD) have been mostly presented as an average of multiple measurement days. However, physical activity is a multi-dimensional construct, which means that it should be described by relevant descriptors and components beside its total amount. We described physical activity measures and hourly patterns in patients with COPD after stratification for generic and COPD-specific characteristics, and, based on multiple physical activity measures, we identified clusters of patients. 1001 patients with COPD were studied cross-sectionally. Daily physical activity measures and hourly patterns (i.e., a graphic representation of the mean intensity of activity per hour during the course of a day) were analysed based on data from a multi-sensor armband. Principal component analysis (PCA) and cluster analysis were applied to physical activity measures to identify clusters of patients with COPD. Age, body mass index (BMI), dyspnoea grade, ADO index (including age, dyspnoea, and airflow obstruction), sex, long-term oxygen therapy use, lung diffusion capacity, and GOLD classification were associated with physical activity measures in patients with COPD (P<0.05 for all), but only the first four were associated with hourly patterns. Five clusters were identified based on three PCA components, which accounted for 60% of variance of the data. Importantly, cluster 1 (i.e., the most inactive patients) was characterized by higher BMI, lower FEV$_1$, worse dyspnoea and higher ADO index compared to other clusters (P<0.05 for all). Daily physical activity measures and hourly patterns are heterogeneous in COPD. Clusters of patients were identified solely based on physical activity data. These findings may be useful to develop interventions aiming to promote physical activity in COPD.
4.1 Introduction

Physical activity levels in patients with chronic obstructive pulmonary disease (COPD) are mostly presented as a total amount or as an average of multiple measurement days [44, 45, 46, 47, 48, 49]. Nevertheless, physical activity is a multi-dimensional construct which should be described by relevant constructs and measures [50]. A more detailed approach to physical activity data analysis could provide complementary information about the physical activity behaviour of patients with COPD. For example, patients with COPD have shown to perform bouts of moderate-to-vigorous physical activity, but the proportion of time in bouts and the frequency of bouts decreased with increasing disease severity [51].

Studies in different patient populations show that a more detailed analysis of physical activity can be achieved by plotting physical activity hourly patterns [50, 52, 53] and by applying cluster analysis to physical activity measures [52, 54, 55]. Physical activity hourly patterns provide a graphic representation of the temporal trends of physical activity intensities over the course of a day [50, 52, 53] and they have shown to provide useful information. Rochester et al [56], for example, observed a delayed morning start and a reduced peak of activity in patients with Parkinson’s disease, while Evering and co-workers [57] observed a less physically active pattern in the afternoon and evening in patients with chronic fatigue syndrome. Cluster analysis [58], in turn, could be useful to identify subgroups of subjects with distinct physical activity characteristics. In middle-aged Chinese adults, Lee et al [52] were able to identify two clusters of subjects, one more active than the other. Male subjects in the least active cluster had higher body fat percentage and older age than those in the active group. These detailed analyses could then lead to new insights regarding subgroups of patients with COPD with specific physical activity patterns, which may be used in further investigations and intervention strategies [49, 59, 60]. Indeed, for specific groups of patients, greater and/or more sustainable results may be achieved if the focus shifts from an increase in moderate-to-vigorous activities towards a reduction in sedentary time [61, 62, 63, 64].

Therefore, the main contributions provided by this work are: to describe physical activity measures and physical activity hourly patterns in patients with COPD after stratification for generic and COPD-specific characteristics; and to identify clusters of patients with COPD based on physical activity measures.

4.2 Materials and methods

4.2.1 Assessment of demographics, anthropometrics, lung function, and clinical data

Age, sex, body mass index (BMI), post-bronchodilator forced expiratory volume in the first 1 second (FEV₁, % of predicted), post-bronchodilator FEV₁ / forced vital capacity (FVC) ratio, diffusion capacity of the lung for carbon monoxide (DLCO, % of predicted), symptoms of dyspnoea by the modified Medical Research Council (mMRC) dyspnoea grade [65], and use of long-term oxygen therapy (LTOT, yes/no) were measured. In addition, the age, dyspnoea, and airflow obstruction (ADO) index was calculated, which predicts COPD mortality [66], and participants were stratified by BMI (underweight, <18.5 kg·m⁻²; normal weight, 18.5 to 24.99
kg·m$^{-2}$; pre-obese, 25 to 29.99 kg·m$^{-2}$; or obese, $\geq$ 30 kg·m$^{-2}$) and by Global Initiative for Chronic Obstructive Lung Disease (GOLD) classifications (2007 [67] 1 to 4; and 2011 [9] A to D). GOLD 2011 classification (A to D) was based on the degree of airflow limitation (GOLD grades 1 to 4) and symptoms (mMRC dyspnoea grades 0 to 4).

4.2.2 Selection of waking hours recordings

Firstly, the data collected with the SenseWear Armband devices were exported in the form of Microsoft Excel spreadsheets with one minute resolution. The data contains information about the sleeping time and, in particular, each minute assessed is marked by the SenseWear software as "sleeping" or "not sleeping" [68]. Then, in order to reduce the variability of the data, only minutes coded as "not sleeping" were selected for analysis. If a minute was coded as "sleeping" but had an intensity value higher than 2.0 metabolic equivalents of task (METs), which is compatible with light intensity, this minute was considered as "not sleeping" since it is very unlikely that a subject present such a high intensity whilst sleeping.

4.2.3 Stratification of physical activity measures

The software SenseWear Professional versions 6.1 and 7.0 were used for data analysis, providing minute-by-minute energy expenditure (EE) and METs. These two measures were stratified according to different criteria (and the combination of them): intensity (e.g., very light, light or moderate-to-vigorous intensity), duration (e.g., bouts of activity), period of the day (e.g., before or after midday), frequency (e.g., number of bouts per day); and quantity (e.g., absolute numbers or percentage of total). A bout of activity was defined as a period of consecutive minutes with a minimum duration (e.g., 10 minutes) and in the same intensity. These stratifications were performed with Matlab R2012b (Mathworks Inc., USA) and led to 180 distinct variables referred to as features, which were used for clustering of patients. Table XVI in the appendix presents the 180 features used for cluster analysis.

4.2.4 Sample size calculation

The main analysis in our study was the identification of clusters based on physical activity data. To the best of our knowledge, currently there are no sample size calculation formulas for cluster analysis as performed in our study. Some authors have suggested that the minimal sample size to include in studies using cluster analysis should be no less than $2^k$ cases, preferably $5 \times 2^k$, with K being the number of variables considered for analysis [69, 70]. In our study, only 3 variables (i.e., the 3 components from the principal component analysis) were used for clustering. Therefore, the minimal sample size in our study should be 40 subjects, which is actually far below the actual number of participants included (i.e., 1001 subjects). Furthermore, our sample size is much larger than that of most previous studies using cluster analysis in COPD,
which were still able to identify heterogeneous groups amongst different samples of patients with COPD [71, 72, 73, 74, 75].

4.2.5 Daily physical activity after stratification for seasons of the year

Daily physical activity measures after stratification for seasons of the year can be found in Table XVII in the appendix.

4.3 Study design and participants

In this retrospective, multicentre, cross-sectional study, objectively assessed physical activity data from ten countries (i.e., United Kingdom, Ireland, the Netherlands, Germany, Switzerland, Italy, Spain, the United States of America (USA), Brazil, and Australia) were analysed. Published and/or unpublished physical activity data from previous studies as assessed by the SenseWear Armband or SenseWear Mini Armband activity monitors (both from BodyMedia Inc., Pittsburgh, PA, USA) were considered for analysis, details of data sources can be found in the appendix. In studies that included longitudinal analyses, only the baseline data were used meaning that the subjects included in the current analysis were not undergoing any specific intervention by the time of assessment. Subjects were included if they had: COPD with a post-bronchodilator forced expiratory volume in the first 1 second (FEV₁) / forced vital capacity (FVC) ratio <0.70 [9], clinical stability at the time of physical activity assessment, and complete data for age, sex, body mass index (BMI) and daily physical activity measures. Ethics Board approval was obtained from the local ethics committees/institutional review boards, and written informed consent was provided by participants, except for the data from Italy (n=23) which were obtained as part of routine clinical assessments. The Italian data, however, were de-identified to protect patient information confidentiality.

4.3.1 Assessment

Demographics, anthropometrics, lung function, and clinical data were assessed. In order to investigate their association with physical activity measures and hourly patterns, these outcomes were stratified according to established criteria or according to the median value (i.e., above or below the median). The SenseWear Armband or SenseWear Mini Armband activity monitors, which use multisensory data in combination with pattern recognition algorithms to reliably estimate energy expenditure (EE) and metabolic equivalents of task (METs) [76], were used to assess physical activity [77, 78, 79, 80]. METs data are divided into activity intensity levels using the thresholds proposed by the American College of Sports Medicine [81]: very light intensity, <2.0 METs; light intensity, 2.0 to 2.9 METs; and moderate-to-vigorous intensity, ≥3.0 METs.

Subjects with a minimum of four recorded days (two weekdays + Saturday + Sunday) [44] with the device being used for ≥22 hours·day⁻¹ [82] were included in the analyses. Only recordings during waking hours of weekdays were considered for the cluster analysis, since physical activity measures during the weekend are known to be different [44] and therefore could bias the analyses. The physical activity measures represent the average of all valid
weekdays. Weekend days were used only for the presentation of daily physical activity hourly patterns. All values are represented by absolute values. Values relative to peak exercise capacity were not presented as measurement of maximal exercise capacity was not available. For the clustering of patients, a set of relevant variables were generated after stratifying averages of physical activity measures according to different criteria (i.e., intensity, duration, period of the day, frequency and quantity, or the combination of these criteria; Table XVI in the appendix).

4.3.2 Statistical analyses

Continuous variables were expressed as median (interquartile range), as most variables presented non-normal distribution. Categorical variables were expressed as absolute and/or relative frequency. Mann-Whitney U test or Kruskal-Wallis test (post hoc Dunn; significant if \( P<0.05 \)) was used for comparing continuous variables, while the chi-square test was used for categorical variables. The influence of seasons on daily physical activity measures was minimal (Table XVII in the appendix) and therefore this was not taken into consideration throughout the analyses. Spearman coefficient was used to investigate correlations, when appropriate. The area under each hourly pattern, named as the Area Under the Curve (AUC), was calculated and presented with its 95% confidence intervals in order to quantitatively represent time-varying averages of the hourly patterns. \( P<0.01 \) was considered significant and all statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, Illinois, USA) or GraphPad Prism 5 (GraphPad Software, La Jolla, California, USA).

Cluster analysis was adopted to identify subgroups with distinct physical activity profiles. Firstly, Principal Component Analysis (PCA) was used to compress the information contained in the high-dimensional feature set (180 dimensions) to a lower subspace (three dimensions) that is both convenient for data visualization and able to account for the desired variance of the data (set to 60%). The features were initially standardized using z-scores. Secondly, a k-means clustering algorithm with automatic selection of the number of clusters was applied to the three principal components to separate the subjects into groups with distinct characteristics. The algorithm selects the number of clusters in a way that the corresponding clustering results are the most stable under small perturbations of the input dataset [58]. The normalized mean over pairwise clustering distances was used as instability measure [58]. Feature extraction, PCA and cluster analysis were performed using Matlab R2012b (Mathworks Inc., USA).

4.4 Results

4.4.1 General characteristics

In total, 1001 patients with COPD were analysed (Table IV). The majority of patients were men, had a normal-to-overweight BMI, moderate-to-severe degree of airflow limitation, and only a small proportion used long-term oxygen therapy (LTOT). Compared to female subjects, male subjects were slightly older (67 (62 – 73) versus 65 (59 – 71) years; \( P<0.0001 \)) and had higher BMI (26.5 (23.3 – 29.9) versus 24.5 (21.1 – 28.6) kg·m\(^{-2}\); \( P<0.0001 \)), but no differences were found in FEV\(_1\), modified Medical Research Council (mMRC) grades, or Global Initiative for
Chronic Obstructive Lung Disease (GOLD) 2007 and 2011 classifications (P>0.01 for all). Characteristics per country can be found in Table XVIII in the appendix.

Table IV General characteristics of patients with COPD (n=1001).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>67 (61 – 72)</td>
</tr>
<tr>
<td>Male, %</td>
<td>65</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>25.8 (22.5 – 29.6)</td>
</tr>
<tr>
<td>BMI classification, %</td>
<td></td>
</tr>
<tr>
<td>Underweight</td>
<td>7</td>
</tr>
<tr>
<td>Normal weight</td>
<td>37</td>
</tr>
<tr>
<td>Overweight</td>
<td>34</td>
</tr>
<tr>
<td>Obese</td>
<td>22</td>
</tr>
<tr>
<td>mMRC dyspnoea grade*</td>
<td>2 (1 – 3)</td>
</tr>
<tr>
<td>Long-term oxygen therapy, %†</td>
<td>10</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.31 (0.91 – 1.79)</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>49 (34 – 64)</td>
</tr>
<tr>
<td>FEV₁/FVC, %</td>
<td>45 (35 – 56)</td>
</tr>
<tr>
<td>DLCO, % predicted‡</td>
<td>51 (37 – 67)</td>
</tr>
<tr>
<td>ADO index, points*</td>
<td>4 (3 – 5)</td>
</tr>
<tr>
<td>GOLD 2007 classification, %</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
</tr>
<tr>
<td>GOLD 2011 classification, %*</td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>29</td>
</tr>
<tr>
<td>B</td>
<td>16</td>
</tr>
<tr>
<td>C</td>
<td>17</td>
</tr>
<tr>
<td>D</td>
<td>38</td>
</tr>
</tbody>
</table>

Data expressed as relative frequency or median (interquartile range). BMI: body mass index; mMRC: modified Medical Research Council; FEV₁: forced expiratory volume in the first second; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide; ADO: age, dyspnoea, and airflow obstruction index; GOLD: Global Initiative for Chronic Obstructive Lung Disease. *Data available for 868 subjects; †Data available for 707 subjects; ‡Data available for 505 subjects.

4.4.2 Daily Physical Activity Measures and Physical Activity Hourly Patterns

The median number of valid days analysed per patient was 6 (6 – 6), resulting in a total of 6074 valid physical activity days, of which 4049 (67%) were weekdays. Table V presents the daily physical activity measures during the weekdays. The daily total time was smallest and the daily total EE was lowest in moderate-to-vigorous intensity. At this intensity, patients spent a median of 6 (0 – 22) min·day⁻¹ in bouts of ≥10 minutes. This value is lower than 10 minutes due to the averaging process, in which days without bouts of ≥10 minutes were also taken into account. Daily hourly patterns were similar between weekdays and weekend days, with the peak of intensity occurring before midday (Figure 17). This similarity was corroborated by similar AUC-values (0.30 for weekdays and 0.29 for weekend days; Table XIX in the appendix).
Figure 17 Daily physical activity hourly patterns of the 1001 patients with chronic obstructive pulmonary disease during weekdays (A) and weekend days (B). Data pooled per hour as mean (95% confidence intervals).

Table V Daily physical activity measures during weekdays in patients with COPD.

<table>
<thead>
<tr>
<th>Physical activity measure</th>
<th>Very light intensity</th>
<th>Light intensity</th>
<th>Moderate-to-vigorous intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>General physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day</td>
<td>803 (710–901)</td>
<td>142 (92–194)</td>
<td>52 (26–99)</td>
</tr>
<tr>
<td>EE, METs·min·day</td>
<td>1032 (822–1327)</td>
<td>435 (291–655)</td>
<td>267 (132–550)</td>
</tr>
<tr>
<td>≥10-minute bouts of physical activity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day</td>
<td>657 (539–780)</td>
<td>7 (0–22)</td>
<td>6 (0–22)</td>
</tr>
<tr>
<td>Frequency, bouts·day−1</td>
<td>18 (16–21)</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
</tr>
<tr>
<td>Average duration, min·bout−1</td>
<td>32 (27–39)</td>
<td>13 (12–14)</td>
<td>14 (12–17)</td>
</tr>
<tr>
<td>EE, METs·min·bout−1</td>
<td>847 (626–1168)</td>
<td>26 (0–77)</td>
<td>36 (0–132)</td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). EE: energy expenditure; MET: metabolic equivalent of task. *The time, frequency and EE in bouts of physical activity were averaged out over the total number of valid days, while the duration of bouts of physical activity was averaged over the total number of bouts available. †P<0.05 vs very light intensity; ‡P<0.05 vs light intensity.

4.4.3 Stratification for Generic and COPD-specific Characteristics

In general, patients of older age, female sex, LTOT users, lower diffusion capacity of the lung for carbon monoxide (DLCO), higher mMRC dyspnoea grade, higher BMI, higher ADO index (including age, dyspnoea, and airflow obstruction), higher GOLD grade and patients from GOLD group D spent the smallest daily total time and lowest daily total EE in moderate-to-vigorous intensity (Table XX-Table XXVIII in the appendix). Daily physical activity hourly patterns after stratification for the abovementioned characteristics are presented in Figure 18-Figure 20, showing a significant influence of age, BMI, mMRC dyspnoea grades, and ADO index scores, as there was little or no overlap between the 95% confidence intervals of the hourly patterns. The AUC-values for these parameters varied between 0.25 and 0.36 (Table XIX in the appendix). The influence of GOLD grades or GOLD groups on these patterns was small. Moreover, only weak associations existed between FEV₁ (% predicted) and the time in activities of very light, light, and moderate-to-vigorous intensities (Figure 21).
Figure 18 Daily physical activity hourly patterns of the patients with chronic obstructive pulmonary disease after stratification for: A and B – modified Medical Research Council (mMRC) grades, data available for 868 subjects only; C and D – body mass index (BMI) classification; E and F – Global Initiative for Chronic Obstructive Lung Disease (GOLD) grades (1 to 4); and G and H – GOLD groups (A to D). Figs. A, C, E, and G represent weekdays, while figs. B, D, F, and H represent weekend days. Data pooled per hour as mean (95% confidence intervals).

4.4 Results
Figure 19 Daily physical activity hourly patterns of the patients with chronic obstructive pulmonary disease after stratification for: A and B – age; C and D – sex; and E and F – LTOT use. Figs. A, C, and E represent weekdays, while figs. B, D, and F represent weekend days. Data pooled per hour as mean (95% confidence intervals). LTOT: long-term oxygen therapy.
Figure 20  Daily physical activity hourly patterns of the patients with chronic obstructive pulmonary disease after stratification for: G and H – DLCO; and I and J – ADO index. Figs. G, and I represent weekdays, while figs. H, and J represent weekend days. Data pooled per hour as mean (95% confidence intervals). DLCO: diffusion capacity of the lung for carbon monoxide; ADO: age, dyspnoea, and airflow obstruction index.
4.4.4 Cluster Analysis of Daily Physical Activity Measures in 1001 Patients with COPD

The PCA identified three components, which accounted for 60% of the total variance in the data (first component, 34%; second component, 17%; third component, 9%). The most relevant features of the 1st component were the daily time in ≥2-min bouts of very light intensity, expressed as percentage of total assessment time; the daily time in ≥10-min bouts of very light intensity, in min·day⁻¹; and the daily time in ≥10-min bouts of very light intensity, expressed as...
percentage of total assessment time. The most relevant of the 2\textsuperscript{nd} component were the daily EE in moderate-to-vigorous intensity, the daily EE in ≥2-min of moderate-to-vigorous intensity, and the daily EE in ≥10-min bouts of moderate-to-vigorous intensity, all expressed as percentage of total EE. The most relevant of the 3\textsuperscript{rd} component were the daily EE in very light intensity after midday, the daily EE in very light intensity, and the daily EE in ≥2-min bouts of very light intensity after midday, all in METs-min·day\textsuperscript{-1}.

Cluster analysis, performed on the three principal components, identified five distinct clusters (Figure 22). Table VI presents the characteristics and physical activity measures of these groups. Cluster 1 (n=216, 22\%) was characterized by higher BMI, more dyspnoea, higher ADO index, more time and EE in very light intensity, and less time and EE in light and moderate-to-vigorous intensities compared to other clusters. Cluster 2 (n=415, 41\%) had more dyspnoea and a higher ADO index than clusters 3 and 5. Similarly to cluster 1, this cluster spent more time and EE in very light intensity and less time and EE in moderate-to-vigorous intensity than other clusters. Cluster 3 (n=184, 18\%) exhibited a higher FEV1 than cluster 2, while cluster 4 (n=165, 17\%) was younger than clusters 1 and 2 and had a lower BMI compared to cluster 2. Moreover, cluster 3 spent more time and EE in light intensity and less time and EE in moderate-to-vigorous intensity than clusters 4 and 5, while cluster 4 spent more time in light intensity compared to cluster 5. Cluster 5 (n=21, 2\%) was characterized by less time in very light intensity and more time in moderate-to-vigorous intensity compared to other clusters. Figure 23 presents the daily time in activities of different intensities by the clusters, highlighting the mixed arrangements of physical activity. Figure 24 presents the daily physical activity hourly patterns of the clusters. In all clusters the peak of intensity during the day occurred before midday, and in general weekdays and weekend days presented a similar pattern, especially in more inactive clusters. Hourly patterns after synchronisation of the waking up moment are presented Figure 25. Moreover, increasing AUC-values were found from clusters 1 to 5 (Table XIX).
Figure 22 The five clusters identified. A: Graph in 3 dimensions presenting the three principal component analysis (PCA) components; B: Graph in 2 dimensions presenting the 1st and 2nd components; C: Graph in 2 dimensions presenting the 1st and 3rd components; and D: Graph in 2 dimensions presenting the 2nd and 3rd components.
4. Physical activity patterns and clusters in 1001 patients with COPD

4.4 Results

Figure 23 Daily time in activities of very light intensity (A), light intensity (B), and moderate-to-vigorous intensity (C) by clusters of patients with chronic obstructive pulmonary disease. Data presented as median (interquartile range).

Figure 24 Daily physical activity hourly pattern of clusters of patients with chronic obstructive pulmonary disease during weekdays (A) and weekend days (B). Data pooled per hour as mean (95% confidence intervals).
Figure 25. Daily physical activity hourly pattern of clusters of patients with chronic obstructive pulmonary disease after synchronisation of the waking up moment during weekdays (A) and weekend days (B). Data pooled per hour as mean (95% confidence intervals).
### Table VI: General characteristics and daily physical activity measures of clusters of patients with COPD.

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>General characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>216</td>
<td>415</td>
<td>184</td>
<td>165</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Age, yrs</td>
<td>68 (62 – 74)</td>
<td>67 (61 – 72)</td>
<td>67 (60 – 72)</td>
<td>63 (58 – 70)</td>
<td>63 (56 – 68)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>67</td>
<td>67</td>
<td>51</td>
<td>76</td>
<td>67</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>30.4 (26.5 – 34.7)</td>
<td>25.7 (22.6 – 29.0)</td>
<td>24.9 (22.2 – 27.4)</td>
<td>23.1 (20.3 – 26.8)</td>
<td>22.5 (18.3 – 30.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>44 (32 – 58)</td>
<td>48 (34 – 61)</td>
<td>57 (41 – 71)</td>
<td>50 (36 – 68)</td>
<td>51 (39 – 70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mMRC dyspnoea grade, points</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>1 (1 – 2)</td>
<td>1 (0 – 3)</td>
<td>1 (0 – 2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GOLD 2007 classification 1 / 2 / 3 / 4, %</td>
<td>4 / 34 / 43 / 19</td>
<td>8 / 38 / 35 / 19</td>
<td>18 / 46 / 23 / 13</td>
<td>9 / 42 / 31 / 18</td>
<td>10 / 43 / 33 / 14</td>
<td>0.17</td>
</tr>
<tr>
<td>GOLD 2011 classification A / B / C / D, %</td>
<td>18 / 19 / 16 / 47</td>
<td>28 / 15 / 17 / 40</td>
<td>44 / 16 / 16 / 24</td>
<td>31 / 13 / 20 / 36</td>
<td>44 / 6 / 28 / 22</td>
<td>0.02</td>
</tr>
<tr>
<td>Physical activity measures in very light intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>955 (904 – 1042)</td>
<td>823 (768 – 879)</td>
<td>706 (641 – 769)</td>
<td>675 (604 – 735)</td>
<td>516 (456 – 621)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs·min⁻¹</td>
<td>1356 (1165 – 1730)</td>
<td>1022 (854 – 1222)</td>
<td>855 (729 – 1118)</td>
<td>789 (692 – 1019)</td>
<td>853 (661 – 1884)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>890 (815 – 968)</td>
<td>680 (622 – 745)</td>
<td>534 (452 – 601)</td>
<td>490 (415 – 561)</td>
<td>340 (254 – 444)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>17 (14 – 20)</td>
<td>20 (17 – 22)</td>
<td>18 (16 – 20)</td>
<td>17 (15 – 20)</td>
<td>12 (11 – 16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>53 (43 – 65)</td>
<td>35 (30 – 41)</td>
<td>29 (25 – 34)</td>
<td>27 (24 – 32)</td>
<td>26 (22 – 32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs·min·day⁻¹</td>
<td>1257 (1068 – 1632)</td>
<td>836 (693 – 1050)</td>
<td>628 (516 – 862)</td>
<td>589 (467 – 779)</td>
<td>704 (420 – 1185)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical activity measures in light intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>57 (35 – 79)</td>
<td>139 (113 – 167)</td>
<td>245 (208 – 282)</td>
<td>167 (134 – 209)</td>
<td>121 (87 – 163)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs·min·day⁻¹</td>
<td>196 (121 – 305)</td>
<td>408 (320 – 517)</td>
<td>725 (591 – 958)</td>
<td>526 (366 – 735)</td>
<td>416 (227 – 1093)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>0 (0 – 3)</td>
<td>8 (3 – 16)</td>
<td>46 (32 – 65)</td>
<td>8 (3 – 16)</td>
<td>0 (0 – 4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
### 4.4 Results

<table>
<thead>
<tr>
<th>Physical Activity Measures in moderate-to-vigorous intensity</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min∙day&lt;sup&gt;−1&lt;/sup&gt; (min -30 to 70)</td>
<td>48 (138 -349)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>235 (138 -349)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>68 (43 -96)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>327 (198 -527)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>9 (3 -18)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts∙day&lt;sup&gt;−1&lt;/sup&gt; (0 -1)</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>12 (11 -14)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min∙bout&lt;sup&gt;−1&lt;/sup&gt; (11 -16)</td>
<td>14 (12 -15)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14 (12 -15)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14 (12 -15)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14 (12 -15)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>14 (12 -15)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs∙min∙day&lt;sup&gt;−1&lt;/sup&gt; (0 -20)</td>
<td>0 (0 -20)</td>
<td>25 (0 -70)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>47 (13 -105)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>300 (171 -513)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1635 (1102 -2596)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Data expressed as absolute/relative frequency, or median (interquartile range). See Table IV and Table V for definition of abbreviations. *Data available for 198 subjects in Cluster 1, 367 subjects in Cluster 2, 128 subjects in Cluster 3, 126 subjects in Cluster 4, and 18 subjects in Cluster 5; †P<0.05 vs Cluster 1; ‡P<0.05 vs Cluster 2; §P<0.05 vs Cluster 3; ‖P<0.05 vs Cluster. The description of the clusters presented at the top of the table was arbitrarily based on the amount of time in very light and moderate-to-vigorous intensities.

**Table IV**

<table>
<thead>
<tr>
<th>Time, min∙day&lt;sup&gt;−1&lt;/sup&gt; (min -30 to 70)</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 (7 -27)</td>
<td>48 (138 -349)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>235 (138 -349)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>68 (43 -96)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>327 (198 -527)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>9 (3 -18)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts∙day&lt;sup&gt;−1&lt;/sup&gt; (0 -1)</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>12 (11 -14)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>1 (0 -1)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

**Table V**

<table>
<thead>
<tr>
<th>Time, min∙day&lt;sup&gt;−1&lt;/sup&gt;</th>
<th>Cluster 1</th>
<th>Cluster 2</th>
<th>Cluster 3</th>
<th>Cluster 4</th>
<th>Cluster 5</th>
</tr>
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<tbody>
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<td>15 (7 -27)</td>
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<td>9 (3 -18)&lt;sup&gt;†&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
4.5 Detailed Analyses of the Components Identified in the PCA

A detailed analysis of the relationship between the three components identified by PCA and the five clusters identified from these components is provided in the following paragraphs.

The first component was clearly able to discriminate clusters 1 and 2 (the most inactive clusters) from the three other clusters (clusters 3, 4 and 5) (Figure 23B and C). The second component was not really useful to identify more inactive patients (clusters 1 and 2), but was able to discriminate the most active cluster (cluster 5) from the rest (Figure 23B and D). For discriminating clusters 3 and 4 from the others it is important to consider the combination of the three components. Indeed, if only the first component was considered, for instance, these clusters would be added to the most active cluster (cluster 5) (Figure 23B and C). On the other hand, if only the second component was considered these clusters would be added to the inactive clusters (i.e., clusters 1 and 2) (Figure 23B and D).

Having a closer look at the most relevant features of each component we can notice that the first component is related to the time spent in bouts of very light intensity, whilst the second component is related to the total daily EE in activities of moderate-to-vigorous intensity, mostly in bouts of physical activity. Therefore, it can be suggested that the time in bouts of moderate-to-vigorous intensity can be a useful marker to discriminate patients who are very active from the others.

4.6 Discussion

The present study provides detailed analyses of objectively measured physical activity in a multinational sample of 1001 patients with COPD. The principal findings show that daily physical activity measures and hourly patterns vary considerably after stratification for generic and COPD-specific characteristics; and that patients with COPD can be clustered based on daily physical activity measures, with five clusters being identified, each with distinct physical activity measures and hourly patterns.

4.6.1 Daily Physical Activity Measures and Physical Activity Hourly Patterns in COPD

Our results clearly show that physical activity is a heterogeneous characteristic in patients with COPD, corroborating previous findings [83, 17]. Distinct levels of physical activity were found after stratification for age (< or ≥ 67 years), sex (male vs. female), BMI (underweight to obese), mMRC dyspnoea grade (0 to 4), LTOT (yes or no), DLCO (< or ≥ 51% predicted), ADO index (< or ≥ 4 points), GOLD grades (1 to 4) and GOLD groups (A to D) (Table XX-Table XVIII in the appendix). Interestingly, comparable time in very light and moderate-to-vigorous intensities was found between GOLD groups A and C, and between GOLD groups B and D (Table XXVIII in the appendix). This suggests that symptoms of dyspnoea, which discriminates between groups A/C and B/D, are better associated with physical activity measures than the degree of airflow
limitation, which discriminates between groups A/B and C/D. Zogg et al [84] also investigated physical activity levels in COPD patients after classification into GOLD groups. These authors observed more preserved physical activity levels in group A compared to the other groups. Nevertheless, the sample size of each group was small and groups C and D had to be combined, compromising more detailed analyses. Despite the significant influence of GOLD groups on physical activity measures, only little or no influence was observed on physical activity hourly patterns. Only a few studies have investigated hourly patterns in COPD. In the study by Hecht et al [53], the authors observed that the highest activity level occurred during the late morning and early afternoon hours, which is corroborated by our findings. Tabak et al [85], in turn, observed a similar pattern of a dip of lower activity in the early afternoon in both employed and unemployed COPD patients, despite differences in the summary values between groups. Together with our findings this suggests that hourly patterns have the potential to complement the information provided by summary values.

4.6.2 Clusters of Patients with COPD Based on Daily Physical Activity Measures

The present study is the first to cluster patients with COPD based only on objectively assessed physical activity measures. Indeed, five clusters were identified, each with distinct physical activity measures and hourly patterns. One very active cluster and one very inactive cluster were identified, but clusters in intermediate categories were also observed.

Only a few studies have used objectively measured physical activity data solely for clustering subjects. In 10-to-12-year-old children, De Bourdeaudhuij and colleagues [86] were able to identify a cluster with a mixed arrangement of physical activity (i.e., less time in moderate-to-vigorous intensity + less sedentary time). In our study, we also found a cluster with resembling characteristics (i.e., cluster 4, long very light intensity/long moderate-to-vigorous intensity), confirming that activities of moderate-to-vigorous intensity and sedentary activities are not two sides of one continuum [86]. Based on the amount of time in 10-min bouts of moderate-to-vigorous physical activity, patients from cluster 4 could be considered physically active [81]. Nonetheless, these patients spent over 11 hours in very light intensity (i.e., sedentary behaviour), and previous studies have shown the detrimental effects of prolonged periods of sedentary behaviour on health outcomes [87]. More inactive clusters were also observed in our study (clusters 1, 2 and 3). In middle-aged Chinese adults, Lee et al [52] observed that male subjects from the least active cluster had higher body fat percentage and older age than those from the active group. In our study, patients from cluster 1 had older age, lower FEV$_1$, higher BMI, worse dyspnoea and higher ADO index than other clusters. Based on their characteristics patients from this cluster may have a worse prognosis, but no follow-up data are available to confirm this hypothesis.

Although there was little or no overlap between the 95% confidence intervals of the hourly patterns of the clusters, confirming that they are statistically different, the patterns were found to be rather similar. Nevertheless, more inactive clusters seem to present less variability in intensity compared to more active clusters, suggesting that they are similarly inactive throughout the day. We also observed that the more inactive a cluster is, the more similar its hourly patterns of weekdays and weekend days are. This corroborates the findings from Lee et al [9], who observed a consistently low physical activity pattern on both weekdays and weekend
days in the least active cluster. Irrespective of the cluster, patients seem to perform the activities with the highest intensity during the morning, which was also observed after stratification for different characteristics (Figure 18, Figure 19 and Figure 20). This should be taken into account when planning interventions such as energy conservation techniques, which have as one of the main aims to reduce unnecessary energy expenditure associated with activities of daily living [88].

4.6.3 Clinical relevance

Patients with COPD spent around 80% of their daily time in activities of very light intensity (Table V). Previous studies in COPD have focused on increasing the time in moderate-to-vigorous intensity [44, 51, 89], but there is emerging literature in other populations suggesting that health benefits can be achieved by decreasing time in very light intensity and increasing the participation in light intensity physical activities [61, 90, 91, 92].

Physical activity hourly patterns and physical activity clustering provide details on the duration and intensity of physical activities over the course of a day, as well as identify groups with specific physical activity patterns, which can broaden the understanding of physical activity in patients with COPD. Indeed, based on the results shown it can be speculated that cluster 1 is probably at increased risk of having a worse prognosis due to the combination of health-threatening characteristics (e.g., more time very light intensity, less time in moderate-to-vigorous intensity). Moreover, identifying groups with specific physical activity patterns seems to be useful information for tailoring physical activity enhancing interventions. Cluster 1, for instance, spent a median of 15 min·day⁻¹ only in moderate-to-vigorous intensity, which is half of the recommended by international guidelines [81], and more than 15 hours in very light intensity (i.e., sedentary behaviour), which is more than two times of what other studies have considered as harmful (i.e., 7 hours) [93, 87]. This cluster therefore, could benefit from an intervention focusing not only on increasing the amount of time in moderate-to-vigorous intensity, but also on reducing the time in very light intensity. Cluster 4, on the other hand, seems to spend enough time in moderate-to-vigorous intensity (i.e., >30 min·day⁻¹ in 10-min bouts), but would probably benefit from an intervention aiming to reduce the time in very light intensity, which is over 11 hours. To date, interventions targeting physical activity enhancement had limited impact in patients with COPD [59, 89, 94], but none of these interventions targeted specific physical activity patterns.

Decreasing the time in very light intensity without necessarily increasing the time in moderate-to-vigorous intensity would mean focusing on light intensity activities. Reductions in sedentary time by increases in light activities might be more realistic for patients with COPD, which in fact could help pave the way to posterior increases in the time in more intense activities [61, 63, 64]. This is supported by a recent study which demonstrated that greater quantity of low-intensity physical activity reduces the risk of COPD hospitalisation [62]. Of note, in that study high-intensity physical activity did not produce any risk reduction.

4.6.4 Strengths and Methodological Considerations

We have analysed a large and diverse sample of patients with COPD with objectively assessed physical activity data. This allowed detailed analyses of daily physical activity, even
identifying clusters of patients with COPD with similar physical activity measures, a novelty within the COPD literature. Physical activity hourly patterns were also investigated for the first time in a large-scale study in COPD, another important advance. All these analyses were only possible due to the use of objective methods of physical activity.

Some methodological considerations need to be taken into account. First, selection and information biases might be present, as the data were collected separately as part of different studies. Moreover, some types of patients with COPD might be underrepresented, such as patients from primary care. Nevertheless, having patients from different studies and countries allowed us to have a more diverse sample, which may enhance the external validity of our findings. Second, the clusters identified in our study were not validated as we were not able to show whether they relate to relevant clinical outcomes, such as COPD-related hospitalisations and deaths due to the lack of follow-up assessments, or whether they could be replicated in another sample. Third, other characteristics which may influence physical activity levels in patients with COPD, such as comorbidities [95], were not available. Finally, some of our findings need to be interpreted in light of the number of multiple comparison tests performed. Nonetheless, multiple findings in the same direction rather than a single statistically significant result are suggestive that these are not due to chance alone.

### 4.7 Conclusion

To conclude, daily physical activity measures and hourly patterns in patients with COPD were found to vary considerably depending on the clinical characteristic. Moreover, five clusters of patients were identified, each with distinct physical activity measures and hourly patterns. The present data show that outcome measures need to be clearly delineated when evaluating interventions aiming to promote physical activity in patients with COPD.
5 Estimated nocturnal sleep impairment in patients with COPD in daily life and its association with daytime physical activity

Sleep disturbance is common in patients with chronic obstructive pulmonary disease (COPD). However, factors associated with objective sleep impairment have not been investigated before in a large patient population nor has the association between sleep impairment and the ability to engage in physical activity on a day-to-day basis been studied. Data were analysed from 932 patients with COPD (65.5% male, 66.4±8.3 years, FEV₁ % predicted = 50.8±20.5). Participants had sleep and physical activity continuously monitored using an activity monitor for a median of six days. The main factors associated with sleep impairment were identified and the association of nocturnal sleep impairment with patients’ subsequent physical activity, and daytime sleep, was investigated. Objectively measured sleep impairment was greater in patients with worse airflow limitation and worse exertional dyspnoea. Nights characterized by more sleeping bouts (>2), shorter sleeping bouts (<225 minutes), lower sleep efficiency (<91%) and more time spent awake after sleep onset (>57 minutes) were followed by days with lower levels of physical activity. There is clear relationship between COPD patients sleep and the amount of activity they undertake during the waking day. Identifying groups with specific sleep characteristics may be useful information when designing physical activity enhancing interventions.
5.1 Introduction

Chronic obstructive pulmonary disease (COPD) is a global health problem and is currently the third leading cause of death worldwide [10]. In addition to progressive chronic airflow limitation, patients with COPD commonly have multiple extra pulmonary effects and comorbidities, which are associated with physical inactivity [16]. Although there is general agreement about the need to assess and improve physical activity in people with COPD, the factors associated with patient’s capability to engage in physical activity are not well established, which may limit the impact of physical activity enhancement interventions [17].

Sleep disturbance, such as sleep fragmentation during the night, is common in patients with COPD [96], and is a major complaint after dyspnoea and fatigue [97]. Despite the high prevalence of disturbed sleep in COPD, night-time symptoms are often underestimated and are not a focus of current disease management [96].

Nocturnal sleep has been shown to be markedly impaired in patients with COPD compared to controls [98]. However, there is scant and discordant information on whether objectively assessed sleep disturbances worsen as the severity of dyspnoea and airflow limitation increases [98, 99]. Therefore, more data and in depth analysis are needed for a better understanding of the factors associated with sleep impairment in patients with COPD.

In healthy individuals, better sleep quality has been associated with higher exercise levels [100, 101]. Even though several studies have investigated the daytime consequences of reduced sleep quality in patients with COPD like fatigue, psychiatric problems and impaired quality of life [102, 103], no published study has objectively investigated the association of disturbed sleep with subsequent physical activity in this patient population.

In this study, data were pooled from different studies resulting in a large sample of patients with mild to very severe COPD who had extended objective measures of sleep and physical activity during daily life assessed using a multi-sensor activity monitor. These data were used to: (1) provide insight into the relationship between objectively determined sleep measures and disease severity, dyspnoea, gender, and day group (i.e. weekdays vs weekends); and (2) investigate whether there was an association between objectively assessed sleep measures and next day activity level. Our hypotheses were that: patients with more severe COPD defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria and higher Modified Medical Research Council (MMRC) dyspnoea score would have more objectively measured sleep disturbances, and that nights of impaired sleep would be followed by days characterized by lower levels of physical activity.

5.2 Material and methods

5.2.1 Participants

In this retrospective, cross-sectional study, data were pooled from previous studies (details can be found in the appendix) as assessed by the SenseWear Armband or SenseWear Mini Armband activity monitors (BodyMedia Inc., Pittsburgh, PA, USA). Data collected across ten countries from 1384 patients diagnosed with mild to very severe COPD defined spirometrically were considered for analysis. Participants were included if they had COPD with a post-
bronchodilator ratio of forced expiratory volume in the first second (FEV₁) to forced vital capacity (FVC) < 0.70 and they were clinically stable (i.e., stable shortness of breath and sputum production). We report baseline data recorded before any specific interventions were undertaken. The data collection was conducted in accordance with the declaration of Helsinki and approved by ethics committees at each of the participating centres, according to local regulations. Written informed consent was provided by all participants.

5.2.2 Sensor measurements

Physical activity levels and sleep were assessed during daily life with the SenseWear Armband devices that include an accelerometer with different physiological sensors [68, 44]. Data were sampled at one minute intervals and, together with demographic characteristics, were used to estimate metabolic equivalent of task (MET) using proprietary algorithms developed by the manufacturer. The use of multisensory data in combination with pattern recognition algorithms ensured that the MET estimation was insensitive to noise and random motion artefacts [104]. METs data were divided into activity intensity levels using the thresholds proposed by the American College of Sports Medicine: very light intensity, < 2.0 METs; light intensity, 2.0 to 2.9 METs; and moderate-to-vigorous intensity, ≥ 3.0 METs [81]. For each minute, the device recorded steps count, information about the sleeping status of a patient (0=awake, 1=sleeping), and posture (0=lying down, 1=not lying down).

5.2.3 Data recordings

Study participants wore the sensor on the upper arm both during daytime and night-time so that continuous, real-life activities were recorded. Participants who wore the device for at least 22 hours per day, with a minimum of four assessed days (two weekdays + Saturday + Sunday) were included [44]. Time in bed and time out of bed were derived from the minutes coded by the activity monitor as “sleeping” and “lying down” using a custom-made algorithm described in the next section. Based on these data the following night-time and daytime sleep measures were derived: total night sleeping time, number of nocturnal sleeping bouts, duration of nocturnal sleeping bouts, sleep efficiency, wake after sleep onset, total day sleeping time, number of daytime sleeping bouts, and average duration of daytime sleeping bouts. In this study, “sleep quality” is used to refer to the collection of these sleep measures which definition is presented in Table VII. Sleeping bouts were defined as consecutive minutes marked by the sensor as sleeping. As physical activity measures, the number of steps performed during day time and the time spent in very light, light and moderate-to-vigorous activities were computed for each assessed day. Participants who did not have their sleep regularly distributed during night-time or who had less than four hours of time in bed were excluded to minimize the inclusion of shift-workers and to reduce the impact of sleep morbidities such as insomnia.
62 5. Estimated nocturnal sleep impairment in patients with COPD in daily life and its association with daytime physical activity

<table>
<thead>
<tr>
<th>Variable name</th>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Night Sleeping Time</td>
<td>TNST</td>
<td>Total night sleeping time is calculated as the sum of all minutes scored as sleep during time in bed.</td>
</tr>
<tr>
<td>Number of Nocturnal Sleeping Bouts</td>
<td>NNSB</td>
<td>Number of nocturnal sleeping bouts during time in bed. A higher NNSB indicates more fragmented sleep.</td>
</tr>
<tr>
<td>Duration of Nocturnal Sleeping Bouts</td>
<td>DNSB</td>
<td>Average duration of nocturnal sleeping bouts during time in bed. A higher DNSB indicates longer sleeping bouts, and, in turn less nocturnal sleeping disturbances.</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>Seff</td>
<td>Sleep efficiency defined as the ratio of TNST and time in bed.</td>
</tr>
<tr>
<td>Wake After Sleep Onset</td>
<td>WASO</td>
<td>Time spent awake during time in bed after the first nocturnal sleep onset.</td>
</tr>
<tr>
<td>Total Day Sleeping Time</td>
<td>TDST</td>
<td>Total day sleeping time defined as the total time spent asleep during the out of bed period.</td>
</tr>
<tr>
<td>Number of Daytime Sleeping Bouts</td>
<td>NDSB</td>
<td>Number of daytime sleeping bouts indicates how many naps a patient takes during the day.</td>
</tr>
<tr>
<td>Duration of Daytime Sleeping Bouts</td>
<td>DDSB</td>
<td>Average duration of daytime sleeping bouts during the day. A higher DDSB indicates longer naps.</td>
</tr>
</tbody>
</table>

5.2.4 Algorithm

In order to calculate sleep measures, actigraphy data need to be segmented and the time in/out of bed needs to be derived. Time in bed is usually defined as the time from lights off to lights on (i.e. time interval comprised between the moment at which participants were lying down with the intention to fall asleep and the moment at which participants stand up from the bed after the night sleep) [68]. Lying down time, in turn, is defined as the time spent lying down while the participants are awake. In practice, the following definitions of time in bed have been used: (1) fixed time interval (from 21:00pm to 06:00am) [105]; (2) Time interval extracted from subject’s daily sleep log [98, 100]; (3) Time interval comprised between the lights off and lights on markers derived from polysomnography (PSG) data [106, 107, 68].

The first two methods are in general not reliable since sleeping behaviour varies from subject to subject and sleeping logs are inaccurate. The last one, when using only actigraphy data, is not possible. Other approaches should be used to guide the analysis of actigraphy data recordings and cluster together sleeping epochs, in a consistent way, in order to compute sleep assessment measures as total night sleeping time or sleep fragmentations (number of sleeping epochs).

Sleep measures are essentially coupled to a biphasic model of human behaviour that assumes, within 24 hours, a sleep and a wake period. It is known that such a model does not
always hold. Therefore, next to finding the light on and light off markers, it is of interest to have an indicator whether such a model is applicable at all.

Multi-sensor activity monitors, such as the SWA, allow the assessment of sleep and wakefulness period. In particular, in the SWA, actigraphy data is classified in a binary form into wake = 0 and sleep = 1 for each specific minute. The same minutes are also classified into lying down = 0 or not lying down = 1 according to the activity monitor’s proprietary algorithm.

The method to find light on and light off markers relies on an algorithm able to segment several days of continuous actigraphy data in time in bed and time out of bed. The algorithm is based on the minutes assessed as lying down moments by the SenseWear armband. A probability distribution and a measure of uncertainty are derived and used to initialize a biphasic model (time in bed-time out of bed). The model is further refined according to the closest lying epochs assessed by the multi-sensor activity monitor.

In a nutshell the algorithm clusters together sleeping epochs related to the time in bed of the subject and it quickly classifies the sleeping pattern of a subject during the assessed days as regular or irregular (i.e. not fitting to the concept of a biphasic model).

In essence the approach is a three-step procedure. In the first step, an average sleep-awake probability distribution or model is created together with an uncertainty distribution or model. The second step is to adapt this average model to each specific day (24 hours sequence) in order to determine the specific time in bed period for that particular sequence. As a third step, the sleep measures depending on the bed/awake segmentation are calculated per day. The first step also directly yields means to generate indicators for the properness of a biphasic model.

Figure 26 shows the output of the SenseWear activity monitor including metabolic equivalent of task (MET), sleep and lying down periods. As can be seen both the lying down (light green) and the sleep (magenta) periods yield fragmented episodes within each 24 hours preventing a straightforward association with desired sleep/awake indicator.

![Figure 26](image)

Figure 26 Several days of data recordings. In yellow: on=standing, in light green: on=lying down, in magenta: on=sleeping, in dark green and red metabolic equivalent of tasks (METs) estimates for weekdays and weekend days, respectively. For clarity, the lying down and standing are scaled to the intervals [0, 1.5] and [0, 2], respectively.

5.2 Material and methods
Based on the activity monitor’s recording of several continuous days the probability of the subject of being in the lying down status for each minute of a 24h day is calculated. Standing epochs during night time (21:00pm-06:00am) that are shorter than 1 hour are removed and considered as sleeping [108, 68]. When calculating quality sleeping measures this assumption will not be taken into account and the real measured epochs of standing and sleeping considered.

For a Bernoulli distribution as the light green line in Figure 26 (i.e., 0 = the subject is not lying down, 1 = the subject is lying down) the probability distribution is equal to the sample mean (blue line in Figure 27). The standard deviation of the sample mean is considered as a measurement of uncertainty (red dashed line in Figure 27). From Figure 27 it can be seen that the probability for the subject to be lying in the bed is maximal around 01:00 am and its maximal uncertainty is around 19:50 pm and 03:00 am (red circles in Figure 27).

A model can be fitted to the data to obtain a smooth curve. In our case, a Gaussian distribution (green line in Figure 27) is fitted to the empirical probability distribution (blue line in Figure 27).

The peaks of the uncertainty distribution closest to the 0.5 crossing point of the fitted Gaussian are used to create a biphasic model that indicates when the subject is likely to be sleeping and when he is likely to be awake (blue line in Figure 28).

Alternatively the two extrema of the first derivative of the fitted Gaussian distribution could be used to create the biphasic model (magenta line in Figure 27).
Figure 28 Biphasic model of time in bed – time out of bed (in blue) derived from the analysis of the assessed days.

The biphasic model is then adapted to the lying down and standing epochs calculated by the activity monitor. In particular, firstly the rising edges of the biphasic model are matched with the closest falling edges of the standing epochs as in Figure 29. Thus, the light-off moments are established.

Figure 29 Finding the start of the time in bed epochs (light off). The rising edges of the biphasic model (green circles) are matched with the closest falling edges of the standing epochs (red circles).

5.2 Material and methods
In the same way the falling edges of the model are matched with the closest rising edges of the standing epochs as in Figure 30.

Figure 30 Finding the end of the time in bed epochs (lights on). The falling edges of the model (green circles) are matched with the closest rising edges of the standing epochs (red circles).

The model is then adapted as shown in Figure 31.

Figure 31 In blue: Segmentation of recorded days in time in bed (on segment of the blue line) and time out of bed (off segment of the blue line).

5.2 Material and methods
The adapted model indicates when the subject starts lying down (light off) and when the subject stands up (light on). It is possible now to calculate indices as sleeping efficiency from data provided by the multi-sensor activity monitor.

The model could be used also to quickly recognise whether a subject didn’t follow a “normal/regular” sleeping pattern. There are several criteria which are inherently computed or derivable within the procedure to give indicators that a biphasic model is not proper for the data. Two simple criteria for a binary setting are the following: (1) if the maximum value of the empirical probability distribution is smaller than a certain threshold (i.e. 0.7 works well for our purpose) it can be assumed that the subject had a very irregular sleep pattern within the observed analysis period; (2) if the distance between the two uncertainty peaks selected is less than two hours the subject had (on an average) too few hours of time in a lying position during the night. The output of the algorithm was qualitatively assessed by visual inspection in 132 cases randomly selected. From the visual inspection we concluded that were no major issues in the functioning of the algorithm.

### 5.3 Statistical analysis

Linear mixed-effect models (LMM) were used to study: (i) which factors influenced sleep quality measures, and (ii) whether and to what extent sleep quality measures were associated with subsequent daily physical activity levels and daytime sleep in patients with COPD.

To study which factors influence measures of sleep quality in people with COPD, we constructed a LMM for each sleep parameter ($S_i$), with GOLD and MMRC as ordinal explanatory variables; smoking status, country of origin, gender and day group (i.e. weekday vs. weekend day) as categorical explanatory variables; age and BMI as continuous explanatory variables. To account for repeated measurements, we used random effects on two levels. On the highest level, we included a random intercept per patient. The second level, within patients, had a random intercept for each day group (weekdays vs. weekends). The residuals then accounted for the differences between days within the same day group.

The model had the form:

$$S_i \sim \text{GOLD} + \text{MMRC} + \text{Smoking status} + \text{Country} + \text{Gender} + \text{Day group} + \text{Age} + \text{BMI} + (1 \mid \text{patient ID}) + (1 \mid \text{Day group: patient ID}) + \epsilon \ (1.1)$$

where $\epsilon$ is a random error and the notations $(1 \mid \text{patient ID})$ and $(1 \mid \text{Day group: patient ID})$ indicate that the model accounts for by-subject and by-day group variability [109].

Next, sleep quality parameters were further categorized into quartiles to examine potential relationships with daytime measurements. Each of the physical activity (PA) measurements was considered the response variable of a separate LMM.

Sleep parameter quartiles (Q) and MMRC were ordinal explanatory variables; smoking status, country of origin, gender and day group were categorical explanatory variables; FEV$_1$, age and BMI were continuous explanatory variables of the model. Repeated measurements and day group were included as random effects.

The model had the form:
Estimated nocturnal sleep impairment in patients with COPD in daily life and its association with daytime physical activity

\[ PA_i \sim Q + MMRC + Smoothing status + Country + Gender + Day group + FEV1 + Age + BMI + (1|patient ID) + (1|Day group:patient ID) + \epsilon \]

This kind of analysis was chosen to focus on differences between effects, while accounting simultaneously for different sources of variance (i.e. controlling for several confounding factors and distinguishing between weekdays and weekend days/nights) and repeated measurements.

Moreover, applying linear mixed effects models on the time-specific data, we assessed the association of sleep quality with physical activity levels during the following day taking into account repeated measurements of sleep and physical activity for each participant without disregarding between-subject variations.

To construct the models we used the lmer function of the package lme4 in R [109]. Least squares means (LS-means) and differences of LS-means of the fixed effects were calculated to present the results. Degrees of freedom and p-values for significant differences (significant if \( p<0.05 \)) were computed using Satterthwaite’s approximation [110]. Comparisons of demographic and clinical characteristics between included and excluded patients were evaluated by Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables.

Analyses were carried out using MATLAB R2015a (The MathWorks, Inc., Natick, Massachusetts, United States) and R (R Core Team, 2012) software.

### 5.4 Results

In total 932 patients with COPD were eligible for analysis. Figure 32 shows the flow of participants through the study. Patients excluded due to irregular sleeping patterns and not enough time in bed had significantly lower \( FEV_1 \% \) predicted compared with included patients \( (46.6\pm19.4 \text{ vs. } 50.8\pm20.5, p<0.05) \). No significant differences between included and excluded patients were observed for age, gender, body mass index (BMI), smoking status and MMRC. The median number of days analysed per patient was six (four weekdays + Saturday and Sunday), resulting in a total of 5646 valid assessed days, of which 3788 (67%) were weekdays. Demographic and clinical characteristics of the patients included in the study are presented in Table VIII, those of excluded patients can be found in Table IX. Comparisons of demographic and clinical characteristics between included and excluded patients were evaluated by Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables.

Patients excluded from the study because of irregular sleeping patterns and too short time spent in bed during the night (column II, Table IX) had lower \( FEV_1 \) compared to included patients. Accordingly, the excluded sample had a higher percentage of patients in GOLD 3 and GOLD 4 and a lower percentage in GOLD 1 and GOLD 2. This is line with the findings of this study showing that patients with impaired sleep had worse COPD severity.

The sample excluded due to missing data (column III, Table IX) had a higher percentage of males, lower percentage of smokers, older age, higher BMI, higher percentage of patients in GOLD 1and GOLD 3, and a lower percentage of patients in GOLD 2 and GOLD 4 compared to the sample of included patients.
Figure 32 Flow of patients through the study.

Table VIII Demographic and clinical characteristics.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Included patients (n=932)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male / female (%)</td>
<td>65.6 / 35.4</td>
</tr>
<tr>
<td>Smokers / non smokers (%)</td>
<td>32.6 / 67.4</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>66.4±8.3</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.3±5.4</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>50.8±20.5</td>
</tr>
<tr>
<td>GOLD 1 - 2 - 3 - 4 (%)</td>
<td>9.6 – 40.2 – 32.4 – 17.8</td>
</tr>
<tr>
<td>MMRC* 0 - 1 - 2 - 3 - 4 (%)</td>
<td>13.9 – 26.8 – 21.9 – 17.6 – 6.1</td>
</tr>
</tbody>
</table>

Data in the table are expressed as percentages, or means ± standard deviation. BMI: Body Mass Index, FEV₁: forced expiratory volume in 1 s, GOLD: Global Initiative for Chronic Obstructive Lung Disease grade, MMRC: modified Medical Research Councils scale. *MMRC data for 805 patients.
### Table VI General characteristics and daily physical activity measures of clusters of patients with COPD.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>General characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>216</td>
<td>415</td>
<td>184</td>
<td>165</td>
<td>21</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>68 (62 – 74)</td>
<td>67 (61 – 72)</td>
<td>67 (60 – 72)</td>
<td>63 (58 – 70)</td>
<td>63 (58 – 70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male, %</td>
<td>67</td>
<td>51</td>
<td>76</td>
<td>76</td>
<td>67</td>
<td>0.32</td>
</tr>
<tr>
<td>BMI, kg·m⁻²</td>
<td>30.4 (26.5 – 34.7)</td>
<td>25.7 (22.6 – 29.0)</td>
<td>24.9 (22.2 – 27.4)</td>
<td>23.1 (20.3 – 26.8)</td>
<td>22.5 (18.3 – 30.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FEV₅ % predicted</td>
<td>44 (32 – 58)</td>
<td>48 (34 – 61)</td>
<td>57 (41 – 71)</td>
<td>50 (36 – 68)</td>
<td>51 (39 – 70)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>mMRC dyspnoea grade, points</td>
<td>2 (1 – 3)</td>
<td>2 (1 – 3)</td>
<td>1 (1 – 2)</td>
<td>1 (0 – 3)</td>
<td>1 (0 – 3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ADO index *</td>
<td>5 (3 – 6)</td>
<td>4 (3 – 5)</td>
<td>4 (3 – 5)</td>
<td>4 (3 – 5)</td>
<td>3 (2 – 4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GOLD 2007 classification A / 2 / 3 / 4, %</td>
<td>18 / 19 / 16 / 47</td>
<td>28 / 15 / 17 / 40</td>
<td>28 / 16 / 16 / 24</td>
<td>31 / 13 / 20 / 36</td>
<td>44 / 6 / 28 / 22</td>
<td>0.02</td>
</tr>
<tr>
<td>GOLD 2011 classification A / B / C / D, %</td>
<td>18 / 19 / 16 / 47</td>
<td>28 / 15 / 17 / 40</td>
<td>28 / 16 / 16 / 24</td>
<td>31 / 13 / 20 / 36</td>
<td>44 / 6 / 28 / 22</td>
<td>0.02</td>
</tr>
<tr>
<td>Physical activity measures in very light intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>955 (904 – 1042)</td>
<td>823 (768 – 879)</td>
<td>706 (641 – 769)</td>
<td>675 (604 – 735)</td>
<td>516 (456 – 621)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs·min·day⁻¹</td>
<td>1356 (1165 – 1730)</td>
<td>1022 (854 – 1222)</td>
<td>855 (729 – 1118)</td>
<td>789 (692 – 1019)</td>
<td>853 (661 – 1884)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>890 (815 – 968)</td>
<td>680 (622 – 745)</td>
<td>534 (452 – 601)</td>
<td>490 (415 – 561)</td>
<td>340 (254 – 444)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>17 (14 – 20)</td>
<td>20 (17 – 22)</td>
<td>18 (16 – 20)</td>
<td>17 (15 – 20)</td>
<td>12 (11 – 16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>53 (43 – 65)</td>
<td>35 (30 – 41)</td>
<td>29 (25 – 34)</td>
<td>27 (24 – 32)</td>
<td>26 (22 – 32)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs·min·day⁻¹</td>
<td>1257 (1068 – 1632)</td>
<td>836 (693 – 1050)</td>
<td>628 (516 – 862)</td>
<td>589 (467 – 779)</td>
<td>704 (420 – 1185)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical activity measures in light intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>57 (35 – 79)</td>
<td>139 (113 – 167)</td>
<td>245 (208 – 282)</td>
<td>167 (134 – 209)</td>
<td>121 (87 – 163)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs·min·day⁻¹</td>
<td>196 (121 – 305)</td>
<td>408 (320 – 517)</td>
<td>725 (591 – 958)</td>
<td>526 (366 – 735)</td>
<td>416 (227 – 1039)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>0 (0 – 3)</td>
<td>8 (3 – 16)</td>
<td>46 (32 – 65)</td>
<td>8 (3 – 16)</td>
<td>0 (0 – 4)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
5.4.1 Sleep measures evaluation in patients with COPD

Figure 33 shows the associations of nighttime and daytime sleep measures with disease severity, dyspnoea, gender, and day group. In particular, the total night sleeping time was significantly higher in women and during weekends (Figure 33A). The number of nocturnal sleeping bouts (Figure 33B) increased both with airflow limitation and exertional dyspnoea. In particular, it was significantly higher in patients who had the most severe airflow limitation and who were the most dyspnoeic. The number of nocturnal sleeping bouts was significantly higher in men and during weekends. Both short duration of nocturnal sleeping bouts and low sleep efficiency were associated with a higher GOLD grade and dyspnoea score (Figure 33C and D). These two sleep measures were significantly higher for women. The time spent awake after the first sleep onset increased both with disease severity and dyspnoea, being worst in patients with GOLD grade 4 and MMRC score 4 (Figure 33E).

During daytime the sleeping time increased significantly with dyspnoea (Figure 33F), as did the number and duration of sleeping bouts (Figure 33G and H). Sleeping time and duration of sleeping bouts were significantly shorter in patients with GOLD grade 4.
5.4.2 Association between objective sleep measures and daytime physical activity

Nocturnal sleep measures were divided into quartiles (Q1, shortest/lowest-Q4, longest/highest) to assess the association with daytime physical activity measures. Table X shows...
the quartile ranges for each sleep quality indicator together with the corresponding least-square average of the daytime actigraphy measures. Spearman’s rank correlation is used to calculate the p-trends between the quartiles for each daytime actigraphy measure.

As shown in Figure 34A, the number of steps performed during the day decreased as the number of sleeping bouts and the minutes spent awake after the sleep onset increased. Patients who had their sleep characterized by long sleeping bouts and high sleep efficiency had a significantly higher number of steps on the following day. Patients who slept more than 480 minutes (Q₄) performed a smaller number of steps than the other patients, but no significant differences were found if the number of steps of each patient is divided by the time spent awake (data not shown). As presented in Figure 34B, the time spent in very light activities was higher in patients who slept more and it increased with sleep fragmentation and time spent awake after the sleep onset. Patients with lower sleep efficiency and shorter sleeping bouts spent more time in very light activities. Patients with a higher number of sleeping bouts per night, shorter sleeping bouts, lower sleep efficiency and longer time spent awake during the night spent less time in light (Figure 34C) and moderate-to-vigorous (Figure 34D) physical activities. Patients who slept more during the night spent less time in light activities, while less time in moderate-to-vigorous was spent by those who slept less during the night.
Estimated nocturnal sleep impairment in patients with COPD in daily life and its association with daytime physical activity

Table X Quartiles of night sleep variables and corresponding LS-means of the daytime actigraphy measures.

<table>
<thead>
<tr>
<th>Quartiles (min)</th>
<th>Total night sleeping time (TNST)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$Q_i &lt; 347$</td>
</tr>
<tr>
<td>STEPS (#)</td>
<td>4952</td>
</tr>
<tr>
<td>TDST (% awake time)</td>
<td>2.26</td>
</tr>
<tr>
<td>TIME VL (% awake time)</td>
<td>73.42</td>
</tr>
<tr>
<td>TIME L (% awake time)</td>
<td>15.3</td>
</tr>
<tr>
<td>TIME MV (% awake time)</td>
<td>7.42</td>
</tr>
</tbody>
</table>

Number of nocturnal sleeping bouts (NNSB)

<table>
<thead>
<tr>
<th>Quartiles (#)</th>
<th>$Q_i \leq 2$</th>
<th>$2 \leq Q_i &lt; 3$</th>
<th>$3 \leq Q_i &lt; 4$</th>
<th>$Q_i \geq 4$</th>
<th>$p$-trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEPS (#)</td>
<td>5136</td>
<td>4874</td>
<td>4664</td>
<td>4484</td>
<td>0.08</td>
</tr>
<tr>
<td>TDST (% awake time)</td>
<td>1.71</td>
<td>1.91</td>
<td>1.94</td>
<td>1.79</td>
<td>0.75</td>
</tr>
<tr>
<td>TIME VL (% awake time)</td>
<td>72.78</td>
<td>73.32</td>
<td>73.60</td>
<td>74.25</td>
<td>0.08</td>
</tr>
<tr>
<td>TIME L (% awake time)</td>
<td>16.00</td>
<td>15.45</td>
<td>15.35</td>
<td>15.08</td>
<td>0.08</td>
</tr>
<tr>
<td>TIME MV (% awake time)</td>
<td>8.18</td>
<td>7.83</td>
<td>7.60</td>
<td>7.39</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Average duration of nocturnal sleeping bouts (DNSB)

<table>
<thead>
<tr>
<th>Quartiles (min)</th>
<th>$Q_i &lt; 86$</th>
<th>$86 \leq Q_i &lt; 136$</th>
<th>$136 \leq Q_i &lt; 225$</th>
<th>$Q_i \geq 225$</th>
<th>$p$-trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEPS (#)</td>
<td>4559</td>
<td>4759</td>
<td>4681</td>
<td>4987</td>
<td>0.08</td>
</tr>
<tr>
<td>TDST (% awake time)</td>
<td>1.97</td>
<td>1.82</td>
<td>1.89</td>
<td>1.70</td>
<td>0.33</td>
</tr>
<tr>
<td>TIME VL (% awake time)</td>
<td>74.05</td>
<td>73.40</td>
<td>73.55</td>
<td>72.98</td>
<td>0.33</td>
</tr>
<tr>
<td>TIME L (% awake time)</td>
<td>15.06</td>
<td>15.56</td>
<td>15.32</td>
<td>15.81</td>
<td>0.33</td>
</tr>
<tr>
<td>TIME MV (% awake time)</td>
<td>7.39</td>
<td>7.76</td>
<td>7.74</td>
<td>8.12</td>
<td>0.33</td>
</tr>
</tbody>
</table>

Sleep efficiency

<table>
<thead>
<tr>
<th>Quartiles (%)</th>
<th>$Q_i &lt; 71$</th>
<th>$71 \leq Q_i &lt; 82$</th>
<th>$82 \leq Q_i &lt; 91$</th>
<th>$Q_i \geq 91$</th>
<th>$p$-trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEPS (#)</td>
<td>4524</td>
<td>4758</td>
<td>4798</td>
<td>5111</td>
<td>0.08</td>
</tr>
<tr>
<td>TDST (% awake time)</td>
<td>2.01</td>
<td>1.81</td>
<td>1.82</td>
<td>1.73</td>
<td>0.33</td>
</tr>
<tr>
<td>TIME VL (% awake time)</td>
<td>73.32</td>
<td>73.50</td>
<td>73.43</td>
<td>72.62</td>
<td>0.08</td>
</tr>
<tr>
<td>TIME L (% awake time)</td>
<td>14.89</td>
<td>15.41</td>
<td>15.54</td>
<td>15.98</td>
<td>0.08</td>
</tr>
<tr>
<td>TIME MV (% awake time)</td>
<td>7.24</td>
<td>7.76</td>
<td>7.76</td>
<td>8.30</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Time awake during time in bed after the first sleeping onset (WASO)

<table>
<thead>
<tr>
<th>Quartiles (min)</th>
<th>$Q_i &lt; 57$</th>
<th>$57 \leq Q_i &lt; 104$</th>
<th>$106 \leq Q_i &lt; 165$</th>
<th>$Q_i \geq 165$</th>
<th>$p$-trends</th>
</tr>
</thead>
<tbody>
<tr>
<td>STEPS (#)</td>
<td>5076</td>
<td>4967</td>
<td>4687</td>
<td>4355</td>
<td>0.08</td>
</tr>
<tr>
<td>TDST (% awake time)</td>
<td>1.75</td>
<td>1.88</td>
<td>1.87</td>
<td>1.89</td>
<td>0.33</td>
</tr>
<tr>
<td>TIME VL (% awake time)</td>
<td>73.02</td>
<td>73.11</td>
<td>73.59</td>
<td>74.23</td>
<td>0.08</td>
</tr>
<tr>
<td>TIME L (% awake time)</td>
<td>15.84</td>
<td>15.56</td>
<td>15.35</td>
<td>15.01</td>
<td>0.08</td>
</tr>
<tr>
<td>TIME MV (% awake time)</td>
<td>8.03</td>
<td>7.98</td>
<td>7.71</td>
<td>7.29</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Daytime actigraphy measures: STEP = Steps performed; TDST = Total Day Sleeping Time, TIME VL = Time spent in Very Light activity, TIME L = Time spent in Light activity, TIME VM = Time spent in Moderate-to-Vigorous activity. $Q_i$ = i-th quartile. Data in the table are expressed as least-square means or percentage of wake time. $p$-trends between quartiles evaluated by Spearman's correlation.

5.4 Results
5.4 Results

Daytime sleep was inversely related to the amount of nocturnal sleep, the duration of sleeping bouts and the sleep efficiency (Figure 35). Patients who showed relatively short sleep duration during the night, who had short sleeping bouts and low sleep efficiency reported more daytime sleep.

Figure 34 Association between nocturnal sleep parameters (TNST = Total Night Sleeping Time; NNSB = Number of Nocturnal Sleeping Bouts; DNSB = average Duration of Nocturnal Sleeping Bouts; Seff = Sleep efficiency; WASO = time awake After the first Sleep Onset) and daytime physical activity measures (A: STEP = Steps performed; B: TIME VL = Time spent in Very Light activity, C: TIME L = Time spent in Light activity, D: TIME MV = Time spent in Moderate-to-Vigorous activity). Data are expressed as least-square means ± standard error. Significance levels for pairwise comparisons are indicated as horizontal bars with *p<0.05, **p<0.01, and ***p<0.001. TIME VL, TIME L, TIME VM are presented in % of the out of bed time.
5.5 Discussion

We describe, to our knowledge, the first study in a large sample of participants with COPD, targeting the association of objectively measured sleep impairment with airflow limitation, exertional dyspnoea, gender, day group and daytime activity levels.

We found that objective sleep quality measures are worse in patients with severe airway obstruction and dyspnoea. This is in agreement with George et al. [111] who showed that subjective sleep disturbances tend to be more severe with advancing disease and with Dodge et al. [112] who showed that patients with dyspnoea are more likely to report persistent sleep disturbance. Conversely, Hartman et al. [99] failed to find a significant association between night’s rest parameters assessed by an accelerometer and both airflow limitation and dyspnoea. However, this latter study did not evaluate sleep quality measures, but rather quantitative parameters such as body movements and number of posture transitions that are not necessarily related to poor sleep quality [99]. Nunes et al. [98] reported that the MMRC score was an important predictor of objectively measured sleep quality in 26 patients with moderate to very severe COPD. However, the small sample size precluded any firm conclusions on the differences between patients with different dyspnoea scores. Furthermore, in this study patient’s daily sleep logs were used. This may be problematic because sleep logs are imprecise in quantifying time in bed and wake time [113].

The strong evidence provided by our findings regarding the association of sleep impairment with the most severe stage of the disease and dyspnoea could be explained by at least two mechanisms. The lying sleeping position assumed by the participants in the study increases both work of breathing and airway resistance, and lowers their threshold for dyspnoea [114]. Moreover, patients with severe COPD frequently experience episodes of worsening symptoms that may also preclude from adequate sleep. It has been shown that one night of sleep deprivation can lead to small but statistically significant falls in FEV₁ and forced vital capacity in a group of patients with COPD [115]. Although a single night’s loss of sleep does not have major clinical consequences, it may be speculated that chronic alterations in sleep would result in cumulative negative effects on the respiratory function, which could become relevant along the prolonged course of this disorder because they occur more likely for those patients who are least able to tolerate any further challenge to their ventilatory capability.

Participants with the most severe disease had worse sleep but they did not seem to compensate it during the day by adding naps. Most dyspnoic patients, in turn, seemed to do so.
Other investigators have also found that daytime sleepiness was related more strongly to the presence of respiratory symptoms than to a diagnosis of lung disease or the degree of airway obstruction [116].

We saw significant gender differences after correction for age, BMI, smoking status, country of origin, GOLD and MMRC. Men had worse sleep quality measures and spent more time sleeping during the day than women. There is currently only limited information regarding the influence of gender on sleep in COPD. In a previous study using actigraphy no significant gender-related differences in sleep quality were found [98]. Other studies have documented that women appear to report more sleep-related complaints [117]. However, objective and subjective assessments of sleep seem to reflect different aspects and may therefore not be necessarily in agreement [118].

During weekends patients had significant more fragmented sleep and spent significantly more time awake after the first sleep onset than during weekdays. Nonetheless, our results showed that impaired sleep during weekends may be compensated by sleeping longer.

This study showed that nights of lower sleep quality were followed by days of lower levels of physical activity in people with COPD. The robustness of the results was verified by controlling for several confounding factors such as severity of airflow limitation and severity of dyspnoea. The association of impaired sleep with worse daytime performance is consistent with findings showing that it could play a substantial role in daytime symptoms and chronic fatigue [119]. Moreover these findings are consistent with other correlational evidence drawn from older adults suggesting that objectively measured poor sleep was associated with worse daytime physical function, yet none of these studies demonstrates a direct effect of sleep on subsequent physical activity [100, 101]. Although inferring a causal relationship was out of the scope of this study, our finding provided a good illustration of the sequential association as it incorporated a clear chronological order of the predictor (sleep quality measure) and the predicted variable (physical activity). However, the possibility that poor daytime performance may be a causative factor for poor sleep quality should be considered.

The deficit in good sleep, in association with changes of sleep architecture, may make sleep not as restorative as needed and may cause a significant sleep deficit [120]. Accordingly, our study provides evidence to suggest that poor sleep efficiency and short sleeping bouts during the night are possibly compensated by additional daytime naps.

The fact that poor sleep quality was associated with reduced physical activity levels may have important consequences with regard to current clinical practice. First, our findings suggest the possibility of increasing spontaneous engagement in physical activity through improving sleep since, in the absence of any intervention, patients having had a better night of sleep spontaneously engaged in more physical activity the following day. Second, existing strategies for promoting physical activity tend to focus on actions during the day. Additional efforts in promoting quality sleep among physically inactive subgroups may increase the overall impact of these interventions. We may speculate that poor sleep quality could make the motivation to exercise by day worse and contribute to the vicious cycle of deconditioning that affects COPD sufferers (see Figure 36). Finally, sleep should be assessed and taken into account when analysing physical activity in COPD, although recent literature is often-overlooking the continuity between night-time sleep and daytime physical activity [121].

This study has some limitations which should be considered when interpreting the results. Our participants were not screened for sleep-related disorders, such as obstructive sleep apnoea (OSA). However, because COPD and OSA are both common chronic conditions, these should be
expected to occur together, particularly among overweight individuals with COPD [122]. Moreover, it has been demonstrated that there are no differences in measures of dyspnoea, sleep quality, sleep efficiency, and sleepiness during the day between patients with COPD only and patients with COPD-OSA overlap [122]. Although we cannot know whether the patients included had OSA, we can rule out that specific interventions influenced quality or quantity of sleep since only baseline data were analysed. Nowadays, sleep assessment in COPD is mainly based on self-reported measures of sleep duration and quality, which have poor precision and reliability when compared to objective measures [96, 100, 103]. Activity monitors provide minimally invasive measures of the continuity and hence quality of sleep and they have the advantage of allowing recording continuously for 24-hours a day for extended periods [103]. However, to the current authors’ knowledge, the SenseWear armband has not been properly validated to study sleep in COPD, even though its reliability has been shown in several sleep studies [68, 123].

In summary, sleep impairment in patients with COPD tends to be more pronounced in patients with severe airflow limitation and in those with worse exertional dyspnoea. Moreover, nocturnal sleep impairment appears to be an important factor associated with the capability to engage in physical activity on a day-to-day basis. In particular, nights of better sleep quality measures were followed by days of higher levels of physical activity. Further research is needed to identify the causal association between night-time sleep and the decline in daytime physical activity, as well as to assess whether the management of night-time symptoms and the reduction of sleep impairment can improve physical activity in COPD patients. Considering both our current understanding of the negative health consequences of sleep disturbance in COPD and the current limited efficacy of interventions in significantly improving and maintain physical activity enhancement, our data suggest that approaches to improve sleep need to be considered as additional targets for tailored interventions and may have a favourable impact on lifestyle in patients with COPD.
Patients experiencing night-time symptoms have their sleep disturbed. A small decline in FEV\textsubscript{1} due to sleep loss itself could have important consequences because it occurs more likely for those patients who are least able to tolerate any further challenge to their ventilatory capability. Although a single night’s loss of sleep does not have major clinical consequences, it may be speculated that chronic alterations in sleep would result in cumulative negative effects on the respiratory function, which could become relevant along the prolonged course of this disorder. This, associated with a not restorative sleep due to sleep disturbance, could make the motivation to exercise during the day worse and contribute to the vicious cycle of deconditioning that affects COPD sufferers.
6 Identifying physical activity profiles in COPD patients using topic models

With the growing amount of physical activity (PA) measures, the need for methods and algorithms that automatically analyse and interpret unannotated data increases. In this work, PA is seen as a combination of multimodal constructs that can co-occur in different ways and proportions during the day. The design of a methodology able to integrate and analyse them is discussed, and its operation is illustrated by applying it to a dataset comprising data from COPD patients and healthy subjects acquired in daily life. The method encompasses different stages. The first stage is a completely automated method of labelling low-level multimodal PA measures. The information contained in the PA labels are further structured using topic modelling techniques, a machine learning method from the text processing community. The topic modelling discovers the main themes that pervade a large set of data. In our case, topic models discover PA routines that are active in the assessed days of the subjects under study. Applying the designed algorithm to our data provides new learnings and insights. As expected, the algorithm discovers that PA routines for COPD patients and healthy subjects are substantially different regarding their composition and moments in time in which transitions occur. Furthermore, it shows consistent trends relating to disease severity as measured by standard clinical practice.

6.1 Introduction

The prevalence of chronic diseases, in general, is rising due to an ageing population, as well as due to environmental and lifestyle changes. This is particularly true for respiratory diseases, such as chronic obstructive pulmonary disease (COPD), which is a progressive and irreversible disease that results in airflow limitation and significant extra pulmonary effects, which limit physical activities [124]. Physical activity (PA), defined as any bodily movement produced by skeletal muscles that requires energy expenditure (EE) [125], is known to be a relevant indicator of COPD patients’ health status. Current COPD treatment guidelines strongly recommend pulmonary rehabilitation programs with the intent of increasing PA and maintaining the changes over time, including when patients are discharged to home [16]. Although learning to exercise and maintaining exercising is really difficult, this is possibly less of an issue for other effective behavioural changes like reducing the sedentary time. New methodologies assessing PA and a better insight into daily PAs of patients with COPD are needed to accurately characterize the disease and assist clinicians in designing targeted therapeutic strategies and personalized coaching programs that do not rely on a priori fixed objectives [51]. Since patients are not able to accurately self-report their physical activities [126], models describing PA should be learned in an unsupervised fashion without the need of user annotations. Moreover, they should be suitable to harmoniously integrate multiple low-level PA measures (such as intensity levels of the activities performed or step counts), and the associated physiological responses into meaningful descriptors [50]. With recent improvements in wearable sensor technologies, it becomes easier in daily life to acquire massive amounts of different sensors data. At the same time, however, it is difficult to combine and extrapolate meaningful information in absence of any supervision or annotation. In this work, measures of PA and physiological responses are presented as the letters composing the words that describe PAs. The co-occurrence of these words in different ways and proportions during the day creates groups of PA constructs describing the main topics that pervade the day of a patient, i.e., PA routines. Routines could also occur at different times and in different proportions across the day for different patients or subgroups of patients, thus characterizing their activity behaviour. In this work, we show that the low-level fusion of sensors data into “words” combined with topic modelling holds the promise of discovering new and clinically relevant insights. In particular, this work provides the following contributions. (1) We propose a methodology to create a vocabulary of meaningful words describing PA from a set of multimodal PA measures without the need of any supervision or parameter tuning. Using the generated vocabulary, we discover PA routines that pervade daily life of healthy control subjects and a subgroup of COPD patients pairwise matched for age, gender, and body mass index (BMI). (2) We infer the underlying PA routine structure of the dataset available (comprising more COPD patients) on day segments of 30 min and on the first 6 h at once describing, respectively, the temporal regularities of the multimodal PA measures, and the estimated time spent by the subjects under study in each of the routines. (3) Finally, we investigate for the first time whether discovered PA routines are related to disease severity, whether they can be deployed to cluster subjects of the matched dataset and, furthermore, to recognize from which group each assessed day comes from.
6.2 Related works

6.2.1 COPD Ambulatory Monitoring

The automatic monitoring and analysis of chronic diseases has always been central in research on wearable sensors. Physical activities in patients with moderate to very severe COPD has been objectively documented using motion sensors, which provide more accurate, individualized, and detailed information on body movement than questionnaires [127]. Liao et al. [128] provided a review focused on describing current wearable technologies for measuring the PA level of COPD patients. In particular, validated devices should be used, since activity monitors can be less accurate in patients whose walking speed is as low as 0.5 miles/h. The use of data from ten wearable sensors as indicator of PA levels and physiological responses to recognize a set of 11 scripted activities is illustrated in [129]. In particular, a comparative study of supervised machine learning techniques is presented with emphasis placed on achieving high recognition accuracy. The number of sensors and the complexity of the algorithms are second to that objective. Research on PA levels of COPD patients usually deploys one single activity monitor to minimize obstructiveness.

6.2.2 COPD Physical Activities

It has been consistently shown that COPD patients have lower PA levels than their healthy peers [130], and that reduced levels of PA are related to an increased risk of hospital admission and mortality [17]. Outcome variables related to this type of analysis are focused mainly on amount and volume parameters, such as number of steps, walking time, volume of PA as expressed by total number of counts, and total EE. Although these are important health markers of patients suffering from COPD, interventions thus far have failed to demonstrate important increases in these outcome variables. Moreover, the relation with severity of the disease, assessed by the forced expiratory volume in the first second (FEV$_1$), is not strong or not significant [45]. Bouts of PA described by their frequency, duration, and intensity were introduced by Gonzalez et al. [51] in order to explore whether these patients meet the general guidelines for PA for older adults. Information about physiological responses was not considered in the analysis.

6.2.3 Symbolic Representation of Data

Alternatively to the selection of statistical attributes (such as mean duration of activity bouts within a day or the time spent in activity bouts of different intensities) which are mainly driven by intuition and experience, other approaches can be used to represent and analyse patient’s data. Symbolic representation of continuous data offers several advantages, such as the possibility to be used in combination of a wide set of algorithms from the text processing community. Symbolic approaches like SAX [131] have been proposed to reduce efficiently a time series to a set of symbols of a vocabulary. In addition to the a priori fixed size of the vocabulary, this method assumes a particular distribution, which may not be always valid and may limit the performance of series mining tasks [132], [133]. In order to construct features for discriminative
tasks, Saria et al. [134] proposed a method that discovers in a time-series recurring sub sequences having similar shape, but that, at the same time, can exhibit significant variability (deformable motifs). Number and length of the motifs need to be specified beforehand and, if applied to multidimensional time series, the method assumes that motifs along all the dimensions are happening synchronously.

6.2.4 Probabilistic Unsupervised Modelling

A probabilistic approach for unsupervised mining of electronic health data has been introduced by Schulam et al. [135]. Time series of clinical markers were clustered taking into account confounding factors that might affect data. In line with the generative modelling of multidimensional time series outlined by the authors and increasing the abstraction level of the activity bouts, we might think of these constructs as primitive descriptors of PA that are latently coupled to each other. Organizing bouts in higher level and coherent structures that co-occur during a day, more informative PA constructs could be described (i.e., PA routines). Topic models suit this goal since they represent a class of algorithms able to discover hidden structures in collections of documents. Due to their pattern discovery capability, they have been explored in the wearable sensor and activity recognition community. Huynh et al. [136] showed that daily routines of activities can be recognized as a probabilistic combination of activity labels, such as walking, discussing at whiteboard, etc. They also addressed the point of avoiding supervised learning approaches by clustering raw sensor data in order to build the vocabulary of activity primitives. Their approach was tested only on data from one single subject, and the vocabulary of primitives had a fixed size chosen a priori. Seiter et al. [137] compared three topic model approaches and analysed three public datasets with different properties affecting the discovery, such as primitive rate, activity composite specificity, primitive sequence similarity, and composite-instance ratio. These authors compared the activity composite discovery performance against the performance of a k-means clustering algorithm providing guidelines for optimal parameter selection. Their results indicated that latent Dirichlet allocation (LDA) shows higher robustness against noise compared to k-means and other topic modelling approaches. The application of a nonparametric framework to create the vocabulary and discover human routines from sensor data was investigated using a Dirichlet process Gaussian mixture model (DPGMM) in [138]. Although this approach does not need to specify the number of unique artificial words, it assumes that data should come from the same distributions used to create the mixture model. In the case of populations with different activity behaviour as healthy subjects and COPD patients at different stages, this might not be true and the mapping of the raw sensor data to vocabulary words might not be correct.

6.3 Background

Topic models are algorithms for discovering the main themes that pervade a large and unstructured collection of documents. Data are treated as observations arising from a generative probabilistic process, in which hidden variables reflect the thematic structure of a collection of documents. The intuition behind using the LDA [139] to discover PA routines is that each day is a mixture of thematically coherent PA measures just as a text document is a mixture of thematically coherent words. The graphical model for LDA is provided in Figure 37. All the
assessed days (also called documents \( d_{1:D} \)) share the same set of daily routines (also called topics \( \beta_{1:K} \)) that are defined as Dirichlet distributions over the observed set of PA descriptors (also called words \( W \) or terms of a fixed vocabulary). Observing activities in patients is a difficult task since it is time intensive and intrusive. At the same time, patients are not able to accurately self-report their physical activities \([126]\), and the training of a classifier requires annotations that in a daily life scenario are difficult to obtain. In order to make the methodology fully unsupervised, we assume that the observed words (input of the model) are composed by multimodal measures coming from a body area sensor network. Each assessed day exhibits PA daily routines in different proportion indicated as \( \theta_{1:D} \), i.e., each day has a different distribution over the routines that also follows a Dirichlet distribution. In such a model, the \( N \) words \( (W_{d,n}) \) that compose the \( D \) documents are the only random variables observed and depend on the per word topic assignment \( (Z_{d,n}) \) and all the \( \beta_k \). The daily routines then are composed indirectly by low-level PA measures that belong, with a certain probability distribution, to different thematic areas. Different routines will have different PA measures with different probabilities. Topic modelling algorithms calculate the hidden structure that likely generated the observed collection of documents. In particular, for this analysis, we use variational inference to approximate the intractable posterior distribution over hidden variables defined by LDA. In a nutshell, variational inference posits a parametrized family of distributions over the hidden structure, and then, finds the member of that family that is closest to the posterior according to the Kullback–Leibler divergence. The reader is invited to refer to \([139]\) for an exhaustive explanation.

**Figure 37** Graphical model for LDA. Each node is a random variable, edges denote possible dependences. The only observed variables (shaded) are the words \((W)\). The distribution of the words in a routine \((\beta)\) and the distribution of the routine in a document \((\theta)\) depend only on the topic hyperparameters \(\eta\) and \(\alpha\) that control the mean shape and sparsity of the distributions. \(Z\) represents the word topic assignment.

### 6.4 Methods

In the application of LDA, a word, defined to be an instance of a vocabulary, is considered as the basic unit of discrete data. In this work, multimodal monitoring signals, composed of PA measures and physiological responses, are symbolized first as letters. Our approach in selecting the letters and then the words composing the vocabulary benefits from a methodology that preserves the interpretability of the vocabulary and that allows the generation of words that could also not appear in the current documents. The multidimensional data space is first divided in subspaces, and for each subspace, we use cluster analysis to divide PA measures and physiological responses into discrete clusters levels (letters) that are then combined to form words. We use soft assignments to link an intensity bout \((IB)\) with the words in the vocabulary.
such that any bout has a probability to belong to each of the terms created. We extract the vocabulary in a subset of COPD and healthy patients and show that the vocabulary chosen can fit the model on a larger cohort of patients. The dataset and the methodology developed are described in detail in the following sections.

6.4.1 Dataset

Data from 1001 patients suffering from mild to very severe COPD were collected across ten countries (United Kingdom, Ireland, The Netherlands, Germany, Switzerland, Italy, Spain, The United States of America, Brazil, and Australia) as part of previous studies (references can be found in the appendix) without overlaps with the current post hoc analysis. Subjects were included if they met the following inclusion criteria: COPD with a postbronchodilator forced expiratory volume in the first 1 s (FEV$_1$) / forced vital capacity (FVC) ratio < 0.70 and stable condition (i.e., no symptoms of increased shortness of breath and sputum production compared to usual). The dataset comprises only baseline data, which means that the COPD patients were not undergoing any specific intervention by the time of the assessment. Centres from The Netherlands and UK also provided data on 66 healthy control subjects that were matched for age, gender, and BMI with a subgroup of 66 COPD patients. On the basis of a 1:1 multivariate matching, the closest possible case:control matches were determined. Subjects matched exactly for age and gender, the median error between BMI values of matching subjects was 0.58 [0.29–1.2] Kg/m$^2$. Subject group characteristics are presented in Table XI. PAs of COPD and healthy subjects were assessed during daily life by mean of the SenseWear Armband and SenseWear Mini Armband activity monitors [140]. These devices combine an accelerometer with different physiological sensors: a heat flux sensor, a galvanic skin response (GSR) sensor, a skin temperature (ST) sensor, and a near-body ambient temperature sensor. Data are sampled in 1-min intervals and together with demographic characteristics (such as gender, age, height, and weight) were used to estimate EE and metabolic equivalent of task (MET) using proprietary algorithms developed by the manufacturer. The use of multisensory data in combination with pattern recognition algorithms ensures that the MET estimation is insensitive to noise and random motion artefacts [104]. For each minute, the associated steps count (SC) and information about the sleeping status of a subject (0 = awake, 1 = sleeping) are also provided by the sensor. The SenseWear Armband has been shown to be valid both in field [77] and in laboratory studies [79]. COPD patients and healthy subjects wore the sensor both during daytime and nighttime so that continuous nonscripted activities were recorded in a natural environment. A minimum of four days (two weekdays + Saturday + Sunday) was considered acceptable to include a subject in the analysis [44], with the device being used for at least 22 h/day. From the minutes coded by the activity monitor as “sleeping,” the longest period of night sleep was extracted, and the awakening point defined as the time instant after such period. Brief awake periods (<10 min) of very light intensity (MET < 2.0) within time intervals coded as “sleeping” longer than 2 h were considered part of the sleeping time. Recorded days were synchronized according to this point in order to minimize the intrinsic variability of the data. Data prior to the awakening point were discarded from the analysis. Subjects with at least 12 h of data after the awakening point were included for a total of 977 COPD patients and 66 healthy controls. The median number of days analysed per patient was 6 (four weekdays, two weekend days), resulting in a total of 5846 valid PA days assessed, of which 3916 (67%) were weekdays.
and 1930 (33%) weekend days. In median, 982 min were analysed per patient each day (992 weekdays, 961 weekend days). Ethics Board approval was obtained from the local ethics committees, and written informed consent was provided by participants.

<table>
<thead>
<tr>
<th>Subject group characteristics. Data are summarized as absolute frequency (n), relative frequency (%), or median and quartiles [Q1–Q3].</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All COPD</strong></td>
</tr>
<tr>
<td>n = 977</td>
</tr>
<tr>
<td>Male/Female (n)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>BMI (Kg/m2)</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
</tr>
<tr>
<td>Assessed days (n)</td>
</tr>
<tr>
<td>Weekend days (%)</td>
</tr>
<tr>
<td>Weekdays (%)</td>
</tr>
</tbody>
</table>

### 6.4.2 Vocabulary

One of the most important choices one has to make when applying LDA to activity data is the nature and number of terms forming the vocabulary. In order to limit the heuristics, we used a data-driven methodology to automatically create the vocabulary without specifying its size beforehand. Sensor data from the 66 healthy subjects and the matched COPD patients subsample were used to automatically create the vocabulary of words without specifying its size beforehand. Each 1-min data point consists of a 7-D measurement vector comprising: MET, ST, GSR, Longitudinal Acceleration (Acc_L), Transversal Acceleration (Acc_T), SC, and Sleeping Status (SL). Acc_L and Acc_T were combined to compute vector magnitude (VM). METs data were first divided into activity intensity categories (IC) using the thresholds proposed by the American College of Sports Medicine [81]: very light intensity (IC_{VL}), < 2.0 METs; light intensity (IC_{L}), 2.0 to 2.9 METs; and moderate-to-vigorous intensity (IC_{MV}), ≥ 3.0 METs. Minutes marked by the sensor as sleeping and with METs < 2.0 formed a separated category named sleeping (IC_S). For simplicity, we will refer to the IC only with subscripts S, VL, L, MV. Figure 38 shows an example of a one day METs data stream with the respective IC superimposed. Consecutive minutes exhibiting the same IC are then grouped together in IB of variable duration (d). In each IB, we calculated the mean (μ) of ST, GSR, VM, and SC. The original sensor data stream is then represented by a series of IBs, where each bout is fully characterized by a six-elements feature vector $\bar{V}$

$$\bar{V} = [IC, d, \mu ST, \mu GSR, \mu VM, \mu SC].$$

Subsequently, for each intensity category (S, VL, L, and VL), the most relevant subset of features was selected such that the multicluster structure of the data can be best preserved. Features were selected using the Multi-Cluster Feature Selection (MCFS) method that deploys spectral regression with $l_1$-norm regularization in order to select features jointly instead of
evaluating each feature independently [141]. The feature vector $\tilde{V}$ can then be simplified according to

\[
V = [IC, f_1, f_2, f_3].
\]

Figure 38 Continuous data stream representing METs value (grey line) is first quantized in IC (blue is sleeping, ciano is very light, green is light, and red is moderate to vigorous intensity). IC of the same intensity form bouts. Features are computed within the bouts, and the most relevant for each intensity, according to the feature selection procedure, will be combined to create PA descriptors.

The features not selected by the feature selection algorithm can be interpreted as wildcard characters representing multiple terms in the vector space ([IC, $f_1$, $f_2$, $f_3$] and [IC, $f_1$, $f_2$, $f_3$, $f_4$, $f_5$] are two such terms of [IC, $f_1$, $f_2$, $f_3$]). As intuitively explained later in this section, wildcarding and the removal of frequent words help in generating sparse topics [139]. The selected features $f_{j_1, j_2, j_3}$ obviously might be different for each intensity. To generate the vocabulary of words, each of the selected features was first standardized, and then, mapped into a set of discrete levels (which could be interpreted as the letters of our words) using a k-means clustering algorithm. The algorithm automatically selects for each feature the number of levels $K_f$ in a way that the resulting clustering levels $L_{p \in \{1, \ldots, K_f\}}$ are the most stable under small perturbations of the input dataset [58]. Levels are sorted according to their mean value $L_p$ in ascending order such that the first level ($L_1$) represents clusters with the smallest feature values, and the last level ($L_{K_f}$) represents clusters with the highest feature values. Features selected and levels are shown in Table XII. Mean value and variance of the levels were stored and used to create the documents as described in section 6.4.4. The vocabulary of terms was built by allowing all the possible
combinations between levels sharing the same IC. For the sleeping category, for example, the feature \( f_1 = d \), \( f_2 = \mu_{\text{GSR}} \), and \( f_3 = \mu_{\text{VM}} \) were selected and divided in \( K_1 = K_2 = 2 \) and \( K_3 = 3 \) levels, respectively. The \( N^S(N_1 \cdot K_2 \cdot K_3) \) terms of the vocabulary describing the sleeping intensity category \( t_1^S \in (1: N^S) \) can be represented by a simplified feature vector according to

\[
\begin{align*}
t^S_1; & \left[ S, \quad L_1^d, \quad L_1^{\text{GSR}}, L_1^{\text{VM}} \right] \\
t^S_2; & \left[ S, \quad L_1^d, \quad L_1^{\text{GSR}}, L_1^{\text{VM}} \right] \\
\vdots & \\
t^S_{12}; & \left[ S, \quad L_2^d, \quad L_2^{\text{GSR}}, L_2^{\text{VM}} \right]
\end{align*}
\]

Table XII: Features selected for each intensity and associated levels.

<table>
<thead>
<tr>
<th>Sleeping</th>
<th>Very light</th>
</tr>
</thead>
<tbody>
<tr>
<td>d</td>
<td>d</td>
</tr>
<tr>
<td>( L_1 ) ( L_2 )</td>
<td>( L_1 ) ( L_2 ) ( L_3 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Light</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>d</td>
<td>d</td>
</tr>
<tr>
<td>( L_1 ) ( L_2 ) ( L_3 )</td>
<td>( L_1 ) ( L_2 ) ( L_3 )</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate to vigorous</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>d</td>
<td>d</td>
</tr>
<tr>
<td>( L_1 ) ( L_2 ) ( L_3 )</td>
<td>( L_1 ) ( L_2 ) ( L_3 )</td>
</tr>
</tbody>
</table>

The sum of terms across different activity levels is the total number of words. In particular, a total of 48 terms were created (12 for S, 8 for VL, 16 for L, and 12 for MV intensity). Note that we did not need to specify the number of unique artificial words (vocabulary size) beforehand. As a last step, we weighted the informativeness of the words in the vocabulary based on their inverse document frequency (IDF) score. Those terms that have a high IDF are considered more informative, because they rarely occur in the collection. In particular, we removed the words occurring in at least 90% of the documents since, occurring so frequently, they are more likely to obscure than facilitate a meaningful decomposition of the collection of documents. The term frequency (TF), usually used in combination with IDF to form the TF-IDF score [142], was not considered because it penalizes words that appear rarely within a document such as words of moderate to vigorous intensity, these words are important in the identification of routines correlated with the disease. The removed terms are \([\text{VL}, L_1^d, L_1^{\text{ST}}, L_2^{\text{MV}}], [\text{VL}, L_1^d, L_2^{\text{ST}}, L_1^{\text{MV}}], \) and \([\text{VL}, L_1^d, L_2^{\text{ST}}, L_2^{\text{MV}}])\). The IDF score of the words, and, subsequently, the set of removed words, are related to the wildcarding procedure previously described. If more letters are used, the words created will be more specific with the consequence of a higher IDF score average for the words in the vocabulary. On the other hand, a higher threshold on the IDF score (i.e., IDF equal to the one of the words present in 70% of documents) could cause the removal of all the terms useful to identify specific patients' subtypes. Although a rigorous methodology would be necessary to select the optimal combination of feature selected and words removed in order to generate sparse topics, we empirically found out that setting a strict threshold on the IDF (90% of documents) and performing feature selection at the level of the letters works well for our purpose.
6.4.3 Routine discovery

For topic discovery, we used the LDA implementation of [139], and we considered each day of assessment as a separate document. Each IB was mapped with an instance of the vocabulary by associating the selected features in V with their closest levels and then concatenating the three closest levels found. The distances for each bout between the feature point \( f_i \) and all the levels \( L_p \) are

\[
d_p(f_j) = \frac{|f_i - L_p|}{\sigma_p}, \quad \forall p = \{1, ..., K_f\}.
\]

Once that a term of the vocabulary was assigned to each IB, documents were created by constructing for each day a histogram of terms. We chose the number of routines (R) equal to 15, and set the hyperparameter \( \alpha \) equal to 0.01 as in [136]. Empirically we found that a number of routines greater than 15 led to duplicated routines. Hyperparameters are optimized with a variational expectation maximization algorithm initialized by randomly choosing a small number of “seed” documents [142]. We selected 18 seeds (nine from healthy subjects and nine from COPD patients). Routines did not change in their overall composition with different seed sets.

6.4.4 Routine inference

Once the routines were calculated, first, we inferred day segments (i.e., in this case, a day segment is considered as the equivalent of a text document) in order to know which routines are active during different parts of the day. For this, we used sliding windows of \( T = 30 \) min of duration as suggested in [137]. From the observations (the bouts) in a sliding window, a histogram of terms has to be created as input for the topic inference. This means that the bouts in the window have to be mapped to terms from the dictionary. We did this by soft assignment as follows. For each bout described by feature vector \( V \), the distances \( d_p(f_i) \) of each particular feature \( f_i \) to the cluster levels \( L_p f_j \) were determined. These distances were converted to feature weights according to

\[
w(f_i, L_p) = \frac{e^{-d_p}}{\sum_{k=1}^{K_f} e^{-d_k}}.
\]

Thus, smaller distances imply higher feature weights, and the sum of the feature weights over the different clusters equals 1. We then create the term weights by summing all the feature weights. The final normalized term weight \( W_t \) is the term weight divided by the sum of all term weights. The normalized term weights are, thus, values between 0 and 1. Normalized term weights of terms associated with other intensity categories were set to 0. Finally, we use the normalized term weights to create the histogram. For each term in the dictionary, we sum all the weights stemming from the all the bouts in the window. Second, we applied routine inference on the first 6 h of the assessed days in order to estimate the minutes spent in each routine during the most active part of the day. The same mapping procedure described for sliding windows of 30 min was applied in the case of a unique fixed window of 6 h.
6.5 Results

Since PA measures during the weekdays and the weekend days are known to be different [44] results were computed separately. Kruskal–Wallis ANOVA test and Dunn’s multiple comparisons test were used to determine significance of the results. A value of $P < 0.05$ was considered significant. Pearson’s coefficient was used to investigate correlations in the entire dataset of 977 COPD patients. The findings are organized as follows. First, an interpretation of the discovered routines using the dataset of matched COPD and healthy subjects is given to highlight differences in intensity composition of routines and associated physiological responses. Second, results from the inference on window segments of 30 min are presented to qualitatively show two examples of daily routines patterns from a healthy subject and a COPD patient. Discovered routines are successively inferred on the first 6 h of all the assessed days of 66 healthy subjects and 977 COPD patients to quantitatively assess differences between selected groups of subjects and trends across different stages of COPD. Finally, the dataset of matched pairs is used to evaluate the routines in discriminative tasks, such as dividing healthy from patients and recognizing to which population each of the assessed days belongs.

6.5.1 Routine interpretation

Figure 39 illustrates the distribution of the discovered routines $\beta_1,..,15$ over the terms of the vocabulary. Three routines related to low intensity levels (R2, R8, R9), nine routines related to moderate-high intensity levels (R1, R3, R4, R5, R6, R10, R12, R14, R15) and one routine composed by a combination of VL, L, and MV descriptors (R7) were discovered in data from 66 COPD patients and 66 healthy subjects. Two separate routines characterizing, respectively, the sleeping behaviour (R11) and high intensity levels (R13) were also found. Each of these routines is characterized by the probability over the terms, where each term is defined by a certain combination of feature levels. For each routine, the three most important terms (i.e., terms of highest probabilities in this routine) can be found in Table XIII. The words composing a particular routine are listed together with their occurrence probability (e.g., the first word of R1: [MV 1 2 2] refers to a simplified feature vector V given by [MV, Ld1 , LST 2 , LV M 2 ] and has occurrence probability equal to 40%). Routines, that might be considered similar by only looking at their intensity composition, are different at the level of the descriptors. As an example, Figure 39 shows that R3 and R5 are formed for the 20% by MV descriptors and for the 50% by L descriptors. Analysing the letters that compose the descriptors shows that both the MV descriptor and the L descriptors of R5 have higher values in the feature level corresponding to the ST (second letter, see Table XIII). This illustrates that some routines differ depending on physiological responses. In absence of appropriate labels for these topics, such insights into routines are relevant for interpreting the inferences of topics per subject.
6.5.2 Daily pattern of routines

Figure 40 illustrates the activation probabilities of the extracted routines when day segments of 30 min are sequentially inferred. The inference on sequential day segments provides a qualitative representation of the temporal behaviour of the routines. The top and the bottom plots show the routine patterns for a COPD and a healthy subject, respectively. It can be seen that three PA routines (R2, R11, and R9) pervade the day of a COPD patient (see top plot of Figure 40). In particular, this patient spent most of his time performing activities that involve a L intensity descriptor of short duration, with high $\mu_{ST}$ and low $\mu_{GSR}$ and a VL intensity descriptor of long duration, with high $\mu_{ST}$ and high $\mu_{VM}$. Three hours after the patient awoke, R9 becomes dominant for about 3 h. This routine includes a L descriptor of short duration, high $\mu_{ST}$, and low $\mu_{GSR}$. The graph also shows that the patient slept in the afternoon for about 1 h (probably he rested after having lunch), and after that he continued with the same behaviour of the morning. After 14 h from the awakening of the subject, R2 starts decreasing and R11, that characterizes the sleeping behaviour, starts to become the most active routine. On the other hand, the day of the healthy subject shows a larger variety of active routine patterns. The bottom plot of Figure 40 shows that the routines R15, R12, R14, R1, R15, R13, and R8 are sequentially active. Around 9 h after his awakening, just before the evening, this subject assumes a behaviour similar to his COPD match, i.e., routine R2 becomes the dominant routine until the sleeping time. From the examples, it can be deduced that this particular day of the COPD patient is more static compared to the one of the healthy subject if the number of transitions between the most active routines is considered. Although we did not use the trajectories of the routines as in Figure 40 in our further analysis they can be used for classification tasks by modelling the trends of routines activation with multitask Gaussian processes [143] or using sequential patterns [144]. In order to extract
cumulative (over several days of assessment) characteristics of a subject we, instead, inferred the routines on the first 6 h of the days of each subject as if it was one day segment. On the right side of Figure 40 the star plots describe the averages of the routines’ activation probabilities across the assessed days of the same two subjects when the inference is performed on the first 6 h after their awakenings. In this case, routines’ activation probabilities can also be considered as an estimate of the time spent in each routine during the most active part of the day. The subjects are represented as a star whose each spoke length is proportional to the average time spent in the associated routine over the assessed weekdays. For clarity, only the most active routines over the assessed days are shown. We see that the shapes of the stars are remarkably different. Routines R11 and R2 were the most active for the COPD patient while, in contrast, the healthy subject spent most of his time performing more active routines such as R1, R12, and R14. Differences in the shapes of the star plot (i.e., time spent in different routines) are consistent across healthy and COPD patients and will be discussed in the next section.

Table XIII Routine matrix. The three dominant words for each of the 15 discovered routines.

<table>
<thead>
<tr>
<th>Routine</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>R1</td>
<td>MV 1 1 2</td>
<td>0.40</td>
<td>L 1 3 1</td>
<td>0.39</td>
<td>L 1 1 2</td>
</tr>
<tr>
<td></td>
<td>L 1 2 1</td>
<td>0.39</td>
<td>VL 2 2 2</td>
<td>0.31</td>
<td>MV 1 1 2</td>
</tr>
<tr>
<td></td>
<td>L 1 3 1</td>
<td>0.07</td>
<td>L 1 2 1</td>
<td>0.10</td>
<td>L 1 2 2</td>
</tr>
<tr>
<td>R6</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>L 1 3 2</td>
<td>0.62</td>
<td>VL 1 1 1</td>
<td>0.41</td>
<td>L 1 3 1</td>
</tr>
<tr>
<td></td>
<td>MV 1 3 2</td>
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<td>MV 1 2 1</td>
<td>0.21</td>
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</tr>
<tr>
<td></td>
<td>L 2 3 2</td>
<td>0.06</td>
<td>L 1 2 1</td>
<td>0.15</td>
<td>L 2 3 1</td>
</tr>
<tr>
<td>R11</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td></td>
<td>S 1 1 3</td>
<td>0.27</td>
<td>L 1 1 1</td>
<td>0.55</td>
<td>MV 1 3 2</td>
</tr>
<tr>
<td></td>
<td>S 1 1 2</td>
<td>0.21</td>
<td>MV 1 1 2</td>
<td>0.15</td>
<td>MV 1 3 1</td>
</tr>
<tr>
<td></td>
<td>S 1 1 1</td>
<td>0.17</td>
<td>MV 1 1 1</td>
<td>0.09</td>
<td>MV 2 3 2</td>
</tr>
</tbody>
</table>

Figure 40 Left: Routine activation probabilities determined from a particular day of a COPD patient (top) and a healthy subject (bottom). Only topics with a maximum activation larger than 0.1 are shown. Right: Star plots illustrating the average time spent on the three most active routines of the same COPD patient and healthy subject during the first 6 h of their assessed days. R2, R11, R12 and R1, R12, R14 are, respectively, the three most active routines for the COPD patient (top) and the healthy subject (bottom).
6.5.3 Trends in routines activation

Figure 41 shows the average values of the estimated time spent in each routine for all the 977 COPD patients, the matched 66 COPD patients, the matched 66 healthy subjects, and for the 977 COPD patients stratified according to their disease severity, where GOLD1 and GOLD4 indicate, respectively, the least and most severe stage of COPD. Each point in the figure identifies the mean over all the subjects of each group, where each subject is represented by the mean of the time spent in the different routines over the assessed weekdays (left) and weekend days (right). Comparison between the time spent in each of the 15 routines in the 977 COPD patients and the subgroup used to extract the routines (see inside the green dashed rectangles in Figure 41) shows that there are no statistical differences ($p > 0.2$) in the time spent in each routine between the two groups in both assessed weekdays and weekend days. This indicates that the model is able to generalize across many COPD patients. When matched COPD and healthy subjects are compared (see inside the red rectangles in Figure 41), we found statistical differences between the two groups ($p < 0.05$) during weekdays in R2, R3, R5, R10, R11, R12, R14, R15. During weekend days, statistical differences were found in R3, R4, R7, R14, R15. A reduced number of statistical differences in the weekend days indicates that the two groups assume a more similar behaviour during these days. This might be due to the fact that healthy subjects could still be active workers or that they perform weekly activities such as grocery shopping. On the contrary, they might use the weekend days to sleep more and rest. These assumptions could be confirmed by an increased value of the time spent in R2 and R11 during the weekend days of healthy subjects. High values of these two routines characterize only the COPD patients group during the weekdays. Comparing healthy subjects and the four different COPD groups (see inside the dashed blue rectangles in Figure 41), we observe five main trends over the different stages of the disease both in weekdays and weekend days. R2 and R11 are increasing with the increase of COPD severity. R2 represents a medium-inactive PA routine composed for the 39% by $[L, L^4, L^ST, L^CSR]$ and by the 31% by $[VL, L^2, L^ST, L^CSR]$. The first PA descriptor represents light intensity movements characterized by short duration that cause a high increase of the temperature. The second term represents very light intensity movements of long duration that cause a moderate increase of physiological responses (high body temperature and high GSR). The positive trend is interrupted in the most severe group of patients that compensate a smaller value for R2 with a higher value of R11 and R15. A high value of the time spent in R11 could be associated with the most severe patients since their conditions might force them to spend more time in bed. R15 is characterized mainly by light intensity PA terms characterized by higher physiological responses if compared with R2. This might indicate a bigger effort in performing activities. The increased value of R2 for healthy subjects during weekend days has been discussed previously. Another rising trend is shown by R11 representing the time spent, while performing very inactive behaviour (mainly sleeping). On the other hand, we note that R3, R12, and R14 decrease with an increase in COPD severity. These three routines indicate movements performed with medium-high activity intensities characterized by small physiological responses. Of particular, interest are R3, R12 since they are weakly, but significantly correlated with FEV$_1$, %predicted ($p = 0.3$, $p = 2 \times 10^{-11}$, $p = 0.2$, $p = 5.8 \times 10^{-12}$, respectively), and R14 weakly correlated with FEV$_1$ ($p = 0.2$, $p = 3 \times 10^{-5}$). No correlation was found with age and BMI indicating that these discovered routines are decoupled from these variables. Statistical differences ($p < 0.0001$) have been found in the percentage of activation of R3 and R14 between healthy subject
and all the COPD severity classes (both weekdays and weekend days). For R3 statistical differences (p < 0.0001) were also found between the first two stage of the disease (GOLD1, GOLD2) and the last two stages (GOLD3 and GOLD4) during the weekdays. For the weekend, only between GOLD1 and the last two stage of disease (GOLD3 GOLD4) and between GOLD2 and GOLD4. For R12, statistical differences (p < 0.0001) have been found between healthy subject and GOLD2, GOLD3, GOLD4 (both weekdays and weekend days). Between the GOLD1 and GOLD3–4 (also during the weekend days), between GOLD2 and GOLD4 (also weekend).

Figure 41 Activation topic averages during weekdays (left) and weekend days (right). The green dashed rectangles indicate the comparison between all the COPD patients (n = 977), and the COPD subset used to generate the routines (n = 66). The red rectangles indicate the comparison between the matched COPD patients (n = 66) and the matched healthy subjects (n = 66). The dashed blue rectangles indicate the comparison between the healthy subjects (n = 66), GOLD1 (n = 89), GOLD2 (n = 385), GOLD3 (n = 330), and GOLD4 (n = 173). Inference was performed in the first 6 h after the awakenings from the night sleep.

6.5.4 Discriminatory power of routines

In order to further validate the findings shown in Figure 41 and assess the discriminatory power of PA routines, we first clustered the 66 patient:control matches and, subsequently, their assessed weekdays. For the first clustering experiment, each of the 66 healthy subjects and 66 matching COPD patients was represented by the average time spent in each routine over the assessed weekdays as symbolically shown in the star plots of Figure 40. Distance-based features were extracted using only R3, R12, and R14 because of their correlation with the FEV1, %predicted and FEV1 : variables used to assess airway obstruction in the current clinical setting. In particular, we calculated the pairwise Kullback–Leibler pairwise distances between all the subjects represented by the averaged time spent in R3, R12, and R14. Using Kruskal’s normalized stress1 criterion, we created a set of locations in three dimensions whose interpoint distances approximate the routine dissimilarities between subjects. We finally clustered the subjects such represented using a k-mean clustering algorithm with k = 2 achieving 86% accuracy in dividing the two groups. For the second experiment, we clustered the 536 assessed weekdays (273 for healthy subjects, 263 for COPD patients), which were represented by the associated daily time spent by the subjects in R3, R12, R14. After extracting the same typology of features, we clustered the days in k = 2 groups achieving 82% of accuracy in discriminating between days that belong to healthy subjects and days belonging to COPD patients. This shows that activity
biomarkers derived from routines can potentially be used in diagnostic decision support systems, but also in monitoring systems providing feedback on a daily basis.

6.6 Conclusion

Unsupervised discovery of latent structures in data from activity monitors is becoming more relevant due to the increasing amount of available multimodal data. Using relatively simple assumptions and settings, we have shown that interpretable and consistent results can be obtained from a large set of unannotated real-life data concerning a large population of COPD and healthy subjects. We have shown that PA routines can be used effectively to integrate and represent the underlying structure of PA measures and physiological responses that characterize the activities of the subjects under study. In particular, it is shown that PA routines in COPD patients and healthy subjects are considerably different regarding their composition and that they show certain consistent trends depending on COPD clinical characteristics. The discovered PA routines were found suitable to label, in an unsupervised way, subjects and assessed days. Moreover, inferring the routine structure on day segments of relatively short duration, it was possible to model PA routine patterns across the day and to identify moments in time in which transitions of the most active routines occur. Some methodological considerations need to be taken into account. First, demographics information (such as working activities) and comorbidities were not available which could influence PA. Second, the routines identified would benefit from a sensitivity study using a new sample of COPD-healthy pairs matching with the same characteristics. Although a more detailed clinical interpretation of the discovered routines is extremely interesting and planned as follow-up of this study, the discovered PA routines apparently reflect the stage of the disease as measured by common clinical practice and could be valid constructs to quantify PA behaviour change in patient with limited exercise capacity such as with COPD. As such, it is an encouraging step into the direction of practical applications of these techniques in daily life to design, for instance, interventions and coaching systems (see Figure 42) with realistic goals for this population.
Figure 42 Envisioned coaching system. Subject’s routines are identified and evaluated by the system without any supervision. The system automatically detects those routines that are considered undesired (within the red rectangle at the bottom of the picture) and suggests the user to minimize the behaviour assumed during their activation time. It is worth noting how routines of the healthy subject and the COPD patient differ in shape. In particular, inactive routines are dominant during the day of the COPD patient and more active routines pervade the day of the healthy subject. The system would be able to provide both real time feedback and summary feedback at the end of each day or assessment session.
7 Classification of patients with COPD using topic models-based features and nighttime data

Night-time symptoms are important indicators of impairment for many diseases and particularly for respiratory diseases as Chronic Obstructive Pulmonary Disease (COPD). This work introduces a technique for predicting the pathological condition in patients with COPD using features extracted from multimodal sensor data during night-time only. Sensor data were discretized and presented as the units composing symbols that describe subjects’ night-time. The co-occurrence of these symbols in different ways and proportions during the night creates thematically coherent groups describing particular sleep modalities used for classification. We demonstrated the capabilities of our approach by applying it to a real-world COPD patient cohort showing its validity in assessing sleep in relation to the pathological condition. The results showed that it is possible to differentiate between healthy subjects and patients with COPD with 94% accuracy and to classifying the level of the disease and dyspnoea severity with an accuracy of 94% and 93%, respectively.
7.1 Introduction

Chronic obstructive pulmonary disease (COPD) is currently the third leading cause of death worldwide [10]. It is caused, among others, by smoking and air pollution and it is characterized by chronic inflammation of the lung airways, and degradation of lung tissue which result in airflow limitation [12]. COPD is a global health problem because of its high prevalence, increasing incidence, and associated socio-economic costs [9]. However, COPD is severely underdiagnosed and therefore undertreated [145]. Spirometry is compulsory for the diagnosis of COPD [9]. Spirometry is now cheap and widely available, but time availability and quality control are often said to limit its implementation, particularly in primary care where there is a great deal of controversy regarding the quality of the tests performed by non-expert professionals [146]. Although detecting the disease at an early stage can increase the survival rate [147], obtaining spirometry for each smoker with or without symptoms of dyspnoea, cough, or sputum production is not a feasible solution. With the advent of health-sensor technologies and advanced data analysis methods there is a gradual permeation of these technologies into actual health care and patients’ homes enabling new care services and their use as supportive systems [7].

In this work we show that the use of multimodal sensor modalities acquired during nighttime only provides a good predictor of the presence of the disease in patients with COPD. In particular, we 1) used data coming from a single activity monitor worn on the upper arm to define new sleep modalities using a data driven methodology, and 2) we showed that these sleep modalities are valid constructs to assess sleep of patients with COPD in relation to their pathological condition. The defined sleep modalities were able to differentiate between nights of patients with COPD vs. nights of healthy subjects and, more in detail, predict the level of the disease and dyspnoea severity. It is worth mentioning that, for the best of our knowledge, to date, this is the first study that introduces the use of night-time data only derived from a single activity monitor for diagnosis of COPD. The objective is to reduce the uncertainty of predictions by fusing multimodal information and the use of data mining techniques.

7.2 Related works

Pervasive healthcare may enable a paradigm shift from the established centralized healthcare model to a pervasive, user-centred and preventive health management [148]. Wearable and unobtrusive technologies make more health-related data available than ever before enabling caregivers to make decisions on a broader basis of information. In clinical settings, data analytics and decision support systems have been established in several data-rich environments [7], among which COPD management.

7.2.1 Automatic classification of patients with COPD

Different machine learning techniques, such as artificial neural networks [149], and multiple instance learning [150] have been used for automatic recognition of COPD based on high resolution computed tomography scanning, which enables the direct evaluation of the lungs and airways. In [151] the authors proposed a method to predict the condition of a patient with COPD.
at an early stage and in absence of a clinician. The predicted physiological parameters such as forced expiratory volume in the first second expressed as percentage of a maximum value (FEV₁%), six-minute walking test, Modified Medical Research Council (MMRC) dyspnoea scale, and body mass index (BMI) are weighed using particle swarm optimization and the state of the patient is fuzzified in accordance to the GOLD criteria. Although useful, all these methods require signals which are only available in hospitals or laboratories and can currently not be provided by automated wireless remote detection.

Newandee et al. [152] have studied COPD severity classification using principal component and cluster analysis on heart rate variability (HRV) parameters using heart rate, blood pressure, and respiration signals. Results demonstrated that these two groups could be differentiated with greater than 99.0% accuracy. Furthermore, differences on the same HRV parameters between all four severity levels of COPD subjects were also investigated. These groups were differentiated with over 88.0% accuracy. However, data were acquired under controlled laboratory conditions.

The CHRONIOUS system [153] offers an intelligent system for the analysis and the real-time evaluation of patient’s condition. A hybrid classifier has been implemented on a personal digital assistant, combining a support vector machine, a random forest, and a rule-based system to provide a categorization scheme for the early and in real-time characterization of a COPD episode. This is followed by a severity estimation algorithm which classifies the identified pathological situation in different levels. The achieved characterization accuracy has been found 94%. Sensor data were acquired by external sensors and several devices attached to a wearable jacket during daytime making the system rather cumbersome and difficult to be used in clinical practice.

In our previous work [154] it has been shown that probabilistic daytime activity biomarkers derived from an unobtrusive activity monitor data by using topic modelling techniques are able to cluster subjects with and without COPD with 86% of accuracy. Patients’ monitoring and classification using night-time data may offer several advantages since, spending one third of their life with sleeping, it belongs to one of the prime activities humans pursue in which disease trends can be better observed. Moreover, compared to daytime hours, sleeping hours may offer a better trade-off between patients’ comfort, sensor unobtrusiveness and signal quality [148].

### 7.2.2 Sleep in patients with COPD

Sleep disturbance, such as sleep fragmentation during the night, is common in patients with COPD [96], and is a major complaint after dyspnoea and fatigue [97]. Despite the high prevalence of disturbed sleep in COPD, night-time symptoms are often underestimated and are not a focus of current disease management [96].

Sleep in patients with COPD is usually assessed using a patient-completed diary that consists of asking patients to record their sleep duration, recalled sleep disruptions, and a sleep score that reflects the degree of perceived sleep disruption [155]. Self-reported measures of sleep duration and quality provide a useful insight into the patient’s perception of the nocturnal burden of their disease, but their precision and reliability are poor compared to objective measures of sleep [96].

Sleep laboratory measurement tests, such as polysomnography (PSG), offer a well-validated, reliable and reproducible method of collecting sleep data, but they are expensive, intrusive and require patients to attend a clinic for overnight recording.
The use of wearable sensors has been mainly limited to coarse-grained methods such as actigraphy, for which limb motions are logged providing some insight in patient’s sleep. Actigraphy correlates well with PSG in differentiating sleep from wake [103], but rather than a replacement for PSG, it should be regarded as another means for assessing sleep, particularly when sleep architecture and extensive physiological monitoring are not necessary.

Activity monitors are useful tools that are becoming popular to objectively assess the sleep–wake cycle. They provide minimally invasive measures of the continuity and hence quality of sleep and other physiological measurements such as energy expenditure, body temperature and galvanic skin response. In this work, metabolic and physiological data recorded during nighttime using an activity monitor are symbolized and presented as the “letters” composing the “words” that describe the night of a subject. The co-occurrence of these words in different ways and proportions during the night creates groups of words describing the modalities in which a subject sleeps. Using these data we extracted patients’ sleep modalities that were valid to assess sleep in relation to the presence of the pathological condition. While previous studies aimed at finding differences between healthy individuals and patients with COPD [98], this study seeks to evaluate severity classification of the disease. This is a challenge because differences in objective sleep measures between COPD classes are subtle [98, 99] making them difficult to detect. The proposed methodology, exclusively defined using data coming from one unobtrusive device, is able to differentiate between COPD and healthy-type of nights, and to discriminate between different GOLD grades and MMRC scores.

**7.3 Background**

Topic models are algorithms for discovering the hidden grouping variables that pervade a large and unstructured collection of documents. LDA is an example of a topic model [139] in which data are treated as observations arising from a generative probabilistic process. In the context of text modelling, given a set of topics defined as distributions over words, the generative process populates the documents with words such that the documents have a particular desired thematic structure. Beside its generative process, LDA can also be used to calculate the hidden variables that likely generated the collection of documents. One of the ways to achieve this is to use variational inference to approximate the posterior distribution over the hidden variables defined by LDA. In a nutshell, variational inference posits a parametrized family of distributions over the hidden structure, and then, finds the member of that family that is closest to the posterior according to the Kullback–Leibler divergence. The intuition behind using LDA [139] for sleep monitoring is that each night is a mixture of thematically coherent measures just as a text document is a mixture of thematically coherent words. The graphical model for LDA is shown in Figure 43. All the assessed nights \(d_{1:D}\) share the same set of sleep modalities \(\beta_{1:K}\) that are defined as Dirichlet distributions over the observed set of symbols \(W\) which are the terms of a fixed vocabulary. The observed symbols (input of the model) are composed by multimodal measures coming from the sensors of an activity monitor. Each assessed night exhibits sleep modalities in different proportion providing an explicit finger print \(\theta\). In particular, each night is a different distribution \(\theta_{1:D}\) over the sleep modalities activation probabilities that also follows a Dirichlet distribution. In such a model, the \(N\) symbols \(W_{d_{1:n}}\) that compose the \(D\) nights are the only random variables observed and depend on the per word sleep modality assignment \(Z_{d_{1:n}}\) and all the \(\theta\). Each sleep modality then is composed indirectly by low-level
sensor measures that belong, with a certain probability distribution, to different thematic areas. Our hypothesis is that nights related to different groups of subjects would have a different distribution over the sleep modalities that in turn would be composed by different distributions over symbolic words defined combining discretized sensor measurements. The proposed methodology will first extract all the $\delta_k$ in a data driven fashion using data from a subset of COPD patients and healthy subjects and then, for each assessed night, it will calculate a probabilistic feature vector $\theta$ composed by the histogram of activation probabilities of all the sleep modalities $\beta_{1:k}$. These probabilistic features will be used to classify a large cohort of patients.

![Graphical model for LDA](image)

Figure 43 Graphical model for LDA. Each node is a random variable, edges denote possible dependences. The only observed variables (shaded) are the symbols ($W$). The distribution of the symbols in a sleep modality ($\beta$) and the distribution of the sleep modalities during a night ($\theta$) depend only on the sleep modality hyperparameters $\eta$ and $\alpha$ that control the mean shape and sparsity of the distributions. $Z$ represents the symbol sleep modality assignment.

### 7.4 Methods

In the application of LDA, a word, defined to be an instance of a vocabulary, is considered as the basic unit of discrete data. In this work, multimodal monitoring signals such us metabolic equivalent of task (MET) [76], temperature, galvanic skin response and number of steps were first converted into a discrete alphabet of letters and then combined into symbolic words. Our approach in selecting the letters and then the words composing the vocabulary benefits from a methodology that preserves the interpretability of the vocabulary and that allows the generation of symbols that actually do not occur in the current documents. The multidimensional data space is first divided in subspaces according to the METs values in order to conveniently define a repertoire of physical activities in which a person may participate [76]. In each subspace, we divided temperature and galvanic skin response data into partitions (letters) that are then combined to form string of symbolic words. We extract the vocabulary in a subset of COPD and healthy patients and show that the constructed vocabulary is able to model the data of a much larger cohort of patients. The dataset and the methodology developed are described in detail in the following sections.

#### 7.4.1 Participants

Data from 1384 patients from ten countries (United Kingdom, Ireland, The Netherlands, Germany, Switzerland, Italy, Spain, The United States of America, Brazil, and Australia) diagnosed with mild to very severe COPD were pooled from previous studies (references can be found in the appendix) and considered for analysis. Participants were included if they had COPD with a post-bronchodilator ratio of forced expiratory volume in the first second ($FEV_1$) to forced vital...
Classification of patients with COPD using topic models-based features and nighttime data

capacity (FVC) < 0.70 and they were clinically stable (i.e., stable shortness of breath and sputum production). We report baseline data recorded before any specific interventions were undertaken. Centres from The Netherlands and UK also provided data on 66 healthy control subjects that were matched for age, gender, and BMI with a subgroup of 66 COPD patients. On the basis of a 1:1 multivariate matching, the closest possible case:control matches were determined. Subjects matched exactly for age and gender, the median error between BMI values of matching subjects was 0.58 [0.29–1.2] kg/m². Subject group characteristics are presented in Table XIV. The data collection was approved by ethics committees at each of the participating centres, according to local regulations. Written informed consent was provided by all participants.

Table XIV Subject group characteristics.

<table>
<thead>
<tr>
<th></th>
<th>All COPD*</th>
<th>Matching healthy</th>
<th>Matching COPD**</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 1059</td>
<td>n = 66</td>
<td>n = 66</td>
<td></td>
</tr>
<tr>
<td>Male/Female (n)</td>
<td>689/370</td>
<td>30/36</td>
<td>30/36</td>
</tr>
<tr>
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<td>65 [61–70]</td>
<td>65 [61–70]</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
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<td>25.2 [23–27.3]</td>
<td>25 [22.5–27.8]</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>49 [34–64]</td>
<td>107 [97–117]</td>
<td>42 [29–63]</td>
</tr>
<tr>
<td>Assessed nights (n)</td>
<td>6446</td>
<td>404</td>
<td>411</td>
</tr>
<tr>
<td>Weekdays (%)</td>
<td>67.3</td>
<td>69</td>
<td>65</td>
</tr>
</tbody>
</table>

Data are summarized as absolute frequency (n), relative frequency (%), or median and quartiles [Q1–Q3]. *MMRC data for 914 subjects. **MMRC data for 59 subjects.

7.4.2 Data recordings

Study participants wore the SenseWear Armband or SenseWear Mini Armband activity monitors [140] (BodyMedia Inc., Pittsburgh, PA, USA) on the upper arm both during daytime and night-time so that continuous, real-life data were recorded in a natural environment. These devices included an accelerometer with different physiological sensors: a heat flux sensor, a galvanic skin response (GSR) sensor, a skin temperature (ST) sensor, and a near-body ambient temperature sensor [68, 44]. Data were sampled at one minute intervals and, together with demographic characteristics, were used to estimate METs using proprietary algorithms developed by the manufacturer. The use of multisensory data in combination with pattern
recognition algorithms ensured that the MET estimation was insensitive to noise and random motion artefacts [104]. For each minute, the device also recorded steps count, information about the sleeping status of a patient (0=awake, 1=sleeping), and posture (0=lying down, 1=not lying down). Night-time sleep was defined as sleep that occurs between 21:00 and 06:00 [105]. For this analysis we considered only MET, ST, GSR, SC, and Sleeping Status (SL) data within this time interval. The following night-time sleep measures were also derived from the sleep status information provided by the sensor: night sleeping time, number of nocturnal sleeping bouts and duration of nocturnal sleeping bouts. Sleeping bouts were defined as consecutive minutes marked by the sensor as sleeping. Participants who wore the device for at least four nights (two weekdays + Saturday + Sunday) were included [44]. In total 1059 patients with COPD and 66 healthy controls were included in the analysis. The median number of nights analysed per patient was six (four during weekdays, two during weekends), resulting in a total of 6446 valid nights assessed, of which 4335 (67.3%) were during weekdays and 2111 (32.7%) during weekends.

7.4.3 Topic models

Sensor data from 66 healthy subjects and 66 matched patients with COPD were used to create the vocabulary of words. METs data were divided into intensity categories (IC) using the thresholds proposed by the American College of Sports Medicine: very light intensity (VL), < 2.0 METs; light intensity (L), 2.0 to 2.9 METs; and moderate-to-vigorous intensity (MV), ≥ 3.0 METs [12]. Minutes marked by the sensor as sleeping and with METs < 2.0 formed a separated category named sleeping (S). Step counts were converted in a binary form depending on whether the participant performed steps in each assessed minute (0=no steps performed, 1=steps performed). Temperature and galvanic skin response data were first cleaned from missing values and outliers (i.e. temperature values outside the range [24-40 °C] and GSR values outside the range [0-8 µSiemens]) and then, for each subject, were centred across the mean over multiple assessed nights. An example of data stream for a single patient night is shown in Figure 44.

In order to have sparse sleep modalities and symbols that best represent the original signal, it is desirable to have a discretization technique that produces symbols with equal probabilities [131] and that minimizes the distortion of the partitioned signal [156]. Therefore,
the empirical cumulative distribution functions (ECDFs) of temperature and galvanic skin response data were estimated separately for each intensity category, and the three breakpoints \( (BE_{i,j=1:3}) \) that divided the data into four equiprobable partitions \( (Pe_{i,j=1:4}) \) were derived. Separately the breakpoints \( (Bd_{i,j=1:3}) \) which divided the same set of data in four partitions \( (Pd_{i,j=1:4}) \) minimizing the mean square distortion of the quantization [156] were also calculated. The final partition breakpoints \( (Bf_{i,j=1:3}) \) were calculated averaging the corresponding pairs of breakpoints \( Bf_i = \frac{Be_i + Bd_i}{2} \) and used to divide the data into four contiguous, non-overlapping ranges of values. Final partition ranges \( (Pf_{i,j=1:4}) \) are sorted in ascending order such that the first range \( (Pf_1) \) represents partition of data with the smallest values, and the last range \( (Pf_4) \) represents data with the highest values. The vocabulary of terms was built by allowing all the possible combinations between partitions ranges of temperature, galvanic skin response data and binary values of steps that share the same IC.

For the sleeping category, for example, the 32 terms of the vocabulary describing the sleeping intensity category can be represented by:

\[
\begin{align*}
\text{t}_{1}^S: [S, \ Pr_{1}^{ST}, \ Pr_{1}^{GSR}, \ Steps_{No}] \\
\text{t}_{2}^S: [S, \ Pr_{1}^{ST}, \ Pr_{2}^{GSR}, \ Steps_{Yes}] \\
\vdots \\
\text{t}_{32}^S: [S, \ Pr_{4}^{ST}, \ Pr_{4}^{GSR}, \ Steps_{No}]
\end{align*}
\]

The sum of terms across different activity levels is the total number of words. In particular, a total of 128 terms were initially created. As a last step, in order to remove nonsense words and increase the frequency of VL and MV words to obtain sparse topics, we pruned the vocabulary adding wildcard characters [139]. We used a wildcard character to replace the symbol related to the steps performed during sleeping IC (i.e. 16 words removed). Considering the neutral wildcard symbols the original 32 terms representing the sleeping category can be represented by 16 terms as:

\[
\begin{align*}
\text{t}_{1}^S: [S, \ Pr_{1}^{ST}, \ Pr_{1}^{GSR}] \\
\text{t}_{2}^S: [S, \ Pr_{1}^{ST}, \ Pr_{2}^{GSR}] \\
\vdots \\
\text{t}_{16}^S: [S, \ Pr_{4}^{ST}, \ Pr_{4}^{GSR}]
\end{align*}
\]

Two wildcard characters replaced the temperature and galvanic skin response symbols during VL and MV intensities (i.e. 60 words removed) to know if the subject was in these two IC because of moving. In view of sparsity we also weighted the informativeness of the remaining words in the vocabulary based on their inverse document frequency (IDF) score. Those terms that have a high IDF are considered more informative, because they rarely occur in the collection. In particular, we removed the words occurring in at least 90% of the documents since, occurring so frequently, they are more likely to obscure than facilitate a meaningful decomposition of the collection of documents. The term frequency (TF), usually used in combination with IDF to form the TF-IDF score [142], was not considered since it penalizes words that rarely appear within a document such as words of light or moderate to vigorous intensity, these words are important in the identification of sleep modalities.
correlated with the disease. The removed term is \([L, \text{Steps}_{Yes}]\). The IDF score of the words, and, subsequently, the set of removed words, are related to the wildcarding procedure previously described. If more letters are used, the words created will be more specific with the consequence of a higher IDF score average for the words in the vocabulary. On the other hand, a higher threshold on the IDF score (i.e., IDF equal to the one of the words present in 70% of documents) could cause the removal of all the terms useful to identify specific patients’ subtypes. We set a threshold on the IDF equal to the one of the words present in 90% of documents as [154]. The variables for each IC and the final associated symbols are shown in Table XV.

Table XV Variables selected for each intensity and associated symbols.

<table>
<thead>
<tr>
<th>Sleeping</th>
<th>Very light</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ST</strong></td>
<td><strong>GSR</strong></td>
</tr>
<tr>
<td>(P_f, P_f, P_f, P_f)</td>
<td>(P_f, P_f, P_f, P_f)</td>
</tr>
</tbody>
</table>

**Light**

<table>
<thead>
<tr>
<th><strong>ST</strong></th>
<th><strong>GSR</strong></th>
<th><strong>SC</strong></th>
<th><strong>ST</strong></th>
<th><strong>GSR</strong></th>
<th><strong>SC</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>(\ast)</td>
<td>(\ast)</td>
<td>(\ast)</td>
<td>(No)</td>
<td>(Yes)</td>
<td>(\ast)</td>
</tr>
</tbody>
</table>

For topic discovery, we used the LDA implementation of [139], and we considered each day of assessment as a separate document. Pre-processed data were received by a symbolization unit which maps the raw, multivariate, continuous-time data stream into a signal which can be handled by LDA. In particular it maps the data contained into each 4-elements vector \(V = [IC, ST, GSR, SC]\) representing one assessed minute into a set of discrete symbols which could be interpreted as the letters of text words. Each assessed minute was mapped with an instance of the vocabulary by associating the selected values in \(V\) with their partitions and then concatenating them. Once that a term of the vocabulary was assigned to each minute, documents were created by constructing for each day a histogram of terms. We computed the results from a number of sleep modalities that varies from 3 to 20, and set the hyperparameter \(\alpha\) equal to 0.01 as in [136]. Hyperparameters are optimized with a variational expectation maximization algorithm initialized by randomly choosing a small number of “seed” documents [142]. We selected 18 seeds (nine from healthy subjects and nine from COPD patients). Routines did not change in their overall composition with different seed sets. Once the routines were calculated and each assessed minute of each night mapped to a symbol of the vocabulary we inferred each night in order to estimate the minutes spent in each routine.

### 7.5 Classification

The evaluation of the results for classifying subjects based on their pathological condition (66 healthy vs. 66 COPD), for distinguishing among different stages of the diseases (healthy, GOLD 1,
1087. Classification of patients with COPD using topic models-based features and nighttime data

GOLD 2, GOLD 3, GOLD 4) and different dyspnoea scores (MMRC 0, MMRC 1, MMRC 2, MMRC 3, MMRC 4) is performed through a 10-fold random-partitioning cross-validation process.

We firstly divided the data from the 132 subjects, comprising healthy subjects and matched COPD patients, into ten subsets. At each iteration, one of the subsets was used as the test set and the other nine subsets formed a training set. From each subject in the training set we randomly selected one night, represented by its characteristic vector of activation probabilities \( \theta = [\theta_1, ..., \theta_n] \) over the sleep modality \( \beta_{j,k} \). We used these distributions to compute a square dissimilarity matrix \( A \) between pairs of nights according to Kullback-Leibler divergence as in [157], in which \( A(i,j) \) denotes the dissimilarity between the \( i \)th and \( j \)th randomly selected nights \( A(i,j) = \sum_k \theta_k^i \log(\frac{\theta_k^i}{\theta_k^j}) \) with \( \theta_k^i \) and \( \theta_k^j \) the activation probabilities of the sleep modality \( \beta_k \) for the nights represented by \( \theta^i \) and \( \theta^j \). The choice of the dissimilarity measure is critical and must fit the nature of the features in question, which in this case are discrete probability functions. Secondly, we calculated the eigenvectors and eigenvalues of \( A \) so that \( AV = DV \), where \( D \) is a diagonal matrix of eigenvalues and \( V \) a matrix whose columns are the corresponding right eigenvectors and there are as many eigenvectors and eigenvalues as there are rows in the initial matrix. Eigenvalues were ranked from the greatest to the least. Using the transformation \( V_TD_T^{-1} \), with \( V_T \) the truncated eigenvector matrix of the first \( n \) eigenvectors of \( V \) and \( D_T \) the associated and truncated eigenvalue matrix, we summarized and attempted to represent inter-nights dissimilarities in a lower dimensional space.

We iteratively projected into \( V_TD_T^{-1} \) all the nights of each subject in the training set and test set such that the between-object dissimilarities are preserved as well as possible. In particular, given a vector of sleep modality activation probabilities \( \theta \) representing one night, we calculated the vector \( x \) of pairwise dissimilarities between \( \theta \) and the nights used to compute \( V_TD_T^{-1} \). Then we assigned to \( \theta \) a location in a low-dimensional space projecting \( x \) into the learned space \( V_TD_T^{-1} \) according to \( v' = xV_TD_T^{-1} \). Iterating this operation for each night in the training set and test, the positions of points relative to each other did not change but the coordinate systems changed resulting in a rotation of the data. In a nutshell we created a transformed feature set which rows represent a night of a patient and columns the projection of the pairwise dissimilarities into the space of the first \( n \) eigenvectors and eigenvalues learned using one single night per subject. We performed class recognition by using a Random Forest (RF) [158] classifier with 50 trees. RFs are ensembles of weakly correlated decision trees that vote on the classification and have been shown to provide good generalization compared to individual decision trees. We used the transformed features representing the nights in the training set to train the ensemble of 50 classification trees. We report the results for the classification of the single nights and of the subjects as results of the vote of his assessed nights.

We applied the same procedure to evaluate the classification of the five disease severity grades (healthy, GOLD 1, GOLD 2, GOLD 3, and GOLD 4) and of the five dyspnoea scores (MMRC 0, MMRC 1, MMRC 2, MMRC 3, and MMRC 4) for a total of 1125 subjects and 690 subjects, respectively. We explored all possible combinations for different number of topics \( \beta_k \) (with \( k \) varying from 2 to 20) and selecting the first \( n \) eigenvectors (with \( n \) varying from 1 to 20).

For comparison we also evaluated the classification performances in the case standard features extracted during night-time such as total night sleeping time, number of nocturnal sleeping bouts and duration of sleeping bouts are used.
7.6 Results

7.6.1 Healthy vs COPD

The average accuracy across all ten cross validation trials in classifying each night as healthy or COPD-type is shown in Figure 45. A total of 815 nights were classified from the 132 matched subjects. The mean accuracy for the single night classification was 0.89 ($SD = 0.008$). The maximum accuracy (0.91, $SD = 0.04$) was achieved setting the number of sleep modalities to 13 and using the first 13 eigenvectors. For this setting we achieved an accuracy of 0.94 ($SD = 0.05$) for the subject classification.

To compare the time spent in each of the 13 sleep modalities in the 1059 COPD patients and the subgroup used to extract the sleep modalities, we constructed a linear mixed-effect model (LMM) for each sleep modality, with GOLD and MMRC as ordinal explanatory variables; subset group (i.e. all COPD vs matched COPD), smoking status, country of origin, gender and day group (i.e. weekday vs. weekend day) as categorical explanatory variables; age and BMI as continuous explanatory variables. Least Squares means (LS-means) and differences of LS-means of the fixed effects were used to compare the two subset groups. To account for repeated measurements, we used random effects on two levels. On the highest level, we included a random intercept per patient. The second level, within patients, had a random intercept for each day group (weekdays vs. weekends). The residuals then accounted for the differences between days within the same day group.

The model accounts for by-subject and by-day group variability. Degrees of freedom and p-values for significant differences (significant if p<0.05) were computed using Satterthwaite’s approximation [110]. To construct the models we used the lmer function of the package lme4 in R [109].

Comparison between the time spent in each of the 13 sleep modalities in the 1059 COPD patients and the subgroup used to extract the sleep modalities (Figure 46) shows that there are no statistical differences (p>0.1) in the time spent in each sleep modality between the two groups. This indicates that the sleep modalities, created using a subset of patients, are able to generalize across many COPD patients.
7.6 Results

Figure 45 Accuracy matrix for differentiating between nights of patients with COPD vs. nights of healthy subjects varying the number of sleep modalities and the number of eigenvectors.

Figure 46 LS-means for time spent (as percentage of the night-time assessed) in each sleep modality (SM) for all the COPD patients (n = 1059), and the COPD subset used to generate the sleep modalities (n = 66).
7.6.2 Disease severity

The average accuracy across all ten cross validation trials in classifying each night as belonging to one of the four disease classes is shown in Figure 47. A total of 6446 nights were classified for a total of 1059 subjects. The mean accuracy for the single night classification was 0.85 ($SD = 0.01$). The maximum accuracy (0.87, $SD = 0.02$) was achieved setting the number of sleep modalities to 16 and using the first 9 eigenvectors. For this setting we achieved an accuracy of 0.94 ($SD = 0.03$) for the subject classification.

![Accuracy matrix for predicting the patients' level of disease severity given each assessed night.](image)

7.6.3 MMRC score

The average accuracy across all ten cross validation trials in classifying each night as belonging to one of the five MMRC classes is shown in Figure 48. A total of 5588 nights were classified for a total of 914 subjects. The mean accuracy for the single night classification was 0.82 ($SD = 0.01$). The maximum accuracy (0.84, $SD = 0.03$) was achieved setting the number of sleep modalities to 19 and using the first 10 eigenvectors. For this setting we achieved an accuracy of 0.93 ($SD = 0.03$) for the subject classification.
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7.6.4 Classification using standard features

The mean accuracy across all ten cross validation trials in classifying each night as healthy or COPD-type is 0.85 (SD = 0.06). For the subject classification the accuracy was 0.92 (SD = 0.07). The average accuracy across all ten cross validation trials in classifying each night as belonging to one of the four disease classes was 0.58 (SD = 0.02). For the subject classification the accuracy was 0.72 (SD = 0.05). The average accuracy across all ten cross validation trials in classifying each night as belonging to one of the five dyspnoea classes was 0.57 (SD = 0.02). For the subject classification the accuracy was 0.76 (SD = 0.05).

7.7 Discussion

Early diagnosis of a disease is probably the most valuable asset in order to prevent damages or stall the progression of the disease by effective interventions. Early stages are difficult to assess. More evidence could typically be obtained by longer observations during daily life and obtained with the smallest burden for the patients. For these reasons such observations should ideally be done by unobtrusive means preferably in a familiar environment. Although it is already possible to collect large amounts of data from a single person during a continuous period of his normal life, it is difficult to merge the data into a set of features enabling diagnosis or assistance in diagnosis. We demonstrated the usefulness of our approach by applying it to a real-world COPD patient cohort of more than 1000 patients and a subset of healthy controls showing its validity in assessing sleep in relation to the pathological condition. In particular, we have shown that by fusing multimodal information derived from a device worn exclusively during the night it is possible to differentiate normal subjects from subjects with COPD with an average accuracy of
94% at the subject level (i.e. using several assessment nights to classify each subject) and an average accuracy of 89% in classifying each single night. In addition, patients were classified as well according to their disease severity level and dyspnoea grade with 94% and 93% accuracies, respectively. Standard features such as total night sleeping time, number of nocturnal sleeping bouts and duration of sleeping bouts were able to differentiate between healthy subjects and patients with COPD with good accuracy. However, in agreement with Hartman et al. [99] who did not find significant associations between night’s rest parameters and GOLD or MMRC, these features were not able to discriminate between different disease severity stages and dyspnoea grades. Discovered latent structures in night-time data, instead, were sufficiently sensitive to pick up subtle differences existing between the four groups of COPD subjects and five groups of dyspnoeic patients. Based on the target outcome, the settings in the latent model should be adapted. In particular, a lower number of latent structures is required to get the best classification performance for a two class problem compared to the classification of more classes. For the four classes and five classes problems, a higher number of latent structures, in turn more specific, led to better classification results. It is worth noting that the classification accuracies were always greater than 80% regardless the number of sleep modalities and eigenvectors selected. We believe our contribution represents a step forward towards a better support to the diagnosis of a complicated disease that will hopefully lead to better patient care. With the aim of learning different disease subspaces in mind, an open question for follow-up work is whether it is possible to use (fully or partially) structures provided by clinicians using known clinical relevant features instead of hidden structures extracted from the data.
8 Conclusions

Pervasive technology has been identified as a strong asset for achieving the goal of a user-centred preventive healthcare [148]. Moreover, pervasive healthcare technologies offer new opportunities beyond traditional disease treatment and may play a major role in the management of chronic patients in their own environment, thus increasing their quality of life by staying in a familiar environment and reducing healthcare costs.

The challenges related to this topic are addressed in this thesis were:

i) the design of new strategies for patient training;
ii) collecting evidence that wearable technology, associated with data recorded during daily life, is a valuable resource to gain insight in patient conditions;
iii) the development of unsupervised methodologies for patient monitoring that may be used as input to motivate active behaviour;
iv) the development of unobtrusive diagnostic support systems able to detect early stages of the disease with the smallest burden for the patient.

The general conclusions are:

- The widespread adoption of smartphones provides a platform for healthcare applications that is directly available to patients. It has been shown that it is a mature technology that could be used as part of clinical routine and daily life monitoring. Future works should aim at creating clinically validated applications running on smartphones to be used also in countries under development where, paradoxically, there is a high economic burden, but a sudden growth of smartphone users. Although, we may consider smartphones not suitable for the current old patient populations, we need to consider that the next generation of chronic patients will be familiar with these technologies.
- Physical activity outcome measures assessed during daily life need to be clearly delineated when evaluating and designing interventions aiming at promoting physical activity in patients with COPD. Based on the results of this research, it is clear that different group of patients with different physical activity patterns exists. They need to be clearly individuated in order to tailor physical activity enhancement interventions. For example, decreasing the time in very light intensity without necessarily increasing the time in moderate-to-vigorous for group of patients that spend enough time in moderate to vigorous activities would mean focusing on light intensity activities. Reductions in sedentary time by increases in light activities might be more realistic for patients with COPD, which in fact could help paving the way to posterior increases in the time in more intense activities. These assumptions should be anyway confirmed in randomized controlled trial intervention studies.
- Identifying groups with specific sleep characteristics may be another source of useful information when designing physical activity enhancing interventions with
realistic goals for this population. Interventions may not be as effective if there is an underlying sleep problem. The use of a simple device to monitor patients’ sleep as they enter the study could actually predict who is going to respond better to the intervention therapy. Additional efforts in improving the quality of sleep among physically inactive subgroups may increase the overall impact of these interventions since we showed that patients having had a better night of sleep spontaneously engaged in more physical activity the following day. We may speculate that poor sleep quality could make the motivation to exercise by day worse and contribute to the vicious cycle of deconditioning that affects COPD sufferers.

- Any apparently unstructured collection of data may hide grouping variables that could be found applying data driven mining algorithms, and therefore organize the collection of data according to thematic coherent groups. These hidden variables can be seen as probabilistic features representing each instance of the collection. This approach, applied to healthcare data, and more specifically to physical activity and sleep data, generates features that could be valid constructs to quantify both physical activity and sleep behaviour changes in patient with limited exercise capacity such as with COPD. The author promotes practical applications of these techniques in daily life to design, for instance, interventions and coaching systems with realistic goals for this population. Moreover, this approach has been demonstrated to be effective in diagnosis support systems. In all likelihood this approach will also be relevant for other diseases than COPD; further studies should aim to confirm this hypothesis.
Appendix

References dataset

The objectively assessed data used in the current analysis were collected as part of previous studies which were developed in 10 different countries (i.e., United Kingdom, Ireland, the Netherlands, Germany, Switzerland, Italy, Spain, the United States of America, Brazil, and Australia). The research groups that contributed to the current study were conveniently selected from recent publications (articles in peer-reviewed journals and abstracts presented at major respiratory congresses) using the SenseWear Armband to assess physical activity in patients with COPD.

The data from the United Kingdom (UK) were collected in three cities, Leicester, Liverpool and London. In Leicester, the data were collected as part of a randomized controlled trial to evaluate the effectiveness of a self-management program of activity coping and education for COPD delivered in primary care (ISRCTN35501175). Ethical approval for the study was granted by Leicestershire, Northamptonshire and Rutland Regional Ethics Committee (reference 07/H0408/114). Participants were assessed between September 2009 and September 2012 at University Hospitals of Leicester NHS Trust. In London, the data were collected as part of two studies: 1) a multicentre study aiming to investigate the compliance of patients with COPD with wearing an activity monitor, and the relationship between physical activity and clinical outcomes (participants were recruited between 2009 and 2011 at the Royal Brompton Hospital; ethical approval was given by the ethics/review board of this institution); and 2) a multicentre study aiming to evaluate the effect of aclidinium bromide on exercise endurance, hyperinflation, and dyspnea at rest and during exercise in patients with moderate to severe COPD (NCT01471171; this study was approved by the Independent Ethics Committees at each site, which were previously detailed by Beeh et al.) [108]. In the latter study, participants were assessed between November 2011 and June 2012. In Liverpool, the data were collected between August 2009 and August 2010 at the University Hospital Aintree, as part of the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) study [159]. Ethical approval was granted by the ethics/review board of the University Hospital Aintree. Some of the participants and data from the UK were part of previous publications [160, 161, 162, 82], however there is no overlapping analysis.

The data from Ireland were collected in Dublin as part of a two-phase longitudinal study to examine the short term effects of pulmonary rehabilitation on standard measures and free-living physical activity in patients with COPD (NCT01530412). The study was approved by the Beaumont Hospital Ethics committee, reference numbers 07/10 and 07/48. Participants were assessed between June 2007 and July 2010 at the Beaumont Hospital. Some of the participants and data from Ireland were part of a previous report [48], however there is no overlapping analysis.

The data from the Netherlands were collected in two cities, Eindhoven and Horn. In Eindhoven, the data were collected between February 2010 and September 2011 at the Catharina Hospital, as part of a clinical trial to investigate the pathophysiologic mechanisms of osteoporosis in COPD (NCT01067248). Approval for the study was obtained from the Medical Ethical Committee of the Catharina Hospital (M09-1971). In Horn, the data were collected
between May 2009 and September 2009 at CIRO+, a Center of Expertise for Chronic Organ Failure, as part of the ECLIPSE study. Ethical approval was granted by the Stichting Therapeutische Evaluatie Geneesmiddelen (STEG/METC). Some of the participants and data from the Netherlands were part of previous publications [82, 163, 164], however there is no overlapping analysis.

The data from Germany were collected in different cities. In Grosshansdorf, the data were collected as part of an ongoing prospective observational study aiming to examine the role of extra-pulmonary effects of COPD [165, 44, 166]. The study was approved by the local ethics committee of Schleswig-Holstein (Germany). Participants included were recruited between 2008 and 2009 at the Pulmonary Research Institute at Lung Clinic Grosshansdorf. A multicenter study aiming to evaluate the effect of aclidinium bromide on exercise endurance, hyperinflation, and dyspnoea at rest and during exercise in patients with moderate to severe COPD (NCT01471171) also contributed to the German database. Ethical approval was granted by the Independent Ethics Committees at each site, which were previously detailed by Beeh et al.1 In this study, participants were recruited in Wiesbaden, Hamburg, Berlin, Lübeck, Hannover, Grosshansdorf, and Frankfurt, and assessed between November 2011 and June 2012. Some of the participants and data from Germany were part of previous publications [160, 108, 161, 165, 44, 166, 167], however there is no overlapping analysis.

The data from Switzerland were collected in two cities, Basel and Zurich. In Basel, the data were collected between July 2011 and January 2012 at the University Hospital Basel, as part of a cross-sectional study aiming to examine the independent association of objectively measured daily physical activity and functional capacity with health-related quality of life in patients with COPD. Ethical approval was granted by the Ethics Committee of Basel (EKBB, 163/11). In Zurich, the data were collected between January 2010 and August 2011 in patients with COPD referred to the Pulmonary Division, University Hospital of Zurich, as part of a study which aimed to investigate if simple tests commonly used in clinical practice could accurately predict daily physical activity in COPD [168]. The study was approved by the Research Ethics Committee of the University Hospital of Zurich, Switzerland (EK-1734). Some of the participants and data from Switzerland were part of a previous report [168, 169, 84], however there is no overlapping analysis.

The data from Italy were collected in Pisa, in the Cardio-Thoracic and Vascular Department, University of Pisa, as part of the baseline evaluation of patients with COPD included in an outpatient pulmonary rehabilitation program. The Italian data were de-identified to protect patient information confidentiality.

The data from Spain were collected in three regions (Catalonia, Euskadi and Balearic Islands) as part of the Phenotype and Course of COPD (PAC-COPD) study, which was a prospective longitudinal study aiming to identify clinically and epidemiologically meaningful COPD subtypes and to validate them by assessing their relationship with clinically relevant outcomes (hospitalization and death) during a 4 year follow-up [170, 71]. Participants were recruited between January 2004 and March 2006 in 9 tertiary hospitals. The study protocol was approved by the Ethics Committees of all the participating hospitals, which were previously listed by Garcia-Aymerich et al [71]. A multicenter study aiming to evaluate the effect of aclidinium bromide on exercise endurance, hyperinflation, and dyspnoea at rest and during exercise in patients with moderate to severe COPD (NCT01471171; this study was approved by the Independent Ethics Committees at each site, which were previously detailed by Beeh et al.1) also contributed to the Spanish database. In this study, participants were recruited in Alicante,
Madrid, and Barcelona, and assessed between November 2011 and June 2012. Some of the participants and data from Spain were part of previous publications [160, 161, 162, 170, 71, 51], however there is no overlapping analysis.

The data from the United States of America (USA) were collected in Rochester, MN, as part of a cross-sectional study aiming to characterize the relationship between the 4 meter gait speed (4MGS) test and various psycho-physiologic measures in a cohort of patients with chronic lung disease. The study was approved by the the Institutional Review Board of the Mayo Clinic College of Medicine (IRB# 11-008157). Participants were recruited between July 2012 and July 2013 at Mayo Clinic. Some of the participants and data from the USA were part of previous publications [47, 171, 172], however there is no overlapping analysis.

The data from Brazil were collected in Londrina, Paraná, as part of an ongoing prospective randomized trial aiming to compare the long term effects of two exercise/training regimens on physical activity in daily life and other relevant outcome measures in patients with COPD. The study was approved by the ethics committee of the State University of Londrina (UEL), Londrina, Brazil. Participants were recruited during the baseline assessment for the outpatient pulmonary rehabilitation program which takes place at the University Hospital of Londrina. Some of the participants and data from Brazil were part of a previous report [173], however there is no overlapping analysis.

The data from Australia were collected in two cities, Perth and Sydney. In both cities the data were collected as part of an ongoing randomized controlled trial evaluating a walking training program versus usual care on quality of life and exercise capacity in patients with COPD (ACTRN12609000472279). Ethical approval was granted by the ethics committees of Sydney South West Area Health Service (lead Human Research Ethics Committee), The University of Sydney, Curtin University, Sir Charles Gairdner Hospital and Bentley Hospital, Australia. Participants were recruited from referrals to hospital outpatient pulmonary rehabilitation programs. Some of the participants and data from Australia were part of a previous report [174], however there is no overlapping analysis.

**Features used for cluster analysis**

Table XVI Features used for cluster analysis.

<table>
<thead>
<tr>
<th>Number</th>
<th>Feature</th>
<th>Number</th>
<th>Feature</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Daily time in moderate-to-vigorous intensity before midday (min·day⁻¹)</td>
<td>91</td>
<td>Daily average duration of 2-min bouts of light intensity before midday (min·bout⁻¹)</td>
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Table XVII Daily physical activity measures after stratification for seasons of the year.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Winter</th>
<th>Spring</th>
<th>Summer</th>
<th>Autumn</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>229</td>
<td>175</td>
<td>264</td>
<td>333</td>
<td>-</td>
</tr>
</tbody>
</table>

**Physical activity measures in very light intensity**

<table>
<thead>
<tr>
<th></th>
<th>Winter</th>
<th>Spring</th>
<th>Summer</th>
<th>Autumn</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min/day</td>
<td>797 (715 – 892)</td>
<td>816 (705 – 927)</td>
<td>802 (707 – 896)</td>
<td>801 (715 – 910)</td>
<td>0.72</td>
</tr>
<tr>
<td>EE, METs-min·day</td>
<td>993 (800 – 1224)</td>
<td>976 (807 – 1219)</td>
<td>1062 (830 – 1464)</td>
<td>1064 (834 – 1509)</td>
<td>0.002</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day</td>
<td>651 (544 – 769)</td>
<td>668 (546 – 812)</td>
<td>662 (531 – 767)</td>
<td>646 (538 – 795)</td>
<td>0.75</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day</td>
<td>18 (15 – 21)</td>
<td>18 (16 – 20)</td>
<td>19 (16 – 21)</td>
<td>18 (16 – 21)</td>
<td>0.33</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout</td>
<td>34 (28 – 42)</td>
<td>36 (29 – 45)</td>
<td>33 (28 – 41)</td>
<td>34 (28 – 43)</td>
<td>0.33</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min·day</td>
<td>797 (615 – 1086)</td>
<td>809 (587 – 1089)</td>
<td>896 (639 – 1242)</td>
<td>869 (647 – 1299)</td>
<td>0.005</td>
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</table>

**Physical activity measures in light intensity**

<table>
<thead>
<tr>
<th></th>
<th>Winter</th>
<th>Spring</th>
<th>Summer</th>
<th>Autumn</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min/day</td>
<td>138 (93 – 200)</td>
<td>138 (82 – 200)</td>
<td>148 (101 – 196)</td>
<td>141 (91 – 184)</td>
<td>0.82</td>
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<tr>
<td>EE, METs-min·day</td>
<td>420 (275 – 577)</td>
<td>433 (272 – 588)</td>
<td>486 (308 – 725)</td>
<td>432 (293 – 711)</td>
<td>0.01</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day</td>
<td>7 (0 – 21)</td>
<td>7 (0 – 26)</td>
<td>8 (3 – 26)</td>
<td>7 (0 – 20)</td>
<td>0.66</td>
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<tr>
<td>Frequency of ≥10-min bouts, bouts·day</td>
<td>1 (0 – 2)</td>
<td>1 (0 – 2)</td>
<td>1 (0 – 2)</td>
<td>1 (0 – 2)</td>
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<tr>
<td>Average duration of ≥10-min bouts, min·bout</td>
<td>12 (11 – 14)</td>
<td>13 (12 – 15)</td>
<td>13 (12 – 14)</td>
<td>12 (11 – 14)</td>
<td>0.03</td>
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<tr>
<td>EE in ≥10-min bouts, METs-min·day</td>
<td>24 (0 – 58)</td>
<td>23 (0 – 79)</td>
<td>32 (6 – 93)</td>
<td>26 (0 – 75)</td>
<td>0.26</td>
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**Physical activity measures in moderate-to-vigorous intensity**

<table>
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<th>Spring</th>
<th>Summer</th>
<th>Autumn</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min/day</td>
<td>57 (26 – 105)</td>
<td>49 (25 – 93)</td>
<td>55 (28 – 95)</td>
<td>49 (25 – 102)</td>
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<td>--------</td>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>EE, METs-min-day⁻¹</td>
<td>260 (129 – 481)</td>
<td>241 (129 – 454)</td>
<td>309 (152 – 649)</td>
<td>266 (123 – 600)</td>
<td>0.10</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min-day⁻¹</td>
<td>8 (0 – 27)</td>
<td>6 (0 – 20)</td>
<td>7 (0 – 22)</td>
<td>6 (0 – 23)</td>
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<td>Frequency of ≥10-min bouts, bouts-day⁻¹</td>
<td>1 (0 – 2)</td>
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<td>0 (0 – 2)</td>
<td>0.25</td>
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<tr>
<td>Average duration of ≥10-min bouts, min-bout⁻¹</td>
<td>14 (12 – 17)</td>
<td>15 (12 – 18)</td>
<td>15 (12 – 18)</td>
<td>14 (12 – 17)</td>
<td>0.83</td>
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<tr>
<td>EE in ≥10-min bouts, METs-min-day⁻¹</td>
<td>44 (0 – 125)</td>
<td>24 (0 – 121)</td>
<td>40 (0 – 145)</td>
<td>32 (0 – 139)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). See Table 2 for definition of abbreviations. *P<0.05 vs winter.
### General characteristics and daily physical activity measures after stratification for country of assessment

Table XVIII General characteristics and daily physical activity measures after stratification for country of assessment.

<table>
<thead>
<tr>
<th>Measure</th>
<th>The United Kingdom (UK)</th>
<th>Ireland</th>
<th>The Netherlands</th>
<th>Germany</th>
<th>Switzerland</th>
<th>Italy</th>
<th>Spain</th>
<th>The United States of America (USA)</th>
<th>Brazil</th>
<th>Australia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
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<td>37</td>
<td>97</td>
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<td>124</td>
<td>23</td>
<td>93</td>
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<thead>
<tr>
<th>General characteristics</th>
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<td>Age, yrs</td>
</tr>
<tr>
<td>66 (61 – 72)</td>
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<td>68 (62 – 74)</td>
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<td>65 (60 – 69)</td>
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<tr>
<td>65 (57 – 71)</td>
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<td>69 (62 – 70)</td>
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<td>65 (60 – 74)</td>
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<td>70 (64 – 75)</td>
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| Male, %                 |
| 60                      |
| 49                      |
| 64                      |
| 69                      |
| 59                      |
| 74                      |
| 94                      |
| 55                      |
| 63                      |
| 65                      |

| BMI, kg·m$^{-2}$        |
| 24.8                    |
| 26.9                    |
| 26.6                    |
| 25.6                    |
| 25.2                    |
| 25.9                    |
| 26.8                    |
| 29.6                    |
| 24.1                    |
| 25.4                    |

<0.000
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<th>Mean (Range)</th>
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<td>48 (34 – 68)</td>
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<td>55 (43 – 68)</td>
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<td>57 (31 – 60)</td>
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<td>52 (42 – 60)</td>
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<td>43 (34 – 62)</td>
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<td>46 (26 – 62)</td>
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<td>43 (32 – 62)</td>
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<td>ADO index</td>
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<tr>
<td>GOLD 2007 classification</td>
<td>13/30/33/11</td>
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<tr>
<td>1 / 2 / 3 / 4, %</td>
<td>4</td>
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<tr>
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<td>0</td>
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<td>Care setting</td>
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<td>Primary / Secondary / Tertiary, %</td>
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<td>GOLD 2011 classification</td>
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<tr>
<td>A / B / C / D, %</td>
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<td></td>
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<td></td>
<td>2</td>
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<td></td>
<td>8</td>
</tr>
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<td></td>
<td>6</td>
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<tr>
<td>Physical activity measures in very light</td>
<td>820</td>
</tr>
<tr>
<td>intensity</td>
<td>862</td>
</tr>
<tr>
<td>Time, min·day(^{-1})</td>
<td>(726 – 917)</td>
</tr>
<tr>
<td></td>
<td>(755 –)</td>
</tr>
<tr>
<td></td>
<td>(735 –)</td>
</tr>
<tr>
<td></td>
<td>(684 – 869)</td>
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<td>(773 –)</td>
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<td>760</td>
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<td>817</td>
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<td>762</td>
</tr>
<tr>
<td></td>
<td>823</td>
</tr>
<tr>
<td></td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

*Significance levels: \(\star\) 0.05, \(\star\) 0.01, \(\star\) 0.001
<table>
<thead>
<tr>
<th></th>
<th>970</th>
<th>922</th>
<th>1007</th>
<th>859</th>
<th>927</th>
<th>970</th>
<th>922</th>
<th>1007</th>
<th>859</th>
<th>927</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EE, METs·min⁻¹·day⁻¹</strong></td>
<td>913</td>
<td>1052</td>
<td>1046</td>
<td>975</td>
<td>1753</td>
<td>1027</td>
<td>950</td>
<td>4543</td>
<td>850</td>
<td>1001</td>
</tr>
<tr>
<td><strong>Time in ≥10-min bouts, min·day⁻¹</strong></td>
<td>666</td>
<td>767</td>
<td>675</td>
<td>630</td>
<td>643</td>
<td>675</td>
<td>629</td>
<td>700</td>
<td>571</td>
<td>686</td>
</tr>
<tr>
<td><strong>Frequency of ≥10-min bouts, bouts·day⁻¹</strong></td>
<td>18</td>
<td>18</td>
<td>20</td>
<td>18</td>
<td>18</td>
<td>18</td>
<td>17</td>
<td>16</td>
<td>21</td>
<td>19</td>
</tr>
<tr>
<td><strong>Average duration of ≥10-min bouts, min·bout⁻¹</strong></td>
<td>36</td>
<td>40</td>
<td>32</td>
<td>33</td>
<td>32</td>
<td>35</td>
<td>35</td>
<td>40</td>
<td>26</td>
<td>34</td>
</tr>
<tr>
<td><strong>EE in ≥10-min bouts, METs·min⁻¹·day⁻¹</strong></td>
<td>762</td>
<td>942</td>
<td>848</td>
<td>766</td>
<td>1397</td>
<td>876</td>
<td>738</td>
<td>3928</td>
<td>607</td>
<td>813</td>
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<tr>
<td><strong>min-bout⁻¹</strong></td>
<td>1036</td>
<td>1201</td>
<td>1034</td>
<td>1024</td>
<td>3120</td>
<td>1137</td>
<td>970</td>
<td>5201</td>
<td>781</td>
<td>1065</td>
</tr>
</tbody>
</table>
### Physical activity measures in light intensity

<table>
<thead>
<tr>
<th>Time, min∙day⁻¹</th>
<th>133 (86 – 184)§§</th>
<th>80 (53 – 158)§§</th>
<th>147 (98 – 194)</th>
<th>155 (109 – 161)</th>
<th>156 (90 – 203)§§</th>
<th>142 (85 – 201)</th>
<th>147 (101 – 205)</th>
<th>112 (60 – 167)§§</th>
<th>208 (135 – 213)</th>
<th>140 (98 – 187)§§</th>
<th>&lt;0.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE, METs∙min⁻¹</td>
<td>356 (252 – 500)¶</td>
<td>224 (159 – 373)§</td>
<td>412 (299 – 584)¶</td>
<td>446 (322 – 612)¶</td>
<td>839 (376 – 1914)¶</td>
<td>400 (183 – 586)¶</td>
<td>433 (272 – 594)¶</td>
<td>1469 (307 – 612)¶</td>
<td>484 (928 – 2136)¶</td>
<td>415 (268 – 552)¶</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min⁻¹</td>
<td>6 (0 – 2)†</td>
<td>0 (0 – 1)</td>
<td>6 (0 – 21)</td>
<td>11 (3 – 28)§§</td>
<td>8 (0 – 26)§§</td>
<td>7 (0 – 25)</td>
<td>11 (0 – 22)</td>
<td>16 (6 – 30)§§</td>
<td>9 (3 – 22)§§</td>
<td>&lt;0.000</td>
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<tr>
<td>Frequency of ≥10-min bouts, bouts⁻¹</td>
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<td>0</td>
<td>1</td>
<td>1</td>
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<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0.002</td>
</tr>
<tr>
<td>Average</td>
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<td>12</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>13</td>
<td>12</td>
<td>0.79</td>
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<tr>
<td>Physical activity measures in moderate-to-vigorous intensity</td>
<td>Time, min∙day⁻¹</td>
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<td>45</td>
<td>45</td>
<td>69</td>
<td>35</td>
<td>32</td>
<td>19</td>
<td>111</td>
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<td>---</td>
</tr>
<tr>
<td>min∙day⁻¹</td>
<td>(23 – 96)</td>
<td>(15 – 46)</td>
<td>(27 – 101)</td>
<td>123</td>
<td>126</td>
<td>122</td>
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</tr>
<tr>
<td>EE, METs-</td>
<td>217</td>
<td>114</td>
<td>262</td>
<td>312</td>
<td>491</td>
<td>241</td>
<td>334</td>
<td>747</td>
<td>304</td>
<td>190</td>
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</tr>
<tr>
<td>min∙day⁻¹</td>
<td>(102 – 405)</td>
<td>(73 – 198)</td>
<td>(131 – 451)</td>
<td>589</td>
<td>1362</td>
<td>563</td>
<td>566</td>
<td>1427</td>
<td>611</td>
<td>307</td>
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</table>

Duration of ≥10-min bouts, min∙bout⁻¹

EE in ≥10-min bouts, METs-min∙day⁻¹
<table>
<thead>
<tr>
<th>Time in ≥10-min bouts, min·day&lt;sup&gt;-1&lt;/sup&gt;</th>
<th>6</th>
<th>0</th>
<th>7</th>
<th>14</th>
<th>4</th>
<th>0</th>
<th>15</th>
<th>7</th>
<th>12</th>
<th>3</th>
<th>&lt;0.000</th>
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</thead>
<tbody>
<tr>
<td>Frequency of ≥10-min bouts, min·bout&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>1</td>
<td>0</td>
<td>1</td>
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<td>0</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>14</td>
<td>14</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>0.40</td>
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</tr>
<tr>
<td>EE in ≥10-min bouts, METs·min·day&lt;sup&gt;-1&lt;/sup&gt;</td>
<td>23</td>
<td>0</td>
<td>31</td>
<td>65</td>
<td>40</td>
<td>0</td>
<td>64</td>
<td>140</td>
<td>40</td>
<td>15</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>

Data expressed as absolute/relative frequency, or median (interquartile range). See Tables 1 and 2 for definition of abbreviations. *Data available for 219 subjects in the United Kingdom, 110 in Germany, 118 in Switzerland, and 64 in Spain; †Data available for 237 subjects in the United Kingdom, 110 in Germany, and 77 in Spain; ‡P<0.05 vs Germany; §P<0.05 vs the Netherlands; ¶P<0.05 vs Spain; ††P<0.05 vs Australia; ‡‡P<0.05 vs the United States of America; †††P<0.05 vs Italy; ††‡P<0.05 vs Switzerland; ††§P<0.05 vs Ireland; ‡*P<0.05 vs Brazil; †P<0.05 vs the United Kingdom.
### Area under the curve from daily physical activity hourly patterns

Table XIX Area under the curve from daily physical activity hourly patterns.

<table>
<thead>
<tr>
<th>Fig.</th>
<th>Period under analysis</th>
<th>Parameter</th>
<th>Category/Group</th>
<th>AUC (95% CI)</th>
</tr>
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<tbody>
<tr>
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<tr>
<td>Figure 17</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>A</td>
<td>Weekdays</td>
<td>-</td>
<td>-</td>
<td>0.30 (95% CI 0.29 to 0.30)</td>
</tr>
<tr>
<td>B</td>
<td>Weekend days</td>
<td>-</td>
<td>-</td>
<td>0.29 (95% CI 0.28 to 0.29)</td>
</tr>
<tr>
<td>Figure 18</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>Weekdays</td>
<td>mMRC</td>
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<td>0.32 (95% CI 0.31 to 0.33)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>1</td>
<td>0.29 (95% CI 0.29 to 0.30)</td>
</tr>
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<td></td>
<td></td>
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<td>2</td>
<td>0.29 (95% CI 0.28 to 0.30)</td>
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<tr>
<td></td>
<td></td>
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<td>3</td>
<td>0.28 (95% CI 0.27 to 0.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>0.28 (95% CI 0.26 to 0.29)</td>
</tr>
<tr>
<td>B</td>
<td>Weekend days</td>
<td>mMRC</td>
<td>0</td>
<td>0.31 (95% CI 0.30 to 0.32)</td>
</tr>
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</tr>
<tr>
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<td></td>
<td></td>
<td>3</td>
<td>0.28 (95% CI 0.27 to 0.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4</td>
<td>0.27 (95% CI 0.26 to 0.28)</td>
</tr>
<tr>
<td>C</td>
<td>Weekdays</td>
<td>BMI</td>
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<td>0.36 (95% CI 0.35 to 0.38)</td>
</tr>
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<td>Normal weight</td>
<td>0.31 (95% CI 0.31 to 0.32)</td>
</tr>
<tr>
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<td>Pre-obese</td>
<td>0.29 (95% CI 0.29 to 0.30)</td>
</tr>
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<td></td>
<td>Obese</td>
<td>0.26 (95% CI 0.25 to 0.26)</td>
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<td>D</td>
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<td>BMI</td>
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<td>0.36 (95% CI 0.34 to 0.37)</td>
</tr>
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</tr>
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<td></td>
<td>Pre-obese</td>
<td>0.28 (95% CI 0.27 to 0.28)</td>
</tr>
<tr>
<td></td>
<td>Weekdays</td>
<td>GOLD grades</td>
<td>Obese</td>
<td></td>
</tr>
<tr>
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<td>----------</td>
<td>-------------</td>
<td>---------</td>
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</tr>
<tr>
<td>E</td>
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<td>0.25 (95% CI 0.24 to 0.25)</td>
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<td>F</td>
<td>Weekend days</td>
<td>GOLD grades</td>
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<td>1 0.31 (95% CI 0.30 to 0.32)</td>
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<td>2 0.30 (95% CI 0.29 to 0.30)</td>
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<td>3 0.29 (95% CI 0.28 to 0.29)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4 0.30 (95% CI 0.29 to 0.31)</td>
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</tr>
<tr>
<td>G</td>
<td>Weekdays</td>
<td>GOLD groups</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>A 0.30 (95% CI 0.29 to 0.31)</td>
<td></td>
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<tr>
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<td></td>
<td>B 0.28 (95% CI 0.27 to 0.29)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C 0.30 (95% CI 0.29 to 0.31)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D 0.29 (95% CI 0.29 to 0.31)</td>
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<tr>
<td>H</td>
<td>Weekend days</td>
<td>GOLD groups</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>A 0.29 (95% CI 0.28 to 0.30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>B 0.27 (95% CI 0.26 to 0.28)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>C 0.29 (95% CI 0.28 to 0.30)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>D 0.28 (95% CI 0.28 to 0.29)</td>
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<table>
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<th>Weekdays</th>
<th>Clusters</th>
<th>Obese</th>
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<tbody>
<tr>
<td>A</td>
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<td>1</td>
<td>0.23 (95% CI 0.23 to 0.23)</td>
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<td></td>
<td>2</td>
<td>0.28 (95% CI 0.28 to 0.28)</td>
</tr>
<tr>
<td>Figure 19</td>
<td>Cluster 1</td>
<td>Cluster 2</td>
<td>Cluster 3</td>
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<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>A</td>
<td>Weekdays</td>
<td>Age</td>
<td>&lt;67 years</td>
</tr>
<tr>
<td>B</td>
<td>Weekend days</td>
<td>Age</td>
<td>&lt;67 years</td>
</tr>
<tr>
<td>C</td>
<td>Weekdays</td>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
<td>D</td>
<td>Weekend days</td>
<td>Sex</td>
<td>Male</td>
</tr>
<tr>
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<td>Weekdays</td>
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<td>Yes</td>
</tr>
<tr>
<td>F</td>
<td>Weekend days</td>
<td>LTOT use</td>
<td>No</td>
</tr>
<tr>
<td>G</td>
<td>Weekdays</td>
<td>D_{LCO}</td>
<td>&lt;51%</td>
</tr>
<tr>
<td>H</td>
<td>Weekend days</td>
<td>D_{LCO}</td>
<td>≥51%</td>
</tr>
<tr>
<td>I</td>
<td>Weekdays</td>
<td>ADO index</td>
<td>&lt;4 points</td>
</tr>
<tr>
<td>J</td>
<td>Weekend days</td>
<td>ADO index</td>
<td>≥4 points</td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Figure 20</td>
<td>No</td>
<td></td>
<td>0.29 (95% CI 0.28 to 0.30)</td>
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</table>
### Daily physical activity measures after stratification for age groups.

Table XX Daily physical activity measures after stratification for age groups.

<table>
<thead>
<tr>
<th>Measure</th>
<th>&lt; median (67 years)</th>
<th>≥ median (67 years)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>495</td>
<td>504</td>
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</tr>
<tr>
<td>Physical activity measures in very light intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day$^{-1}$</td>
<td>792 (697 – 891)</td>
<td>813 (730 – 908)</td>
<td>0.01</td>
</tr>
<tr>
<td>EE, METs·min·day$^{-1}$</td>
<td>1020 (807 – 1341)</td>
<td>1040 (832 – 1308)</td>
<td>0.53</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day$^{-1}$</td>
<td>636 (507 – 772)</td>
<td>678 (564 – 798)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day$^{-1}$</td>
<td>19 (16 – 21)</td>
<td>18 (15 – 21)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

AUC: area under the curve; CI: confidence intervals; mMRC: modified Medical Research Council; BMI: body mass index; GOLD: Global Initiative for Chronic Obstructive Lung Disease; COPD: chronic obstructive pulmonary disease; LTOT: long-term oxygen therapy; DLCO: diffusion capacity of the lung for carbon monoxide; ADO: age, dyspnoea, and airflow obstruction index
<table>
<thead>
<tr>
<th>Activity Measure</th>
<th>Group 1 Median (IQR)</th>
<th>Group 2 Median (IQR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average duration of ≥10-min bouts, min∙bout⁻¹</td>
<td>32 (26 – 40)</td>
<td>36 (30 – 46)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min∙day⁻¹</td>
<td>801 (601 – 1163)</td>
<td>877 (658 – 1177)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Physical activity measures in light intensity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min∙day⁻¹</td>
<td>148 (97 – 203)</td>
<td>137 (87 – 184)</td>
<td>0.003</td>
</tr>
<tr>
<td>EE, METs-min∙day⁻¹</td>
<td>457 (311 – 689)</td>
<td>417 (264 – 621)</td>
<td>0.03</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min∙day⁻¹</td>
<td>7 (2 – 22)</td>
<td>8 (0 – 23)</td>
<td>0.62</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts∙day⁻¹</td>
<td>1 (0 – 2)</td>
<td>1 (0 – 2)</td>
<td>0.24</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min∙bout⁻¹</td>
<td>13 (11 – 14)</td>
<td>13 (12 – 14)</td>
<td>0.20</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min∙day⁻¹</td>
<td>25 (4 – 74)</td>
<td>26 (0 – 83)</td>
<td>0.48</td>
</tr>
<tr>
<td><strong>Physical activity measures in moderate-to-vigorous intensity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min∙day⁻¹</td>
<td>58 (32 – 121)</td>
<td>45 (23 – 81)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs-min∙day⁻¹</td>
<td>308 (153 – 638)</td>
<td>241 (114 – 448)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min∙day⁻¹</td>
<td>7 (0 – 30)</td>
<td>6 (0 – 19)</td>
<td>0.04</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts∙day⁻¹</td>
<td>1 (0 – 2)</td>
<td>1 (0 – 1)</td>
<td>0.03</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min∙bout⁻¹</td>
<td>15 (12 – 18)</td>
<td>14 (12 – 17)</td>
<td>0.64</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min∙day⁻¹</td>
<td>40 (0 – 166)</td>
<td>32 (0 – 107)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). See Table V for definition of abbreviations.
**Daily physical activity measures after stratification for sex**

Table XXI Daily physical activity measures after stratification for sex.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Male</th>
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<th>P-value</th>
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<tbody>
<tr>
<td>N</td>
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<td>347</td>
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</tr>
<tr>
<td>Physical activity measures in very light intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min-day⁻¹</td>
<td>807 (711 – 911)</td>
<td>790 (706 – 879)</td>
<td>0.09</td>
</tr>
<tr>
<td>EE, METs-min-day⁻¹</td>
<td>1091 (877 – 1358)</td>
<td>875 (737 – 1258)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min-day⁻¹</td>
<td>666 (547 – 789)</td>
<td>646 (527 – 770)</td>
<td>0.07</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>18 (16 – 21)</td>
<td>18 (16 – 21)</td>
<td>0.60</td>
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<tr>
<td>Average duration of ≥10-min bouts, min-bout⁻¹</td>
<td>35 (28 – 43)</td>
<td>33 (28 – 41)</td>
<td>0.08</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min-day⁻¹</td>
<td>894 (676 – 1200)</td>
<td>734 (554 – 1128)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Physical activity measures in light intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min-day⁻¹</td>
<td>137 (89 – 185)</td>
<td>155 (102 – 205)</td>
<td>0.002</td>
</tr>
<tr>
<td>EE, METs-min-day⁻¹</td>
<td>443 (294 – 652)</td>
<td>420 (276 – 663)</td>
<td>0.36</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min-day⁻¹</td>
<td>6 (0 – 18)</td>
<td>13 (3 – 29)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>1 (0 – 1)</td>
<td>1 (0 – 2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min-bout⁻¹</td>
<td>12 (11 – 14)</td>
<td>13 (12 – 14)</td>
<td>0.008</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min-day⁻¹</td>
<td>21 (0 – 65)</td>
<td>35 (6 – 96)</td>
<td>0.001</td>
</tr>
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</table>
Physical activity measures in moderate-to-vigorous intensity

<table>
<thead>
<tr>
<th>Measure</th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Pre-obese</th>
<th>Obese</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min-day$^{-1}$</td>
<td>53 (27 – 106)</td>
<td>48 (23 – 87)</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE, METs-min-day$^{-1}$</td>
<td>297 (147 – 600)</td>
<td>235 (100 – 448)</td>
<td>&lt;0.0001</td>
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</tr>
<tr>
<td>Time in ≥10-min bouts, min-day$^{-3}$</td>
<td>8 (0 – 26)</td>
<td>5 (0 – 19)</td>
<td>0.004</td>
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<tr>
<td>Frequency of ≥10-min bouts, bouts-day$^{-3}$</td>
<td>1 (0 – 2)</td>
<td>0 (0 – 1)</td>
<td>0.004</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min-bout$^{-3}$</td>
<td>15 (13 – 18)</td>
<td>14 (12 – 17)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min-day$^{-1}$</td>
<td>42 (0 – 149)</td>
<td>22 (0 – 91)</td>
<td>&lt;0.0001</td>
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<td></td>
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</tbody>
</table>

Data expressed as median (interquartile range). See Table V for definition of abbreviations.

**Daily physical activity measures after stratification for body mass index classification**

Table XXII Daily physical activity measures after stratification for body mass index classification.

<table>
<thead>
<tr>
<th>Measure</th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Pre-obese</th>
<th>Obese</th>
<th>P-value</th>
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<tbody>
<tr>
<td>N</td>
<td>68</td>
<td>366</td>
<td>342</td>
<td>225</td>
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</table>

Physical activity measures in very light intensity

<table>
<thead>
<tr>
<th>Measure</th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Pre-obese</th>
<th>Obese</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min-day$^{-1}$</td>
<td>739 (668 – 816)</td>
<td>769 (688 – 863)</td>
<td>789 (704 – 881)$^*$</td>
<td>891 (812 – 974)$^{<em>,</em>,*}$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs-min-day$^{-1}$</td>
<td>716 (616 – 806)</td>
<td>857 (736 – 1036)$^*$</td>
<td>1057 (904 – 1256)$^{<em>,</em>}$</td>
<td>1438 (1223 – 1753)$^{<em>,</em>,*}$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min-day$^{-3}$</td>
<td>535 (413 – 631)</td>
<td>605 (502 – 712)$^*$</td>
<td>657 (552 – 768)$^{<em>,</em>}$</td>
<td>789 (693 – 897)$^{<em>,</em>,*}$</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts-day$^{-3}$</td>
<td>20 (17 – 22)</td>
<td>19 (16 – 22)</td>
<td>18 (16 – 20)$^{<em>,</em>}$</td>
<td>17 (14 – 19)$^{<em>,</em>,*}$</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
### Average duration of ≥10-min bouts, min∙bout$^{-1}$

<table>
<thead>
<tr>
<th></th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Pre-obese</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE in ≥10-min bouts, METs-min∙day$^{-1}$</td>
<td>35 (30–42)$^*$</td>
<td>31 (26–37)$^*$</td>
<td>26 (22–31)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Physical activity measures in light intensity

<table>
<thead>
<tr>
<th>Time, min∙day$^{-1}$</th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Pre-obese</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE, METs-min∙day$^{-1}$</td>
<td>440 (230–441)</td>
<td>444 (310–615)$^*$</td>
<td>489 (334–714)$^*$</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

### Physical activity measures in moderate-to-vigorous intensity

<table>
<thead>
<tr>
<th>Time, min∙day$^{-1}$</th>
<th>Underweight</th>
<th>Normal weight</th>
<th>Pre-obese</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE, METs-min∙day$^{-1}$</td>
<td>315 (151–675)</td>
<td>258 (121–534)</td>
<td>277 (155–556)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). See Table V for definition of abbreviations. *P<0.05 vs Underweight; †P<0.05 vs Normal weight; ‡P<0.05 vs Pre-obese.
### Daily physical activity measures after stratification for modified Medical Research Council (mMRC) grades*

Table XXII Daily physical activity measures after stratification for modified Medical Research Council (mMRC) grades.

<table>
<thead>
<tr>
<th>Measure</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>137</td>
<td>268</td>
<td>221</td>
<td>181</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td><strong>Physical activity measures in very light intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min⋅day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>743 (675 – 853)</td>
<td>804 (714 – 895)</td>
<td>819 (718 – 886)</td>
<td>847 (760 – 934)</td>
<td>884 (756 – 1001)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs-min⋅day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1027 (829 – 1325)</td>
<td>1045 (822 – 1349)</td>
<td>1028 (822 – 1464)</td>
<td>1063 (852 – 1580)</td>
<td>1092 (777 – 1268)</td>
<td>0.4</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min⋅day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>588 (507 – 714)</td>
<td>662 (548 – 780)</td>
<td>669 (548 – 776)</td>
<td>711 (604 – 834)</td>
<td>748 (575 – 899)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts⋅day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>18 (16 – 20)</td>
<td>18 (15 – 21)</td>
<td>18 (16 – 21)</td>
<td>19 (16 – 22)</td>
<td>20 (17 – 22)</td>
<td>0.0</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min⋅bout&lt;sup&gt;1&lt;/sup&gt;</td>
<td>32 (27 – 40)</td>
<td>35 (28 – 45)</td>
<td>34 (28 – 42)</td>
<td>35 (29 – 50)</td>
<td>36 (30 – 46)</td>
<td>0.0</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min⋅day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>843 (626 – 889)</td>
<td>889 (627 – 851)</td>
<td>851 (640 – 899)</td>
<td>899 (683 – 940)</td>
<td>940 (557 – 1001)</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>1093)</td>
<td>1201)</td>
<td>1278)</td>
<td>1428)</td>
<td>1159)</td>
<td>8</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-------</td>
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<td>-------</td>
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<td>-------</td>
<td>-----</td>
</tr>
<tr>
<td><strong>Physical activity measures in light intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day(^{-1})</td>
<td>167 (124 – 211)</td>
<td>141 (94 – 199) (\dagger)</td>
<td>138 (92 – 188) (\dagger)</td>
<td>127 (71 – 174) (\dagger,\dagger)</td>
<td>104 (62 – 163) (\dagger,\dagger,\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs-min·day(^{-1})</td>
<td>549 (394 – 762)</td>
<td>478 (307 – 691) (\dagger)</td>
<td>410 (272 – 676) (\dagger)</td>
<td>373 (246 – 575) (\dagger,\dagger)</td>
<td>275 (163 – 391) (\dagger,\dagger,\dagger,\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day(^{-1})</td>
<td>13 (3 – 31)</td>
<td>11 (3 – 26) (\dagger)</td>
<td>7 (0 – 22) (\dagger)</td>
<td>4 (0 – 14) (\dagger,\dagger)</td>
<td>3 (0 – 8) (\dagger,\dagger,\dagger,\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day(^{-1})</td>
<td>1 (0 – 2)</td>
<td>1 (0 – 2) (\dagger)</td>
<td>1 (0 – 2) (\dagger)</td>
<td>0 (0 – 1) (\dagger,\dagger)</td>
<td>0 (0 – 1) (\dagger,\dagger,\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout(^{-1})</td>
<td>13 (12 – 14)</td>
<td>13 (12 – 14) (\dagger)</td>
<td>13 (11 – 14) (\dagger)</td>
<td>12 (11 – 14) (\dagger)</td>
<td>12 (11 – 15) (\dagger)</td>
<td>0.3</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min·day(^{-1})</td>
<td>49 (12 – 115)</td>
<td>32 (10 – 93) (\dagger)</td>
<td>22 (0 – 66) (\dagger)</td>
<td>11 (0 – 47) (\dagger,\dagger)</td>
<td>7 (0 – 23) (\dagger,\dagger,\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Physical activity measures in moderate-to-vigorous intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day(^{-1})</td>
<td>74 (43 – 134)</td>
<td>53 (31 – 93) (\dagger)</td>
<td>45 (26 – 82) (\dagger)</td>
<td>33 (17 – 76) (\dagger,\dagger)</td>
<td>21 (11 – 72) (\dagger,\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>EE, METs-min·day(^{-1})</td>
<td>374 (211 – 293)</td>
<td>293 (165 – 224) (\dagger)</td>
<td>224 (122 – 209) (\dagger)</td>
<td>209 (78 – 108) (\dagger)</td>
<td>108 (47 – 108) (\dagger)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Measure</td>
<td>Yes</td>
<td>No</td>
<td>P-value</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------------------</td>
<td>-------------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>67</td>
<td>640</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical activity measures in very light intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min-day(^{1})</td>
<td>836 (749 – 925)</td>
<td>804 (711 – 896)</td>
<td>0.04</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EE, METs-min-day(^{1})</td>
<td>1082 (845 – 1308)</td>
<td>1051 (836 – 1434)</td>
<td>0.65</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). See Table 2 for definition of abbreviations. *Data available for 868 subjects; †P<0.05 vs mMRC0; ‡P<0.05 vs mMRC1; §P<0.05 vs mMRC2; ǁP<0.05 vs mMRC3.

**Daily physical activity measures after stratification for long-term oxygen therapy use*.**

Table XXIV Daily physical activity measures after stratification for long-term oxygen therapy use.
<table>
<thead>
<tr>
<th>Physical activity measures in ≥10-min bouts, min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</th>
<th>709 (581 – 837)</th>
<th>662 (550 – 774)</th>
<th>0.08</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency of ≥10-min bouts, bouts∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>18 (16 – 21)</td>
<td>18 (16 – 21)</td>
<td>0.65</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min∙bout&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>39 (28 – 51)</td>
<td>35 (29 – 44)</td>
<td>0.15</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>948 (667 – 1244)</td>
<td>878 (647 – 1239)</td>
<td>0.67</td>
</tr>
</tbody>
</table>

**Physical activity measures in light intensity**

<table>
<thead>
<tr>
<th>Time, min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</th>
<th>113 (65 – 171)</th>
<th>141 (93 – 196)</th>
<th>0.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE, METs-min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>341 (196 – 605)</td>
<td>453 (299 – 699)</td>
<td>0.02</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>3 (0 – 8)</td>
<td>8 (2 – 23)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>0 (0 – 1)</td>
<td>1 (0 – 2)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min∙bout&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>12 (11 – 15)</td>
<td>13 (12 – 14)</td>
<td>0.60</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>10 (0 – 51)</td>
<td>29 (5 – 84)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

**Physical activity measures in moderate-to-vigorous intensity**

<table>
<thead>
<tr>
<th>Time, min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</th>
<th>37 (17 – 68)</th>
<th>53 (28 – 95)</th>
<th>0.005</th>
</tr>
</thead>
<tbody>
<tr>
<td>EE, METs-min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>176 (79 – 400)</td>
<td>298 (149 – 577)</td>
<td>0.004</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>2 (0 – 9)</td>
<td>7 (0 – 22)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>0 (0 – 1)</td>
<td>1 (0 – 2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min∙bout&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>13 (11 – 16)</td>
<td>15 (12 – 18)</td>
<td>0.02</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min∙day&lt;sup&gt;⁻¹&lt;/sup&gt;</td>
<td>5 (0 – 59)</td>
<td>40 (0 – 146)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). See Table V for definition of abbreviations. *Data available for 707 subjects.
**Daily physical activity measures after stratification for diffusion capacity of the lung for carbon monoxide (DLCO) groups*.**

Table XXV Daily physical activity measures after stratification for diffusion capacity of the lung for carbon monoxide (DLCO) groups.

<table>
<thead>
<tr>
<th>Measure</th>
<th>&lt; median (51 % predicted)</th>
<th>≥ median (51 % predicted)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>241</td>
<td>264</td>
<td></td>
</tr>
<tr>
<td>Physical activity measures in very light intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>819 (735 – 919)</td>
<td>802 (708 – 886)</td>
<td>0.05</td>
</tr>
<tr>
<td>EE, METs-min·day⁻¹</td>
<td>944 (788 – 1198)</td>
<td>1112 (902 – 1455)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>666 (552 – 790)</td>
<td>663 (556 – 768)</td>
<td>0.52</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>19 (16 – 21)</td>
<td>18 (15 – 20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>34 (29 – 42)</td>
<td>36 (29 – 45)</td>
<td>0.12</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min·day⁻¹</td>
<td>767 (567 – 1058)</td>
<td>928 (698 – 1227)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Physical activity measures in light intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>139 (88 – 187)</td>
<td>146 (94 – 197)</td>
<td>0.34</td>
</tr>
<tr>
<td>EE, METs-min·day⁻¹</td>
<td>390 (260 – 540)</td>
<td>512 (342 – 712)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Physical activity measures in moderate-to-vigorous intensity</td>
<td>Time, min·day⁻¹</td>
<td>EE, METs·min⁻¹·day⁻¹</td>
<td></td>
</tr>
<tr>
<td>-------------------------------------------------------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td></td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>7 (0–20)</td>
<td>11 (3–27)</td>
<td></td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td></td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>13 (12–14)</td>
<td>35 (11–104)</td>
<td></td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs·min⁻¹·day⁻¹</td>
<td>1 (0–2)</td>
<td>1 (0–2)</td>
<td></td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>13 (12–14)</td>
<td>35 (11–104)</td>
<td></td>
</tr>
</tbody>
</table>

Data expressed as median (interquartile range). See Table V for definition of abbreviations. *Data available for 505 subjects.
## Daily physical activity measures after stratification for ADO index groups.

Table XXVI Daily physical activity measures after stratification for ADO index groups.

<table>
<thead>
<tr>
<th>Measure</th>
<th>&lt; median (4 points)</th>
<th>≥ median (4 points)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>317</td>
<td>551</td>
<td></td>
</tr>
</tbody>
</table>

### Physical activity measures in very light intensity

<table>
<thead>
<tr>
<th>Measure</th>
<th>&lt; median (4 points)</th>
<th>≥ median (4 points)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min·day(^1)</td>
<td>783 (690 – 879)</td>
<td>827 (739 – 922)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>EE, METs·min·day(^1)</td>
<td>1079 (835 – 1415)</td>
<td>1047 (823 – 1344)</td>
<td>0.38</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day(^1)</td>
<td>642 (516 – 752)</td>
<td>689 (571 – 813)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day(^1)</td>
<td>18 (16 – 21)</td>
<td>18 (16 – 21)</td>
<td>0.51</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout(^1)</td>
<td>33 (27 – 41)</td>
<td>35 (29 – 45)</td>
<td>0.003</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs·min·day(^1)</td>
<td>882 (631 – 1226)</td>
<td>874 (645 – 1201)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

### Physical activity measures in light intensity

<table>
<thead>
<tr>
<th>Measure</th>
<th>&lt; median (4 points)</th>
<th>≥ median (4 points)</th>
<th>(P)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time, min·day(^1)</td>
<td>156 (108 – 204)</td>
<td>132 (82 – 182)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>EE, METs·min·day(^1)</td>
<td>517 (333 – 734)</td>
<td>393 (252 – 579)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Physical activity measures in moderate-to-vigorous intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------------------------------------------------</td>
<td>---</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>62 (36 – 115)</td>
<td>42 (20 – 78)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>EE, METs·min·day⁻¹</td>
<td>348 (191 – 687)</td>
<td>215 (89 – 425)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>9 (0 – 31)</td>
<td>4 (0 – 16)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>1 (0 – 2)</td>
<td>0 (0 – 1)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>15 (13 – 18)</td>
<td>14 (12 – 17)</td>
<td>0.002</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs·min·day⁻¹</td>
<td>54 (0 – 173)</td>
<td>20 (0 – 89)</td>
<td>&lt;0.000</td>
</tr>
</tbody>
</table>
Data expressed as median (interquartile range). See Table V for definition of abbreviations. *Data available for 868 subjects.

**Daily physical activity measures after stratification for Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification.**

Table XXVII Daily physical activity measures after stratification for Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2007 classification.

<table>
<thead>
<tr>
<th>Measure</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>91</td>
<td>395</td>
<td>340</td>
<td>175</td>
<td></td>
</tr>
<tr>
<td><strong>Physical activity measures in very light intensity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min∙day⁻¹</td>
<td>751 (680 –)</td>
<td>791 (706 –)</td>
<td>817 (731 –)</td>
<td>822 (720 –)</td>
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</tr>
<tr>
<td></td>
<td>846)</td>
<td>882)</td>
<td>922)</td>
<td>929)</td>
<td>04</td>
</tr>
<tr>
<td>EE, METs-min∙day⁻¹</td>
<td>1019 (800 –)</td>
<td>1079 (845 –)</td>
<td>1027 (824 –)</td>
<td>960 (759 –)</td>
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</tr>
<tr>
<td></td>
<td>1405)</td>
<td>1409)</td>
<td>1308)</td>
<td>1181)†</td>
<td>8</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min∙day⁻¹</td>
<td>625 (511 –)</td>
<td>653 (543 –)</td>
<td>677 (548 –)</td>
<td>656 (530 –)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>720)</td>
<td>769)</td>
<td>805)</td>
<td>808)</td>
<td></td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts ∙day⁻¹</td>
<td>17 (15 – 20)</td>
<td>18 (15 – 21)</td>
<td>18 (16 – 21)</td>
<td>20 (16 –)</td>
<td>0.00</td>
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</table>
### Physical activity measures in light intensity

<table>
<thead>
<tr>
<th>Measure</th>
<th>Time, min·day⁻¹</th>
<th>EE, METs-min·day⁻¹</th>
<th>Time in ≥10-min bouts, min·day⁻¹</th>
<th>Frequency of ≥10-min bouts, bouts·day⁻¹</th>
<th>Average duration of ≥10-min bouts, min·bout⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>13 (12 – 14)</td>
<td>13 (12 – 14)</td>
<td>12 (11 – 14)</td>
<td>13 (12 – 14)</td>
<td>13 (12 – 14)</td>
</tr>
<tr>
<td>EE in ≥10-min bouts, METs-min·day⁻¹</td>
<td>820 (625 – 1152)</td>
<td>878 (652 – 1246)</td>
<td>849 (653 – 1052)</td>
<td>1152 (1052)</td>
<td>1152 (1052)</td>
</tr>
<tr>
<td>Physical activity measures in light intensity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min·day⁻¹</td>
<td>181 (117 – 230)</td>
<td>578 (416 – 843)</td>
<td>20 (6 – 41)</td>
<td>2 (1 – 3)</td>
<td>13 (12 – 14)</td>
</tr>
<tr>
<td>EE, METs-min·day⁻¹</td>
<td>147 (105 – 198)</td>
<td>505 (328 – 727)</td>
<td>10 (3 – 27)</td>
<td>1 (0 – 2)</td>
<td>1 (0 – 2)</td>
</tr>
<tr>
<td>Time in ≥10-min bouts, min·day⁻¹</td>
<td>132 (80 – 182)</td>
<td>389 (253 – 564)</td>
<td>6 (0 – 17)</td>
<td>1 (0 – 1)</td>
<td>1 (0 – 1)</td>
</tr>
<tr>
<td>Frequency of ≥10-min bouts, bouts·day⁻¹</td>
<td>137 (88 – 137)</td>
<td>374 (237 – 519)</td>
<td>4 (0 – 11)</td>
<td>0 (0 – 1)</td>
<td>0 (0 – 1)</td>
</tr>
<tr>
<td>Average duration of ≥10-min bouts, min·bout⁻¹</td>
<td>137 (88 – 137)</td>
<td>374 (237 – 519)</td>
<td>4 (0 – 11)</td>
<td>0 (0 – 1)</td>
<td>0 (0 – 1)</td>
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### Physical activity measures in moderate-to-vigorous intensity

<table>
<thead>
<tr>
<th>Measure</th>
<th>Mean (95% CI)</th>
<th>95% CI</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td><strong>EE in ≥10-min bouts, METs-min·day⁻¹</strong></td>
<td>71 (21 – 141)</td>
<td>103 *</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td></td>
<td>35 (10 – 135)</td>
<td>57 *; †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19 (0 – 93)</td>
<td>11 *; †; ‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (0 – 29)</td>
<td>11 *; †; ‡</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Time, min·day⁻¹</strong></td>
<td>75 (44 – 117)</td>
<td>78 *; †</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td></td>
<td>59 (33 – 108)</td>
<td>105 *; †</td>
<td></td>
</tr>
<tr>
<td><strong>EE, METs-min·day⁻¹</strong></td>
<td>364 (225 – 684)</td>
<td>450 *; †</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td></td>
<td>328 (183 – 644)</td>
<td>450 *; †</td>
<td></td>
</tr>
<tr>
<td><strong>Time in ≥10-min bouts, min·day⁻¹</strong></td>
<td>12 (3 – 31)</td>
<td>4 (0 – 17) *; †</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td></td>
<td>11 (3 – 28)</td>
<td>3 (0 – 18) *; †</td>
<td></td>
</tr>
<tr>
<td><strong>Frequency of ≥10-min bouts, bouts·day⁻¹</strong></td>
<td>1 (0 – 2)</td>
<td>0 (0 – 1) *; †</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td></td>
<td>1 (0 – 2)</td>
<td>0 (0 – 1) *; †</td>
<td></td>
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<td><strong>Average duration of ≥10-min bouts, min·bout⁻¹</strong></td>
<td>15 (12 – 19)</td>
<td>14 (12 – 17)</td>
<td>0.47</td>
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<tr>
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<td>14 (13 – 18)</td>
<td>14 (12 – 17)</td>
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</tr>
<tr>
<td><strong>EE in ≥10-min bouts, METs-min·day⁻¹</strong></td>
<td>71 (14 – 165)</td>
<td>93 *; †</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td></td>
<td>64 (13 – 171)</td>
<td>79 *; †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20 (0 – 93)</td>
<td>79 *; †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>11 (0 – 29)</td>
<td>79 *; †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;0.001</td>
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<td></td>
</tr>
</tbody>
</table>
Data expressed as median (interquartile range). See Table V for definition of abbreviations. *P<0.05 vs 1; †P<0.05 vs 2; ‡P<0.05 vs 3.

**Daily physical activity measures after stratification for Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011 classification**.

Table XXVIII Daily physical activity measures after stratification for Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2011.

<table>
<thead>
<tr>
<th>Measure</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>P-value</th>
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<tbody>
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<td>N</td>
<td>255</td>
<td>137</td>
<td>150</td>
<td>326</td>
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<tr>
<td><strong>Physical activity measures in very light intensity</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time, min∙day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>775 (694–869)</td>
<td>830 (746–)</td>
<td>799 (700–899)</td>
<td>832 (738–)</td>
<td>&lt;0.0</td>
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<tr>
<td></td>
<td></td>
<td>899&lt;sup&gt;†&lt;/sup&gt;</td>
<td></td>
<td>937&lt;sup&gt;†,‡&lt;/sup&gt;</td>
<td>0.001</td>
</tr>
<tr>
<td>EE, METs-min∙day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>1104 (841–)</td>
<td>1213 (912–)</td>
<td>1000 (789–)</td>
<td>1005 (800–)</td>
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<tr>
<td></td>
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<td>1369</td>
<td>1803</td>
<td>1236&lt;sup&gt;†&lt;/sup&gt;</td>
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<td>Time in ≥10-min bouts, min∙day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>645 (530–759)</td>
<td>700 (593–)</td>
<td>629 (519–775)</td>
<td>689 (560–823)&lt;sup&gt;†&lt;/sup&gt;</td>
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<td></td>
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<td>808&lt;sup&gt;†&lt;/sup&gt;</td>
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<td>Frequency of ≥10-min bouts, bouts∙day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>18 (15–20)</td>
<td>18 (15–20)</td>
<td>18 (16–21)</td>
<td>19 (16–22)&lt;sup&gt;†,‡&lt;/sup&gt;</td>
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<td>Average duration of ≥10-min bouts, min∙bout&lt;sup&gt;1&lt;/sup&gt;</td>
<td>35 (28–42)</td>
<td>36 (31–51)</td>
<td>34 (26–43)&lt;sup&gt;‡&lt;/sup&gt;</td>
<td>34 (28–43)&lt;sup&gt;†&lt;/sup&gt;</td>
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<td>EE in ≥10-min bouts, METs-min∙day&lt;sup&gt;1&lt;/sup&gt;</td>
<td>895 (638–)</td>
<td>1052 (740–)</td>
<td>824 (587–)</td>
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### Physical activity measures in light intensity

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<td><strong>Time, min·day(^1)</strong></td>
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<td><strong>EE, METs-min·day(^1)</strong></td>
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<td>480</td>
<td>429</td>
<td>352</td>
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<tr>
<td><strong>Time in ≥10-min bouts, min·day(^1)</strong></td>
<td>13</td>
<td>8</td>
<td>7</td>
<td>4</td>
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<tr>
<td><strong>Frequency of ≥10-min bouts, bouts·day(^1)</strong></td>
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<tr>
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<tr>
<td><strong>Average duration of ≥10-min bouts, min·bout(^1)</strong></td>
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<td>29</td>
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<td>11</td>
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### Physical activity measures in moderate-to-vigorous intensity

<table>
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<tbody>
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<td><strong>Time, min·day(^1)</strong></td>
<td>64</td>
<td>44</td>
<td>51</td>
<td>37</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
<td>001</td>
</tr>
<tr>
<td><strong>EE, METs-min·day(^1)</strong></td>
<td>348</td>
<td>296</td>
<td>243</td>
<td>175</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>001</td>
</tr>
<tr>
<td><strong>Time in ≥10-min bouts, min·day(^1)</strong></td>
<td>10</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>&lt;0.0</td>
</tr>
<tr>
<td></td>
<td>A</td>
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<td>C</td>
<td>P</td>
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<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
<td>------</td>
<td></td>
</tr>
<tr>
<td><strong>Frequency of ≥10-min bouts, bouts·day$^{-1}$</strong></td>
<td>1 (0 – 2)</td>
<td>0 (0 – 1)$^\dagger$</td>
<td>0 (0 – 1)$^\dagger$</td>
<td>&lt;0.0</td>
<td></td>
</tr>
<tr>
<td><strong>Average duration of ≥10-min bouts, min·bout$^{-1}$</strong></td>
<td>15 (13 – 18)</td>
<td>14 (12 – 17)</td>
<td>15 (12 – 20)</td>
<td><strong>0.00</strong></td>
<td></td>
</tr>
<tr>
<td><strong>EE in ≥10-min bouts, METs·min·day$^{-1}$</strong></td>
<td>58 (15 – 165)</td>
<td>50 (0 – 135)</td>
<td>29 (0 – 122)$^\dagger$</td>
<td><strong>&lt;0.0</strong></td>
<td></td>
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</tbody>
</table>

Data expressed as median (interquartile range). See Table V for definition of abbreviations. *Data available for 868 subjects; †P<0.05 vs A; ‡P<0.05 vs B; §P<0.05 vs C.
References


N. Y. Hammerla, R. Kirkham, P. Andras, and T. Ploetz, “On preserving statistical characteristics of accelerometry data using their empirical cumulative distribution,” in


Acknowledgments

Four years (it is in the nature of an engineer to approximate the reality) have passed. I remember exactly the day of the interview for this PhD position. In particular, I remember exactly how I felt that morning and that evening. In the morning, while walking to the Potential building of TU/e before giving my presentation, I confess I was a bit stressed. I had not slept much the night before because I still had to prepare the presentation and practice it “at least once”. However, I was reinsured by wearing the new “lucky charm shirt” my mother offered me for the special occasion. While walking I was also fascinated by the combination of the blue and sunny sky on top of my head, the icy cold wind surely more powerful than the coffee I had had for breakfast, and a cracking white snow under my shoes. Everything looked very beautiful and I really thought that I could be happy in that place. Everything during the interview went smoothly. The same day, in the late afternoon, I took the airplane to go back to Genova where I was living. At the airport, I discovered that the “lucky charm shirt” still had attached the security tag. That small piece of plastic made my life quite difficult that afternoon, but I managed to fly back without ripping the shirt. In the evening, while driving on the highway from the airport to my house, an unlucky deer stepped in front of me causing a car accident from which, miraculously, I walked away without a scratch. Today I still don’t know whether they were all signs given to me to take the decision to go and stay in the Netherlands in case of a positive feedback, but this is how my adventure started and it is the first of many stories that I have locked in the deepest part of my heart and my mind. Our lives are made of stories and we will be remembered mostly because someone will continue telling them. Here I would like to acknowledge the people that made the stories related to the years of my PhD an incredible experience and who helped me to grow, think, invent, share, smile, and love.

First and foremost, I would like to thank my supervisor Bert den Brinker who guided me through the rough road to finish this thesis with his great humanity, skills proper of a great scientist, and a lot 9:00-o-clock-Friday-meetings that stopped my Thursday evening borrels, but that stimulated me intellectually and pushed me week by week to achieve this goal. Bert, I am very grateful to you and I really enjoyed working with you every single day. I thank my promoter Ronald Aarts, and the head of SPS group Jan Bergmans for their priceless advices on both my research as well as on my career. This work would not have the spirit it has without the invaluable academic, educational, and belief in me as researcher provided by Emilie Wouters and Martijn Spruit who, in particular, gave me the possibility to analyse a huge amount of interesting data and helped me to see the problems not only from an engineering point of view – hard job, but I think it was successful. I would also like to thank Pieter Wijn and Tjalling Tjalkens for their efforts as members of the PhD-committee. I would like to thank in a special way Pierluigi Casale who has been of amazing help all this time with his competences and his South-Italian touch in applying machine learning to every problem.

My time as PhD student was made enjoyable in large part thanks to the many friends that became a part of my life. I would like to thank all the colleagues of the ACTlab@TU/e together with whom I started this experience, to Rafael from CIRO+, and all the SPS members – they all have my esteem. A special thank you is for all generations of Philips interns and master students that I have seen in the room 1.014 of HTC 34 with whom I shared not only many funny, stressful and successful moments, but especially lunch culinary experiences – discovering that it exists.
something else besides pasta. A special acknowledgement goes to my German house-office mate and buddy Florian and my German born-Dutch during the world cup-party animal Steffen. You both are fantastic people with whom I have lived in harmony for two unforgettable years. Unfortunately our lives at some point took different paths, but I am sure that we will continue sending each other postcards and meeting with real pleasure every time.

A big thank you goes to all my Italian friends in The Netherlands, responsible (in part) for not having learned Dutch (yet). In particular, this time in Eindhoven would not have been the same without Ciccio, Pirro, Betty, Vale, Saporito e Christian. I cannot really count all the parties, festivals, laughs, texts, nonsense that we had together. Sometime I ask myself what if I had not met Christian during the Dutch course who introduced me to the mayor, who introduced me to the Italian gang and opened the doors of his house when I could move in... but to be honest I prefer don’t think about it. The Italian family includes the best photographer-physicist Nico whose company several times made me falling asleep with my clothes on and with the light on, the best DAE designer Pace able to transform any space in the house in a better place for the entire humanity, the best-in-everything Dani who gave me the template of this thesis (that does not take into account landscape tables), countless suggestions, and that several times I used as a human google, Agnese and her sweetness, hugs and smiles, Ginny and her Albe, Minicass and his 19 years old vitality, Luca and his efforts in social causes, Cristian for welcoming in his house during the last period.

People that should change their passport after having spent so much time in Nieuwstraat and that I would like to thank are Laura for having shared with me many important moments, Ester for just being as she is in a world totally different, DJ Juana for instilling in me his passion for music and vinyl records, Joyce rare example of Dutch living in Eindhoven. I don’t forget all my university friends Paolone, Jucia, Covi, Pauletta, Ale, Bij, the bombers Marco & Miki, the radiant Giorgia, i cug. (non sta per cugini) Broccoli & Mirko. Each of you my dear (new and old) friends taught me something different and your friendship is one of the most valuable rewards I could ever wish.

Nothing could be ever possible without my family. I have an amazing family, unique in many ways, and the stereotype of the southern Italian family in many others. Their support has been unconditional all these years and I need to thank them in Italian now... Mamma, Papà, Cristina non sarei qui senza di voi, senza il vostro supporto, senza i vostri incitamenti, senza le chiamate su skype con internet che “non va”, senza i messaggi per sapere se va tutto bene, consigli e preoccupazioni. Sappiate che la distanza è stata solo un mezzo per raggiungere tutto questo, non una scelta, tantomeno un piacere. Vivere a migliaia di chilometri di distanza è difficile, ma spero state orgogliosi dei nostri traguardi come famiglia e felici nell'affrontare il futuro. Vi ringrazio davvero di cuore e vi dedico questo lavoro che potete e dovete sentire vostro. Grazie a tutta la mia famiglia in generale, agli Spina ed ai Marino che hanno sempre creduto in me, raggiungendomi dove possibile e cercando di essere sempre presenti nelle fasi più importanti della mia vita.

Lastly, I would like to thank my loved Sandra where the most basic source of my life energy resides. We were born at almost 10000 kilometers of distance. We would not have been able to meet even in a dream because when you were sleeping I was awake, still somehow we crossed each other’s lives. If it happened, it is because we are meant to be happy together, and I want this from the bottom of my heart. Thank you for being with me.

With love,
Gabbo
List of Publications

Journal articles:
4. Gabriele Spina et al. Topic models-based features from nighttime data for classification of patients with COPD, To be submitted to Biomedical and Health Informatics, IEEE Journal, 2016

Proceedings and conference contributions:
1. Gabriele Spina, Guannan Huang, Anouk Vaes, Martijn Spruit and Oliver Amft COPDTrainer: A smartphone-based motion rehabilitation training system with real-time acoustic feedback Ubicomp 2013, ACM International Joint Conference on Pervasive and Ubiquitous Computing, 8-12 September, 2013, Zurich, Switzerland.

Patent applications:
1. Apparatus and methods relating to monitoring or assisting breathing in patients, European Patent application 28-01-2016, Philips Internal Reference 2015PF01649, 2016
2. Breathing support system for COPD patients to overcome shortness of breath (breathing tool with feedback), European Patent application 30-10-2015, Philips Internal Reference 2015PF01437, 2015
4. System and method to detect respiration markers, European and USA Patent application 12-12-2014, Philips Internal Reference 2014PF01453, 2014

Other contributions:
Summary

The research activities reported in this thesis concern many aspects related to the use of wearable and unobtrusive technologies to monitor and train physical inactive patients such as patients with COPD in daily life. Data mining algorithms and machine learning approaches were deployed both to provide insight into daily activities of patients and to develop accurate support for diagnosis with the goal to pave the way for a pervasive, user-centred and preventive healthcare model, whilst coping with increasing healthcare costs and shortage of healthcare staff.

Two smartphone-based frameworks have been implemented and validated for the rapid prototyping of healthcare applications. The first framework was designed to interconnect external devices and therefore enabling multiple sensing modalities especially suitable for long term patient monitoring [175]. The second framework utilizes only the smartphone internal sensors to monitor patient’s exercise execution and provides acoustic feedback on exercise performance and exercise errors [176].

Driven by the certainty that data acquired in daily life are extremely valuable, data analysis was performed on daily physical activity data from a large cohort of patients with COPD in order to generate insights that may allow the design of more effective physical activity enhancement interventions. Daily physical activity measures and hourly patterns were found to vary considerably depending on the clinical characteristic. Moreover, five clusters of patients were identified, each with distinct physical activity measures and hourly patterns showing that outcome measures need to be clearly delineated when evaluating interventions aiming to promote physical activity in patients with COPD [177]. Moreover, relations between sleep and daytime physical activity data were investigated showing a clear relationship between sleep of patients with COPD and the amount of activity they undertake during the next waking day. In particular, it has been demonstrated that patients having had a better night of sleep spontaneously engaged in more physical activity the following day [178].

Clinical relevant holistic metrics that integrate physiological parameters were derived using data driven, generative probabilistic models in order to allow a comprehensive and automatic assessment of the patient health status, which is currently non-existent, as an element in new preventive and treatment approaches. A methodology able to integrate and analyse physical activity measures and physiological parameters was developed [154]. The methodology is based on the assumption that any apparently unstructured collection of data hides grouping variables that could be found applying data driven mining algorithms, and therefore organize the collection of data according to thematic coherent groups. The proposed approach was applied to discover the main physical activity routines that characterize the day of the subjects under study. In particular, it has been shown that the discovered physical activity routines are considerably different for COPD patients and healthy subjects regarding their composition and moments in time at which transitions occur. Moreover, they show certain consistent trends depending on COPD clinical characteristics and were found suitable to label, in an unsupervised way, subjects and assessed days according to the pathological condition. In addition, inferring the routine structure on day segments of relatively short duration, it was possible to model activity patterns across the day. Motivated by the results of [178] and [154] we applied a similar approach but now using only night-time data to predict the pathological condition in patients with COPD, and,
more in detail, to predict the level of the disease and dyspnoea severity. Compared to daytime hours, sleeping hours may offer a better trade-off between patients’ comfort, sensor unobtrusiveness and signal quality. The results showed that, by using probabilistic features extracted from multimodal sensor data during night-time, it is possible to differentiate between healthy and patients with COPD with 94% accuracy and between disease severity and dyspnoea severity with an accuracy of 94% and 93%, respectively [179].
Curriculum Vitae

Gabriele Spina was born on October 22nd, 1986 in Palermo, Italy.

After completing high school at the “Liceo Scientifico Galielo Galilei” in 2005 in Palermo, he studied biomedical engineering at the Campus Bio-medico University of Rome, Rome, Italy.

In 2012, he received his Master’s degree cum laude in biomedical engineering, with a specialization in biomechatronics and biomicrosystems, and he moved to the Netherlands to pursue a Doctoral degree at the Eindhoven University of Technology within the Signal Processing Systems group.

In 2014, he joined Philips Research as visiting PhD student, where he continued working on his PhD project under the supervision of Dr. Albertus den Brinker.

In 2016, he started working as Data Scientist at Philips Research.

During his PhD, he focused on the use of emerging technologies (mobile, ubiquitous sensor and network technology), data mining and machine learning algorithms in healthcare to monitor patient’s status and provide insight into daily activities that is needed to interpret the patients’ vital data and disease trends. The results of his effort on this topic are described in this dissertation.