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PROTOCOL

Overview of a Sleep Monitoring Protocol for a Large Natural Population

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Abstract

A standard operating procedure for studying the sleep phenotypes in a large population cohort is proposed. It is intended for academic researchers in investigating the sleep phenotypes in conjunction with the clinical sleep disorders assessment guidelines. The protocol refers to the definitive American Academy of Sleep Medicine (AASM) manual for setting polysomnography (PSG) technical specifications, scoring of sleep and associated events, etc. On this basis, it not only provides a standardized procedure of sleep interview, sleep-relevant questionnaires, and laboratory-based PSG test, but also offers a comprehensive process of sleep data analysis, phenotype extraction, and data storage. Both the objective sleep data recorded by PSG test and subjective sleep information obtained by the sleep interview and sleep questionnaires are involved in the data acquisition procedure. Subsequently, sleep phenotypes can be characterized by observable/inconspicuous physiological patterns during sleep from PSG test or can be marked by sleeping habits like sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, daytime dysfunction, etc., from sleep interview or questionnaires derived. In addition, solutions to the problems that may be encountered during the protocol are summarized and addressed. With the protocol, it can significantly improve scientific research efficiency and reduce unnecessary workload in large population cohort studies. Moreover, it is also expected to provide a valuable reference for researchers to conduct systematic sleep research.

Keywords Sleep phenotype · Standard operating procedure · Polysomnography · Questionnaire · Cohort study

Abbreviations

PSG	Polysomnography
SOP	Standard operating procedure
EEG	Electroencephalography
ECG	Electrocardiography
EMG	Electromyography
EOG	Electrooculography
REM	Rapid eye movement
NREM	Non-rapid eye movement
ADHD	Attention deficit hyperactivity disorder
AHI	Apnea–hypopnea index
OSA	Obstructive sleep apnea
PLM	Periodic leg movement
RLS	Restless legs syndrome
SpO_2	Oxygen saturation
LM	Leg movement
TST	Total sleep time
TRT	Total recording time
WASO	Wake after sleep onset
PSQI	Pittsburgh Sleep Quality Index
TOVC	Total volatile organic compounds
ISI	Insomnia severity index
MEQ	Morning and evening questionnaire
FSS	Fatigue severity scale
GAD-7	Generalized anxiety disorder scale
ESS	Epworth sleepiness scale
BAI	Beck anxiety inventory
BDI	Beck depression inventory
POE	Power over ethernet
DS	Down syndrome
BMI	Body mass index

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Introduction

Sleep serves as an important function for self-regulation and self-recovery in physiological and psychological health. In addition to adequate sleep duration, healthy sleep requires good quality, appropriate timing, regularity, etc. (Ramar et al. 2021). Sleep deprivation, sleep restriction, circadian rhythm disorders, and untreated sleep disorders can have detrimental effects on physical health, mental health, mood, and public safety. To illustrate, fatigue due to lack of sleep can lead to dangers such as traffic accidents, construction site accidents, etc. (Liew and Aung 2021; Moradi et al. 2019; Shiferaw et al. 2018); chronic sleep deprivation increases the risk of death and contributes to various diseases, including cardiovascular disease, diabetes, obesity, and cancer (Kocevska et al. 2021). Especially during the COVID-19 pandemic, sleep disorders are likely to exacerbate pneumonia, and pneumonia can also affect sleep quality and exacerbate sleep-disordered breathing. Salles Cristina et al. reported the relationship between COVID-19 and sleep apnea, and verified that obstructive sleep apnea and sleep deprivation could add to the severity of the pulmonary inflammatory process of COVID-19 (Salles and Mascarenhas Barbosa 2020). Not surprisingly, significant changes in sleep patterns were found during and after the COVID-19 pandemic lockdown. Longer sleep latency, less ease of falling asleep, increased amount of time spent in bed, and higher dream recall frequency were observed during lockdown (Alfonsi et al. 2022). Besides, patients with confirmed or suspected sleep-disordered breathing were more likely to undergo sleep difficulties like frequent awakenings during lockdown (Pinto et al. 2020). The characteristics of the sleep disorders or the sudden/persistent change in sleep patterns can be reflected in various sleep phenotypes.

Sleep phenotypes include objective indicators derived from electrophysiological signals and subjective sleep trajectories reflected by questionnaires. Objective indicators can reflect physiological or pathological characteristics during sleep via multi-physiological signals like electroencephalography (EEG), electrocardiography (ECG), electromyography (EMG), electrooculography (EOG), etc. According to *AASM Manual for the Scoring of Sleep and Associated Events* (Berry et al. 2020) issued by the AASM and updated every one or two years, the overnight sleep consists of distinct stages, namely wakefulness (stage W), and sleep onset (stage N1), light sleep period (stage N2), deep sleep period (stage N3), and rapid eye movement period (REM), among which N1, N2, and N3 are also collectively referred to as non-rapid eye movement period (NREM). Each sleep stage has its own characteristics. These features are also reflected in bioelectrical signals, which are then manifested in sleep phenotypes. For example, in the stage W, people are awake. The EEG is mainly characterized by posterior dominant rhythm, usually accompanied by rapid eye movement and high-amplitude mandibular EMG activity. In addition to these objective indicators, subjective sleep trajectories that comprehensively reflect an individual's sleep and living habits can be obtained via sleep interview or questionnaires, for example, Pittsburgh Sleep Quality Index (PSQI) questionnaire can measure the sleep quality, sleep latency, sleep duration, sleep disturbances, etc., of the volunteers over the past month, and the post-sleep questionnaire can assess the overall sleep quality of the previous night, etc. The aforementioned objective indicators and subjective sleep trajectories provide a reliable basis for sleep assessment and sleep disorders diagnosis.

Currently, in clinical practice, to obtain comprehensive sleep phenotypes and provide a precise diagnosis, physicians will combine the medical history, sleep history, and/or PSG test. PSG, as the gold standard to quantify sleep and diagnose sleep disorders, records multi-physiological signals including brain activity, eye movement, breathing, heart rhythm, leg movements, and oxygen level, etc. It enables physicians to evaluate sleep architecture and assess sleep by manually interpreting the recorded signals. However, PSG is expensive and requires professional technicians to administer and interpret. Thus, it may be inaccessible in many health professional shortage areas and medically underserved areas. For these areas, sleep interview or questionnaires that reflects people's sleep quality, sleep habits, etc., are used for sleep analysis. Inspired by the clinical sleep assessment procedure, studies attempt to assess the sleep-related manifestations by extracting various sleep phenotypes. To illustrate, Miano et al. found that multiple sleep phenotypes of attention deficit hyperactivity disorder (ADHD) patients differed from controls by conducting comprehensive sleep assessments, including PSG and sleep questionnaires, in 30 patients and 25 healthy controls, and proposed that chronic sleep deprivation should be evaluated as a possible unifying marker of ADHD (Miano et al. 2019). Nakayama et al. recruited 210 men with moderate or severe obstructive sleep apnea (OSA) and without any concomitant heart or psychosomatic disease, and they obtained phenotypes such as apnea–hypopnea index (AHI), event duration, degree of oxygen desaturation, and occurrence and timing of arousals during whole sleep and/or each sleep stage by recording polysomnography, and then identify useful parameters other than AHI to classify OSA subgroups to study the heterogeneity of OSA patients (Nakayama et al. 2019). In 2019, Ononye et al. proposed an OSA screening protocol (Ononye et al. 2019). They identified and classified OSA population by measuring AHI, blood pressure,

neck circumference, and other phenotypes and filling in questionnaires in at-risk groups, which improved the diagnostic rate and the accuracy of diagnosis. Although these studies focus on sleep phenotypes, excavating the association between sleep phenotypes and certain diseases, and providing a more phenotypic basis for the diagnosis of these diseases, the standardized procedures for the extraction of objective and subjective sleep phenotypes are not systematically described. Second, current research mainly focused on studying sleep phenotypes within a specific sleep disease, or comparing phenotypes between patients and healthy controls. Hence, a very limited number of sleep phenotypes are extracted in most of the research, and these phenotypes may also be restricted to the specific clinical manifestations. However, our study explored the association between sleep phenotypes and other phenomes by extracting large amounts of phenotypic data and performing statistical analyses. On this basis, part of the phenotypes can also be selected for the study of special diseases. Our research is more flexible and the scope of research is wider. Finally, the phenotypes were mostly extracted manually, which is time consuming and labor intensive.

In this study, a systematic sleep phenotypes acquisition procedure is proposed for 1000 participants in natural population cohort studies currently. In the future, it can be flexibly modified for different disease studies, such as adding questionnaires or measurement items. The protocol is different from previous studies and contributes to the sleep research domain in the following two aspects.

(1) A standardized sleep monitoring protocol that aims to offer detailed procedures in sleep data acquisition, sleep phenotypes extraction, data storage, etc., is proposed in this study. Both objective sleep indicators that can be characterized by physiological signals from PSG test and subjective sleep trajectories that can be marked from sleep interview or questionnaires are provided.
(2) Our study is designed for a large cohort of natural populations that involves about 1000 volunteers. In contrast to the previous studies, relative comprehensive sleep phenotypes that are not limited to specific clinical manifestations are presented. These phenotypes are extracted automatically.

The remaining sections of this paper are organized in order as follows: *Materials and Methods* presents the overview of sleep phenotypes, materials, equipment, and environmental settings required for sleep phenotypes extraction. *Procedure* describes the complete process of sleep monitoring, and *Data Processing* introduces the method of phenotypes extraction in detail. *Troubleshooting* provides the problems that may be encountered in the process of data acquisition and processing, and the corresponding solutions, and discussion and conclusion are given in the *Discussion*.

Materials and Methods

This section describes the human subject, sleep phenotypes list, the materials and equipment required for sleep phenotype collection, and an overview of the collection methods and procedures.

Human Subject

In our study, there are approximately 1000 participants without specific disease, including 60% women and 40% men.

List of Sleep Phenotypes

Sleep phenotype is a macro-phenotype, which includes all the external traits that can be monitored during sleep and the psychological characteristics related to sleep. The former belongs to objective sleep phenotypes, while the latter belongs to subjective sleep trajectories. Objective sleep phenotypes are mainly derived from the various physiological signals such as EEG, ECG, EOG, EMG, respiration, etc., recorded by PSG. Subjective sleep trajectories are mainly inspired by the sleep questionnaires. Objective sleep phenotypes include a special class of phenotypes—event-related phenotypes. Event-related phenotypes are mainly used to describe important and special sleep events (respiratory events and leg movement events) during sleep. For example, the number of apneas is an important indicator of respiratory events, which is used to characterize the situation of apnea events during sleep. Other objective phenotypes record a subject's sleep time and physiological state during the sleep, including sleep time, heart rate, snore and body position, etc. We summarized all phenotypes into the following nine categories and described the significance. The list of phenotypes in each category is shown in Table 1.

- Respiratory event: This is a class of event-related phenotypes, which are extracted from the breathing signals (e.g., nasal and oral airflow) during sleep, and they are mainly used to describe respiration pattern or identify interruptions in breathing. Respiratory events are important indicators for the diagnosis of sleep apnea (Magalang et al. 2013). Apnea is a severe sleep respiratory disorder, but people are often unaware of its seriousness in their daily lives.
- Leg movement event: Leg movement event is a class of event-related phenotypes which are obtained from leg EMG. It is of great significance for the diagnosis of sleep

Table 1 List of sleep phenotypes

Phenotypic category	Sleep phenotypes
Respiratory event	AHI
	Number of apnea
	Average duration of apneas
	Longest duration of apneas
	Number of apnea in stage NREM
	Number of apnea in stage REM
	Hypopnea index
	Number of hypopnea
	Average duration of hypopneas
	Longest duration of hypopneas
	Number of hypopneas in stage NREM
	Number of hypopneas in stage REM
Leg movement event	Number of leg movement events (LM)
	LM index
	Number of PLM
	PLM Index
Sleep time and sleep stage	Time to turn off the lights
	Time to turn on the lights
	Total sleep time (TST)
	Total recording time (TRT)
	Wake after sleep onset (WASO)
	Percent sleep efficiency (TST/TRT (%))
	Sleep latency
	Time proportion of N1 stage in the total sleep time
	Time proportion of N2 stage in the total sleep time
	Time proportion of N3 stage in the total sleep time
	Time proportion of REM stage in the total sleep time
	Stage N1 latency
	Stage N2 latency
	Stage N3 latency
	Stage REM latency
Micro-arousal	Respiratory effort related arousals
	Leg movement related arousals
	Spontaneous arousals
	PLM-related arousals
	Arousals
	Respiratory effort related arousal index
	Feet movement related arousal index
	Spontaneous arousal index
	PLM Related arousal index
	Arousal index
Snore	Occurrence of snoring
	Occurrence of snoring during sleep
	Occurrence of snoring during NREM
	Occurrence of snoring during REM
	Snoring index
	Snoring index during sleep
	Snoring index during NREM
	Snoring index during REM

Table 1 (continued)

Phenotypic category	Sleep phenotypes
Body position	Supine position
	Left side position
	Right side position
	Prone position
Heart rate	Average heart rate during sleep (highest/lowest)
	Highest heart rate during recording
	Average heart rate during NREM
	Average heart rate during REM
	Respiratory event-related average heart rate (apnea/hypopnea)
	Number of bradycardia/tachycardia
	Cardiac asystole
	Bradycardia
	Sinus tachycardia
	Atrial fibrillation
SpO_2	Minimum SpO_2
	Average SpO_2 during sleep
	Average SpO_2 during awake
	Minimum SpO_2 during sleep
	Average SpO_2 level drop
	Duration of SpO_2 level fall below 90%
	Duration of SpO_2 level fall below 85%
	Duration of SpO_2 level fall below 80%
	Duration of SpO_2 level fall below 75%
	Oxygen desaturations $\geq 3\%$
	Oxygen desaturations $\geq 4\%$
Questionnaire	PSQI
	Insomnia severity index (ISI)
	Morning and evening questionnaire (MEQ)
	Fatigue severity scale (FSS)
	Generalized anxiety disorder scale (GAD-7)
	Epworth sleepiness scale (ESS)
	Beck anxiety inventory (BAI)
	Beck depression inventory (BDI)
	Post-sleep questionnaire

disorders. For example, periodic leg movement (PLM) during sleep is one of the important causes of sleep disorders. It can be used to measure the severity of restless legs syndrome (RLS), which also occurs frequently in narcolepsy, sleep apnea syndrome, and REM sleep behavior disorder (Ferri et al. 2017; Hornyak et al. 2006; Mendelson 1996).

- Sleep time and sleep stage: It characterizes important time points of sleep and different sleep stages. These are significant indicators to quantify the sleep architecture and assess sleep quality.
- Micro-arousal: Micro-arousal characterizes the transient changes in EEG during sleep, and it is often related to leg movements, respiratory events, etc. It is important for judging sleep fragmentation.
- Snore: Snoring was recorded through a microphone, and the phenotypes including the number of snores and snoring in each sleep stage are presented.
- Body position: PSG records four common sleeping positions during sleep, afterward sleep phenotypes such as breathing, leg movements, and micro-arousals in different sleeping positions can be extracted.
- Heart rate: This part of the phenotypes are extracted from the ECG signal during sleep and characterizes the heart rate in different sleep stages.
- Oxygen saturation (SpO_2): Sleep blood oxygen is recorded by the fingertip blood oxygen detector. The

blood oxygen can reflect the hypoxia in sleep, which is usually related to snoring and sleep apnea. Therefore, sleep blood oxygen saturation is an important basis for the diagnosis of sleep apnea (Zamarrón et al. 2003).

- Questionnaires: In addition to the above objective indicators, subjective questionnaires, as another kind of important phenotypes, reflect the volunteers' sleep habits, mood and sleep quality, etc.

The list of phenotypes is shown in Table 1.

Protocol Process

The whole protocol process to collect sleep phenotypes above in this study is shown in Fig. 1. The main steps can be summarized as follows.

- **Preparations:** First, technicians need to configure equipment and inform volunteers about precautions in advance. At the same time, volunteers need to sign an informed consent form.
- **Health checks and interviews:** Technicians conduct simple interviews with volunteers. Then volunteers have health checks, which include measuring blood pressure, heart rate, etc. In this step, you can design the interview questions and health check items according to the actual scientific research/clinical needs.
- **Sleep monitoring:** Volunteers enter the sleep monitoring room and fill out questionnaires in addition to the post-sleep questionnaire. Technicians install electrodes on the volunteers. After overnight data collection, technicians remove electrodes and volunteers fill out post-sleep questionnaires. In this step, data collection equipment and questionnaires can be replaced according to research/clinical needs.
- **Data review, processing, and storage:** Technicians first check the accuracy and integrity of the data. Then the sleep phenotypes were extracted by automatic software extraction and self-developed algorithm extraction. Finally, the data are stored both locally and in the cloud. In this step, the way of phenotypes extraction can be chosen according to the actual needs. The specific implementation method will be described in detail in section Procedure and Data Processing.

Equipment and Environment Settings

In this section, we describe the details of the equipment used and how to configure it. The following are commercial research devices used for sleep data recordings.

Grael PSG Device

PSG is the gold standard for diagnosing sleep disorders. Compared with other sleep monitoring devices (such actigraphy, portable PSG, watch, etc.), the sleep phenotypes measured by PSG are more comprehensive and can meet our scientific research needs. Therefore, we choose PSG equipment with 48 channels produced by the Australian

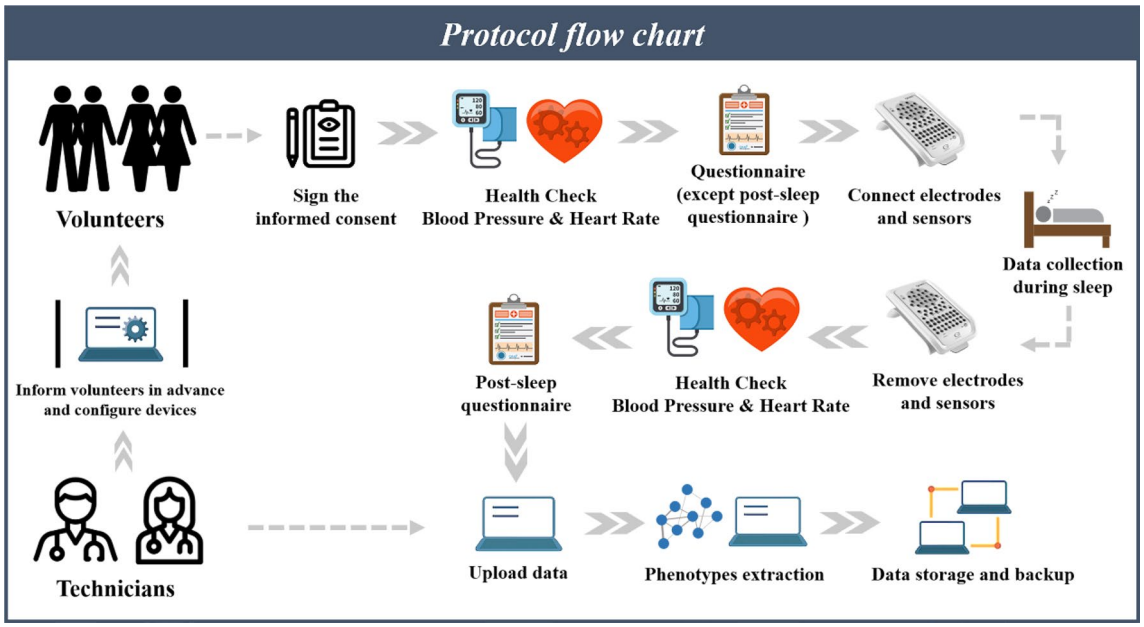

Fig. 1 Protocol procedure

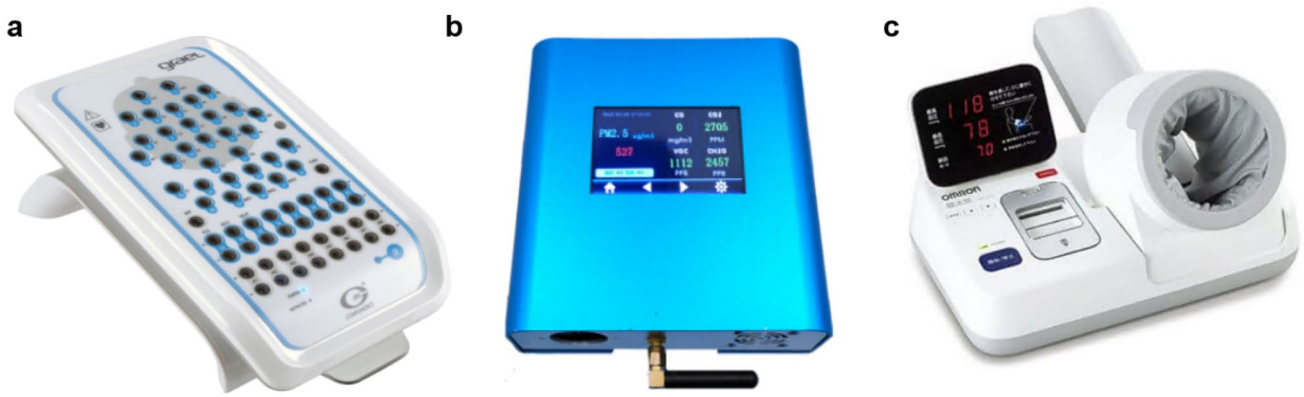

Fig. 2 Measurement devices. **a** PSG devices, **b** Lanno UMINI500 Indoor Ambient Air Quality Monitoring Terminal, **c** OMRON Medical Automatic Electronic Blood Pressure Monitor HBP-9020

Table 2 Electrode and sampling rate requirements

Signal	Channel	Sampling rate (Hz)
EEG	F3-M2, F4-M1, Fz, C3-M2, C4-M1, Cz, O1-M2, O2-M1, Pz, Fp1, Fp2	512
EOG	E1-M2, E2-M2	512
EMG (Chin)	Chin 1-Chin 2, Chin 3-Chin 2	512
EMG (Leg)	Leg/L, Leg/R	512
ECG	ECG −, ECG +	512
Respiratory inductance plethysmography	Chest and abdominal girdle	128
Respiration	Nasal cannula airflow	128
Snore	Microphone	512
SpO_2	Oximeter probe	32

Compumedics Company, which is shown in Fig. 2a. It is a relatively advanced product at present. It can detect a set of indicators during human sleep, including EEG, EOG, jaw EMG, lower limb EMG, ECG, chest and abdominal movement, nasal cannula airflow, body position, blood oxygen saturation, etc. The results are displayed on the supporting computer screen in the form of waveform diagram, and the original data can also be saved locally. The instrument needs to use consumables such as conductive paste and electrode patches. The usage of PSG and the position of electrode placement in this paper refer to the *Grael v2 User Guide* (Compumedics 2016). You can also replace other sleep monitoring devices as needed. Table 2 shows the electrode and sampling rate requirements.

Then select device type: "Compumedics Grael V2 Driver" and select configuration: "Grael2-PSG.xml" before wiring. After wiring, check the impedance of each electrode of the EEG, try to make it below 5 kΩ, and not higher than 10 kΩ. If the signal of a channel cannot be reduced below 10 kΩ, it needs to be recorded in the "Night Sleep Monitoring Record Form".

Table 3 Testing environment requirements

Item	Requirements
Temperature	16–28℃
Relative humidity	40–60% RH
CH_2O	0.08 mg/m^3
Particulate matter 2.5 (PM2.5)	< 5.3 μg/m^3
Total volatile organic compounds (TVOC)	≤ 0.6 mg/m^3
CO_2	≤ 1000 PPM

Lanno UMINI500 Indoor Ambient Air Quality Monitoring Terminal

As is known to all, changes in the environment will affect people's psychological state and sleep quality. To obtain more reliable results in the follow-up study, environmental monitoring equipment needs to be set up. We placed this monitor in the interview room to record the environment and air conditions on the day of the experiment.

UMINI500 is a small multi-monitoring parameter indoor environment monitoring (collection) terminal which is shown in Fig. 2b. It adopts independent high-sensitivity sensors, high-reliability microcircuit design, and professional intelligent detection and analysis algorithms. It has the advantages of strong anti-interference ability, good consistency, and high accuracy.

The environment requirements are given in Table 3.

OMRON Medical Automatic Electronic Blood Pressure Monitor HBP-9020

Studies have shown a strong association between blood pressure and sleep. Both sleep deprivation and insomnia have been linked to increases in the incidence and prevalence of hypertension. Likewise, sleep disruption attributable to restless legs syndrome increases the likelihood of having hypertension. There is a strong correlation between the severity of OSA and the risk and severity of hypertension (Calhoun and Harding 2010). Therefore, blood pressure before and after sleep is measured.

The sphygmomanometer is shown in Fig. 2c. It measures blood pressure by detecting the pulse wave generated by the heartbeat. It is equipped with the "Accurate Measurement Assist" function to prevent measurement errors caused by wrong posture.

Environment Settings

The environment settings are shown in Fig. 3. There are one main control room shown in Fig. 3a, one interview room shown in Fig. 3b, and nine sleep monitoring rooms shown in Fig. 3c and d in the administrative building of Zhangjiang campus of Fudan University. The PSG devices are placed in the sleep monitoring rooms and they will record a whole night's sleep data of volunteers. Lanno UMINI500 and OMRON HBP-9020 are placed in the interview room. The technician monitors the conditions of sleep monitoring rooms in the main control room and asks volunteers for basic information and measures blood pressure in the interview room.

Questionnaires

In this protocol, we choose these questionnaires by integrating clinical recommendations and referring to the diagnosis and treatment plans of domestic authoritative hospitals to comprehensively evaluate sleep status from the aspects of sleep duration, sleep quality, and psychological state. This protocol contains the following nine questionnaires.

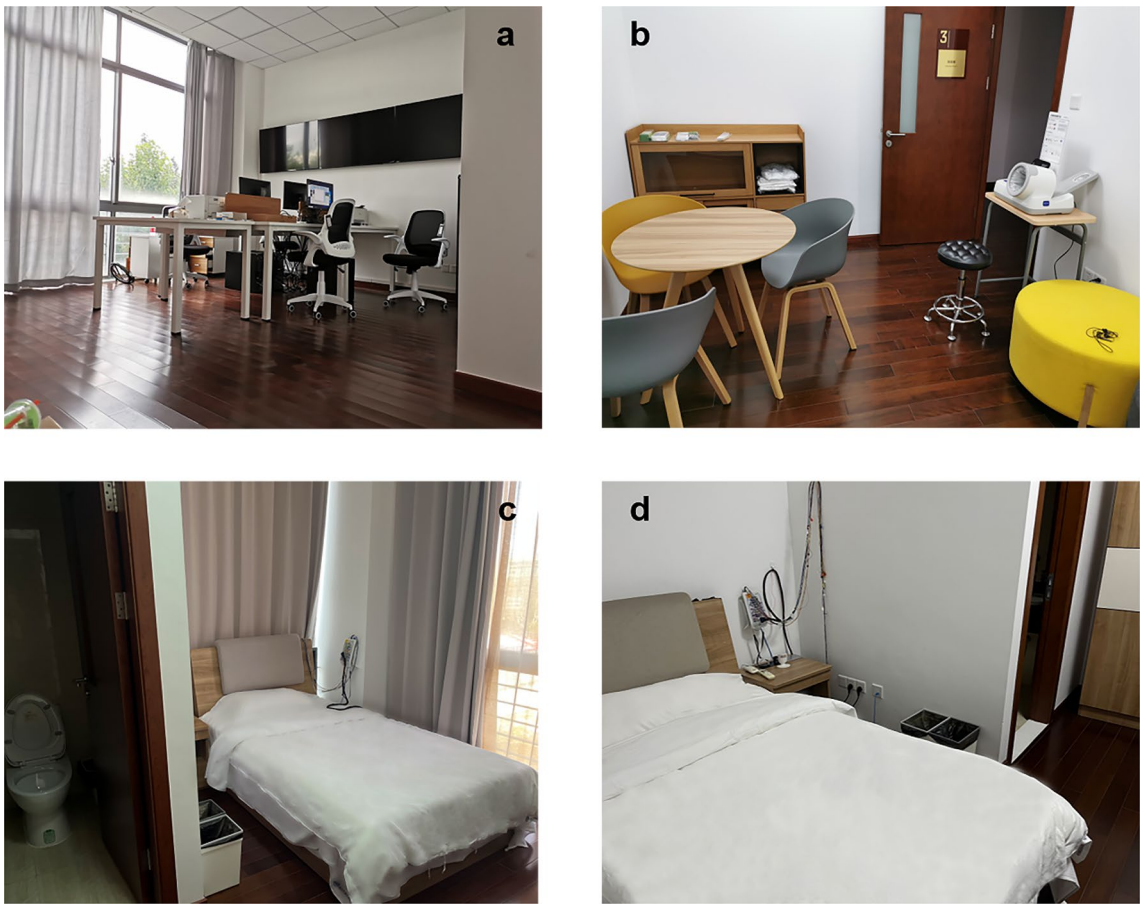

Fig. 3 Environment settings. **a** Main control room, **b** interview room, **c** and **d** sleep monitoring room

- PSQI: PSQI is a self-rated questionnaire that can assess sleep quality and disturbances over a 1-month time interval (Buysse et al. 1989). It contains nine items.
- Insomnia severity index (ISI): The ISI is a brief self-report questionnaire measuring the patient's perception of his or her insomnia. The ISI comprises seven items assessing the severity of sleep-onset and sleep maintenance difficulties (both nocturnal and early morning awakenings) (Bastien et al. 2001).
- Morning and evening questionnaire (MEQ): MEQ is a self-assessment questionnaire to determine morningness–eveningness in human circadian rhythms (Horne and Östberg 1976). It contains 19 items.
- Fatigue severity scale (FSS): The FSS is a scale used to measure the severity of fatigue, and it consists of nine items (Krupp et al. 1989).
- Generalized anxiety disorder scale (GAD-7): GAD-7 is a brief self-report scale to identify probable cases of generalized anxiety disorder (GAD) which contains seven items (Spitzer et al. 2006).
- Epworth sleepiness scale (ESS): ESS is a simple, self-administered questionnaire that provides a measurement of the subject's genera1 level of daytime sleepiness (Johns 1991). It contains eight items.
- Beck anxiety inventory (BAI): BAI is a self-assessment questionnaire used to assess subjects' anxiety level (Beck et al. 1988a). It contains 21 items.
- Beck depression inventory (BDI): The BDI is a questionnaire used to screen for depression or to assess the severity of depression according to the situation of the subjects in the past two weeks which contains 21 items (Beck et al. 1988b).
- Post-sleep questionnaire: This is a questionnaire to assess the sleep quality of subjects last night. It contains 11 items. This questionnaire assesses sleep quality during the test by recording how the subjects felt during the previous night's sleep, how many times they woke up, how they felt after waking up, what they ate before going to bed, etc.

Through sleep-related scales, we can get important information about volunteers' recent sleep habits and sleep quality. Combined with the information obtained from the questionnaire after waking up, sleep state can be assessed whether that of the volunteers during sleep monitoring is consistent with usual. In addition, psychological-related scales also play an important role. Anxiety and depression often lead to insomnia, and insomnia can exacerbate depression. Therefore, studying the relationship between psychological state and sleep is also important and promising.

Procedure

This section will describe the flow of the protocol in chronological order which lasted from 5:30 pm to 7:30 am the next day. Before all experiments begin, the following things need to be informed to volunteers.

- Due to stay overnight, essential daily necessities need to be prepared: loose pajamas and a change of clothes.
- Do not drink alcohol, tea, coffee, cola, and other beverages on the test day, and it is strictly forbidden to take sleeping drugs.
- Enter the sleep laboratory in advance to familiarize with the environment, and prepare for electrode placement and equipment debugging.

Then the experimental process is summarized in the following parts and steps.

Preparation Works (3–4 h)

This stage includes preparations for sleep monitoring and takes about 3–4 h.

1. Volunteers have dinner at 5:30 pm and measure blood pressure half an hour after the meal.
2. The technician asks the volunteers some questions, including whether they had a cold, nasal congestion, medical history, etc., and record them in the "Night Sleep Monitoring Record Form" in the interview room.
3. Volunteers returned to the sleep monitoring room and filled out the questionnaires (except the post-sleep questionnaire). This process lasts about half to one hour.
4. The volunteers then need to wash their hair and bathe. But they could not use conditioner or skin care products.

Sleep Monitoring (10–12 h)

5. The technician checks again if the polysomnography is normal. The power indicator and cable indicator of the polysomnography have the following three states.

   (1) Power indicator blue: the computer is not connected.
   (2) Power indicator green and network cable indicator yellow: the computer is connected.
   (3) All indicators are off: the network cable port is not connected.

6. Place electrodes on the body of volunteers to collect EEG, ECG, EMG, EOG, respiration, and sound signals.

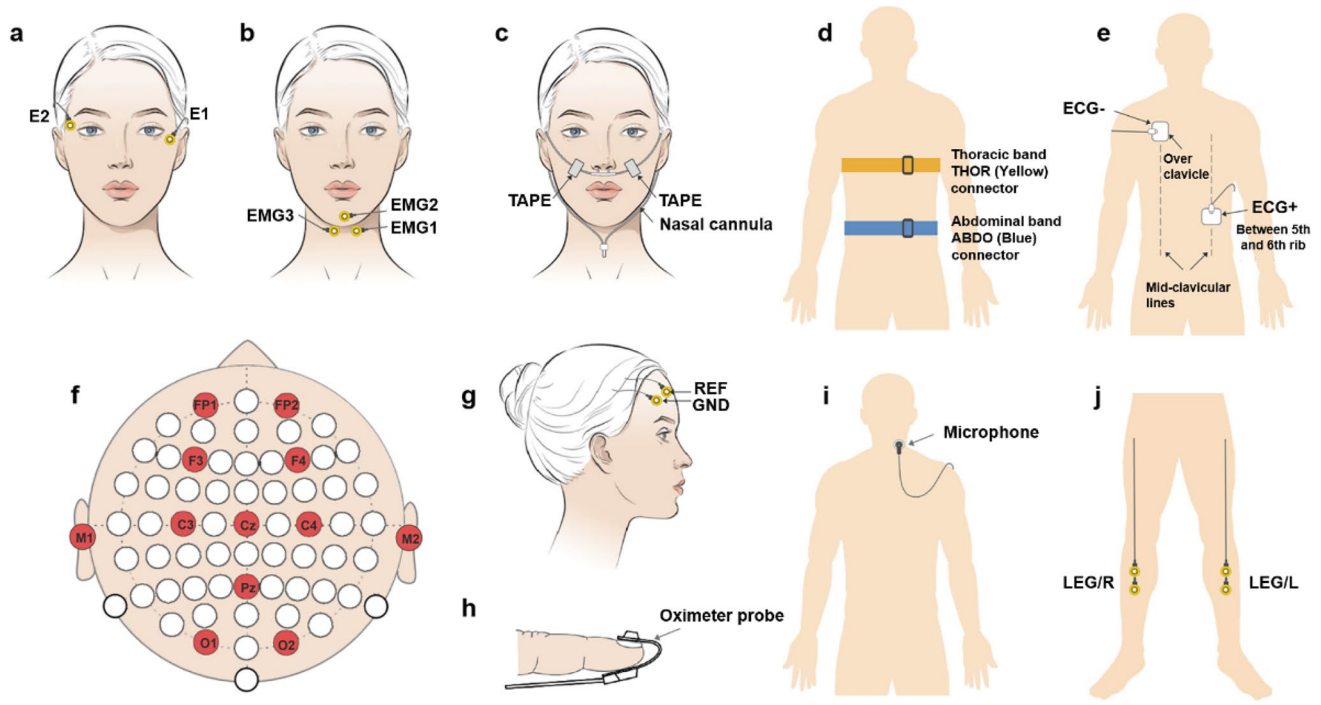

Fig. 4 Electrode placement position. **a** EOG electrode placement: E1 and E2, **b** chin EMG electrode placement: EMG1, EMG2 and EMG3, **c** nasal cannula placement, **d** respiratory band placement, **e** ECG electrode placement: ECG + and ECG − , **f** EEG electrode placement which are marked red, **g** ground and reference electrode placement: GND and REF, **h** oximeter probe placement, **i** microphone placement, **j** leg EMG electrode placement: LEG/R and LEG/L

The electrode placement position is shown in Fig. 4. This process lasts about half to 1 h.

CRITICAL
Correct electrode placement and strong connections are critical.

7. Carry out the first calibration work.

CRITICAL
The purpose of the first calibration is to calibrate and understand the subjects' daily EEG, eye movement, and other waveforms.

8. Inform volunteers in advance of the following.

(1) Please consciously turn off electronic devices such as mobile phones and radios after the inspection starts; for those with dentures, please remove the dentures before the inspection.
(2) Obey the arrangement of the operator, and do not disassemble the equipment and the placed electrodes without permission.
(3) Wake up by the technician through the summon bell the next morning, and remove the electrodes and sensors with the help of the technician.

9. Start to record data.

The software operation method of data logging is as follows. The schematic diagram of the software interface is shown in Fig. 5.

(1) Open the software Device Manager and then choose to create a new study file;
(2) Enter the basic information of the volunteer collected in preparation works;
(3) Select the gender and save path;
(4) Select the configuration, waveform layout, and the name of the recorded video, and then click the OK button;
(5) Click the impedance and real-time video in the < Record > option;
(6) Click the < Record > option to start recording;
(7) Click the technician's annotation toolbar to perform biological calibration according to the technician's annotation;
(8) Click the < Close > in the < Record > option after the biological calibration in the next morning;
(9) Click "Yes" in the pop-up window to close the recording;
(10) Shut down the host and monitoring probe.

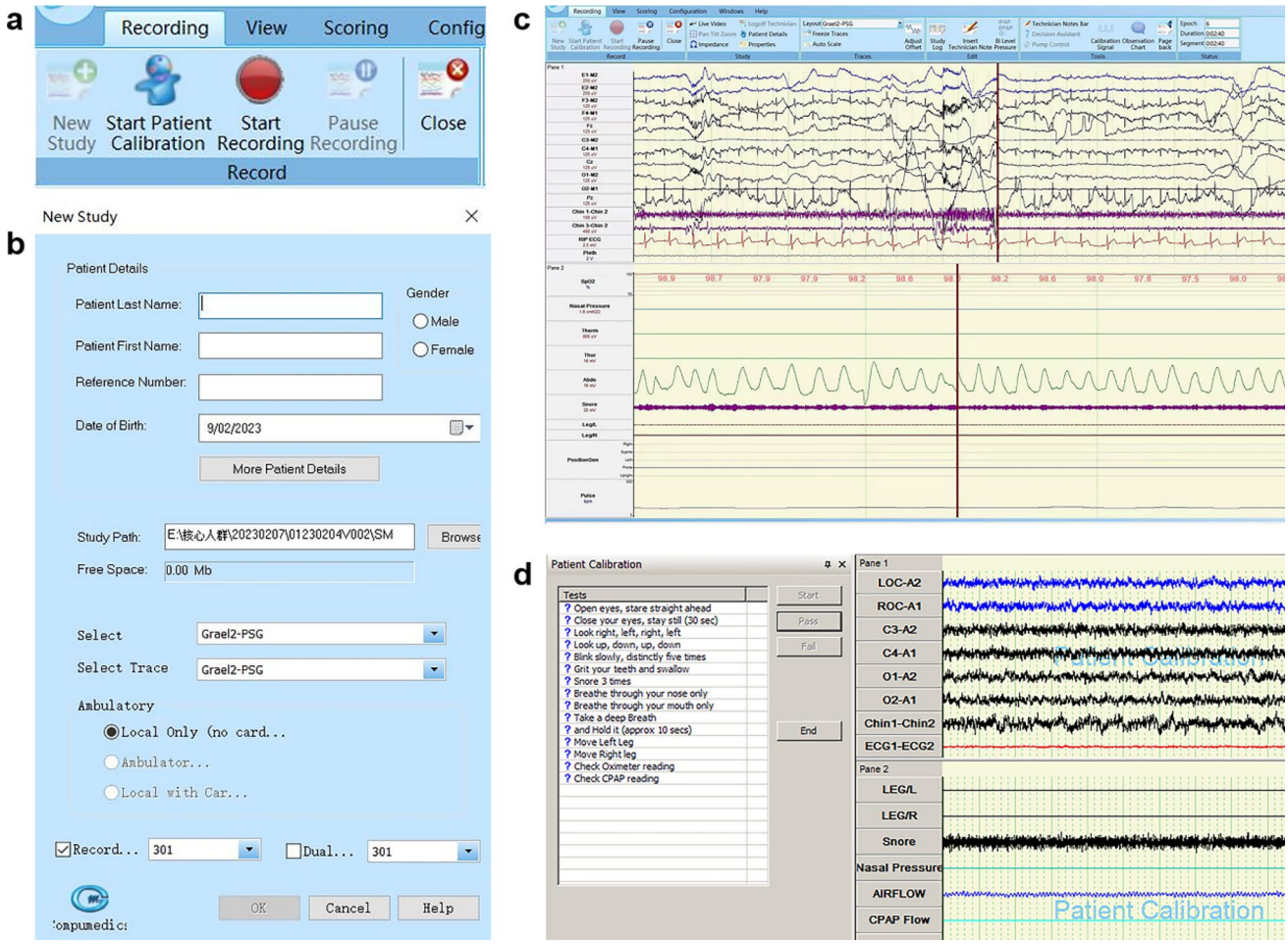

Fig. 5 Schematic diagram of software operation. **a** Toolbar, **b** < New Study > dialogue box, fill in the basic information of volunteers here, **c** waveform layout, **d** biological calibration

After Waking Up (About 1 h)

The technician will wake up volunteers between 6:00 am and 6:30 am the next morning.

10. The technician wakes up volunteers and records the time of turn-on light.
11. Second calibration.

> **CRITICAL**
> The second calibration is necessary which helps us to reconfirm the subjects' daily bioelectrical waveforms, provides support for the results of the first calibration and helps us understand the changes before and after the sleep.

12. Remove the electrodes and clean the subject's skin and the equipment with alcohol;
13. Measure blood pressure again.
14. Volunteers need to fill out post-sleep questionnaires.
15. Volunteers need to wash their hair and take a bath.
16. The technician needs to maintain the equipment and disinfect the sleep monitoring room with UV for 30 min after the volunteers leave.

Data Processing

This section describes how to upload and save raw data and extract sleep phenotypes from it. The data processing flow chart is shown in Fig. 6. The whole process includes two parts: data integrity review and data quality control and phenotypes extraction. In the data integrity review, technicians needs to check the number of volunteers and the number of cases of sleep data. Next, in the data quality control step, it is necessary to record the incomplete data, and eliminate the data with poor signal quality in the complete data. For good quality signals, phenotype extraction will be performed, including self-developed algorithm extraction and automatic

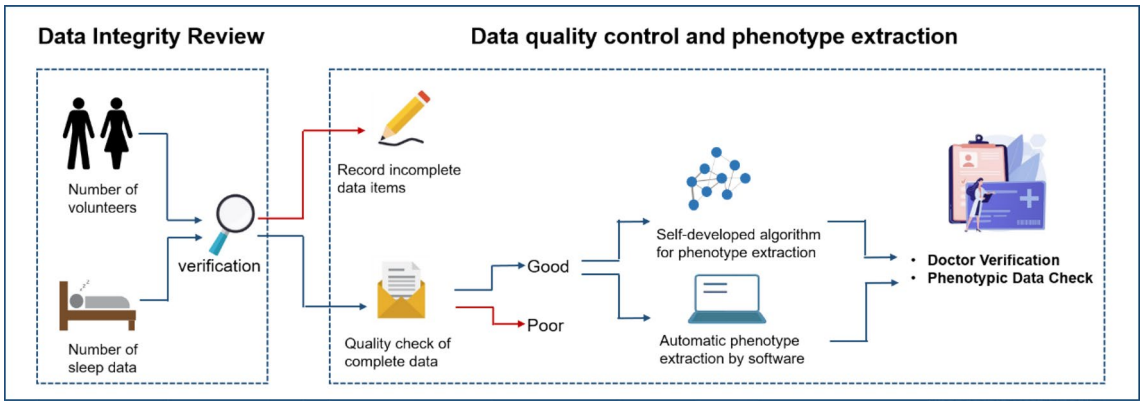

Fig. 6 Data processing flow chart

software extraction. Finally, the extracted phenotypes are submitted to a physician for verification.

Data Quality Control

Data quality checks and controls are mainly performed in two phases, during detection and after phenotypes extraction.

During detection, the data need to be checked for three times.

(1) Before detection: check whether the corresponding waveform is normal after calibration, and adjust it in time if the waveform is abnormal.
(2) During detection: monitor whether the corresponding waveform is normal in real time. If the signal is abnormal, check the impedance. If the signal does not return to normal after 10 min (the impedance is greater than 10 kΩ), record it in time. If multiple waveforms are abnormal, adjust them in time according to the regulations.
(3) After detection: check whether the corresponding waveform is normal; if the waveform is abnormal, make an annotation and record it in time.

After the phenotypes are extracted, the phenotype data need to be checked regularly by sampling. If one of the following situations occur in the phenotype data, it is determined that the phenotype data are abnormal, and the abnormal phenotype data must be reported and recorded in time.

(1) Phenotypic data are missing or blank.
(2) The phenotypic data are outside the normal range.

Table 4 Format of the data

Raw data	Format
Physiological electrical signal data of PSG	EDF +
Output of data automatic analysis (statistics, stage graphs, scoring events)	ASCII
Environment data of lanno UMINI500	xlsx

Export and Save

The raw data consist of physiological signals measured by PSG and environmental data collected by Lanno UMINI500. The format of the data is shown in Table 4.

In this study, the data exported through PSG are in EDF + format, and the basic information and air quality data of the subjects are in xlsx format. EDF is the only digital format that has become widely accepted in commercially available equipment and scientific studies. EDF + is a new data format developed on the basis of EDF, which solves the limitations that EDF does not support events and annotations (Kemp and Olivan 2003). To have the universality of data processing methods and better realize data sharing, the signal formats of PSG output we use are all EDF + . We can then analyze the raw data using software Matlab.

After data collection is completed, start analyzing and saving the data. First, open the software Profusion PSG 4, select the < Study File > , then select < Tool > , click < Auto-Analyze > button. Second, in the < Tools > tab, select to output raw edf data, statistical data, stage graphs, and scoring events after the automatic analysis is completed; the file names are raw, statistics, stages and events, respectively. The software operation process is shown in Fig. 7. The data of Lanno UMINI500 are exported to excel.

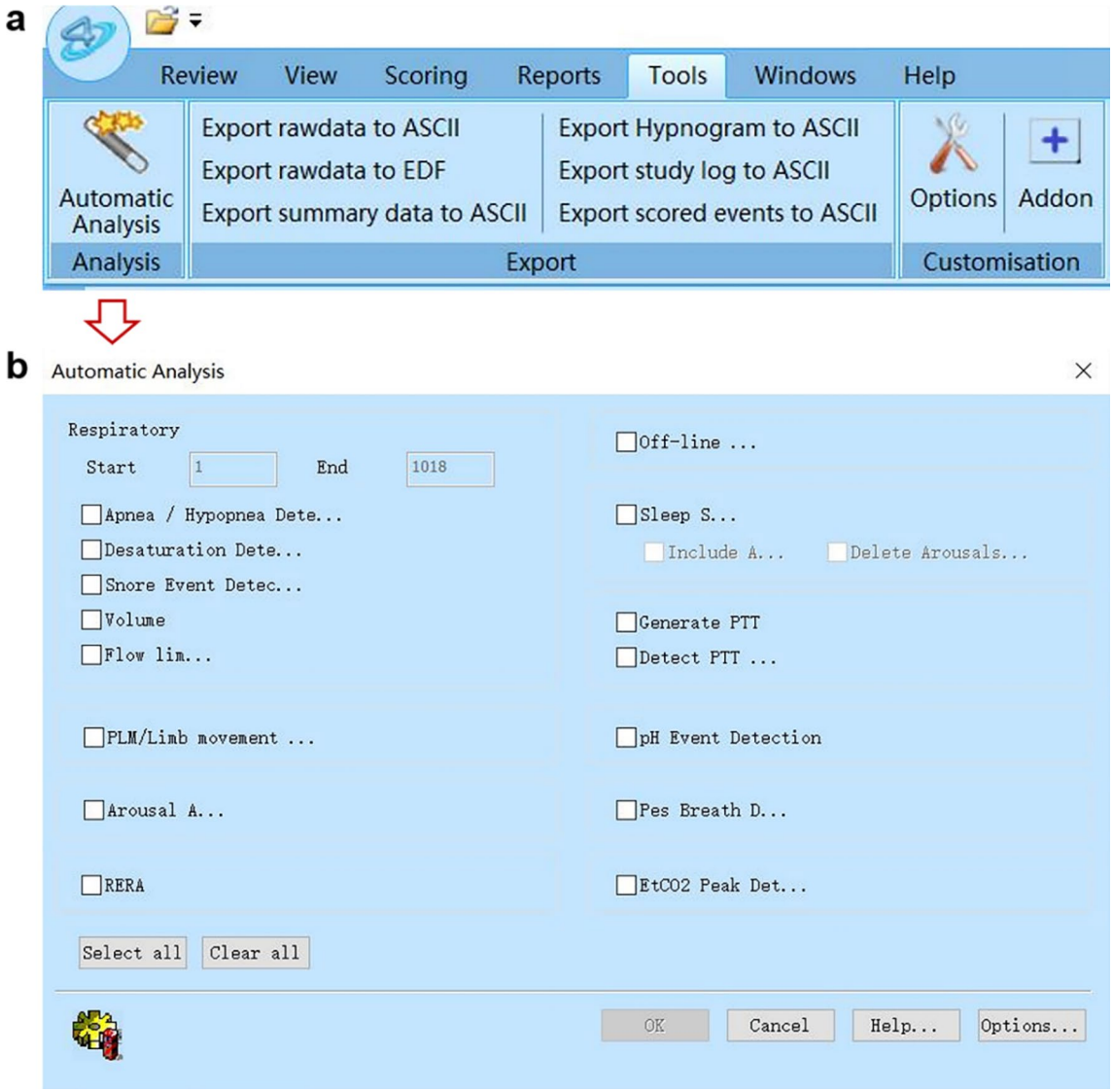

Fig. 7 Software screenshots of data analysis and storage. **a** Data Analysis and Export Toolbar **b** Automatic Analysis Settings Dialog Box

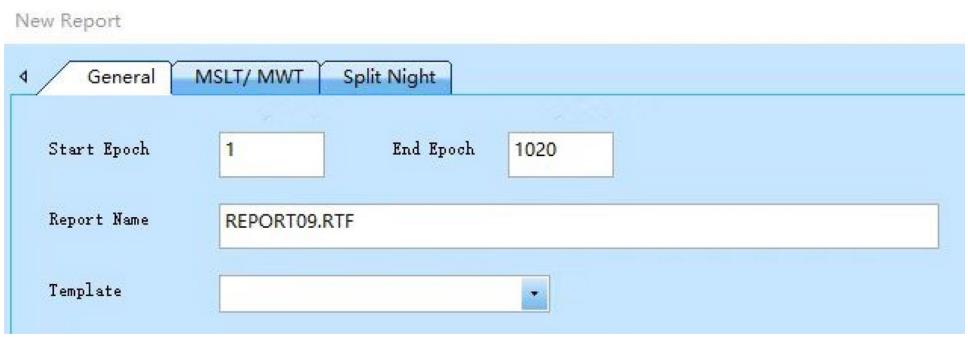

Fig. 8 Automatic analysis report export dialog

Finally, it must be noted that, to confirm that the data are successfully saved, please go to the path "E:\date\ID number\SM" to check whether it exists and whether the memory is consistent with the time length.

Extraction of Sleep Phenotypes

There are two main ways to extract sleep phenotypes, one is automatic extraction through software, and the other is extraction using self-developed algorithms. The automatic extraction of phenotypes by software can also be replaced by self-developed algorithms, which is more flexible and extensible. To ensure accuracy, data review is required before phenotypes extraction, as shown in Fig. 6.

Automatic Analysis

The export of the sleep phenotype still uses the software Profusion PSG 4. Export sleep phenotypes by selecting < study file > → < Report > → < New > (modify start frame and end frame) → < Template > → choose "Fudan University (Sleep).rtf" → < OK > . Automatic analysis report export dialog is shown in Fig. 8.

After exporting the sleep phenotypes, upload the verified and accurate data to the designated server, and then perform file analysis in the human phenotype data collection system and review and check whether the phenotype data are complete, back up regularly and save it properly.

Self-Developed Algorithms

In addition to the automatically extracted sleep phenotypes by software, we also proposed deep learning-based algorithms for sleep staging and sleep event extraction.

We proposed a multi-level neural network architecture for sleep stage classification based on comprehensive feature learning and multi-flow sequence learning (Sun et al. 2019b). This method integrates the feature knowledge of sleep waveforms in clinical medicine, the waveform feature recognition of sleep staging by clinicians, and the time series analysis of sleep stage transformation into the machine learning model, which greatly improves the accuracy of the sleep staging system. Based on this model architecture, we also proposed a two-stage neural network (Sun et al. 2019c) and a hierarchical sequential neural network with feature fusion based on EOG and R–R interval signals (Sun et al. 2019a) for sleep staging. To solve the problem of sleep data imbalance, we proposed a representative EEG data augmentation algorithm (Fan et al. 2020), which considers five data augmentation methods: random copy of few samples, morphological changes, signal segmentation and recombination, transfer learning between datasets, and generative adversarial networks and use it for sleep staging. In addition, we proposed a novel hybrid expert scheme to identify sleep micro-event K-complex by integrating signal morphology with expert knowledge into the decision-making process (Zhao et al. 2021).

Finally, we submitted the results of the phenotypes extracted by the algorithm to the doctor to check and evaluate again. In the future, we will continue to improve the performance of our self-developed algorithms to ensure the accuracy of the results. Combining software automatic extraction of phenotypes with self-developed phenotype extraction methods can build a more complete cohort of sleep phenotypes.

Post-processing

After the phenotypes extraction, verification is performed again, including the inspection of the data and the verification of the doctor. During data inspection, if one of the following situations occurs, the original data and extracted sleep phenotypes need to be reviewed.

(1) The proportion of any sleep stage is 0%;
(2) The proportion of any NREM sleep stage is more than 90%;
(3) The proportion of REM stage is > 60%;
(4) AHI = 0;
(5) Obstructive apnea index > 80;
(6) Central apnea index > 40;
(7) Minimum oxygen saturation during sleep < 40%;
(8) Apnea or hypopnea time < 5 s;
(9) PLM index during sleep > 25;
(10) The length of the respiratory event is > 30 s.

Troubleshooting

Throughout the process, some technical and operational issues may be encountered during the data acquisition, data retrieval, sleep marking, report export, and data saving phases. Troubleshooting advice can be found in Table 5.

Anticipated Results

We anticipate that this protocol can efficiently collect high-quality and reliable phenotypic data from a large population, and establish a sleep phenotype data set with broad population coverage and diverse sleep phenotype types that can be easily used for scientific research. We anticipate obtaining the following results if the recordings are correctly performed:

Table 5 Troubleshooting advice

Stage of the problem	Problem	Solution
Data collection	The device could not be found	Check the IP settings of the software, and set the IP addresses of the computer and the device to the same network segment Check if the power or network cable of the power over Ethernet (POE) switch are disconnected Check all network cable ports to see if the network is normal Check the power and network indicators in the lower left corner of the host Turn off the window firewall of the computer
	Video not showing	Check whether the camera power supply and network cable are disconnected In < Tools > -< Options > -< Digital Video > , select < Use Local Digital Video > and add the camera name
Data retrieval	The waveform is disturbed	The filter setting is wrong: double-click on the waveform label to adjust the filter; Electrode impedance is too high: use proper site and installation techniques to ensure impedance is low enough when recording
	Waveforms not visible on polysomnography	Select the correct file layout name in the layout dialog box of the review menu; in the waveform layout properties dialog box, select Insert to add a waveform, and use the drop-down menu to select the desired insert signal name, such as the drop-down menu of the insert signal. The required insertion signal is not present, that is, it is not recorded
	The waveform is too small or too large	Zoom with mouse scroll
	Waveforms appear to have no undulations	Adjust the screen sharpness or resolution on your computer, the recommended display setting is 1920×1080
	Research files could not be found	Incorrect guide path to acquire data: at the bottom of the open study file dialog, change the guide path to the correct path; select rebuild study file index to refresh the file list
	Incomplete display of pane signals	After adjusting the display to an appropriate format, select < Display > -< Waveform Layout Properties > -< Save As > , and enter the new waveform layout properties file name
Sleep marker	Events cannot be marked on the waveform	Incorrect input signal assignment: In < Tools > -< Options > -< Input Channel Assignment > , select the exact input signal name
	No automatic breath analysis	The input signal parameter settings are incorrect: in < Tools > -< Options > -< Input Channel Assignment > -< Respiration > , select the corresponding breathing channel input
Report export	Report could not be generated	Offline research summary is not formed: make offline research summary in automatic analysis The report template folder path is defined incorrectly: in < Tools > -< Options > -< System Settings > -< General > -< Report Template > Folder, use < Browse > to set the correct report template folder The signal contained in the report does not exist: confirm all the data in the report is exist and correct
	Report does not form correct information	Check whether the definition of the report code is accurate, input the correct report code; the input signal assignment is incorrect: go to Tools-Options-Input Channel Assignment, select the correct input signal; the format of the report code is incorrect, the format must be [@**] which indicates that the code corresponds to the correct reporting code; use a comma and dot after the code and insert the correct modification code
Data saving	Data could not be written to the hard drive	Disk full: delete non-permanently archived research data files from hard disk Storage path setting error: make sure the destination drive is correct Hard disk contains excessive fragmented files: defragment the hard disk regularly

- This protocol gives a standard procedure and conforms to clinical norms in the collection of sleep phenotype data, and the obtained results can be widely used in scientific research and are authoritative.
- Software automatic analysis and self-developed algorithm analysis method can obtain accurate and reliable sleep phenotype data.

- Compared with manual extraction of phenotypes, the process of this protocol has the advantages of high efficiency, high quality, and less errors.
- The sleep phenotype date set is rich and diverse.

Discussion

In this study, a standardized sleep monitoring protocol for large population cohort is proposed. It not only offers detailed procedures in sleep data acquisition and sleep phenotypes extraction, but also provided a dedicated solution for data preservation to protect the privacy of volunteers. After sleep phenotypes extraction, raw data and phenotypes will be uploaded to the server that can ensure the security of the data and the demand for high-performance computing of massive data. In addition, currently, sleep phenotypes extraction mainly includes automatic extraction and self-developed algorithm extraction. Automatic extraction by software can quickly and easily obtain most phenotypes; however, the software automatic extraction method lacks specificity and cannot provide different methods for different situations, which may lead to a little error in the accuracy of the phenotype. The self-developed algorithms introduced in section Data Processing can compensate for this limitation. The self-developed algorithms can be adjusted for different groups of people, so this method has higher adaptability, accuracy, and flexibility and can be better applied to scientific research according to actual needs. Therefore, in this protocol, both the sleep phenotypes extracted by software and self-developed algorithms are involved.

Although this protocol is relatively complete, there are still some points that can be further improved. First, the verification procedure is a semi-auto process. The two types of phenotypes extraction approaches, namely software automatic extraction and self-developed algorithm extraction, are performed separately, then integrated and submitted to the physician for verification. In the future, a fully automated procedure can be developed and added to integrate and accelerate the verification process. Second, although over 380 phenotypes are extracted in this protocol, more innovative and discriminative phenotypes can be derived, such as blood pressure and sleep-related phenotypes, micro-sleep events, etc. More self-developed algorithms can be explored to enhance sleep phenotypes, or combine clinical experience to design more sleep-related questionnaires, such as exploring the impact of recent diet and exercise on sleep. Third, the distribution of participants is uneven. On one hand, there is an uneven distribution of gender. Among the existing volunteers, female volunteers account for the majority, and males account for about 40%. Obviously, women are more willing to participate in such trials. On the other hand, the age distribution is uneven, and the proportion of older volunteers is very low. The average age of all volunteers is 33 years old, about 13% are over 50 years old, and only 0.7% are over 60 years old. Therefore, in the follow-up study, attracting more volunteers, increasing the response rate, and expanding the scope of the population are key issues that need to be considered.

Establishing a large cohort for phenotypic analysis is of great significance, and this protocol can broad the sleep research in the following prospects. First, through the correlation analysis between sleep phenotypes, the external phenotypes of sleep diseases can be familiarized. Then targeted interventions can be proposed in time to avoid more serious diseases after a long time, and reduce the time cost and economic pressure of clinical diagnosis. To illustrate, Goldman et al. simultaneously recorded PSG, questionnaires, and daytime behavior reports of children with autism spectrum disorders (ASD) (Goldman et al. 2009). They identified associations between the sleep phenotypes and daytime behavior, with poor sleepers with ASD showing more hyperactivity and compulsive and ritualistic behavior than good sleepers with ASD. This work provides the foundation for focused studies of pathophysiology and targeted interventions to improve sleep in this population. Second, the association between sleep disorders and other diseases is often not a simple and clear causal relationship, but a complex the interaction mechanism of multiple factors. Therefore, analyzing sleep phenotypes and their associations with other phenotypes can help us to explore the intrinsic links between sleep disorders and other diseases, and thus explain the pathogenesis more comprehensively. A study of sleep in children with down syndrome (DS) showed that children with DS also had a higher incidence of OSA (Nisbet et al. 2015). This leads to sleep fragmentation in children with DS, which in turn leads to worsening cognitive function. Finally, phenotypic differences in different ethnic groups can be studied. People of different races have different physiological structures and psychological states. For example, the mechanisms that cause OSA differ among patients and are likely to differ across ethnicities. Much of the epidemiological data describing the association between OSA and an elevated body mass index (BMI) have been collected primarily in Caucasian populations (Punjabi 2008). O'Driscoll et al. conducted a study that indicated that the physiological phenotypes of OSA differs between Caucasian and Chinese patients (O'Driscoll et al. 2019). Thus, with this protocol, it can not only provide a standardized procedure for exploring sleep phenotypes, but also can assist the sleep research in the aforementioned aspects from a basic understanding of phenotypic characteristics of the Chinese group, to comprehending pathophysiology and pathogenesis of sleep disorders, the discovery of new diagnostic indicators, etc. At

present, our research is still on natural populations. In the future, it can be flexibly modified for different disease studies, such as adding questionnaires or measurement items. This research has great development space and scientific research potential.

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Declarations

Conflicts of Interest WC is the editorial board member and CC is the youth editorial board member of Phenomics, and they were not involved in reviewing this paper.

Competing Interests Wei Chen and Chen Chen are the Members of Phenomics, and they were not involved in reviewing this paper.

Ethical Approval This study was in agreement with the ethical guidelines of the 1975 Declaration of Helsinki and approved by the institutional review board of Fudan University.

Consent to Participants Written informed consents are obtained from all research participants.

Consent for Publication Not applicable.

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