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Sleep behavior and cardiorespiratory fitness in patients after percutaneous coronary intervention during cardiac rehabilitation: protocol for a longitudinal study

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Sleep behavior and cardiorespiratory fitness in patients after percutaneous coronary intervention during cardiac rehabilitation: protocol for a longitudinal study

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Abstract

Introduction: Most patients with coronary heart disease experience sleep disturbances and low cardiorespiratory fitness (CRF), but the relationship between them during cardiac rehabilitation (CR) is still unclear. This article details a protocol for the study of sleep trajectory in patients with coronary heart disease during CR and the relationship between sleep and CRF. A better understanding of the relationship between sleep and CRF on patient outcomes can improve sleep management strategies.

Methods and analysis: This is a longitudinal study with a recruitment target of 101 patients after percutaneous cardiac intervention (PCI) from the Seventh People's Hospital of Shanghai, China. Data collection will include socio-demographic information, diseases, medications and the results of cardiopulmonary exercise tests (CPETs). The information provided by a six-minute walk test (6MWT) will be used to supplement the CPET. The Pittsburgh sleep quality index (PSQI) will be used to understand the sleep conditions of the participants in the past month. The Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder Scale (GAD-7) will be used to assess depression and anxiety, respectively. All participants will be required

to wear a motion recorder on their wrists for 72 h to monitor objective sleep conditions. This information will be collected four times within six months of CR, and patients will be followed up for one year. Mplus 7.1 software will be used to analyze the longitudinal sleep data. The generalized estimating equation will be used to examine the associations between sleep and CRF during CR.

Ethics and dissemination: Ethical approval for this observational longitudinal study was granted by the Shanghai Seventh People's Hospital Ethics Committee on 23 April 2021, (2021-7th-HIRB-012). Study results will be disseminated in peer-reviewed journal articles.

Keywords: sleep disturbance, cardiopulmonary fitness, percutaneous coronary intervention, cardiac rehabilitation, coronary heart disease, protocol

Strengths and limitations of this study

1. This is a longitudinal study of patients in cardiac rehabilitation, assessing sleep trajectory and the relationship between sleep and cardiorespiratory fitness.
2. The use of cardiopulmonary exercise testing and the 6-minute walk test will provide accurate and objective cardiorespiratory fitness outcomes.
3. The Pittsburgh sleep quality Index and actigraphy will be used to comprehensively assess sleep quality and quantity, improving the power to discover patients with sleep disorders.
4. This is a single-centre study, the sample source will only include participants from one tertiary hospital in China.
5. The sample has selection bias, as only patients who voluntarily choose to undergo a cardiac rehabilitation program after percutaneous cardiac intervention.

INTRODUCTION

In recent years, the incidence and mortality of cardiovascular diseases have continued to increase, and they have become the main cause of death worldwide. Chronic ischemic heart disease (IHD) has remained a major health concern for decades. One of the most widely used treatments for patients with IHD is percutaneous coronary intervention (PCI), which has been shown to significantly

reduce patient mortality from acute myocardial infarction. However, after complete or incomplete revascularization procedures, patients may still encounter stent thrombosis, angina and symptoms related to psychological and somatic stress. Sleep disturbance or insomnia is quite common in patients with IHD. It is estimated that 1/3 of patients who have undergone PCI suffer from a sleep disturbance. [1] Difficulty falling asleep and having several awakenings during the night are the most common symptoms. Sleep disturbances are an independent prognostic marker for cardiac outcomes. [2] Study results have demonstrated that patients undergoing PCI have an increased risk of adverse cardiovascular events and mortality after experiencing long-term sleep disturbances. [3 4] In addition, sleep disturbances may have a negative impact on physical and mental health status and may reduce patient compliance with cardiac rehabilitation (CR), thereby influencing the course of rehabilitation. [5-9]

CR is a highly regarded program of secondary prevention measures, which has been endorsed by the European Society of Cardiology, the American Heart Association and the American College of Cardiology. [10-12] Exercise is a core component of CR. [13] Relevant studies have found that adherence to exercise-based CR can effectively reduce the risk of further cardiac insults, improve sleep quality, enhance cardiorespiratory fitness (CRF) and minimize hospital re-admission and mortality. [14-16] In the process of CR, CRF is used to assess the severity of the patient's cardiac limitation and the recovery after a cardiac event, and it is an important independent risk factor for cardiovascular disease. [17 18] However, limited knowledge exists on the relationship between sleep and CRF. In a large cross-sectional study of 51,000 participants, peak oxygen uptake (VO_{2peak}) was used to estimate CRF, showing a modest inverse association between having difficulty falling asleep at night and VO_{2peak}. [19] In contrast, another study used a symptom-limited cardiopulmonary exercise test (CPET) to objectively measure CRF and used accelerometry to monitor sleep patterns. The study reported that CRF and sleep characteristics were not significantly correlated in adults with primary hypertension. [20]

In general, most studies so far are limited cross-sectional surveys; thus, the

interactive relationship between sleep and CRF remains to be established. Moreover, subjective reports are used to assess perceptions of sleep quality in most studies, but they may not accurately measure sleep duration and efficiency. Within this context, clinicians cannot provide targeted guidance for patients undergoing CR after PCI.

Therefore, the purposes of this study are to: 1) investigate the sleep quality and efficiency of patients undergoing CR for the first time after PCI; 2) determine the sleep trajectory and influencing factors of patients undergoing CR for the first three months after PCI; and 3) investigate the longitudinal correlation between objectively measured sleep quality and CRF in patients undergoing CR after PCI.

METHODS

Patient and public involvement

On the basis of literature review in related fields, the research questions and outcome measures were evaluated and discussed by researchers. Patients were not involved in the design of the study, but their cooperation was required during the implementation phase of the study, and their needs and preferences were fully taken into account. Test results will be communicated verbally or in writing to participants.

Study design

This is a longitudinal study of patients in CR, which collects data at five time points as follows: 1) T1, patients will have completed the first CPET one month after PCI and will have begun CR program, based on the risk evaluation by the physicians; 2) T2, one month after the beginning of CR program; 3) T3, three months after the beginning of CR program; 4) T4, six months after the beginning of CR program; and 5) T5, twelve months after the beginning of CR program. This study explores the time-varying effects of sleep structure in patients after PCI during CR and the potential relationship between sleep and CRF. The data will be collected in person at the time of the four scheduled visits. Twelve months after the start of CR, disease prognosis will be followed up over phone. The study framework is shown in Figure 1.

Participants

This study will be conducted at the Seventh People's Hospital of Shanghai, China. A convenience sampling method will be used to recruit patients after PCI in the rehabilitation department. We hope to recruit at least 101 patients who meet the eligibility criteria. We plan to recruit patients in CR over an 18-month period beginning in May 2021.

General inclusion criteria

The inclusion criteria are as follows: 1) diagnosed with coronary heart disease and underwent PCI; 2) clinically stable; 3) aged 18–75 years; 4) no contraindications to exercise rehabilitation; and 5) capable and mentally able to communicate with the investigator in verbal or written form and provide written informed consent.

General exclusion criteria

The exclusion criteria are as follows: 1) unable to participate in regular exercise training on time; 2) have cardiogenic shock or severe arrhythmia; 3) have severe lung diseases; and 4) have severe liver and kidney dysfunction, infection, tumor or anemia.

Recruitment

Recruitment posters with research details will be placed at the front of the rehabilitation clinic. Medical staff will introduce this study to eligible patients undergoing CPET. Patients who are post-PCI will be invited to participate in this study after signing a written informed consent form.

Study procedures

After a patient is enrolled in the study, the medical staff will conduct a baseline assessment including sociodemographic information such as age, sex, education, socioeconomic status, comorbidities and medication use, as well as CPET results. The baseline assessment will include the Pittsburgh sleep quality index (PSQI) to understand the sleep conditions of the participants in the past month. The mental states of depression and anxiety will be assessed with the Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorder Scale (GAD-7), respectively. All enrolled participants will be required to wear a motion recorder on their wrists for 72 h to objectively monitor sleep conditions. The physical therapist will prescribe

a personalized exercise program for each participant, based on CPET results and the patient's disease state. The patient will then undergo a CR exercise program three times a week for a total of 6 months. During the CR process, data will be collected again in the 1st, 3rd and 6th months. In addition, the 6-minute walk test (6MWT) will be performed in the 1st and 3rd months of the CR program. Except for this, other assessment contents will be the same as those listed in the baseline assessments. At the 12th month, a telephonic follow-up will also be required. The follow-up content includes major adverse cardiovascular events (MACEs) and the number of rehospitalizations. Table 1 shows the data collection details.

Sample size

The calculations of the sample size were based on an estimate of the correlation coefficient between sleep quality and CRF in patients from previous studies. [21] With a two-sided significance level of 5% and a minimum correlation coefficient of 0.37 between sleep quality and CRF, 84 patients after PCI would be included. Considering an attrition rate of 20%, the final total sample size will be at least 101 patients.

Measurements

Cardiopulmonary exercise testing (CPET)

The CPET will be performed by professional physicians with operating qualifications using COSMED S.R.L Pulmonary Function Equipment (The Metabolic company, Guangzhou, China). Patients will not need to stop cardiovascular drugs (including β-blockers) on the day of the CPET test and must avoid drinking caffeine beverages and smoking 2 h before the test. According to the American Thoracic Society (ATS) guidelines, CPET uses a continuous load escalation program for symptomatic self-limiting cycling exercise. [22] The patient sits on a cycle ergometer and first rests for 3 minutes and then performs a zero-load idling warm-up for at least 1 minute, followed by the load-increasing exercise phase with an incremental power of 10 W/min or 20 W/min, so that the patient can reach maximum exercise intensity for self-limiting symptoms. The speed of the treadmill is maintained at 55–65 r/min throughout the test. electrocardiogram, blood pressure and respiratory

status will be continually monitored during the recovery period for at least 3 minutes after the load exercise stops, until the end of the test. The main measured outcomes include the anaerobic threshold, peak oxygen uptake, peak oxygen pulse, minute ventricular load and maximum exercise load. The V-slope method will be used to calculate the anaerobic threshold.

Six-minute walk test (6MWT)

Functional exercise capacity is objectively evaluated by the 6MWT. This test records the distance that a patient can quickly walk along a long and flat corridor in 6 min. During this test, patients are permitted to decide their walking speed but are still required to walk as far as possible for 6 min. Every minute, physiotherapists will call out a standardized phrase of verbal encouragement. The 6MWT process is based on guidelines from the ATS. [23]

Actigraphy for the assessment of sleep

Actigraphy (Respironics Inc, Murrysville, America) will be continuously monitored for 24 h to analyze patients' sleep and waking data. The recording frequency interval for actigraphy will be 30 s/frame, and the recording time will be 3 days. The exported sleep report will comprise daily sleep data and average sleep data. Sleep data will include: 1) sleep time and wake-up time; 2) time in bed; 3) actual sleep time; 4) sleep latency; 5) sleep efficiency; 6) the number of minutes and times of awakening after the start of sleep. Finally, the averaged sleep data will be included in the statistical analysis.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a self-rated questionnaire designed and revised by scholars including Buysse to measure patients' sleep quality in the past month. [24] The questionnaire has a total of 18 items, which are used to measure the following: 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) sleep efficiency; 5) sleep disturbances; 6) use of sleeping medication; and 7) daytime dysfunction.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a reliable and effective indicator for measuring the severity of depression, and its items correspond to the DSM-IV diagnostic criteria for

depression.[25] The PHQ-9 total score ranges from 0 to 27 points, and the scores 5, 10 and 20 are the cut-off values for mild, moderate and severe depression, respectively.

General anxiety disorder scale (GAD-7)

The GAD-7 is used to determine whether the patients have psychological symptoms of anxiety and their frequency within 2 weeks. [26] This scale includes seven items, each with a score of 0–3 points for a total score of 21 points, of which a score of 10–21 points denotes having an anxious mental state.

Statistical analysis

We will use the growth mixture model (GMM) to analyze the participants' longitudinal sleep data with Mplus 7.1 software (Muthén & Muthén, Los Angeles, America) and identify the longitudinal development trajectory of sleep during CR. We will explore the characteristics of sleep trajectory in the sample population over time based on the consideration of population heterogeneity. The generalized estimating equation (GEE) will be used to examine the associations between sleep and cardiopulmonary function during CR, adjusting for potential covariates.

DISCUSSION

Sleep disturbance after PCI can cause both acute and chronic physiological and psychological burden to patients. Following PCI, patients must reduce their risk of cardiac events and sleep disturbance through secondary prevention strategies. [27] CR is helpful for reducing the deleterious effects of sleep disorders and improving CRF. This protocol describes a longitudinal observational study to explore the time-varying effect of sleep structure and the potential relationship between sleep and CRF in patients after PCI and during CR. The results of this study will help patients implement effective sleep management during the CR period. A key strength of this study is its prospective and longitudinal design, which will help resolve the question of the potential relationship between sleep and CRF.

As far as we know, this is the first longitudinal study to explore the trajectory of patients' sleep structure changes after PCI and during CR. The advantages of this study include the use of the PSQI and actigraphy to comprehensively assess sleep quality and quantity. Actigraphy is an objective sleep measure that improves data

accuracy. CPET will also be used to non-invasively monitor the electrocardiogram, pulse oximetry (SpO_2), O_2 inhalation and CO_2 output at rest and during exercise. Cardiopulmonary reserve function and exercise tolerance will be analyzed by combining multiple indicators.

There are some limitations to this study. The sample source will only include participants from one hospital in China. Due to the limitations of research sites and recruitment strategies, our sample may be prone to selection bias and random-sampling recruitment may be difficult. The study will only include patients who voluntarily choose to undergo a CR program after PCI. Patients who meet the conditions but have a fear of exercise will be excluded.

This study aims to investigate the sleep conditions of patients during CR and the relationship with CRF as the preliminary basis of clinical intervention. The results of this study will provide useful knowledge for exploring targeted sleep management during the CR period in future.

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Contributors

Lan Huang is the principal investigator of the study and is responsible for protocol design, data collection and analysis and presentation of findings. She was also responsible for drafting this manuscript. Jing Wu obtained funding. Jie Zhou、Husheng Li and Yiyan Wang participated in data collection and analysis. Xubo Wu and Jing Wu contributed to the protocol design and revisions of the manuscript. All authors have read and approved the final manuscript.

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Competing interests

None declared.

Data sharing

No additional data are available.

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TABLE 1 Data collection in the study

Items	T1	T2	T3	T4	T5
Demographic characteristic	√				
Baseline status	√				
CPET	√			√	
6MWT		√	√		
Actigraphy	√	√	√	√	
PSQI	√	√	√	√	
PHQ-9	√	√	√	√	
GAD-7	√	√	√	√	
MACEs					√
Rehospitalizations					√

Notes: T1: Baseline assessment and enrolment; T2: one month after the beginning of CR program; T3: three months after the beginning of CR program; T4: six months after the beginning of CR program; T5: twelve months after the beginning of CR program.

Abbreviations: CPET: cardiopulmonary exercise testing; 6MWT: six-minute walk test; PSQI: Pittsburgh Sleep Quality Index; PHQ-9: Patient Health Questionnaire; GAD-7: General anxiety disorder scale; MACEs: major adverse cardiovascular events

FIGURE 1 Study framework

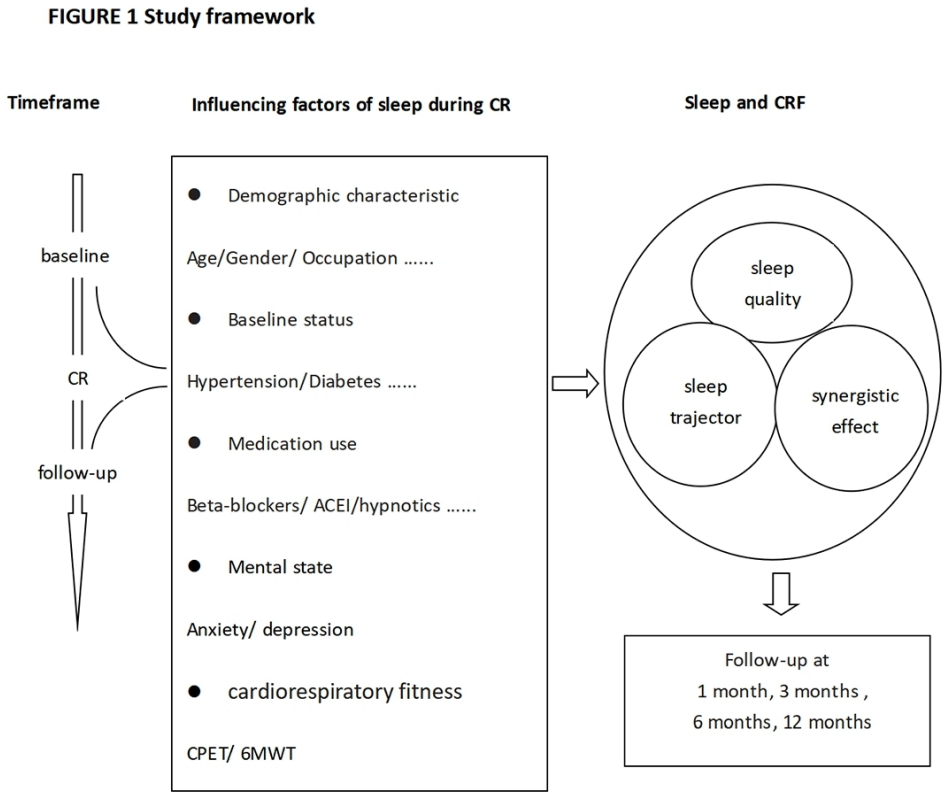

FIGURE 1 Study framework

199x187mm (144 x 144 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Sleep behavior and cardiorespiratory fitness in patients after percutaneous coronary intervention during cardiac rehabilitation: protocol for a longitudinal study

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Abstract

Introduction: Most patients with coronary heart disease experience sleep disturbances and low cardiorespiratory fitness (CRF), but their relationship during cardiac rehabilitation (CR) is still unclear. This article details a protocol for the study of sleep trajectory in patients with coronary heart disease during CR and the relationship between sleep and CRF. A better understanding of the relationship between sleep and CRF on patient outcomes can improve sleep management strategies.

Methods and analysis: This is a longitudinal study with a recruitment target of 101 patients after percutaneous cardiac intervention (PCI) from the Seventh People's Hospital of Shanghai, China. Data collection will include demographic characteristics, medical history, physical examination, blood sampling, echocardiography, and the results of cardiopulmonary exercise tests (CPETs). The information provided by a six-minute walk test (6MWT) will be used to supplement the CPET. The Pittsburgh sleep quality index (PSQI) will be used to understand the sleep conditions of the participants in the past month. The Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder Scale (GAD-7) will be used to assess depression and

anxiety, respectively. All participants will be required to wear an actigraphy on their wrists for 72 h to monitor objective sleep conditions. This information will be collected four times within six months of CR, and patients will be followed up for one year. The growth mixture model will be used to analyze the longitudinal sleep data. The generalized estimating equation will be used to examine the associations between sleep and CRF during CR.

Ethics and dissemination: Ethical approval for this observational longitudinal study was granted by the Shanghai Seventh People's Hospital Ethics Committee on 23 April 2021, (2021-7th-HIRB-012). Study results will be disseminated in peer-reviewed journal articles.

Keywords: sleep disturbance, cardiopulmonary fitness, percutaneous coronary intervention, cardiac rehabilitation, coronary heart disease, protocol

Strengths and limitations of this study

1. This is a longitudinal study of patients in cardiac rehabilitation, assessing sleep trajectory and the relationship between sleep and cardiorespiratory fitness.
2. The use of cardiopulmonary exercise testing and the 6-minute walk test will provide accurate and objective cardiorespiratory fitness outcomes.
3. The Pittsburgh sleep quality Index and actigraphy will be used to comprehensively assess sleep quality and quantity, improving the power to discover patients with sleep disorders.
4. This is a single-center study, the sample source will only include participants from one tertiary hospital in China.
5. The sample has selection bias, as only patients who voluntarily choose to undergo a cardiac rehabilitation program after the percutaneous cardiac intervention.

INTRODUCTION

Cardiovascular mortality, mostly attributable to ischemic heart disease (IHD), is expected to increase more dramatically in the next decade globally. [1] According to the 2018 ESC/EACTS Guidelines on myocardial revascularization, timely percutaneous coronary intervention (PCI) of the infarct-related artery is still the

priority treatment of IHD patients. [2] However, after complete or incomplete revascularization procedures, patients may still encounter stent thrombosis, angina, and symptoms related to psychological and somatic stress. Sleep disturbances such as insomnia, obstructive sleep apnea (OSA) are quite common in patients with IHD. [3-5] Evidence from an epidemiological survey demonstrated that over 1/3 of post-PCI patients with the confession of sleep disturbance. [6 7] Sleep trait abnormalities include difficulty in falling asleep, periods of breathing cessation, or multiple awakenings during the night, which resulted in insufficient sleep durations and poor sleep quality.[3 8] It is established that disturbed sleep is associated with adverse cardiac events after PCI. [9-11] Previous studies have predominantly focused on sleep duration as an isolated risk factor for cardiovascular disease. [12] However, sleep is multidimensional and multi-causal. It is not only associated with cardiovascular outcome but also affects the patient compliance and prognosis during the cardiac rehabilitation (CR) program.[12-16]

CR is a highly regarded program of secondary prevention measures, which has been endorsed by the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. [17-19] Exercise is a core component of CR. [20] Relevant studies have found that adherence to exercise-based CR can effectively reduce the risk of further cardiac insults, improve sleep quality, enhance cardiorespiratory fitness (CRF) and minimize hospital re-admission and mortality. [21-24] In the process of CR, CRF is used to assess the severity of the patient's cardiac limitation and the recovery after a cardiac event, and it is an important independent risk factor for cardiovascular disease. [25 26] Moreover, the risk of long-term major adverse cardiovascular events (MACE) is further increased when Sleep disturbances and decreased cardiorespiratory fitness (CRF) co-occur. [27] The number of studies evaluating sleep in relation to CRF is limited, with the majority of research being of cross-sectional design. In a large cross-sectional study of 51,000 participants, peak oxygen uptake (VO_{2peak}) was used to estimate CRF, showing a modest inverse association between having difficulty falling asleep at night and VO_{2peak}. [28] In contrast, another study used a symptom-limited cardiopulmonary

exercise test (CPET) to objectively measure CRF and used accelerometry to monitor sleep patterns. The study reported that CRF and sleep characteristics were not significantly correlated in adults with primary hypertension. [29] Lindegård et al found similary results in a longitudinal cohort study of women diagnosed with stress-related exhaustion disorder. [30]

Although prior observational evidence exists, none included the prospective, multi-time assessment of sleep and CRF during the CR program of post-PCI patients. There is still limited information on the relationship between patients' sleep traits and the joint effects of CRF. Moreover, subjective reports are used to assess perceptions of sleep quality in most studies, but they may not accurately measure sleep duration and efficiency. Within this context, clinicians cannot provide targeted guidance for patients undergoing CR after PCI.

Therefore, the purposes of this study are to: 1) investigate the sleep quality and efficiency of patients undergoing CR for the first time after PCI; 2) determine the sleep trajectory and influencing factors of patients undergoing CR for the first six months after PCI; and 3) investigate the longitudinal correlation between objectively measured sleep quality and CRF in patients undergoing CR after PCI.

METHODS

Patient and public involvement

Based on literature review in related fields, the research questions and outcome measures were evaluated and discussed by researchers. Patients were not involved in the design of the study, but their cooperation was required during the implementation phase of the study, and their needs and preferences were fully taken into account. Test results will be communicated verbally or in writing to participants.

Study design

This is a longitudinal study of patients in CR, which collects data at five-time points as follows: 1) T1, patients will have completed the first CPET one month after PCI and will have begun CR program, based on the risk evaluation by the physicians; 2) T2, one month after the beginning of CR program; 3) T3, three months after the

beginning of CR program; 4) T4, six months after the beginning of CR program; and 5) T5, twelve months after the beginning of CR program. This study explores the time-varying effects of sleep structure in patients after PCI during CR and the potential relationship between sleep and CRF. The data will be collected in person at the time of the four scheduled visits. Twelve months after the start of CR, the disease prognosis will be followed up over the phone. The study framework is shown in Figure 1.

Participants

This study will be conducted at the Seventh People's Hospital of Shanghai, China. A convenience sampling method will be used to recruit patients after PCI in the rehabilitation department. We hope to recruit at least 101 patients who meet the eligibility criteria. We plan to recruit patients in CR over an 18-month period beginning in May 2021.

General inclusion criteria

The inclusion criteria are as follows: 1) diagnosed with coronary heart disease and underwent PCI; 2) clinically stable; 3) aged 18–75 years; 4) no contraindications to exercise rehabilitation, and 5) capable and mentally able to communicate with the investigator in verbal or written form and provide written informed consent.

General exclusion criteria

The exclusion criteria are as follows: 1) unable to participate in regular exercise training on time; 2) have a cardiogenic shock or severe arrhythmia; 3) have severe lung diseases; and 4) have severe liver and kidney dysfunction, infection, tumor, or anemia.

Recruitment

Recruitment posters with research details will be placed at the front of the rehabilitation clinic. Medical staff will introduce this study to eligible patients undergoing CPET. Patients who are post-PCI will be invited to participate in this study after signing a written informed consent form.

Study procedures

At the baseline selection prior to the study, subjects provided a self-report of

demographic characteristics and medical history. The medical staff will conduct clinical examination including physical examination, blood sampling, echocardiography, as well as CPET results. Body mass index (BMI) and Waist circumference (WC) were determined during physical examination. The fasting serum of each subject was collected in the morning, the measurements of fasting plasma glucose (FPG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were recorded. Cardiac biomarkers including B-type natriuretic peptide (BNP), serum high-sensitivity C-reactive protein (hsCRP), and Homocysteine (HCY) were measured in a laboratory. Data from echocardiography examination were collected, including left ventricular ejection fraction (LVEF), left atrium diameter (LAD), left ventricular internal diameter at end-diastole (LVIDd), interventricular septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT).

CPET will be assessed by a physician, focusing on recording peak oxygen uptake (VO2 peak), oxygen consumption divided by heart rate (known as the oxygen pulse: VO2/HR), metabolic equivalents (METs), minute ventilation divided by carbon dioxide production (VE/VCO2 slope), oxygen uptake efficiency slope (OUES), anaerobic threshold (AT), heart rate recovery at 1 minute after exercise (HRR 1 minute), maximal heart rate reserve (HRR Max).

The baseline assessment will also include the Pittsburgh sleep quality index (PSQI) to understand the sleep conditions of the participants in the past month. The mental states of depression and anxiety will be assessed with the Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorder Scale (GAD-7), respectively. The scales are in the Chinese version. All enrolled participants will be required to wear an actigraphy on their wrists for 72 h to objectively monitor sleep conditions. The physical therapist will prescribe a personalized exercise program for each participant, based on the CPET result and the patient's disease state. Then the patient will undergo a CR exercise program three times a week in the rehabilitation clinic for a total of 6 months. Patients perform 40 minutes of aerobic training on a treadmill or bicycle each time and use a heart rate monitor and Borg ratings of perceived exertion scale to assess exercise intensity. During the CR process, data

(physical examination, echocardiography, blood sampling, actigraphy for the assessment of sleep, PSQI, PHQ-9, and GAD-7) will be collected again in the 1st, 3rd, and 6th months. In addition, CEPT will be performed again in the 6th month of the CR program and the 6-minute walk test (6MWT) will be performed in the 1st and 3rd months of the CR program to supplement the CPET. Except for this, other assessment contents will be the same as those listed in the baseline assessments. At the 12th month, a telephonic follow-up will also be required. The follow-up content includes major adverse cardiovascular events (MACEs) and the number of rehospitalizations. Table 1 shows the data collection details.

Sample size

The calculations of the sample size were based on an estimate of the correlation coefficient between sleep quality and CRF in participants from previous studies. [31] With a two-sided significance level of 5% and a minimum correlation coefficient of 0.37 between sleep quality and CRF, 84 patients after PCI would be included. Considering an attrition rate of 20%, the final total sample size will be at least 101 patients.

Measurements

Cardiopulmonary exercise testing (CPET)

The CPET will be performed by professional physicians with operating qualifications using COSMED S.R.L Pulmonary Function Equipment (The Metabolic company, Guangzhou, China). Patients will not need to stop cardiovascular drugs (including β-blockers) on the day of the CPET test and must avoid drinking caffeine beverages and smoking 2 h before the test. According to the American Thoracic Society (ATS) guidelines, CPET uses a continuous load escalation program for symptomatic self-limiting cycling exercise. [32] The patient sits on a cycle ergometer and first rests for 3 minutes and then performs a zero-load idling warm-up for at least 1 minute, followed by the load-increasing exercise phase with an incremental power of 10 W/min or 20 W/min, so that the patient can reach maximum exercise intensity for self-limiting symptoms. The speed of the treadmill is maintained at 55–65 r/min throughout the test. electrocardiogram, blood pressure, and respiratory

status will be continually monitored during the recovery period for at least 3 minutes after the loading exercise stops, until the end of the test. The main measured outcomes include the anaerobic threshold, peak oxygen uptake, peak oxygen pulse, minute ventricular load, and maximum exercise load. The V-slope method will be used to calculate the anaerobic threshold.

Six-minute walk test (6MWT)

Functional exercise capacity is objectively evaluated by the 6MWT. This test records the distance that a patient can quickly walk along a long and flat corridor in 6 min. During this test, patients are permitted to decide their walking speed but are still required to walk as far as possible for 6 min. Every minute, physiotherapists will call out a standardized phrase of verbal encouragement. The 6MWT process is based on guidelines from the ATS. [33]

Actigraphy for the assessment of sleep

Actigraphy (Respironics Inc, Murrysville, America) will be continuously monitored for 24 h to analyze patients' sleep and waking data. The recording frequency interval for actigraphy will be 30 s/frame, and the recording time will be 3 days. The exported sleep report will comprise daily sleep data and average sleep data. Sleep data will include: 1) sleep time and wake-up time; 2) time in bed; 3) actual sleep time; 4) sleep latency; 5) sleep efficiency; 6) the number of minutes and times of awakening after the start of sleep. Finally, the averaged sleep data will be included in the statistical analysis.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a sleep self-rated questionnaire designed and revised by scholars including Buysse. [34] In this study, the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) was used to measure the sleep quality of patients in the past month. [35] The questionnaire has a total of 18 items, which are used to measure the following: 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) sleep efficiency; 5) sleep disturbances; 6) use of sleeping medication, and 7) daytime dysfunction.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a reliable and effective indicator for measuring the severity of

depression, and its items correspond to the DSM-IV diagnostic criteria for depression. [36] In this study, the Chinese version of the PHQ-9 was used to assess the severity of depression in patients in the last two weeks through nine questions. [37] The PHQ-9 total score ranges from 0 to 27 points, and the scores 5, 10, and 20 are the cut-off values for mild, moderate, and severe depression, respectively.

General anxiety disorder scale (GAD-7)

The GAD-7 is used to determine whether the patients have psychological symptoms of anxiety and their frequency within 2 weeks. [38] The Chinese version of GAD-7 showed good reliability and validity in cardiovascular patients. [37] This scale includes seven items, each with a score of 0–3 points for a total score of 21 points, of which a score of 10–21 points denotes having an anxious mental state.

Statistical analysis

The results will be statistically analyzed using SPSS 25.0 software (SPSS Inc., Chicago, Illinois, USA) and Mplus 7.1 software (Muthén & Muthén, Los Angeles, America). Continuous variables are expressed as mean ± standard deviation and categorical variables as proportions. We will use the growth mixture model (GMM) to analyze the participants' longitudinal sleep data and identify the longitudinal development trajectory of sleep during CR. And we will explore the characteristics of sleep trajectory in the sample population over time based on the consideration of population heterogeneity. GMM combines aspects of latent growth curve modeling and finite mixture modeling to identify discrete trajectories in longitudinal data. [39 40] The generalized estimating equation (GEE) will be used to examine the association between sleep and cardiopulmonary function during CR, adjusting for potential covariates which include age, sex, education, socioeconomic status, comorbidities, drug use, and psychological status. Cox regression model was used to calculate hazard ratios (HRs) and 95% confidence interval (CI) for the incident of major adverse cardiovascular events after 12 months of CR in relation to sleep.

DISCUSSION

Sleep disturbance after PCI can cause both acute and chronic physiological and psychological burdens to patients. Following PCI, patients must reduce their risk of

cardiac events and sleep disturbance through secondary prevention strategies. [41] CR is helpful for reducing the deleterious effects of sleep disorders and improving CRF. This protocol describes a longitudinal observational study to explore the time-varying effect of sleep structure and the potential relationship between sleep and CRF in patients after PCI and during CR. Compared to the longitudinal study by Mazaki T et al., the sleep data collected by actigraphy and PSQI are more extensive and comprehensive. [11] Moreover, multi-time-point sleep data can display the dynamic changes of sleep in patients after PCI during CR, helping patients to implement effective sleep management during the CR period. Additionally, given the importance of CRF for cardiovascular disease, a key strength of this study is addressing the longitudinal underlying relationship between sleep and CRF. As far as we know, this is the first longitudinal study to explore the trajectory of patients' sleep structure changes after PCI and during CR. The advantages of this study include the use of the PSQI and actigraphy to comprehensively assess sleep quality and quantity. Actigraphy is an objective sleep measure that improves data accuracy. CPET will also be used to non-invasively monitor the electrocardiogram, pulse oximetry (SpO_2), O_2 inhalation, and CO_2 output at rest and during exercise. Cardiopulmonary reserve function and exercise tolerance will be analyzed by combining multiple indicators.

There are some limitations to this study. First, the sample source will only include participants from one hospital in China. Due to the limitations of research sites and recruitment strategies, our sample may be prone to selection bias and random-sampling recruitment may be difficult. Second, the study will only include patients who voluntarily choose to undergo a CR program after PCI. Patients who meet the conditions but have a fear of exercise will be excluded. This part of the patient information may have an impact on the study results. Finally, we did not use the gold standard sleep assessment technique, polysomnography (PSG). PSG is difficult and expensive due to the fact that the patient is out of hospital for a long period of time and the cardiac rehabilitation takes place in a rehabilitation clinic. Although actigraphy cannot replace PSG in terms of diagnostic accuracy and

reliability, it has shown good performance for tracking sleep and wakefulness. [42 43]

Poor CRF is considered a possible adverse health outcome associated with poor sleep. This study aims to investigate the sleep conditions of patients during CR and the relationship with CRF as the preliminary basis of clinical intervention. The exploration of the dynamic fluctuations of sleep and its relationship with CRF may provide useful reference for targeted cardiac rehabilitation management. During CR management, medical staff can timely detect and adjust the patient's adverse state through objective sleep and CRF monitoring, and speed up the recovery process.

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Contributors

Lan Huang is the principal investigator of the study and is responsible for protocol design, data collection and analysis, and presentation of findings. She was also responsible for drafting this manuscript. Jing Wu obtained funding. Jie Zhou、Husheng Li and Yiyan Wang participated in data collection and analysis. Xubo Wu and Jing Wu contributed to the protocol design and revisions of the manuscript. All authors have read and approved the final manuscript.

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Competing interests

None declared.

Data sharing

No additional data are available.

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TABLE 1 Data collection in the study

Items	T1	T2	T3	T4	T5
Demographic characteristic	√				
Medical history	√				
Physical examination	√	√	√	√	
Blood sampling	√	√	√	√	
Echocardiography	√	√	√	√	
CPET	√			√	
6MWT		√	√		
Actigraphy	√	√	√	√	
PSQI	√	√	√	√	
PHQ-9	√	√	√	√	
GAD-7	√	√	√	√	
MACEs					√
Rehospitalizations					√

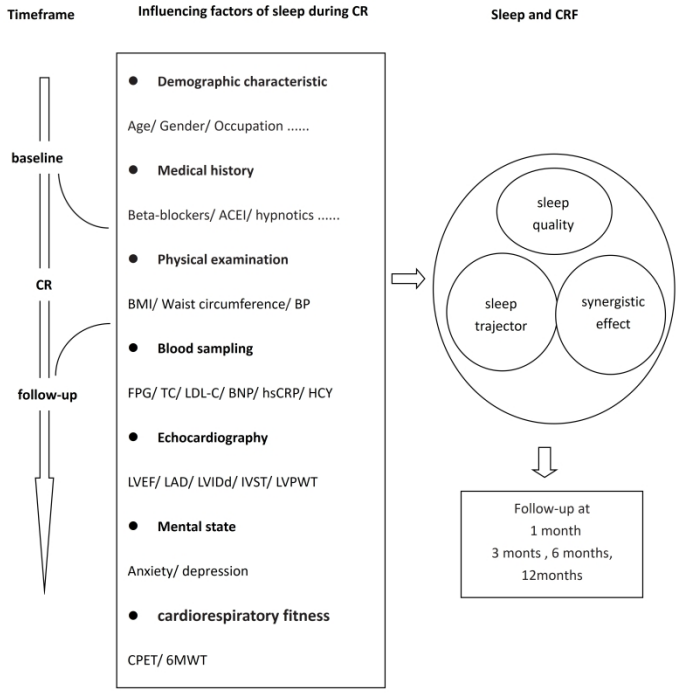
Notes: T1: Baseline assessment and enrolment; T2: one month after the beginning of CR program; T3: three months after the beginning of CR program; T4: six months after the beginning of CR program; T5: twelve months after the beginning of CR program. Physical examination: Body mass index (BMI) , Waist circumference (WC), blood pressure (BP); Blood sampling: fasting plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), B-type natriuretic peptide (BNP), serum high-sensitivity C-reactive protein (hsCRP), Homocysteine

(HCY); Echocardiography: left ventricular ejection fraction (LVEF), left atrium diameter (LAD), left ventricular internal diameter at end-diastole (LVIDd), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT)

Abbreviations: CPET: cardiopulmonary exercise testing; 6MWT: six-minute walk test; PSQI: Pittsburgh Sleep Quality Index; PHQ-9: Patient Health Questionnaire; GAD-7: General anxiety disorder scale; MACEs: major adverse cardiovascular events

FIGURE 1 Study framework

FIGURE 1 Study framework



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4-5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	

Continued on next page

Results			
Participants	13 *	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14 *	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15 *	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	
Generalisability	21	Discuss the generalisability (external validity) of the study results	
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Sleep behavior and cardiorespiratory fitness in patients after percutaneous coronary intervention during cardiac rehabilitation: protocol for a longitudinal study

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Sleep behavior and cardiorespiratory fitness in patients after percutaneous coronary intervention during cardiac rehabilitation: protocol for a longitudinal study

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Abstract

Introduction: Most patients with coronary heart disease experience sleep disturbances and low cardiorespiratory fitness (CRF), but their relationship during cardiac rehabilitation (CR) is still unclear. This article details a protocol for the study of sleep trajectory in patients with coronary heart disease during CR and the relationship between sleep and CRF. A better understanding of the relationship between sleep and CRF on patient outcomes can improve sleep management strategies.

Methods and analysis: This is a longitudinal study with a recruitment target of 101 patients after percutaneous cardiac intervention (PCI) from the Seventh People's Hospital of Shanghai, China. Data collection will include demographic characteristics, medical history, physical examination, blood sampling, echocardiography, and the results of cardiopulmonary exercise tests (CPETs). The information provided by a six-minute walk test (6MWT) will be used to supplement the CPET. The Pittsburgh sleep quality index (PSQI) will be used to understand the sleep conditions of the participants in the past month. The Patient Health Questionnaire (PHQ-9) and General Anxiety Disorder Scale (GAD-7) will be used to assess depression and

anxiety, respectively. All participants will be required to wear an actigraphy on their wrists for 72 h to monitor objective sleep conditions. This information will be collected four times within six months of CR, and patients will be followed up for one year. The growth mixture model will be used to analyze the longitudinal sleep data. The generalized estimating equation will be used to examine the associations between sleep and CRF during CR.

Ethics and dissemination: Ethical approval for this observational longitudinal study was granted by the Shanghai Seventh People's Hospital Ethics Committee on 23 April 2021, (2021-7th-HIRB-012). Study results will be disseminated in peer-reviewed journal articles.

Keywords: sleep disturbance, cardiopulmonary fitness, percutaneous coronary intervention, cardiac rehabilitation, coronary heart disease, protocol

Strengths and limitations of this study

1. This is a longitudinal study of patients in cardiac rehabilitation, assessing sleep trajectory and the relationship between sleep and cardiorespiratory fitness.
2. The use of cardiopulmonary exercise testing and the 6-minute walk test will provide accurate and objective cardiorespiratory fitness outcomes.
3. The Pittsburgh sleep quality Index and actigraphy will be used to comprehensively assess sleep quality and quantity, improving the power to discover patients with sleep disorders.
4. This is a single-center study, the sample source will only include participants from one tertiary hospital in China.
5. The sample has selection bias, as only patients who voluntarily choose to undergo a cardiac rehabilitation program after the percutaneous cardiac intervention.

INTRODUCTION

Cardiovascular mortality, mostly attributable to ischemic heart disease (IHD), is expected to increase more dramatically in the next decade globally. [1] According to the 2018 ESC/EACTS Guidelines on myocardial revascularization, timely percutaneous coronary intervention (PCI) of the infarct-related artery is still the

priority treatment of IHD patients. [2] However, after complete or incomplete revascularization procedures, patients may still encounter stent thrombosis, angina, and symptoms related to psychological and somatic stress. Sleep disturbances such as insomnia, obstructive sleep apnea (OSA) are quite common in patients with IHD. [3-5] Evidence from an epidemiological survey demonstrated that over 1/3 of post-PCI patients with the confession of sleep disturbance. [6 7] Sleep trait abnormalities include difficulty in falling asleep, periods of breathing cessation, or multiple awakenings during the night, which resulted in insufficient sleep durations and poor sleep quality.[3 8] It is established that disturbed sleep is associated with adverse cardiac events after PCI. [9-11] Previous studies have predominantly focused on sleep duration as an isolated risk factor for cardiovascular disease. [12] However, sleep is multidimensional and multi-causal. It is not only associated with cardiovascular outcome but also affects the patient compliance and prognosis during the cardiac rehabilitation (CR) program.[12-16]

CR is a highly regarded program of secondary prevention measures, which has been endorsed by the European Society of Cardiology, the American Heart Association, and the American College of Cardiology. [17-19] Exercise is a core component of CR. [20] Relevant studies have found that adherence to exercise-based CR can effectively reduce the risk of further cardiac insults, improve sleep quality, enhance cardiorespiratory fitness (CRF) and minimize hospital re-admission and mortality. [21-24] In the process of CR, CRF is used to assess the severity of the patient's cardiac limitation and the recovery after a cardiac event, and it is an important independent risk factor for cardiovascular disease. [25 26] Moreover, the risk of long-term major adverse cardiovascular events (MACE) is further increased when Sleep disturbances and decreased cardiorespiratory fitness (CRF) co-occur. [27] The number of studies evaluating sleep in relation to CRF is limited, with the majority of research being of cross-sectional design. In a large cross-sectional study of 51,000 participants, peak oxygen uptake (VO_{2peak}) was used to estimate CRF, showing a modest inverse association between having difficulty falling asleep at night and VO_{2peak}. [28] In contrast, another study used a symptom-limited cardiopulmonary

exercise test (CPET) to objectively measure CRF and used accelerometry to monitor sleep patterns. The study reported that CRF and sleep characteristics were not significantly correlated in adults with primary hypertension. [29] Lindegård et al found similary results in a longitudinal cohort study of women diagnosed with stress-related exhaustion disorder. [30]

Although prior observational evidence exists, none included the prospective, multi-time assessment of sleep and CRF during the CR program of post-PCI patients. There is still limited information on the relationship between patients' sleep traits and the joint effects of CRF. Moreover, subjective reports are used to assess perceptions of sleep quality in most studies, but they may not accurately measure sleep duration and efficiency. Within this context, clinicians cannot provide targeted guidance for patients undergoing CR after PCI.

Therefore, the purposes of this study are to: 1) investigate the sleep quality and efficiency of patients undergoing CR for the first time after PCI; 2) determine the sleep trajectory and influencing factors of patients undergoing CR for the first six months after PCI; and 3) investigate the longitudinal correlation between objectively measured sleep quality and CRF in patients undergoing CR after PCI.

METHODS

Patient and public involvement

Based on literature review in related fields, the research questions and outcome measures were evaluated and discussed by researchers. Patients were not involved in the design of the study, but their cooperation was required during the implementation phase of the study, and their needs and preferences were fully taken into account. Test results will be communicated verbally or in writing to participants.

Study design

This is a longitudinal study of patients in CR, which collects data at five-time points as follows: 1) T1, patients will have completed the first CPET one month after PCI and will have begun CR program, based on the risk evaluation by the physicians; 2) T2, one month after the beginning of CR program; 3) T3, three months after the

beginning of CR program; 4) T4, six months after the beginning of CR program; and 5) T5, twelve months after the beginning of CR program. This study explores the time-varying effects of sleep structure in patients after PCI during CR and the potential relationship between sleep and CRF. The data will be collected in person at the time of the four scheduled visits. Twelve months after the start of CR, the disease prognosis will be followed up over the phone. The study framework is shown in Figure 1.

Participants

This study will be conducted at the Seventh People's Hospital of Shanghai, China. A convenience sampling method will be used to recruit patients after PCI in the rehabilitation department. We hope to recruit at least 101 patients who meet the eligibility criteria. We plan to recruit patients in CR over an 18-month period beginning in May 2021.

General inclusion criteria

The inclusion criteria are as follows: 1) diagnosed with coronary heart disease and underwent PCI; 2) clinically stable; 3) aged 18–75 years; 4) no contraindications to exercise rehabilitation, and 5) capable and mentally able to communicate with the investigator in verbal or written form and provide written informed consent.

General exclusion criteria

The exclusion criteria are as follows: 1) unable to participate in regular exercise training on time; 2) have a cardiogenic shock or severe arrhythmia; 3) have severe lung diseases; and 4) have severe liver and kidney dysfunction, infection, tumor, or anemia.

Recruitment

Recruitment posters with research details will be placed at the front of the rehabilitation clinic. Medical staff will introduce this study to eligible patients undergoing CPET. Patients who are post-PCI will be invited to participate in this study after signing a written informed consent form.

Study procedures

At the baseline selection prior to the study, subjects provided a self-report of

demographic characteristics and medical history. The medical staff will conduct clinical examination including physical examination, blood sampling, echocardiography, as well as CPET results. Body mass index (BMI) and Waist circumference (WC) were determined during physical examination. The fasting serum of each subject was collected in the morning, the measurements of fasting plasma glucose (FPG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) were recorded. Cardiac biomarkers including B-type natriuretic peptide (BNP), serum high-sensitivity C-reactive protein (hsCRP), and Homocysteine (HCY) were measured in a laboratory. Data from echocardiography examination were collected, including left ventricular ejection fraction (LVEF), left atrium diameter (LAD), left ventricular internal diameter at end-diastole (LVIDd), interventricular septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT).

CPET will be assessed by a physician, focusing on recording peak oxygen uptake (VO2 peak), oxygen consumption divided by heart rate (known as the oxygen pulse: VO2/HR), metabolic equivalents (METs), minute ventilation divided by carbon dioxide production (VE/VCO2 slope), oxygen uptake efficiency slope (OUES), anaerobic threshold (AT), heart rate recovery at 1 minute after exercise (HRR 1 minute), maximal heart rate reserve (HRR Max).

The baseline assessment will also include the Pittsburgh sleep quality index (PSQI) to understand the sleep conditions of the participants in the past month. The mental states of depression and anxiety will be assessed with the Patient Health Questionnaire (PHQ-9) and the General Anxiety Disorder Scale (GAD-7), respectively. The scales are in the Chinese version. All enrolled participants will be required to wear an actigraphy on their wrists for 72 h to objectively monitor sleep conditions. The physical therapist will prescribe a personalized exercise program for each participant, based on the CPET result and the patient's disease state. Then the patient will undergo a CR exercise program three times a week in the rehabilitation clinic for a total of 6 months. Patients perform 40 minutes of aerobic training on a treadmill or bicycle each time and use a heart rate monitor and Borg ratings of perceived exertion scale to assess exercise intensity. During the CR process, data

(physical examination, echocardiography, blood sampling, actigraphy for the assessment of sleep, PSQI, PHQ-9, and GAD-7) will be collected again in the 1st, 3rd, and 6th months. In addition, CEPT will be performed again in the 6th month of the CR program and the 6-minute walk test (6MWT) will be performed in the 1st and 3rd months of the CR program to supplement the CPET. Except for this, other assessment contents will be the same as those listed in the baseline assessments. At the 12th month, a telephonic follow-up will also be required. The follow-up content includes major adverse cardiovascular events (MACEs) and the number of rehospitalizations. Table 1 shows the data collection details.

Sample size

The calculations of the sample size were based on an estimate of the correlation coefficient between sleep quality and CRF in participants from previous studies. [31] With a two-sided significance level of 5% and a minimum correlation coefficient of 0.37 between sleep quality and CRF, 84 patients after PCI would be included. Considering an attrition rate of 20%, the final total sample size will be at least 101 patients.

Measurements

Cardiopulmonary exercise testing (CPET)

The CPET will be performed by professional physicians with operating qualifications using COSMED S.R.L Pulmonary Function Equipment (The Metabolic company, Guangzhou, China). Patients will not need to stop cardiovascular drugs (including β-blockers) on the day of the CPET test and must avoid drinking caffeine beverages and smoking 2 h before the test. According to the American Thoracic Society (ATS) guidelines, CPET uses a continuous load escalation program for symptomatic self-limiting cycling exercise. [32] The patient sits on a cycle ergometer and first rests for 3 minutes and then performs a zero-load idling warm-up for at least 1 minute, followed by the load-increasing exercise phase with an incremental power of 10 W/min or 20 W/min, so that the patient can reach maximum exercise intensity for self-limiting symptoms. The speed of the treadmill is maintained at 55–65 r/min throughout the test. electrocardiogram, blood pressure, and respiratory

status will be continually monitored during the recovery period for at least 3 minutes after the loading exercise stops, until the end of the test. The main measured outcomes include the anaerobic threshold, peak oxygen uptake, peak oxygen pulse, minute ventricular load, and maximum exercise load. The V-slope method will be used to calculate the anaerobic threshold.

Six-minute walk test (6MWT)

Functional exercise capacity is objectively evaluated by the 6MWT. This test records the distance that a patient can quickly walk along a long and flat corridor in 6 min. During this test, patients are permitted to decide their walking speed but are still required to walk as far as possible for 6 min. Every minute, physiotherapists will call out a standardized phrase of verbal encouragement. The 6MWT process is based on guidelines from the ATS. [33]

Actigraphy for the assessment of sleep

Actigraphy (Respironics Inc, Murrysville, America) will be continuously monitored for 24 h to analyze patients' sleep and waking data. The recording frequency interval for actigraphy will be 30 s/frame, and the recording time will be 3 days. The exported sleep report will comprise daily sleep data and average sleep data. Sleep data will include: 1) sleep time and wake-up time; 2) time in bed; 3) actual sleep time; 4) sleep latency; 5) sleep efficiency; 6) the number of minutes and times of awakening after the start of sleep. Finally, the averaged sleep data will be included in the statistical analysis.

Pittsburgh Sleep Quality Index (PSQI)

The PSQI is a sleep self-rated questionnaire designed and revised by scholars including Buysse. [34] In this study, the Chinese version of the Pittsburgh Sleep Quality Index (CPSQI) was used to measure the sleep quality of patients in the past month. [35] The questionnaire has a total of 18 items, which are used to measure the following: 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) sleep efficiency; 5) sleep disturbances; 6) use of sleeping medication, and 7) daytime dysfunction.

Patient Health Questionnaire (PHQ-9)

The PHQ-9 is a reliable and effective indicator for measuring the severity of

depression, and its items correspond to the DSM-IV diagnostic criteria for depression. [36] In this study, the Chinese version of the PHQ-9 was used to assess the severity of depression in patients in the last two weeks through nine questions. [37] The PHQ-9 total score ranges from 0 to 27 points, and the scores 5, 10, and 20 are the cut-off values for mild, moderate, and severe depression, respectively.

General anxiety disorder scale (GAD-7)

The GAD-7 is used to determine whether the patients have psychological symptoms of anxiety and their frequency within 2 weeks. [38] The Chinese version of GAD-7 showed good reliability and validity in cardiovascular patients. [37] This scale includes seven items, each with a score of 0–3 points for a total score of 21 points, of which a score of 10–21 points denotes having an anxious mental state.

Statistical analysis

The results will be statistically analyzed using SPSS 25.0 software (SPSS Inc., Chicago, Illinois, USA) and Mplus 7.1 software (Muthén & Muthén, Los Angeles, America). Continuous variables are expressed as mean ± standard deviation and categorical variables as proportions. We will use the growth mixture model (GMM) to analyze the participants' longitudinal sleep data and identify the longitudinal development trajectory of sleep during CR. And we will explore the characteristics of sleep trajectory in the sample population over time based on the consideration of population heterogeneity. GMM combines aspects of latent growth curve modeling and finite mixture modeling to identify discrete trajectories in longitudinal data. [39 40] The generalized estimating equation (GEE) will be used to examine the association between sleep and cardiopulmonary function during CR, adjusting for potential covariates which include age, sex, education, socioeconomic status, comorbidities, drug use, and psychological status. Cox regression model was used to calculate hazard ratios (HRs) and 95% confidence interval (CI) for the incident of major adverse cardiovascular events after 12 months of CR in relation to sleep.

DISCUSSION

Sleep disturbance after PCI can cause both acute and chronic physiological and psychological burdens to patients. Following PCI, patients must reduce their risk of

cardiac events and sleep disturbance through secondary prevention strategies. [41] CR is helpful for reducing the deleterious effects of sleep disorders and improving CRF. This protocol describes a longitudinal observational study to explore the time-varying effect of sleep structure and the potential relationship between sleep and CRF in patients after PCI and during CR. Compared to the longitudinal study by Mazaki T et al., the sleep data collected by actigraphy and PSQI are more extensive and comprehensive. [11] Moreover, multi-time-point sleep data can display the dynamic changes of sleep in patients after PCI during CR, helping patients to implement effective sleep management during the CR period. Additionally, given the importance of CRF for cardiovascular disease, a key strength of this study is addressing the longitudinal underlying relationship between sleep and CRF. As far as we know, this is the first longitudinal study to explore the trajectory of patients' sleep structure changes after PCI and during CR. The advantages of this study include the use of the PSQI and actigraphy to comprehensively assess sleep quality and quantity. Actigraphy is an objective sleep measure that improves data accuracy. CPET will also be used to non-invasively monitor the electrocardiogram, pulse oximetry (SpO_2), O_2 inhalation, and CO_2 output at rest and during exercise. Cardiopulmonary reserve function and exercise tolerance will be analyzed by combining multiple indicators.

There are some limitations to this study. First, the sample source will only include participants from one hospital in China. Due to the limitations of research sites and recruitment strategies, our sample may be prone to selection bias and random-sampling recruitment may be difficult. Second, the study will only include patients who voluntarily choose to undergo a CR program after PCI. Patients who meet the conditions but have a fear of exercise will be excluded. This part of the patient information may have an impact on the study results. Finally, we did not use the gold standard sleep assessment technique, polysomnography (PSG). PSG is difficult and expensive due to the fact that the patient is out of hospital for a long period of time and the cardiac rehabilitation takes place in a rehabilitation clinic. Although actigraphy cannot replace PSG in terms of diagnostic accuracy and

reliability, it has shown good performance for tracking sleep and wakefulness. [42 43]

Poor CRF is considered a possible adverse health outcome associated with poor sleep. This study aims to investigate the sleep conditions of patients during CR and the relationship with CRF as the preliminary basis of clinical intervention. The exploration of the dynamic fluctuations of sleep and its relationship with CRF may provide useful reference for targeted cardiac rehabilitation management. During CR management, medical staff can timely detect and adjust the patient's adverse state through objective sleep and CRF monitoring, and speed up the recovery process.

ETHICS AND DISSEMINATION

This article describes a prospective, longitudinal study protocol to assess sleep trajectory and the relationship between sleep and cardiorespiratory fitness for CR patients. Ethical approval for this observational longitudinal study was granted by the Shanghai Seventh People's Hospital Ethics Committee on 23 April 2021, (2021-7th-HIRB-012). All participants will be provided with a full understanding of the study and will be made aware that participation is strictly voluntary. Informed consent and information sheets will be provided for patients before the onset of this research. The study results will be disseminated in peer-reviewed journal articles.

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Contributors

Lan Huang is the principal investigator of the study and is responsible for protocol design, data collection and analysis, and presentation of findings. She was also responsible for drafting this manuscript. Jing Wu obtained funding. Jie Zhou、Husheng Li and Yiyan Wang participated in data collection and analysis. Xubo Wu and Jing Wu contributed to the protocol design and revisions of the manuscript. All authors have read and approved the final manuscript.

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Competing interests

None declared.

Data sharing

No additional data are available.

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TABLE 1 Data collection in the study

Items	T1	T2	T3	T4	T5
Demographic characteristic	√				
Medical history	√				
Physical examination	√	√	√	√	
Blood sampling	√	√	√	√	
Echocardiography	√	√	√	√	
CPET	√			√	
6MWT		√	√		
Actigraphy	√	√	√	√	
PSQI	√	√	√	√	
PHQ-9	√	√	√	√	
GAD-7	√	√	√	√	
MACEs					√
Rehospitalizations					√

Notes: T1: Baseline assessment and enrolment; T2: one month after the beginning of CR program; T3: three months after the beginning of CR program; T4: six months after the beginning of CR program; T5: twelve months after the beginning of CR program. Physical examination: Body mass index (BMI) , Waist circumference (WC), blood pressure (BP); Blood sampling: fasting

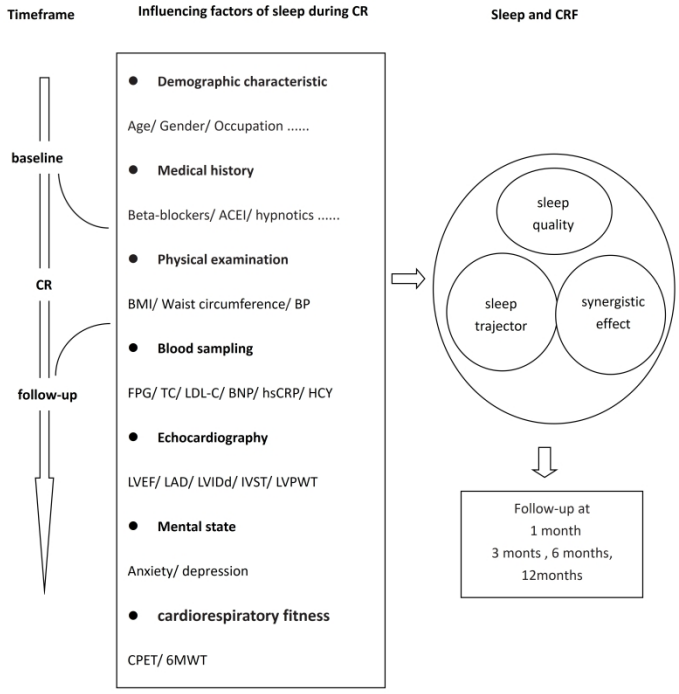
plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), B-type natriuretic peptide (BNP), serum high-sensitivity C-reactive protein (hsCRP), Homocysteine (HCY); Echocardiography: left ventricular ejection fraction (LVEF), left atrium diameter (LAD), left ventricular internal diameter at end-diastole (LVIDd), interventricular septal thickness (IVST), left ventricular posterior wall thickness (LVPWT)

Abbreviations: CPET: cardiopulmonary exercise testing; 6MWT: six-minute walk test; PSQI: Pittsburgh Sleep Quality Index; PHQ-9: Patient Health Questionnaire; GAD-7: General anxiety disorder scale; MACEs: major adverse cardiovascular events

FIGURE 1 Study framework

Abbreviations: BMI: Body mass index; BP: blood pressure; FPG: fasting plasma glucose; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; BNP: B-type natriuretic peptide; hsCRP: serum high-sensitivity C-reactive protein; HCY: Homocysteine; LVEF: left ventricular ejection fraction; LAD: left atrium diameter; LVIDd: left ventricular internal diameter at end-diastole; IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; CPET: cardiopulmonary exercise testing; 6MWT: six-minute walk test

FIGURE 1 Study framework



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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	2-4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Study design	4	Present key elements of study design early in the paper	4-5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-7
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	n/a
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-9
Bias	9	Describe any efforts to address potential sources of bias	n/a
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	9
		(*c*) Explain how missing data were addressed	n/a
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a

Continued on next page

Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	n/a
		(b) Give reasons for non-participation at each stage	n/a
		(c) Consider use of a flow diagram	n/a
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	n/a
		(b) Indicate number of participants with missing data for each variable of interest	n/a
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	n/a n/a
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	n/a
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	9-10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10-11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.