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# BMJ Open

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

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4 **Sleep behavior and cardiorespiratory fitness in patients after**  
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6 **percutaneous coronary intervention during cardiac rehabilitation:**  
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9 **protocol for a longitudinal study**  
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28  
29 **Abstract**

30  
31 **Introduction:** Most patients with coronary heart disease experience sleep  
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33 disturbances and low cardiorespiratory fitness (CRF), but the relationship between  
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35 them during cardiac rehabilitation (CR) is still unclear. This article details a protocol  
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37 for the study of sleep trajectory in patients with coronary heart disease during CR  
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39 and the relationship between sleep and CRF. A better understanding of the  
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41 relationship between sleep and CRF on patient outcomes can improve sleep  
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43 management strategies.

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45 **Methods and analysis:** This is a longitudinal study with a recruitment target of 101  
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47 patients after percutaneous cardiac intervention (PCI) from the Seventh People's  
48  
49 Hospital of Shanghai, China. Data collection will include socio-demographic  
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51 information, diseases, medications and the results of cardiopulmonary exercise tests  
52  
53 (CPETs). The information provided by a six-minute walk test (6MWT) will be used to  
54  
55 supplement the CPET. The Pittsburgh sleep quality index (PSQI) will be used to  
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57 understand the sleep conditions of the participants in the past month. The Patient  
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59 Health Questionnaire (PHQ-9) and General Anxiety Disorder Scale (GAD-7) will be  
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used to assess depression and anxiety, respectively. All participants will be required

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4 to wear a motion recorder on their wrists for 72 h to monitor objective sleep  
5 conditions. This information will be collected four times within six months of CR, and  
6 patients will be followed up for one year. Mplus 7.1 software will be used to analyze  
7 the longitudinal sleep data. The generalized estimating equation will be used to  
8 examine the associations between sleep and CRF during CR.  
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13 **Ethics and dissemination:** Ethical approval for this observational longitudinal study  
14 was granted by the Shanghai Seventh People's Hospital Ethics Committee on 23 April  
15 2021, (2021-7<sup>th</sup>-HIRB-012). Study results will be disseminated in peer-reviewed  
16 journal articles.  
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21 **Keywords:** sleep disturbance, cardiopulmonary fitness, percutaneous coronary  
22 intervention, cardiac rehabilitation, coronary heart disease, protocol  
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### 25 **Strengths and limitations of this study**

- 26  
27 1. This is a longitudinal study of patients in cardiac rehabilitation, assessing sleep  
28 trajectory and the relationship between sleep and cardiorespiratory fitness.  
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31 2. The use of cardiopulmonary exercise testing and the 6-minute walk test will  
32 provide accurate and objective cardiorespiratory fitness outcomes.  
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35 3. The Pittsburgh sleep quality Index and actigraphy will be used to comprehensively  
36 assess sleep quality and quantity, improving the power to discover patients with  
37 sleep disorders.  
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40 4. This is a single-centre study, the sample source will only include participants from  
41 one tertiary hospital in China.  
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44 5. The sample has selection bias, as only patients who voluntarily choose to undergo  
45 a cardiac rehabilitation program after percutaneous cardiac intervention.  
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## 50 **INTRODUCTION**

51  
52 In recent years, the incidence and mortality of cardiovascular diseases have  
53 continued to increase, and they have become the main cause of death worldwide.  
54 Chronic ischemic heart disease (IHD) has remained a major health concern for  
55 decades. One of the most widely used treatments for patients with IHD is  
56 percutaneous coronary intervention (PCI), which has been shown to significantly  
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4 reduce patient mortality from acute myocardial infarction. However, after complete  
5 or incomplete revascularization procedures, patients may still encounter stent  
6 thrombosis, angina and symptoms related to psychological and somatic stress. Sleep  
7 disturbance or insomnia is quite common in patients with IHD. It is estimated that  
8 1/3 of patients who have undergone PCI suffer from a sleep disturbance.<sup>1</sup> Difficulty  
9 falling asleep and having several awakenings during the night are the most common  
10 symptoms. Sleep disturbances are an independent prognostic marker for cardiac  
11 outcomes.<sup>2</sup> Study results have demonstrated that patients undergoing PCI have an  
12 increased risk of adverse cardiovascular events and mortality after experiencing  
13 long-term sleep disturbances.<sup>3 4</sup> In addition, sleep disturbances may have a negative  
14 impact on physical and mental health status and may reduce patient compliance  
15 with cardiac rehabilitation (CR), thereby influencing the course of rehabilitation.<sup>5-9</sup>

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27 CR is a highly regarded program of secondary prevention measures, which has  
28 been endorsed by the European Society of Cardiology, the American Heart  
29 Association and the American College of Cardiology.<sup>10-12</sup> Exercise is a core  
30 component of CR.<sup>13</sup> Relevant studies have found that adherence to exercise-based  
31 CR can effectively reduce the risk of further cardiac insults, improve sleep quality,  
32 enhance cardiorespiratory fitness (CRF) and minimize hospital re-admission and  
33 mortality.<sup>14-16</sup> In the process of CR, CRF is used to assess the severity of the patient's  
34 cardiac limitation and the recovery after a cardiac event, and it is an important  
35 independent risk factor for cardiovascular disease.<sup>17 18</sup> However, limited knowledge  
36 exists on the relationship between sleep and CRF. In a large cross-sectional study of  
37 51,000 participants, peak oxygen uptake ( $VO_{2peak}$ ) was used to estimate CRF,  
38 showing a modest inverse association between having difficulty falling asleep at  
39 night and  $VO_{2peak}$ .<sup>19</sup> In contrast, another study used a symptom-limited  
40 cardiopulmonary exercise test (CPET) to objectively measure CRF and used  
41 accelerometry to monitor sleep patterns. The study reported that CRF and sleep  
42 characteristics were not significantly correlated in adults with primary hypertension.

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

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4 interactive relationship between sleep and CRF remains to be established. Moreover,  
5 subjective reports are used to assess perceptions of sleep quality in most studies,  
6 but they may not accurately measure sleep duration and efficiency. Within this  
7 context, clinicians cannot provide targeted guidance for patients undergoing CR after  
8 PCI.  
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13 Therefore, the purposes of this study are to: 1) investigate the sleep quality and  
14 efficiency of patients undergoing CR for the first time after PCI; 2) determine the  
15 sleep trajectory and influencing factors of patients undergoing CR for the first three  
16 months after PCI; and 3) investigate the longitudinal correlation between objectively  
17 measured sleep quality and CRF in patients undergoing CR after PCI.  
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## 23 **METHODS**

### 24 **Patient and public involvement**

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

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

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

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

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

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

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45 After a patient is enrolled in the study, the medical staff will conduct a baseline  
46 assessment including sociodemographic information such as age, sex, education,  
47 socioeconomic status, comorbidities and medication use, as well as CPET results. The  
48 baseline assessment will include the Pittsburgh sleep quality index (PSQI) to  
49 understand the sleep conditions of the participants in the past month. The mental  
50 states of depression and anxiety will be assessed with the Patient Health  
51 Questionnaire (PHQ-9) and the General Anxiety Disorder Scale (GAD-7), respectively.  
52 All enrolled participants will be required to wear a motion recorder on their wrists  
53 for 72 h to objectively monitor sleep conditions. The physical therapist will prescribe  
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4 a personalized exercise program for each participant, based on CPET results and the  
5 patient's disease state. The patient will then undergo a CR exercise program three  
6 times a week for a total of 6 months. During the CR process, data will be collected  
7 again in the 1<sup>st</sup>, 3<sup>rd</sup> and 6<sup>th</sup> months. In addition, the 6-minute walk test (6MWT) will  
8 be performed in the 1<sup>st</sup> and 3<sup>rd</sup> months of the CR program. Except for this, other  
9 assessment contents will be the same as those listed in the baseline assessments. At  
10 the 12<sup>th</sup> month, a telephonic follow-up will also be required. The follow-up content  
11 includes major adverse cardiovascular events (MACEs) and the number of  
12 rehospitalizations. Table 1 shows the data collection details.

### 21 **Sample size**

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

### 34 **Measurements**

#### 36 **Cardiopulmonary exercise testing (CPET)**

37  
38 The CPET will be performed by professional physicians with operating  
39 qualifications using COSMED S.R.L Pulmonary Function Equipment (The Metabolic  
40 company, Guangzhou, China). Patients will not need to stop cardiovascular drugs  
41 (including  $\beta$ -blockers) on the day of the CPET test and must avoid drinking caffeine  
42 beverages and smoking 2 h before the test. According to the American Thoracic  
43 Society (ATS) guidelines, CPET uses a continuous load escalation program for  
44 symptomatic self-limiting cycling exercise.<sup>22</sup> The patient sits on a cycle ergometer  
45 and first rests for 3 minutes and then performs a zero-load idling warm-up for at  
46 least 1 minute, followed by the load-increasing exercise phase with an incremental  
47 power of 10 W/min or 20 W/min, so that the patient can reach maximum exercise  
48 intensity for self-limiting symptoms. The speed of the treadmill is maintained at 55–  
49 60 65 r/min throughout the test. electrocardiogram, blood pressure and respiratory



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4 status will be continually monitored during the recovery period for at least 3 minutes  
5 after the load exercise stops, until the end of the test. The main measured outcomes  
6 include the anaerobic threshold, peak oxygen uptake, peak oxygen pulse, minute  
7 ventricular load and maximum exercise load. The V-slope method will be used to  
8 calculate the anaerobic threshold.  
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### 13 Six-minute walk test (6MWT)

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15 Functional exercise capacity is objectively evaluated by the 6MWT. This test  
16 records the distance that a patient can quickly walk along a long and flat corridor in 6  
17 min. During this test, patients are permitted to decide their walking speed but are  
18 still required to walk as far as possible for 6 min. Every minute, physiotherapists will  
19 call out a standardized phrase of verbal encouragement. The 6MWT process is based  
20 on guidelines from the ATS.<sup>23</sup>  
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### 27 Actigraphy for the assessment of sleep

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

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47 The PSQI is a self-rated questionnaire designed and revised by scholars  
48 including Buysse to measure patients' sleep quality in the past month.<sup>24</sup> The  
49 questionnaire has a total of 18 items, which are used to measure the following: 1)  
50 subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) sleep efficiency; 5)  
51 sleep disturbances; 6) use of sleeping medication; and 7) daytime dysfunction.  
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### 56 Patient Health Questionnaire (PHQ-9)

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58 The PHQ-9 is a reliable and effective indicator for measuring the severity of  
59 depression, and its items correspond to the DSM-IV diagnostic criteria for  
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4 depression.<sup>25</sup> The PHQ-9 total score ranges from 0 to 27 points, and the scores 5, 10  
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6 and 20 are the cut-off values for mild, moderate and severe depression, respectively.

#### 7 8 **General anxiety disorder scale (GAD-7)**

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

#### 17 18 **Statistical analysis**

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20 We will use the growth mixture model (GMM) to analyze the participants'  
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22 longitudinal sleep data with Mplus 7.1 software (Muthén & Muthén, Los Angeles,  
23  
24 America) and identify the longitudinal development trajectory of sleep during CR.  
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26 We will explore the characteristics of sleep trajectory in the sample population over  
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28 time based on the consideration of population heterogeneity. The generalized  
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30 estimating equation (GEE) will be used to examine the associations between sleep  
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32 and cardiopulmonary function during CR, adjusting for potential covariates.

#### 33 34 **DISCUSSION**

35  
36 Sleep disturbance after PCI can cause both acute and chronic physiological and  
37  
38 psychological burden to patients. Following PCI, patients must reduce their risk of  
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40 cardiac events and sleep disturbance through secondary prevention strategies.<sup>27</sup> CR  
41  
42 is helpful for reducing the deleterious effects of sleep disorders and improving CRF.  
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44 This protocol describes a longitudinal observational study to explore the  
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46 time-varying effect of sleep structure and the potential relationship between sleep  
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48 and CRF in patients after PCI and during CR. The results of this study will help  
49  
50 patients implement effective sleep management during the CR period. A key  
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52 strength of this study is its prospective and longitudinal design, which will help  
53  
54 resolve the question of the potential relationship between sleep and CRF.

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56 As far as we know, this is the first longitudinal study to explore the trajectory of  
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58 patients' sleep structure changes after PCI and during CR. The advantages of this  
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60 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

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4 accuracy. CPET will also be used to non-invasively monitor the electrocardiogram,  
5 pulse oximetry (SpO<sub>2</sub>), O<sub>2</sub> inhalation and CO<sub>2</sub> output at rest and during exercise.  
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7 Cardiopulmonary reserve function and exercise tolerance will be analyzed by  
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9 combining multiple indicators.  
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12 There are some limitations to this study. The sample source will only include  
13 participants from one hospital in China. Due to the limitations of research sites and  
14 recruitment strategies, our sample may be prone to selection bias and  
15 random-sampling recruitment may be difficult. The study will only include patients  
16 who voluntarily choose to undergo a CR program after PCI. Patients who meet the  
17 conditions but have a fear of exercise will be excluded.  
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24 This study aims to investigate the sleep conditions of patients during CR and the  
25 relationship with CRF as the preliminary basis of clinical intervention. The results of  
26 this study will provide useful knowledge for exploring targeted sleep management  
27 during the CR period in future.  
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### 40 41 **Contributors**

42  
43 Lan Huang is the principal investigator of the study and is responsible for  
44 protocol design, data collection and analysis and presentation of findings. She was  
45 also responsible for drafting this manuscript. Jing Wu obtained funding. Jie Zhou,  
46 Husheng Li and Yiyang Wang participated in data collection and analysis. Xubo Wu  
47 and Jing Wu contributed to the protocol design and revisions of the manuscript. All  
48 authors have read and approved the final manuscript.  
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59

### 60 **Competing interests**

None declared.

### Data sharing

No additional data are available.

### REFERENCES

1. Rouleau CR, Horsley KJ, Morse E, et al. The Association Between Insomnia Symptoms and Mood Changes During Exercise Among Patients Enrolled in Cardiac Rehabilitation. *J Cardiopulm Rehabil Prev* 2015;35(6):409-16. doi: 10.1097/hcr.000000000000138 [published Online First: 2015/09/18]
2. Clark A, Lange T, Hallqvist J, et al. Sleep impairment and prognosis of acute myocardial infarction: a prospective cohort study. *Sleep* 2014;37(5):851-8. doi: 10.5665/sleep.3646 [published Online First: 2014/05/03]
3. Fernandes NM, Nield LE, Popel N, et al. Symptoms of disturbed sleep predict major adverse cardiac events after percutaneous coronary intervention. *Can J Cardiol* 2014;30(1):118-24. doi: 10.1016/j.cjca.2013.07.009 [published Online First: 2013/10/22]
4. Strand LB, Tsai MK, Gunnell D, et al. Self-reported sleep duration and coronary heart disease mortality: A large cohort study of 400,000 Taiwanese adults. *Int J Cardiol* 2016;207:246-51. doi: 10.1016/j.ijcard.2016.01.044 [published Online First: 2016/01/26]
5. Soehner AM, Harvey AG. Prevalence and functional consequences of severe insomnia symptoms in mood and anxiety disorders: results from a nationally representative sample. *Sleep* 2012;35(10):1367-75. doi: 10.5665/sleep.2116 [published Online First: 2012/10/02]
6. Meijer A, Conradi HJ, Bos EH, et al. Adjusted prognostic association of depression following myocardial infarction with mortality and cardiovascular events: individual patient data meta-analysis. *Br J Psychiatry* 2013;203(2):90-102. doi: 10.1192/bjp.bp.112.111195 [published Online First: 2013/08/03]
7. Cappuccio FP, Cooper D, D'Elia L, et al. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32(12):1484-92. doi: 10.1093/eurheartj/ehr007 [published Online First: 2011/02/09]
8. Madsen MT, Huang C, Zangger G, et al. Sleep Disturbances in Patients With Coronary Heart Disease: A Systematic Review. *J Clin Sleep Med* 2019;15(3):489-504. doi: 10.5664/jcsm.7684 [published Online First: 2019/03/12]
9. Banack HR, Holly CD, Lowensteyn I, et al. The association between sleep disturbance, depressive symptoms, and health-related quality of life among cardiac rehabilitation participants. *J Cardiopulm Rehabil Prev* 2014;34(3):188-94. doi: 10.1097/hcr.000000000000054 [published Online First: 2014/04/01]
10. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary heart disease: an American Heart Association scientific statement from the Council on Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical Activity), in collaboration with the American association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2005;111(3):369-76. doi: 10.1161/01.Cir.0000151788.08740.5c [published Online First: 2005/01/26]
11. Corrà U, Piepoli MF, Carré F, et al. Secondary prevention through cardiac rehabilitation: physical

- activity counselling and exercise training: key components of the position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur Heart J* 2010;31(16):1967-74. doi: 10.1093/eurheartj/ehq236 [published Online First: 2010/07/21]
12. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation* 2013;128(8):873-934. doi: 10.1161/CIR.0b013e31829b5b44 [published Online First: 2013/07/24]
13. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary prevention programs: 2007 update: a scientific statement from the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention, and Nutrition, Physical Activity, and Metabolism; and the American Association of Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007;115(20):2675-82. doi: 10.1161/circulationaha.106.180945 [published Online First: 2007/05/22]
14. Kirchberger I, Hunger M, Stollenwerk B, et al. Effects of a 3-year nurse-based case management in aged patients with acute myocardial infarction on rehospitalisation, mortality, risk factors, physical functioning and mental health. a secondary analysis of the randomized controlled KORINNA study. *PLoS One* 2015;10(3):e0116693. doi: 10.1371/journal.pone.0116693 [published Online First: 2015/03/27]
15. Rutledge T, Redwine LS, Linke SE, et al. A meta-analysis of mental health treatments and cardiac rehabilitation for improving clinical outcomes and depression among patients with coronary heart disease. *Psychosom Med* 2013;75(4):335-49. doi: 10.1097/PSY.0b013e318291d798 [published Online First: 2013/05/01]
16. Zhang L, Zhang L, Wang J, et al. Community health service center-based cardiac rehabilitation in patients with coronary heart disease: a prospective study. *BMC Health Serv Res* 2017;17(1):128. doi: 10.1186/s12913-017-2036-3 [published Online First: 2017/02/12]
17. Laddu D, Ozemek C, Lamb B, et al. Factors Associated With Cardiorespiratory Fitness at Completion of Cardiac Rehabilitation: Identification of Specific Patient Features Requiring Attention. *Can J Cardiol* 2018;34(7):925-32. doi: 10.1016/j.cjca.2018.03.015 [published Online First: 2018/06/05]
18. Thompson PD, Arena R, Riebe D, et al. ACSM's new preparticipation health screening recommendations from ACSM's guidelines for exercise testing and prescription, ninth edition. *Curr Sports Med Rep* 2013;12(4):215-7. doi: 10.1249/JSR.0b013e31829a68cf [published Online First: 2013/07/16]
19. Strand LB, Laugsand LE, Wisløff U, et al. Insomnia symptoms and cardiorespiratory fitness in healthy individuals: the Nord-Trøndelag Health Study (HUNT). *Sleep* 2013;36(1):99-108. doi: 10.5665/sleep.2310 [published Online First: 2013/01/05]
20. Martinez-Aguirre-Betolaza A, Maldonado-Martín S, Corres P, et al. Actigraphy-based sleep analysis in sedentary and overweight/obese adults with primary hypertension: data from the EXERDIET-HTA study. *Sleep Breath* 2019;23(4):1265-73. doi: 10.1007/s11325-019-01813-7 [published Online First: 2019/03/01]
21. Crowley SK, Rebellon J, Huber C, et al. Cardiorespiratory fitness, sleep, and physiological responses to stress in women. *Eur J Sport Sci* 2020;20(10):1368-77. doi: 10.1080/17461391.2020.1716855 [published Online First: 2020/01/16]

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22. Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med* 2003;167(10):1451; author reply 51. doi: 10.1164/ajrccm.167.10.950 [published Online First: 2003/05/10]
23. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166(1):111-7. doi: 10.1164/ajrccm.166.1.at1102 [published Online First: 2002/07/02]
24. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213. doi: 10.1016/0165-1781(89)90047-4 [published Online First: 1989/05/01]
25. Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for screening to detect major depression: individual participant data meta-analysis. *Bmj* 2019;365:l1476. doi: 10.1136/bmj.l1476 [published Online First: 2019/04/11]
26. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-7. doi: 10.1001/archinte.166.10.1092 [published Online First: 2006/05/24]
27. Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmacoeconomic burden. *Am J Manag Care* 2009;15(2 Suppl):S36-41. [published Online First: 2009/04/16]

**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

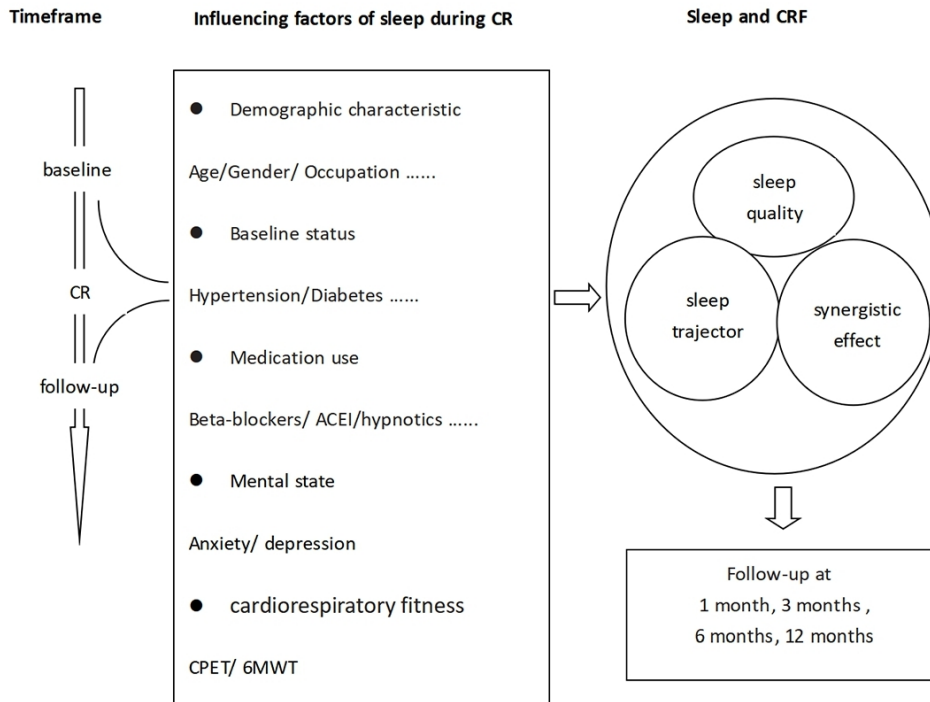


FIGURE 1 Study framework  
199x187mm (144 x 144 DPI)



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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Continued on next page

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
	*	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	
<b>Discussion</b>			
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	
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2021-057117.R1
Article Type:	Protocol
Date Submitted by the Author:	16-Mar-2022
Complete List of Authors:	Huang, Lan; Shanghai University of Traditional Chinese Medicine, Nursing Zhou, Jie; Shanghai University of Traditional Chinese Medicine, Nursing Li, Husheng; Shanghai University of Traditional Chinese Medicine, Nursing Wang, Yiyan; Shanghai University of Traditional Chinese Medicine, Nursing Wu, Xubo; Shanghai Seventh People's Hospital, Rehabilitation; Shanghai University of Traditional Chinese Medicine, Rehabilitation Wu, Jing; Shanghai University of Traditional Chinese Medicine, Nursing; Shanghai Seventh People's Hospital, Rehabilitation
<b>Primary Subject Heading</b>:	Cardiovascular medicine
Secondary Subject Heading:	Rehabilitation medicine
Keywords:	Coronary heart disease < CARDIOLOGY, REHABILITATION MEDICINE, Ischaemic heart disease < CARDIOLOGY

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Manuscripts

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4 1 **Sleep behavior and cardiorespiratory fitness in patients after**  
5  
6 2 **percutaneous coronary intervention during cardiac rehabilitation:**  
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8  
9 3 **protocol for a longitudinal study**

10  
11 4 **Lan Huang <sup>a</sup>、 Jie Zhou <sup>a</sup>、 Husheng Li <sup>a</sup>、 Yiyang Wang <sup>a</sup>、 Xubo Wu <sup>b\*</sup>、 Jing Wu <sup>ab\*</sup>**

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27 11 The study was funded by the Nature Science Foundation of China (No. 71904127).

28  
29 12 **Abstract**

30  
31 13 **Introduction:** Most patients with coronary heart disease experience sleep  
32  
33 14 disturbances and low cardiorespiratory fitness (CRF), but their relationship during  
34  
35 15 cardiac rehabilitation (CR) is still unclear. This article details a protocol for the study  
36  
37 16 of sleep trajectory in patients with coronary heart disease during CR and the  
38  
39 17 relationship between sleep and CRF. A better understanding of the relationship  
40  
41 18 between sleep and CRF on patient outcomes can improve sleep management  
42  
43 19 strategies.

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45 20 **Methods and analysis:** This is a longitudinal study with a recruitment target of 101  
46  
47 21 patients after percutaneous cardiac intervention (PCI) from the Seventh People's  
48  
49 22 Hospital of Shanghai, China. Data collection will include demographic characteristics,  
50  
51 23 medical history, physical examination, blood sampling, echocardiography, and the  
52  
53 24 results of cardiopulmonary exercise tests (CPETs). The information provided by a six-  
54  
55 25 minute walk test (6MWT) will be used to supplement the CPET. The Pittsburgh sleep  
56  
57 26 quality index (PSQI) will be used to understand the sleep conditions of the  
58  
59 27 participants in the past month. The Patient Health Questionnaire (PHQ-9) and  
60  
28 General Anxiety Disorder Scale (GAD-7) will be used to assess depression and

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4 29 anxiety, respectively. All participants will be required to wear an actigraphy on their  
5  
6 30 wrists for 72 h to monitor objective sleep conditions. This information will be  
7  
8 31 collected four times within six months of CR, and patients will be followed up for one  
9  
10 32 year. The growth mixture model will be used to analyze the longitudinal sleep data.  
11  
12 33 The generalized estimating equation will be used to examine the associations  
13  
14 34 between sleep and CRF during CR.

15  
16 35 **Ethics and dissemination:** Ethical approval for this observational longitudinal study  
17  
18 36 was granted by the Shanghai Seventh People's Hospital Ethics Committee on 23 April  
19  
20 37 2021, (2021-7<sup>th</sup>-HIRB-012). Study results will be disseminated in peer-reviewed  
21  
22 38 journal articles.

23  
24 39 **Keywords:** sleep disturbance, cardiopulmonary fitness, percutaneous coronary  
25  
26 40 intervention, cardiac rehabilitation, coronary heart disease, protocol

#### 27 41 **Strengths and limitations of this study**

- 28  
29 42 1. This is a longitudinal study of patients in cardiac rehabilitation, assessing sleep  
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31 43 trajectory and the relationship between sleep and cardiorespiratory fitness.  
32  
33 44 2. The use of cardiopulmonary exercise testing and the 6-minute walk test will  
34  
35 45 provide accurate and objective cardiorespiratory fitness outcomes.  
36  
37 46 3. The Pittsburgh sleep quality Index and actigraphy will be used to comprehensively  
38  
39 47 assess sleep quality and quantity, improving the power to discover patients with  
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41 48 sleep disorders.  
42  
43 49 4. This is a single-center study, the sample source will only include participants from  
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45 50 one tertiary hospital in China.  
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47 51 5. The sample has selection bias, as only patients who voluntarily choose to undergo  
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49 52 a cardiac rehabilitation program after the percutaneous cardiac intervention.

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#### 52 54 **INTRODUCTION**

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54 55 Cardiovascular mortality, mostly attributable to ischemic heart disease (IHD), is  
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56 56 expected to increase more dramatically in the next decade globally. <sup>1</sup> According to  
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58 57 the 2018 ESC/EACTS Guidelines on myocardial revascularization, timely  
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60 58 percutaneous coronary intervention (PCI) of the infarct-related artery is still the

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4 59 priority treatment of IHD patients.<sup>2</sup> However, after complete or incomplete  
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6 60 revascularization procedures, patients may still encounter stent thrombosis, angina,  
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8 61 and symptoms related to psychological and somatic stress. Sleep disturbances such  
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10 62 as insomnia, obstructive sleep apnea (OSA) are quite common in patients with IHD.<sup>3-</sup>  
11  
12 63 <sup>5</sup> Evidence from an epidemiological survey demonstrated that over 1/3 of post-PCI  
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14 64 patients with the confession of sleep disturbance.<sup>6 7</sup> Sleep trait abnormalities  
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16 65 include difficulty in falling asleep, periods of breathing cessation, or multiple  
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18 66 awakenings during the night, which resulted in insufficient sleep durations and poor  
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20 67 sleep quality.<sup>3 8</sup> It is established that disturbed sleep is associated with adverse  
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22 68 cardiac events after PCI.<sup>9-11</sup> Previous studies have predominantly focused on sleep  
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24 69 duration as an isolated risk factor for cardiovascular disease.<sup>12</sup> However, sleep is  
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26 70 multidimensional and multi-causal. It is not only associated with cardiovascular  
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28 71 outcome but also affects the patient compliance and prognosis during the cardiac  
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30 72 rehabilitation (CR) program.<sup>12-16</sup>

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33 73 CR is a highly regarded program of secondary prevention measures, which has  
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35 74 been endorsed by the European Society of Cardiology, the American Heart  
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37 75 Association, and the American College of Cardiology.<sup>17-19</sup> Exercise is a core  
38  
39 76 component of CR.<sup>20</sup> Relevant studies have found that adherence to exercise-based  
40  
41 77 CR can effectively reduce the risk of further cardiac insults, improve sleep quality,  
42  
43 78 enhance cardiorespiratory fitness (CRF) and minimize hospital re-admission and  
44  
45 79 mortality.<sup>21-24</sup> In the process of CR, CRF is used to assess the severity of the patient's  
46  
47 80 cardiac limitation and the recovery after a cardiac event, and it is an important  
48  
49 81 independent risk factor for cardiovascular disease.<sup>25 26</sup> Moreover, the risk of long-  
50  
51 82 term major adverse cardiovascular events (MACE) is further increased when Sleep  
52  
53 83 disturbances and decreased cardiorespiratory fitness (CRF) co-occur.<sup>27</sup> The number  
54  
55 84 of studies evaluating sleep in relation to CRF is limited, with the majority of research  
56  
57 85 being of cross-sectional design. In a large cross-sectional study of 51,000  
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59 86 participants, peak oxygen uptake ( $VO_{2peak}$ ) was used to estimate CRF, showing a  
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87 modest inverse association between having difficulty falling asleep at night and  
88  $VO_{2peak}$ .<sup>28</sup> In contrast, another study used a symptom-limited cardiopulmonary

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4 89 exercise test (CPET) to objectively measure CRF and used accelerometry to monitor  
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6 90 sleep patterns. The study reported that CRF and sleep characteristics were not  
7  
8 91 significantly correlated in adults with primary hypertension.<sup>29</sup> Lindegård et al found  
9  
10 92 similar results in a longitudinal cohort study of women diagnosed with stress-  
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12 93 related exhaustion disorder.<sup>30</sup>

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14 94 Although prior observational evidence exists, none included the prospective,  
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16 95 multi-time assessment of sleep and CRF during the CR program of post-PCI patients.  
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18 96 There is still limited information on the relationship between patients' sleep traits  
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20 97 and the joint effects of CRF. Moreover, subjective reports are used to assess  
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22 98 perceptions of sleep quality in most studies, but they may not accurately measure  
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24 99 sleep duration and efficiency. Within this context, clinicians cannot provide targeted  
25  
26 100 guidance for patients undergoing CR after PCI.

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28 101 Therefore, the purposes of this study are to: 1) investigate the sleep quality and  
29  
30 102 efficiency of patients undergoing CR for the first time after PCI; 2) determine the  
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32 103 sleep trajectory and influencing factors of patients undergoing CR for the first six  
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34 104 months after PCI; and 3) investigate the longitudinal correlation between objectively  
35  
36 105 measured sleep quality and CRF in patients undergoing CR after PCI.

## 37 106 **METHODS**

### 38 39 107 **Patient and public involvement**

40  
41 108 Based on literature review in related fields, the research questions and  
42  
43 109 outcome measures were evaluated and discussed by researchers. Patients were not  
44  
45 110 involved in the design of the study, but their cooperation was required during the  
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47 111 implementation phase of the study, and their needs and preferences were fully  
48  
49 112 taken into account. Test results will be communicated verbally or in writing to  
50  
51 113 participants.

### 52 53 114 **Study design**

54  
55 115 This is a longitudinal study of patients in CR, which collects data at five-time  
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57 116 points as follows: 1) T1, patients will have completed the first CPET one month after  
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59 117 PCI and will have begun CR program, based on the risk evaluation by the physicians;  
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118 2) T2, one month after the beginning of CR program; 3) T3, three months after the

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4 119 beginning of CR program; 4) T4, six months after the beginning of CR program; and  
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6 120 5) T5, twelve months after the beginning of CR program. This study explores the  
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8 121 time-varying effects of sleep structure in patients after PCI during CR and the  
9  
10 122 potential relationship between sleep and CRF. The data will be collected in person at  
11  
12 123 the time of the four scheduled visits. Twelve months after the start of CR, the  
13  
14 124 disease prognosis will be followed up over the phone. The study framework is shown  
15  
16 125 in Figure 1.

## 126 **Participants**

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

## 132 **General inclusion criteria**

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

## 137 **General exclusion criteria**

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

## 142 **Recruitment**

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

## 147 **Study procedures**

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



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4 149 demographic characteristics and medical history. The medical staff will conduct  
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6 150 clinical examination including physical examination, blood sampling,  
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8 151 echocardiography, as well as CPET results. Body mass index (BMI) and Waist  
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10 152 circumference (WC) were determined during physical examination. The fasting  
11  
12 153 serum of each subject was collected in the morning, the measurements of fasting  
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14 154 plasma glucose (FPG), total cholesterol (TC), and low-density lipoprotein cholesterol  
15  
16 155 (LDL-C) were recorded. Cardiac biomarkers including B-type natriuretic peptide  
17  
18 156 (BNP), serum high-sensitivity C-reactive protein (hsCRP), and Homocysteine (HCY)  
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20 157 were measured in a laboratory. Data from echocardiography examination were  
21  
22 158 collected, including left ventricular ejection fraction (LVEF), left atrium diameter  
23  
24 159 (LAD), left ventricular internal diameter at end-diastole (LVIDd), interventricular  
25  
26 160 septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT).

27 161 CPET will be assessed by a physician, focusing on recording peak oxygen uptake  
28  
29 162 ( $VO_2$  peak), oxygen consumption divided by heart rate (known as the oxygen pulse:  
30  
31 163  $VO_2/HR$ ), metabolic equivalents (METs), minute ventilation divided by carbon  
32  
33 164 dioxide production ( $VE/VCO_2$  slope), oxygen uptake efficiency slope (OUES),  
34  
35 165 anaerobic threshold (AT), heart rate recovery at 1 minute after exercise (HRR 1  
36  
37 166 minute), maximal heart rate reserve (HRR Max).

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39 167 The baseline assessment will also include the Pittsburgh sleep quality index  
40  
41 168 (PSQI) to understand the sleep conditions of the participants in the past month. The  
42  
43 169 mental states of depression and anxiety will be assessed with the Patient Health  
44  
45 170 Questionnaire (PHQ-9) and the General Anxiety Disorder Scale (GAD-7), respectively.  
46  
47 171 The scales are in the Chinese version. All enrolled participants will be required to  
48  
49 172 wear an actigraphy on their wrists for 72 h to objectively monitor sleep conditions.  
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51 173 The physical therapist will prescribe a personalized exercise program for each  
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53 174 participant, based on the CPET result and the patient's disease state. Then the  
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55 175 patient will undergo a CR exercise program three times a week in the rehabilitation  
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57 176 clinic for a total of 6 months. Patients perform 40 minutes of aerobic training on a  
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59 177 treadmill or bicycle each time and use a heart rate monitor and Borg ratings of  
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178 perceived exertion scale to assess exercise intensity. During the CR process, data

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4 179 (physical examination, echocardiography, blood sampling, actigraphy for the  
5 180 assessment of sleep, PSQI, PHQ-9, and GAD-7) will be collected again in the 1<sup>st</sup>, 3<sup>rd</sup>,  
6 181 and 6<sup>th</sup> months. In addition, CEPT will be performed again in the 6<sup>th</sup> month of the CR  
7 182 program and the 6-minute walk test (6MWT) will be performed in the 1<sup>st</sup> and 3<sup>rd</sup>  
8 183 months of the CR program to supplement the CPET. Except for this, other  
9 184 assessment contents will be the same as those listed in the baseline assessments. At  
10 185 the 12<sup>th</sup> month, a telephonic follow-up will also be required. The follow-up content  
11 186 includes major adverse cardiovascular events (MACEs) and the number of  
12 187 rehospitalizations. Table 1 shows the data collection details.

### 188 Sample size

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

### 195 Measurements

#### 196 Cardiopulmonary exercise testing (CPET)

197 The CPET will be performed by professional physicians with operating  
198 qualifications using COSMED S.R.L Pulmonary Function Equipment (The Metabolic  
199 company, Guangzhou, China). Patients will not need to stop cardiovascular drugs  
200 (including  $\beta$ -blockers) on the day of the CPET test and must avoid drinking caffeine  
201 beverages and smoking 2 h before the test. According to the American Thoracic  
202 Society (ATS) guidelines, CPET uses a continuous load escalation program for  
203 symptomatic self-limiting cycling exercise.<sup>32</sup> The patient sits on a cycle ergometer  
204 and first rests for 3 minutes and then performs a zero-load idling warm-up for at  
205 least 1 minute, followed by the load-increasing exercise phase with an incremental  
206 power of 10 W/min or 20 W/min, so that the patient can reach maximum exercise  
207 intensity for self-limiting symptoms. The speed of the treadmill is maintained at 55–  
208 65 r/min throughout the test. electrocardiogram, blood pressure, and respiratory

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4 209 status will be continually monitored during the recovery period for at least 3 minutes  
5  
6 210 after the loading exercise stops, until the end of the test. The main measured  
7  
8 211 outcomes include the anaerobic threshold, peak oxygen uptake, peak oxygen pulse,  
9  
10 212 minute ventricular load, and maximum exercise load. The V-slope method will be  
11  
12 213 used to calculate the anaerobic threshold.

#### 13 214 Six-minute walk test (6MWT)

15 215 Functional exercise capacity is objectively evaluated by the 6MWT. This test  
16  
17 216 records the distance that a patient can quickly walk along a long and flat corridor in 6  
18  
19 217 min. During this test, patients are permitted to decide their walking speed but are  
20  
21 218 still required to walk as far as possible for 6 min. Every minute, physiotherapists will  
22  
23 219 call out a standardized phrase of verbal encouragement. The 6MWT process is based  
24  
25 220 on guidelines from the ATS.<sup>33</sup>

#### 27 221 Actigraphy for the assessment of sleep

29 222 Actigraphy (Respironics Inc, Murrysville, America) will be continuously  
30  
31 223 monitored for 24 h to analyze patients' sleep and waking data. The recording  
32  
33 224 frequency interval for actigraphy will be 30 s/frame, and the recording time will be 3  
34  
35 225 days. The exported sleep report will comprise daily sleep data and average sleep  
36  
37 226 data. Sleep data will include: 1) sleep time and wake-up time; 2) time in bed; 3)  
38  
39 227 actual sleep time; 4) sleep latency; 5) sleep efficiency; 6) the number of minutes and  
40  
41 228 times of awakening after the start of sleep. Finally, the averaged sleep data will be  
42  
43 229 included in the statistical analysis.

#### 44 230 Pittsburgh Sleep Quality Index (PSQI)

46 231 The PSQI is a sleep self-rated questionnaire designed and revised by scholars  
47  
48 232 including Buysse.<sup>34</sup> In this study, the Chinese version of the Pittsburgh Sleep Quality  
49  
50 233 Index (CPSQI) was used to measure the sleep quality of patients in the past month.<sup>35</sup>  
51  
52 234 The questionnaire has a total of 18 items, which are used to measure the following:  
53  
54 235 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) sleep efficiency; 5)  
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56 236 sleep disturbances; 6) use of sleeping medication, and 7) daytime dysfunction.

#### 58 237 Patient Health Questionnaire (PHQ-9)

60 238 The PHQ-9 is a reliable and effective indicator for measuring the severity of

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4 239 depression, and its items correspond to the DSM-IV diagnostic criteria for  
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6 240 depression.<sup>36</sup> In this study, the Chinese version of the PHQ-9 was used to assess the  
7  
8 241 severity of depression in patients in the last two weeks through nine questions.<sup>37</sup>  
9  
10 242 The PHQ-9 total score ranges from 0 to 27 points, and the scores 5, 10, and 20 are  
11  
12 243 the cut-off values for mild, moderate, and severe depression, respectively.

#### 244 **General anxiety disorder scale (GAD-7)**

15 245 The GAD-7 is used to determine whether the patients have psychological  
16  
17 246 symptoms of anxiety and their frequency within 2 weeks.<sup>38</sup> The Chinese version of  
18  
19 247 GAD-7 showed good reliability and validity in cardiovascular patients.<sup>37</sup> This scale  
20  
21 248 includes seven items, each with a score of 0–3 points for a total score of 21 points, of  
22  
23 249 which a score of 10–21 points denotes having an anxious mental state.

#### 250 **Statistical analysis**

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

#### 266 **DISCUSSION**

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

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4 269 cardiac events and sleep disturbance through secondary prevention strategies.<sup>41</sup> CR  
5  
6 270 is helpful for reducing the deleterious effects of sleep disorders and improving CRF.  
7  
8 271 This protocol describes a longitudinal observational study to explore the time-  
9  
10 272 varying effect of sleep structure and the potential relationship between sleep and  
11  
12 273 CRF in patients after PCI and during CR. Compared to the longitudinal study by  
13  
14 274 Mazaki T et al., the sleep data collected by actigraphy and PSQI are more extensive  
15  
16 275 and comprehensive.<sup>11</sup> Moreover, multi-time-point sleep data can display the  
17  
18 276 dynamic changes of sleep in patients after PCI during CR, helping patients to  
19  
20 277 implement effective sleep management during the CR period. Additionally, given the  
21  
22 278 importance of CRF for cardiovascular disease, a key strength of this study is  
23  
24 279 addressing the longitudinal underlying relationship between sleep and CRF. As far as  
25  
26 280 we know, this is the first longitudinal study to explore the trajectory of patients'  
27  
28 281 sleep structure changes after PCI and during CR. The advantages of this study include  
29  
30 282 the use of the PSQI and actigraphy to comprehensively assess sleep quality and  
31  
32 283 quantity. Actigraphy is an objective sleep measure that improves data accuracy.  
33  
34 284 CPET will also be used to non-invasively monitor the electrocardiogram, pulse  
35  
36 285 oximetry (SpO<sub>2</sub>), O<sub>2</sub> inhalation, and CO<sub>2</sub> output at rest and during exercise.  
37  
38 286 Cardiopulmonary reserve function and exercise tolerance will be analyzed by  
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40 287 combining multiple indicators.

41 288 There are some limitations to this study. First, the sample source will only  
42  
43 289 include participants from one hospital in China. Due to the limitations of research  
44  
45 290 sites and recruitment strategies, our sample may be prone to selection bias and  
46  
47 291 random-sampling recruitment may be difficult. Second, the study will only include  
48  
49 292 patients who voluntarily choose to undergo a CR program after PCI. Patients who  
50  
51 293 meet the conditions but have a fear of exercise will be excluded. This part of the  
52  
53 294 patient information may have an impact on the study results. Finally, we did not use  
54  
55 295 the gold standard sleep assessment technique, polysomnography (PSG). PSG is  
56  
57 296 difficult and expensive due to the fact that the patient is out of hospital for a long  
58  
59 297 period of time and the cardiac rehabilitation takes place in a rehabilitation clinic.  
60  
298 Although actigraphy cannot replace PSG in terms of diagnostic accuracy and

299 reliability, it has shown good performance for tracking sleep and wakefulness.<sup>42 43</sup>

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

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### 312 **Contributors**

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

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### 322 **Competing interests**

323 None declared.

### 324 **Data sharing**

325 No additional data are available.

326

### 327 **REFERENCES**

328 1. Du X, Patel A, Anderson CS, et al. Epidemiology of Cardiovascular Disease in China and  
329 Opportunities for Improvement: JACC International. *J Am Coll Cardiol* 2019;73(24):3135-47.

- 1  
2  
3 330 doi: 10.1016/j.jacc.2019.04.036 [published Online First: 2019/06/22]  
4  
5 331 2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial  
6 332 revascularization. *Eur Heart J* 2019;40(2):87-165. doi: 10.1093/eurheartj/ehy394 [published  
7 333 Online First: 2018/08/31]  
8 334 3. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive Sleep Apnea and Cardiovascular Disease: A  
9 335 Scientific Statement From the American Heart Association. *Circulation* 2021;144(3):e56-e67.  
10 336 doi: 10.1161/cir.0000000000000988 [published Online First: 2021/06/22]  
11 337 4. Wang X, Fan JY, Zhang Y, et al. Association of obstructive sleep apnea with cardiovascular outcomes  
12 338 after percutaneous coronary intervention: A systematic review and meta-analysis. *Medicine*  
13 339 (*Baltimore*) 2018;97(17):e0621. doi: 10.1097/md.00000000000010621 [published Online First:  
14 340 2018/04/29]  
15 341 5. Frøjd LA, Munkhaugen J, Moum T, et al. Insomnia in patients with coronary heart disease:  
16 342 prevalence and correlates. *J Clin Sleep Med* 2021;17(5):931-38. doi: 10.5664/jcsm.9082  
17 343 [published Online First: 2021/01/06]  
18 344 6. Rouleau CR, Horsley KJ, Morse E, et al. The Association Between Insomnia Symptoms and Mood  
19 345 Changes During Exercise Among Patients Enrolled in Cardiac Rehabilitation. *J Cardiopulm*  
20 346 *Rehabil Prev* 2015;35(6):409-16. doi: 10.1097/hcr.000000000000138 [published Online  
21 347 First: 2015/09/18]  
22 348 7. Le Grande MR, Beauchamp A, Driscoll A, et al. Prevalence of obstructive sleep apnoea in acute  
23 349 coronary syndrome patients: systematic review and meta-analysis. *BMC Cardiovasc Disord*  
24 350 2020;20(1):147. doi: 10.1186/s12872-020-01430-3 [published Online First: 2020/03/27]  
25 351 8. St-Onge MP, Grandner MA, Brown D, et al. Sleep Duration and Quality: Impact on Lifestyle  
26 352 Behaviors and Cardiometabolic Health: A Scientific Statement From the American Heart  
27 353 Association. *Circulation* 2016;134(18):e367-e86. doi: 10.1161/cir.0000000000000444  
28 354 [published Online First: 2016/11/02]  
29 355 9. Fernandes NM, Nield LE, Popel N, et al. Symptoms of disturbed sleep predict major adverse cardiac  
30 356 events after percutaneous coronary intervention. *Can J Cardiol* 2014;30(1):118-24. doi:  
31 357 10.1016/j.cjca.2013.07.009 [published Online First: 2013/10/22]  
32 358 10. Strand LB, Tsai MK, Gunnell D, et al. Self-reported sleep duration and coronary heart disease  
33 359 mortality: A large cohort study of 400,000 Taiwanese adults. *Int J Cardiol* 2016;207:246-51.  
34 360 doi: 10.1016/j.ijcard.2016.01.044 [published Online First: 2016/01/26]  
35 361 11. Mazaki T, Kasai T, Yokoi H, et al. Impact of Sleep-Disordered Breathing on Long-Term Outcomes in  
36 362 Patients With Acute Coronary Syndrome Who Have Undergone Primary Percutaneous  
37 363 Coronary Intervention. *J Am Heart Assoc* 2016;5(6) doi: 10.1161/jaha.116.003270 [published  
38 364 Online First: 2016/06/17]  
39 365 12. Cappuccio FP, Cooper D, D'Elia L, et al. Sleep duration predicts cardiovascular outcomes: a  
40 366 systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32(12):1484-  
41 367 92. doi: 10.1093/eurheartj/ehr007 [published Online First: 2011/02/09]  
42 368 13. Soehner AM, Harvey AG. Prevalence and functional consequences of severe insomnia symptoms  
43 369 in mood and anxiety disorders: results from a nationally representative sample. *Sleep*  
44 370 2012;35(10):1367-75. doi: 10.5665/sleep.2116 [published Online First: 2012/10/02]  
45 371 14. Meijer A, Conradi HJ, Bos EH, et al. Adjusted prognostic association of depression following  
46 372 myocardial infarction with mortality and cardiovascular events: individual patient data meta-  
47 373 analysis. *Br J Psychiatry* 2013;203(2):90-102. doi: 10.1192/bjp.bp.112.111195 [published  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

- 1  
2  
3 374 Online First: 2013/08/03]  
4 375 15. Madsen MT, Huang C, Zangger G, et al. Sleep Disturbances in Patients With Coronary Heart  
5 376 Disease: A Systematic Review. *J Clin Sleep Med* 2019;15(3):489-504. doi: 10.5664/jcsm.7684  
6 377 [published Online First: 2019/03/12]  
7 378 16. Banack HR, Holly CD, Lowensteyn I, et al. The association between sleep disturbance, depressive  
8 379 symptoms, and health-related quality of life among cardiac rehabilitation participants. *J*  
9 380 *Cardiopulm Rehabil Prev* 2014;34(3):188-94. doi: 10.1097/hcr.000000000000054 [published  
10 381 Online First: 2014/04/01]  
11 382 17. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary  
12 383 heart disease: an American Heart Association scientific statement from the Council on  
13 384 Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and  
14 385 the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical  
15 386 Activity), in collaboration with the American association of Cardiovascular and Pulmonary  
16 387 Rehabilitation. *Circulation* 2005;111(3):369-76. doi: 10.1161/01.Cir.0000151788.08740.5c  
17 388 [published Online First: 2005/01/26]  
18 389 18. Corrà U, Piepoli MF, Carré F, et al. Secondary prevention through cardiac rehabilitation: physical  
19 390 activity counselling and exercise training: key components of the position paper from the  
20 391 Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and  
21 392 Rehabilitation. *Eur Heart J* 2010;31(16):1967-74. doi: 10.1093/eurheartj/ehq236 [published  
22 393 Online First: 2010/07/21]  
23 394 19. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific  
24 395 statement from the American Heart Association. *Circulation* 2013;128(8):873-934. doi:  
25 396 10.1161/CIR.0b013e31829b5b44 [published Online First: 2013/07/24]  
26 397 20. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary  
27 398 prevention programs: 2007 update: a scientific statement from the American Heart  
28 399 Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on  
29 400 Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention,  
30 401 and Nutrition, Physical Activity, and Metabolism; and the American Association of  
31 402 Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007;115(20):2675-82. doi:  
32 403 10.1161/circulationaha.106.180945 [published Online First: 2007/05/22]  
33 404 21. Kirchnerberger I, Hunger M, Stollenwerk B, et al. Effects of a 3-year nurse-based case management in  
34 405 aged patients with acute myocardial infarction on rehospitalisation, mortality, risk factors,  
35 406 physical functioning and mental health. a secondary analysis of the randomized controlled  
36 407 KORINNA study. *PLoS One* 2015;10(3):e0116693. doi: 10.1371/journal.pone.0116693  
37 408 [published Online First: 2015/03/27]  
38 409 22. Rutledge T, Redwine LS, Linke SE, et al. A meta-analysis of mental health treatments and cardiac  
39 410 rehabilitation for improving clinical outcomes and depression among patients with coronary  
40 411 heart disease. *Psychosom Med* 2013;75(4):335-49. doi: 10.1097/PSY.0b013e318291d798  
41 412 [published Online First: 2013/05/01]  
42 413 23. Zhang L, Zhang L, Wang J, et al. Community health service center-based cardiac rehabilitation in  
43 414 patients with coronary heart disease: a prospective study. *BMC Health Serv Res*  
44 415 2017;17(1):128. doi: 10.1186/s12913-017-2036-3 [published Online First: 2017/02/12]  
45 416 24. Loboda D, Stepanik M, Golba A, et al. The beneficial impact of cardiac rehabilitation on obstructive  
46 417 sleep apnea in patients with coronary artery disease. *J Clin Sleep Med* 2021;17(3):403-12.



- 1  
2  
3 418 doi: 10.5664/jcsm.8900 [published Online First: 2020/10/23]  
4  
5 419 25. Laddu D, Ozemek C, Lamb B, et al. Factors Associated With Cardiorespiratory Fitness at  
6 420 Completion of Cardiac Rehabilitation: Identification of Specific Patient Features Requiring  
7 421 Attention. *Can J Cardiol* 2018;34(7):925-32. doi: 10.1016/j.cjca.2018.03.015 [published  
8 422 Online First: 2018/06/05]  
9  
10 423 26. Thompson PD, Arena R, Riebe D, et al. ACSM's new preparticipation health screening  
11 424 recommendations from ACSM's guidelines for exercise testing and prescription, ninth  
12 425 edition. *Curr Sports Med Rep* 2013;12(4):215-7. doi: 10.1249/JSR.0b013e31829a68cf  
13 426 [published Online First: 2013/07/16]  
14  
15 427 27. Barillas-Lara MI, Medina-Inojosa JR, Kolla BP, et al. The Association of Sleep Apnea and  
16 428 Cardiorespiratory Fitness With Long-Term Major Cardiovascular Events. *Mayo Clin Proc*  
17 429 2021;96(3):636-47. doi: 10.1016/j.mayocp.2020.03.040 [published Online First: 2021/03/07]  
18  
19 430 28. Strand LB, Laugsand LE, Wisløff U, et al. Insomnia symptoms and cardiorespiratory fitness in  
20 431 healthy individuals: the Nord-Trøndelag Health Study (HUNT). *Sleep* 2013;36(1):99-108. doi:  
21 432 10.5665/sleep.2310 [published Online First: 2013/01/05]  
22  
23 433 29. MartinezAguirre-Betolaza A, Maldonado-Martín S, Corres P, et al. Actigraphy-based sleep analysis  
24 434 in sedentary and overweight/obese adults with primary hypertension: data from the  
25 435 EXERDIET-HTA study. *Sleep Breath* 2019;23(4):1265-73. doi: 10.1007/s11325-019-01813-7  
26 436 [published Online First: 2019/03/01]  
27  
28 437 30. Lindegård A, Wastensson G, Hadzibajramovic E, et al. Longitudinal associations between  
29 438 cardiorespiratory fitness and stress-related exhaustion, depression, anxiety and sleep  
30 439 disturbances. *BMC Public Health* 2019;19(1):1726. doi: 10.1186/s12889-019-8081-6  
31 440 [published Online First: 2019/12/25]  
32  
33 441 31. Crowley SK, Rebellon J, Huber C, et al. Cardiorespiratory fitness, sleep, and physiological responses  
34 442 to stress in women. *Eur J Sport Sci* 2020;20(10):1368-77. doi:  
35 443 10.1080/17461391.2020.1716855 [published Online First: 2020/01/16]  
36  
37 444 32. Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*  
38 445 2003;167(10):1451; author reply 51. doi: 10.1164/ajrccm.167.10.950 [published Online First:  
39 446 2003/05/10]  
40  
41 447 33. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*  
42 448 2002;166(1):111-7. doi: 10.1164/ajrccm.166.1.at1102 [published Online First: 2002/07/02]  
43  
44 449 34. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument  
45 450 for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213. doi: 10.1016/0165-  
46 451 1781(89)90047-4 [published Online First: 1989/05/01]  
47  
48 452 35. Tsai PS, Wang SY, Wang MY, et al. Psychometric evaluation of the Chinese version of the  
49 453 Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life*  
50 454 *Res* 2005;14(8):1943-52. doi: 10.1007/s11136-005-4346-x [published Online First:  
51 455 2005/09/13]  
52  
53 456 36. Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for  
54 457 screening to detect major depression: individual participant data meta-analysis. *Bmj*  
55 458 2019;365:l1476. doi: 10.1136/bmj.l1476 [published Online First: 2019/04/11]  
56  
57 459 37. Lin Q, Bonkano O, Wu K, et al. The Value of Chinese Version GAD-7 and PHQ-9 to Screen Anxiety  
58 460 and Depression in Chinese Outpatients with Atypical Chest Pain. *Ther Clin Risk Manag*  
59 461 2021;17:423-31. doi: 10.2147/tcrm.S305623 [published Online First: 2021/05/28]

- 1  
2  
3 462 38. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety  
4 463 disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-7. doi:  
5 464 10.1001/archinte.166.10.1092 [published Online First: 2006/05/24]  
6  
7 465 39. Gilthorpe MS, Dahly DL, Tu YK, et al. Challenges in modelling the random structure correctly in  
8 466 growth mixture models and the impact this has on model mixtures. *J Dev Orig Health Dis*  
9 467 2014;5(3):197-205. doi: 10.1017/s2040174414000130 [published Online First: 2014/06/06]  
10  
11 468 40. Muthén B, Asparouhov T. Growth mixture modeling with non-normal distributions. *Stat Med*  
12 469 2015;34(6):1041-58. doi: 10.1002/sim.6388 [published Online First: 2014/12/17]  
13  
14 470 41. Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmaco-economic burden.  
15 471 *Am J Manag Care* 2009;15(2 Suppl):S36-41. [published Online First: 2009/04/16]  
16  
17 472 42. Haghayegh S, Khoshnevis S, Smolensky MH, et al. Accuracy of Wristband Fitbit Models in  
18 473 Assessing Sleep: Systematic Review and Meta-Analysis. *J Med Internet Res*  
19 474 2019;21(11):e16273. doi: 10.2196/16273 [published Online First: 2019/11/30]  
20  
21 475 43. Chinoy ED, Cuellar JA, Huwa KE, et al. Performance of seven consumer sleep-tracking devices  
22 476 compared with polysomnography. *Sleep* 2021;44(5) doi: 10.1093/sleep/zsaa291 [published  
23 477 Online First: 2020/12/31]  
24 478  
25  
26 479  
27  
28 480  
29  
30 481  
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32 482  
33  
34 483  
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36 484  
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500 **TABLE 1 Data collection in the study**

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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					√

502

503 **Notes:** T1: Baseline assessment and enrolment; T2: one month after the beginning of CR

504 program; T3: three months after the beginning of CR program; T4: six months after the beginning

505 of CR program; T5: twelve months after the beginning of CR program. Physical examination: Body

506 mass index (BMI) , Waist circumference (WC), blood pressure (BP); Blood sampling: fasting

507 plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), B-type

508 natriuretic peptide (BNP), serum high-sensitivity C-reactive protein (hsCRP), Homocysteine

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4 509 (HCY); Echocardiography: left ventricular ejection fraction (LVEF), left atrium diameter (LAD), left  
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6 510 ventricular internal diameter at end-diastole (LVIDd), interventricular septal thickness (IVST), left  
7  
8 511 ventricular posterior wall thickness (LVPWT)

9  
10 512 **Abbreviations:** CPET: cardiopulmonary exercise testing; 6MWT: six-minute walk test; PSQI:  
11  
12 513 Pittsburgh Sleep Quality Index; PHQ-9: Patient Health Questionnaire; GAD-7: General anxiety  
13  
14 514 disorder scale; MACEs: major adverse cardiovascular events

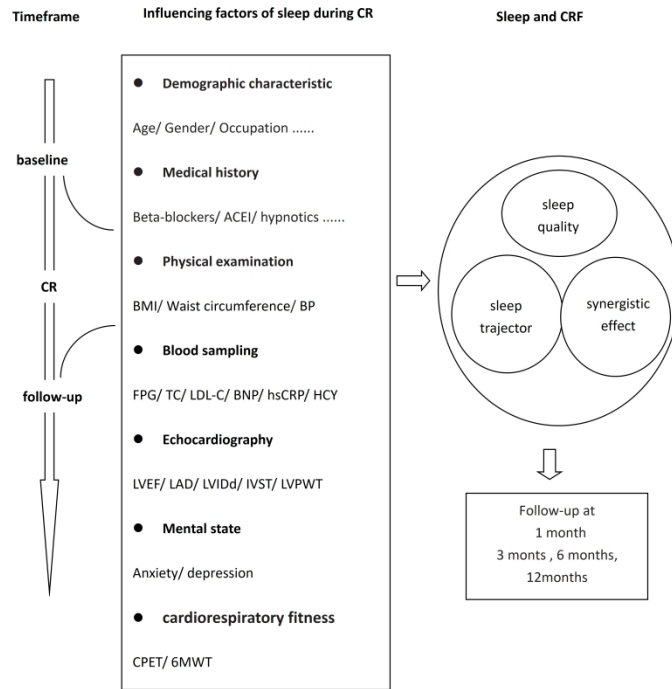
15 515

16 516 **FIGURE 1 Study framework**

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For peer review only

FIGURE 1 Study framework



532x753mm (227 x 227 DPI)

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	4-5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	
		(e) Describe any sensitivity analyses	

Continued on next page

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	
Outcome data	15	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	
	*	<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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	
<b>Discussion</b>			
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	
<b>Other information</b>			
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](http://www.strobe-statement.org).

# BMJ Open

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

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4 1 **Sleep behavior and cardiorespiratory fitness in patients after**  
5  
6 2 **percutaneous coronary intervention during cardiac rehabilitation:**  
7  
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9 3 **protocol for a longitudinal study**

10 4 **Lan Huang <sup>a</sup>、 Jie Zhou <sup>a</sup>、 Husheng Li <sup>a</sup>、 Yiyan Wang <sup>a</sup>、 Xubo Wu <sup>b\*</sup>、 Jing Wu <sup>ab\*</sup>**

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17 11 The study was funded by the Nature Science Foundation of China (No. 71904127).

18 12 **Abstract**

19 13 **Introduction:** Most patients with coronary heart disease experience sleep  
20 14 disturbances and low cardiorespiratory fitness (CRF), but their relationship during  
21 15 cardiac rehabilitation (CR) is still unclear. This article details a protocol for the study  
22 16 of sleep trajectory in patients with coronary heart disease during CR and the  
23 17 relationship between sleep and CRF. A better understanding of the relationship  
24 18 between sleep and CRF on patient outcomes can improve sleep management  
25 19 strategies.

26 20 **Methods and analysis:** This is a longitudinal study with a recruitment target of 101  
27 21 patients after percutaneous cardiac intervention (PCI) from the Seventh People's  
28 22 Hospital of Shanghai, China. Data collection will include demographic characteristics,  
29 23 medical history, physical examination, blood sampling, echocardiography, and the  
30 24 results of cardiopulmonary exercise tests (CPETs). The information provided by a six-  
31 25 minute walk test (6MWT) will be used to supplement the CPET. The Pittsburgh sleep  
32 26 quality index (PSQI) will be used to understand the sleep conditions of the  
33 27 participants in the past month. The Patient Health Questionnaire (PHQ-9) and  
34 28 General Anxiety Disorder Scale (GAD-7) will be used to assess depression and

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4 29 anxiety, respectively. All participants will be required to wear an actigraphy on their  
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6 30 wrists for 72 h to monitor objective sleep conditions. This information will be  
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8 31 collected four times within six months of CR, and patients will be followed up for one  
9  
10 32 year. The growth mixture model will be used to analyze the longitudinal sleep data.  
11  
12 33 The generalized estimating equation will be used to examine the associations  
13  
14 34 between sleep and CRF during CR.

15  
16 35 **Ethics and dissemination:** Ethical approval for this observational longitudinal study  
17  
18 36 was granted by the Shanghai Seventh People's Hospital Ethics Committee on 23 April  
19  
20 37 2021, (2021-7<sup>th</sup>-HIRB-012). Study results will be disseminated in peer-reviewed  
21  
22 38 journal articles.

23  
24 39 **Keywords:** sleep disturbance, cardiopulmonary fitness, percutaneous coronary  
25  
26 40 intervention, cardiac rehabilitation, coronary heart disease, protocol

#### 27 41 **Strengths and limitations of this study**

- 28  
29 42 1. This is a longitudinal study of patients in cardiac rehabilitation, assessing sleep  
30  
31 43 trajectory and the relationship between sleep and cardiorespiratory fitness.  
32  
33 44 2. The use of cardiopulmonary exercise testing and the 6-minute walk test will  
34  
35 45 provide accurate and objective cardiorespiratory fitness outcomes.  
36  
37 46 3. The Pittsburgh sleep quality Index and actigraphy will be used to comprehensively  
38  
39 47 assess sleep quality and quantity, improving the power to discover patients with  
40  
41 48 sleep disorders.  
42  
43 49 4. This is a single-center study, the sample source will only include participants from  
44  
45 50 one tertiary hospital in China.  
46  
47 51 5. The sample has selection bias, as only patients who voluntarily choose to undergo  
48  
49 52 a cardiac rehabilitation program after the percutaneous cardiac intervention.

#### 50 53 51 54 **INTRODUCTION**

52  
53  
54 55 Cardiovascular mortality, mostly attributable to ischemic heart disease (IHD), is  
55  
56 56 expected to increase more dramatically in the next decade globally. <sup>1</sup> According to  
57  
58 57 the 2018 ESC/EACTS Guidelines on myocardial revascularization, timely  
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60 58 percutaneous coronary intervention (PCI) of the infarct-related artery is still the

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4 59 priority treatment of IHD patients.<sup>2</sup> However, after complete or incomplete  
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6 60 revascularization procedures, patients may still encounter stent thrombosis, angina,  
7  
8 61 and symptoms related to psychological and somatic stress. Sleep disturbances such  
9  
10 62 as insomnia, obstructive sleep apnea (OSA) are quite common in patients with IHD.<sup>3-</sup>  
11  
12 63 <sup>5</sup> Evidence from an epidemiological survey demonstrated that over 1/3 of post-PCI  
13  
14 64 patients with the confession of sleep disturbance.<sup>6 7</sup> Sleep trait abnormalities  
15  
16 65 include difficulty in falling asleep, periods of breathing cessation, or multiple  
17  
18 66 awakenings during the night, which resulted in insufficient sleep durations and poor  
19  
20 67 sleep quality.<sup>3 8</sup> It is established that disturbed sleep is associated with adverse  
21  
22 68 cardiac events after PCI.<sup>9-11</sup> Previous studies have predominantly focused on sleep  
23  
24 69 duration as an isolated risk factor for cardiovascular disease.<sup>12</sup> However, sleep is  
25  
26 70 multidimensional and multi-causal. It is not only associated with cardiovascular  
27  
28 71 outcome but also affects the patient compliance and prognosis during the cardiac  
29  
30 72 rehabilitation (CR) program.<sup>12-16</sup>

31  
32  
33 73 CR is a highly regarded program of secondary prevention measures, which has  
34  
35 74 been endorsed by the European Society of Cardiology, the American Heart  
36  
37 75 Association, and the American College of Cardiology.<sup>17-19</sup> Exercise is a core  
38  
39 76 component of CR.<sup>20</sup> Relevant studies have found that adherence to exercise-based  
40  
41 77 CR can effectively reduce the risk of further cardiac insults, improve sleep quality,  
42  
43 78 enhance cardiorespiratory fitness (CRF) and minimize hospital re-admission and  
44  
45 79 mortality.<sup>21-24</sup> In the process of CR, CRF is used to assess the severity of the patient's  
46  
47 80 cardiac limitation and the recovery after a cardiac event, and it is an important  
48  
49 81 independent risk factor for cardiovascular disease.<sup>25 26</sup> Moreover, the risk of long-  
50  
51 82 term major adverse cardiovascular events (MACE) is further increased when Sleep  
52  
53 83 disturbances and decreased cardiorespiratory fitness (CRF) co-occur.<sup>27</sup> The number  
54  
55 84 of studies evaluating sleep in relation to CRF is limited, with the majority of research  
56  
57 85 being of cross-sectional design. In a large cross-sectional study of 51,000  
58  
59 86 participants, peak oxygen uptake ( $VO_{2peak}$ ) was used to estimate CRF, showing a  
60  
87 modest inverse association between having difficulty falling asleep at night and  
88  $VO_{2peak}$ .<sup>28</sup> In contrast, another study used a symptom-limited cardiopulmonary

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4 89 exercise test (CPET) to objectively measure CRF and used accelerometry to monitor  
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6 90 sleep patterns. The study reported that CRF and sleep characteristics were not  
7  
8 91 significantly correlated in adults with primary hypertension.<sup>29</sup> Lindegård et al found  
9  
10 92 similar results in a longitudinal cohort study of women diagnosed with stress-  
11  
12 93 related exhaustion disorder.<sup>30</sup>

13  
14 94 Although prior observational evidence exists, none included the prospective,  
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16 95 multi-time assessment of sleep and CRF during the CR program of post-PCI patients.  
17  
18 96 There is still limited information on the relationship between patients' sleep traits  
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20 97 and the joint effects of CRF. Moreover, subjective reports are used to assess  
21  
22 98 perceptions of sleep quality in most studies, but they may not accurately measure  
23  
24 99 sleep duration and efficiency. Within this context, clinicians cannot provide targeted  
25  
26 100 guidance for patients undergoing CR after PCI.

27  
28 101 Therefore, the purposes of this study are to: 1) investigate the sleep quality and  
29  
30 102 efficiency of patients undergoing CR for the first time after PCI; 2) determine the  
31  
32 103 sleep trajectory and influencing factors of patients undergoing CR for the first six  
33  
34 104 months after PCI; and 3) investigate the longitudinal correlation between objectively  
35  
36 105 measured sleep quality and CRF in patients undergoing CR after PCI.

## 37 106 **METHODS**

### 38 39 107 **Patient and public involvement**

40  
41 108 Based on literature review in related fields, the research questions and  
42  
43 109 outcome measures were evaluated and discussed by researchers. Patients were not  
44  
45 110 involved in the design of the study, but their cooperation was required during the  
46  
47 111 implementation phase of the study, and their needs and preferences were fully  
48  
49 112 taken into account. Test results will be communicated verbally or in writing to  
50  
51 113 participants.

### 52 53 114 **Study design**

54  
55 115 This is a longitudinal study of patients in CR, which collects data at five-time  
56  
57 116 points as follows: 1) T1, patients will have completed the first CPET one month after  
58  
59 117 PCI and will have begun CR program, based on the risk evaluation by the physicians;  
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118 2) T2, one month after the beginning of CR program; 3) T3, three months after the

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4 119 beginning of CR program; 4) T4, six months after the beginning of CR program; and  
5  
6 120 5) T5, twelve months after the beginning of CR program. This study explores the  
7  
8 121 time-varying effects of sleep structure in patients after PCI during CR and the  
9  
10 122 potential relationship between sleep and CRF. The data will be collected in person at  
11  
12 123 the time of the four scheduled visits. Twelve months after the start of CR, the  
13  
14 124 disease prognosis will be followed up over the phone. The study framework is shown  
15  
16 125 in Figure 1.

## 126 **Participants**

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

## 132 **General inclusion criteria**

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

## 137 **General exclusion criteria**

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

## 142 **Recruitment**

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

## 147 **Study procedures**

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

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4 149 demographic characteristics and medical history. The medical staff will conduct  
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6 150 clinical examination including physical examination, blood sampling,  
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8 151 echocardiography, as well as CPET results. Body mass index (BMI) and Waist  
9  
10 152 circumference (WC) were determined during physical examination. The fasting  
11  
12 153 serum of each subject was collected in the morning, the measurements of fasting  
13  
14 154 plasma glucose (FPG), total cholesterol (TC), and low-density lipoprotein cholesterol  
15  
16 155 (LDL-C) were recorded. Cardiac biomarkers including B-type natriuretic peptide  
17  
18 156 (BNP), serum high-sensitivity C-reactive protein (hsCRP), and Homocysteine (HCY)  
19  
20 157 were measured in a laboratory. Data from echocardiography examination were  
21  
22 158 collected, including left ventricular ejection fraction (LVEF), left atrium diameter  
23  
24 159 (LAD), left ventricular internal diameter at end-diastole (LVIDd), interventricular  
25  
26 160 septal thickness (IVST), and left ventricular posterior wall thickness (LVPWT).

27 161 CPET will be assessed by a physician, focusing on recording peak oxygen uptake  
28  
29 162 ( $VO_2$  peak), oxygen consumption divided by heart rate (known as the oxygen pulse:  
30  
31 163  $VO_2/HR$ ), metabolic equivalents (METs), minute ventilation divided by carbon  
32  
33 164 dioxide production ( $VE/VCO_2$  slope), oxygen uptake efficiency slope (OUES),  
34  
35 165 anaerobic threshold (AT), heart rate recovery at 1 minute after exercise (HRR 1  
36  
37 166 minute), maximal heart rate reserve (HRR Max).

38  
39 167 The baseline assessment will also include the Pittsburgh sleep quality index  
40  
41 168 (PSQI) to understand the sleep conditions of the participants in the past month. The  
42  
43 169 mental states of depression and anxiety will be assessed with the Patient Health  
44  
45 170 Questionnaire (PHQ-9) and the General Anxiety Disorder Scale (GAD-7), respectively.  
46  
47 171 The scales are in the Chinese version. All enrolled participants will be required to  
48  
49 172 wear an actigraphy on their wrists for 72 h to objectively monitor sleep conditions.  
50  
51 173 The physical therapist will prescribe a personalized exercise program for each  
52  
53 174 participant, based on the CPET result and the patient's disease state. Then the  
54  
55 175 patient will undergo a CR exercise program three times a week in the rehabilitation  
56  
57 176 clinic for a total of 6 months. Patients perform 40 minutes of aerobic training on a  
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59 177 treadmill or bicycle each time and use a heart rate monitor and Borg ratings of  
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178 perceived exertion scale to assess exercise intensity. During the CR process, data

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4 179 (physical examination, echocardiography, blood sampling, actigraphy for the  
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6 180 assessment of sleep, PSQI, PHQ-9, and GAD-7) will be collected again in the 1<sup>st</sup>, 3<sup>rd</sup>,  
7  
8 181 and 6<sup>th</sup> months. In addition, CEPT will be performed again in the 6<sup>th</sup> month of the CR  
9  
10 182 program and the 6-minute walk test (6MWT) will be performed in the 1<sup>st</sup> and 3<sup>rd</sup>  
11  
12 183 months of the CR program to supplement the CPET. Except for this, other  
13  
14 184 assessment contents will be the same as those listed in the baseline assessments. At  
15  
16 185 the 12<sup>th</sup> month, a telephonic follow-up will also be required. The follow-up content  
17  
18 186 includes major adverse cardiovascular events (MACEs) and the number of  
19  
20 187 rehospitalizations. Table 1 shows the data collection details.

### 21 188 **Sample size**

22  
23 189 The calculations of the sample size were based on an estimate of the  
24  
25 190 correlation coefficient between sleep quality and CRF in participants from previous  
26  
27 191 studies.<sup>31</sup> With a two-sided significance level of 5% and a minimum correlation  
28  
29 192 coefficient of 0.37 between sleep quality and CRF, 84 patients after PCI would be  
30  
31 193 included. Considering an attrition rate of 20%, the final total sample size will be at  
32  
33 194 least 101 patients.

### 34 195 **Measurements**

#### 35 196 **Cardiopulmonary exercise testing (CPET)**

36  
37 197 The CPET will be performed by professional physicians with operating  
38  
39 198 qualifications using COSMED S.R.L Pulmonary Function Equipment (The Metabolic  
40  
41 199 company, Guangzhou, China). Patients will not need to stop cardiovascular drugs  
42  
43 200 (including  $\beta$ -blockers) on the day of the CPET test and must avoid drinking caffeine  
44  
45 201 beverages and smoking 2 h before the test. According to the American Thoracic  
46  
47 202 Society (ATS) guidelines, CPET uses a continuous load escalation program for  
48  
49 203 symptomatic self-limiting cycling exercise.<sup>32</sup> The patient sits on a cycle ergometer  
50  
51 204 and first rests for 3 minutes and then performs a zero-load idling warm-up for at  
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53 205 least 1 minute, followed by the load-increasing exercise phase with an incremental  
54  
55 206 power of 10 W/min or 20 W/min, so that the patient can reach maximum exercise  
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57 207 intensity for self-limiting symptoms. The speed of the treadmill is maintained at 55–  
58  
59 208 65 r/min throughout the test. electrocardiogram, blood pressure, and respiratory  
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4 209 status will be continually monitored during the recovery period for at least 3 minutes  
5  
6 210 after the loading exercise stops, until the end of the test. The main measured  
7  
8 211 outcomes include the anaerobic threshold, peak oxygen uptake, peak oxygen pulse,  
9  
10 212 minute ventricular load, and maximum exercise load. The V-slope method will be  
11  
12 213 used to calculate the anaerobic threshold.

#### 13 214 Six-minute walk test (6MWT)

15 215 Functional exercise capacity is objectively evaluated by the 6MWT. This test  
16  
17 216 records the distance that a patient can quickly walk along a long and flat corridor in 6  
18  
19 217 min. During this test, patients are permitted to decide their walking speed but are  
20  
21 218 still required to walk as far as possible for 6 min. Every minute, physiotherapists will  
22  
23 219 call out a standardized phrase of verbal encouragement. The 6MWT process is based  
24  
25 220 on guidelines from the ATS.<sup>33</sup>

#### 27 221 Actigraphy for the assessment of sleep

29 222 Actigraphy (Respironics Inc, Murrysville, America) will be continuously  
30  
31 223 monitored for 24 h to analyze patients' sleep and waking data. The recording  
32  
33 224 frequency interval for actigraphy will be 30 s/frame, and the recording time will be 3  
34  
35 225 days. The exported sleep report will comprise daily sleep data and average sleep  
36  
37 226 data. Sleep data will include: 1) sleep time and wake-up time; 2) time in bed; 3)  
38  
39 227 actual sleep time; 4) sleep latency; 5) sleep efficiency; 6) the number of minutes and  
40  
41 228 times of awakening after the start of sleep. Finally, the averaged sleep data will be  
42  
43 229 included in the statistical analysis.

#### 44 230 Pittsburgh Sleep Quality Index (PSQI)

46 231 The PSQI is a sleep self-rated questionnaire designed and revised by scholars  
47  
48 232 including Buysse.<sup>34</sup> In this study, the Chinese version of the Pittsburgh Sleep Quality  
49  
50 233 Index (CPSQI) was used to measure the sleep quality of patients in the past month.<sup>35</sup>  
51  
52 234 The questionnaire has a total of 18 items, which are used to measure the following:  
53  
54 235 1) subjective sleep quality; 2) sleep latency; 3) sleep duration; 4) sleep efficiency; 5)  
55  
56 236 sleep disturbances; 6) use of sleeping medication, and 7) daytime dysfunction.

#### 58 237 Patient Health Questionnaire (PHQ-9)

60 238 The PHQ-9 is a reliable and effective indicator for measuring the severity of



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4 239 depression, and its items correspond to the DSM-IV diagnostic criteria for  
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6 240 depression.<sup>36</sup> In this study, the Chinese version of the PHQ-9 was used to assess the  
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8 241 severity of depression in patients in the last two weeks through nine questions.<sup>37</sup>  
9  
10 242 The PHQ-9 total score ranges from 0 to 27 points, and the scores 5, 10, and 20 are  
11  
12 243 the cut-off values for mild, moderate, and severe depression, respectively.

#### 244 **General anxiety disorder scale (GAD-7)**

15 245 The GAD-7 is used to determine whether the patients have psychological  
16  
17 246 symptoms of anxiety and their frequency within 2 weeks.<sup>38</sup> The Chinese version of  
18  
19 247 GAD-7 showed good reliability and validity in cardiovascular patients.<sup>37</sup> This scale  
20  
21 248 includes seven items, each with a score of 0–3 points for a total score of 21 points, of  
22  
23 249 which a score of 10–21 points denotes having an anxious mental state.

#### 250 **Statistical analysis**

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

#### 266 **DISCUSSION**

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

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4 269 cardiac events and sleep disturbance through secondary prevention strategies.<sup>41</sup> CR  
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6 270 is helpful for reducing the deleterious effects of sleep disorders and improving CRF.  
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8 271 This protocol describes a longitudinal observational study to explore the time-  
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10 272 varying effect of sleep structure and the potential relationship between sleep and  
11  
12 273 CRF in patients after PCI and during CR. Compared to the longitudinal study by  
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14 274 Mazaki T et al., the sleep data collected by actigraphy and PSQI are more extensive  
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16 275 and comprehensive.<sup>11</sup> Moreover, multi-time-point sleep data can display the  
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18 276 dynamic changes of sleep in patients after PCI during CR, helping patients to  
19  
20 277 implement effective sleep management during the CR period. Additionally, given the  
21  
22 278 importance of CRF for cardiovascular disease, a key strength of this study is  
23  
24 279 addressing the longitudinal underlying relationship between sleep and CRF. As far as  
25  
26 280 we know, this is the first longitudinal study to explore the trajectory of patients'  
27  
28 281 sleep structure changes after PCI and during CR. The advantages of this study include  
29  
30 282 the use of the PSQI and actigraphy to comprehensively assess sleep quality and  
31  
32 283 quantity. Actigraphy is an objective sleep measure that improves data accuracy.  
33  
34 284 CPET will also be used to non-invasively monitor the electrocardiogram, pulse  
35  
36 285 oximetry (SpO<sub>2</sub>), O<sub>2</sub> inhalation, and CO<sub>2</sub> output at rest and during exercise.  
37  
38 286 Cardiopulmonary reserve function and exercise tolerance will be analyzed by  
39  
40 287 combining multiple indicators.

41 288 There are some limitations to this study. First, the sample source will only  
42  
43 289 include participants from one hospital in China. Due to the limitations of research  
44  
45 290 sites and recruitment strategies, our sample may be prone to selection bias and  
46  
47 291 random-sampling recruitment may be difficult. Second, the study will only include  
48  
49 292 patients who voluntarily choose to undergo a CR program after PCI. Patients who  
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51 293 meet the conditions but have a fear of exercise will be excluded. This part of the  
52  
53 294 patient information may have an impact on the study results. Finally, we did not use  
54  
55 295 the gold standard sleep assessment technique, polysomnography (PSG). PSG is  
56  
57 296 difficult and expensive due to the fact that the patient is out of hospital for a long  
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59 297 period of time and the cardiac rehabilitation takes place in a rehabilitation clinic.  
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298 Although actigraphy cannot replace PSG in terms of diagnostic accuracy and

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4 299 reliability, it has shown good performance for tracking sleep and wakefulness.<sup>42 43</sup>

5 300 Poor CRF is considered a possible adverse health outcome associated with poor  
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7 301 sleep. This study aims to investigate the sleep conditions of patients during CR and  
8  
9 302 the relationship with CRF as the preliminary basis of clinical intervention. The  
10  
11 303 exploration of the dynamic fluctuations of sleep and its relationship with CRF may  
12  
13 304 provide useful reference for targeted cardiac rehabilitation management. During CR  
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15 305 management, medical staff can timely detect and adjust the patient's adverse state  
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17 306 through objective sleep and CRF monitoring, and speed up the recovery process.

### 19 307 **ETHICS AND DISSEMINATION**

21 308 This article describes a prospective, longitudinal study protocol to assess sleep  
22  
23 309 trajectory and the relationship between sleep and cardiorespiratory fitness for CR  
24  
25 310 patients. Ethical approval for this observational longitudinal study was granted by  
26  
27 311 the Shanghai Seventh People's Hospital Ethics Committee on 23 April 2021, (2021-  
28  
29 312 7th-HIRB-012). All participants will be provided with a full understanding of the study  
30  
31 313 and will be made aware that participation is strictly voluntary. Informed consent and  
32  
33 314 information sheets will be provided for patients before the onset of this research.  
34  
35 315 The study results will be disseminated in peer-reviewed journal articles.

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### 46 321 **Contributors**

47  
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50  
51 323 protocol design, data collection and analysis, and presentation of findings. She was  
52  
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55 325 Husheng Li and Yiyan Wang participated in data collection and analysis. Xubo Wu  
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57 326 and Jing Wu contributed to the protocol design and revisions of the manuscript. All  
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59 327 authors have read and approved the final manuscript.

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7  
8 331 **Competing interests**

9  
10 332 None declared.

11  
12 333 **Data sharing**

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14 334 No additional data are available.

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18 336 **REFERENCES**

- 19 337 1. Du X, Patel A, Anderson CS, et al. Epidemiology of Cardiovascular Disease in China and  
20 338 Opportunities for Improvement: JACC International. *J Am Coll Cardiol* 2019;73(24):3135-47.  
21 339 doi: 10.1016/j.jacc.2019.04.036 [published Online First: 2019/06/22]
- 22 340 2. Neumann FJ, Sousa-Uva M, Ahlsson A, et al. 2018 ESC/EACTS Guidelines on myocardial  
23 341 revascularization. *Eur Heart J* 2019;40(2):87-165. doi: 10.1093/eurheartj/ehy394 [published  
24 342 Online First: 2018/08/31]
- 25 343 3. Yeghiazarians Y, Jneid H, Tietjens JR, et al. Obstructive Sleep Apnea and Cardiovascular Disease: A  
26 344 Scientific Statement From the American Heart Association. *Circulation* 2021;144(3):e56-e67.  
27 345 doi: 10.1161/cir.0000000000000988 [published Online First: 2021/06/22]
- 28 346 4. Wang X, Fan JY, Zhang Y, et al. Association of obstructive sleep apnea with cardiovascular outcomes  
29 347 after percutaneous coronary intervention: A systematic review and meta-analysis. *Medicine*  
30 348 (*Baltimore*) 2018;97(17):e0621. doi: 10.1097/md.00000000000010621 [published Online First:  
31 349 2018/04/29]
- 32 350 5. Frøjd LA, Munkhaugen J, Moum T, et al. Insomnia in patients with coronary heart disease:  
33 351 prevalence and correlates. *J Clin Sleep Med* 2021;17(5):931-38. doi: 10.5664/jcsm.9082  
34 352 [published Online First: 2021/01/06]
- 35 353 6. Rouleau CR, Horsley KJ, Morse E, et al. The Association Between Insomnia Symptoms and Mood  
36 354 Changes During Exercise Among Patients Enrolled in Cardiac Rehabilitation. *J Cardiopulm*  
37 355 *Rehabil Prev* 2015;35(6):409-16. doi: 10.1097/hcr.0000000000000138 [published Online  
38 356 First: 2015/09/18]
- 39 357 7. Le Grande MR, Beauchamp A, Driscoll A, et al. Prevalence of obstructive sleep apnoea in acute  
40 358 coronary syndrome patients: systematic review and meta-analysis. *BMC Cardiovasc Disord*  
41 359 2020;20(1):147. doi: 10.1186/s12872-020-01430-3 [published Online First: 2020/03/27]
- 42 360 8. St-Onge MP, Grandner MA, Brown D, et al. Sleep Duration and Quality: Impact on Lifestyle  
43 361 Behaviors and Cardiometabolic Health: A Scientific Statement From the American Heart  
44 362 Association. *Circulation* 2016;134(18):e367-e86. doi: 10.1161/cir.0000000000000444  
45 363 [published Online First: 2016/11/02]
- 46 364 9. Fernandes NM, Nield LE, Popel N, et al. Symptoms of disturbed sleep predict major adverse cardiac  
47 365 events after percutaneous coronary intervention. *Can J Cardiol* 2014;30(1):118-24. doi:  
48 366 10.1016/j.cjca.2013.07.009 [published Online First: 2013/10/22]
- 49 367 10. Strand LB, Tsai MK, Gunnell D, et al. Self-reported sleep duration and coronary heart disease  
50 368 mortality: A large cohort study of 400,000 Taiwanese adults. *Int J Cardiol* 2016;207:246-51.  
51 369 doi: 10.1016/j.ijcard.2016.01.044 [published Online First: 2016/01/26]
- 52  
53  
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55  
56  
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- 1  
2  
3 370 11. Mazaki T, Kasai T, Yokoi H, et al. Impact of Sleep-Disordered Breathing on Long-Term Outcomes in  
4 371 Patients With Acute Coronary Syndrome Who Have Undergone Primary Percutaneous  
5 372 Coronary Intervention. *J Am Heart Assoc* 2016;5(6) doi: 10.1161/jaha.116.003270 [published  
6 373 Online First: 2016/06/17]  
7  
8 374 12. Cappuccio FP, Cooper D, D'Elia L, et al. Sleep duration predicts cardiovascular outcomes: a  
9 375 systematic review and meta-analysis of prospective studies. *Eur Heart J* 2011;32(12):1484-  
10 376 92. doi: 10.1093/eurheartj/ehr007 [published Online First: 2011/02/09]  
11  
12 377 13. Soehner AM, Harvey AG. Prevalence and functional consequences of severe insomnia symptoms  
13 378 in mood and anxiety disorders: results from a nationally representative sample. *Sleep*  
14 379 2012;35(10):1367-75. doi: 10.5665/sleep.2116 [published Online First: 2012/10/02]  
15  
16 380 14. Meijer A, Conradi HJ, Bos EH, et al. Adjusted prognostic association of depression following  
17 381 myocardial infarction with mortality and cardiovascular events: individual patient data meta-  
18 382 analysis. *Br J Psychiatry* 2013;203(2):90-102. doi: 10.1192/bjp.bp.112.111195 [published  
19 383 Online First: 2013/08/03]  
20  
21 384 15. Madsen MT, Huang C, Zangger G, et al. Sleep Disturbances in Patients With Coronary Heart  
22 385 Disease: A Systematic Review. *J Clin Sleep Med* 2019;15(3):489-504. doi: 10.5664/jcsm.7684  
23 386 [published Online First: 2019/03/12]  
24  
25 387 16. Banack HR, Holly CD, Lowensteyn I, et al. The association between sleep disturbance, depressive  
26 388 symptoms, and health-related quality of life among cardiac rehabilitation participants. *J*  
27 389 *Cardiopulm Rehabil Prev* 2014;34(3):188-94. doi: 10.1097/hcr.000000000000054 [published  
28 390 Online First: 2014/04/01]  
29  
30 391 17. Leon AS, Franklin BA, Costa F, et al. Cardiac rehabilitation and secondary prevention of coronary  
31 392 heart disease: an American Heart Association scientific statement from the Council on  
32 393 Clinical Cardiology (Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention) and  
33 394 the Council on Nutrition, Physical Activity, and Metabolism (Subcommittee on Physical  
34 395 Activity), in collaboration with the American association of Cardiovascular and Pulmonary  
35 396 Rehabilitation. *Circulation* 2005;111(3):369-76. doi: 10.1161/01.Cir.0000151788.08740.5c  
36 397 [published Online First: 2005/01/26]  
37  
38 398 18. Corrà U, Piepoli MF, Carré F, et al. Secondary prevention through cardiac rehabilitation: physical  
39 399 activity counselling and exercise training: key components of the position paper from the  
40 400 Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and  
41 401 Rehabilitation. *Eur Heart J* 2010;31(16):1967-74. doi: 10.1093/eurheartj/ehq236 [published  
42 402 Online First: 2010/07/21]  
43  
44 403 19. Fletcher GF, Ades PA, Kligfield P, et al. Exercise standards for testing and training: a scientific  
45 404 statement from the American Heart Association. *Circulation* 2013;128(8):873-934. doi:  
46 405 10.1161/CIR.0b013e31829b5b44 [published Online First: 2013/07/24]  
47  
48 406 20. Balady GJ, Williams MA, Ades PA, et al. Core components of cardiac rehabilitation/secondary  
49 407 prevention programs: 2007 update: a scientific statement from the American Heart  
50 408 Association Exercise, Cardiac Rehabilitation, and Prevention Committee, the Council on  
51 409 Clinical Cardiology; the Councils on Cardiovascular Nursing, Epidemiology and Prevention,  
52 410 and Nutrition, Physical Activity, and Metabolism; and the American Association of  
53 411 Cardiovascular and Pulmonary Rehabilitation. *Circulation* 2007;115(20):2675-82. doi:  
54 412 10.1161/circulationaha.106.180945 [published Online First: 2007/05/22]  
55  
56 413 21. Kirchnerberger I, Hunger M, Stollenwerk B, et al. Effects of a 3-year nurse-based case management in  
57  
58  
59  
60

- 1  
2  
3 414 aged patients with acute myocardial infarction on rehospitalisation, mortality, risk factors,  
4 415 physical functioning and mental health. a secondary analysis of the randomized controlled  
5 416 KORINNA study. *PLoS One* 2015;10(3):e0116693. doi: 10.1371/journal.pone.0116693  
6 417 [published Online First: 2015/03/27]  
7  
8 418 22. Rutledge T, Redwine LS, Linke SE, et al. A meta-analysis of mental health treatments and cardiac  
9 419 rehabilitation for improving clinical outcomes and depression among patients with coronary  
10 420 heart disease. *Psychosom Med* 2013;75(4):335-49. doi: 10.1097/PSY.0b013e318291d798  
11 421 [published Online First: 2013/05/01]  
12  
13 422 23. Zhang L, Zhang L, Wang J, et al. Community health service center-based cardiac rehabilitation in  
14 423 patients with coronary heart disease: a prospective study. *BMC Health Serv Res*  
15 424 2017;17(1):128. doi: 10.1186/s12913-017-2036-3 [published Online First: 2017/02/12]  
16  
17 425 24. Loboda D, Stepanik M, Golba A, et al. The beneficial impact of cardiac rehabilitation on obstructive  
18 426 sleep apnea in patients with coronary artery disease. *J Clin Sleep Med* 2021;17(3):403-12.  
19 427 doi: 10.5664/jcsm.8900 [published Online First: 2020/10/23]  
20  
21 428 25. Laddu D, Ozemek C, Lamb B, et al. Factors Associated With Cardiorespiratory Fitness at  
22 429 Completion of Cardiac Rehabilitation: Identification of Specific Patient Features Requiring  
23 430 Attention. *Can J Cardiol* 2018;34(7):925-32. doi: 10.1016/j.cjca.2018.03.015 [published  
24 431 Online First: 2018/06/05]  
25  
26 432 26. Thompson PD, Arena R, Riebe D, et al. ACSM's new preparticipation health screening  
27 433 recommendations from ACSM's guidelines for exercise testing and prescription, ninth  
28 434 edition. *Curr Sports Med Rep* 2013;12(4):215-7. doi: 10.1249/JSR.0b013e31829a68cf  
29 435 [published Online First: 2013/07/16]  
30  
31 436 27. Barillas-Lara MI, Medina-Inojosa JR, Kolla BP, et al. The Association of Sleep Apnea and  
32 437 Cardiorespiratory Fitness With Long-Term Major Cardiovascular Events. *Mayo Clin Proc*  
33 438 2021;96(3):636-47. doi: 10.1016/j.mayocp.2020.03.040 [published Online First: 2021/03/07]  
34  
35 439 28. Strand LB, Laugsand LE, Wisløff U, et al. Insomnia symptoms and cardiorespiratory fitness in  
36 440 healthy individuals: the Nord-Trøndelag Health Study (HUNT). *Sleep* 2013;36(1):99-108. doi:  
37 441 10.5665/sleep.2310 [published Online First: 2013/01/05]  
38  
39 442 29. MartinezAguirre-Betolaza A, Maldonado-Martín S, Corres P, et al. Actigraphy-based sleep analysis  
40 443 in sedentary and overweight/obese adults with primary hypertension: data from the  
41 444 EXERDIET-HTA study. *Sleep Breath* 2019;23(4):1265-73. doi: 10.1007/s11325-019-01813-7  
42 445 [published Online First: 2019/03/01]  
43  
44 446 30. Lindegård A, Wastensson G, Hadzibajramovic E, et al. Longitudinal associations between  
45 447 cardiorespiratory fitness and stress-related exhaustion, depression, anxiety and sleep  
46 448 disturbances. *BMC Public Health* 2019;19(1):1726. doi: 10.1186/s12889-019-8081-6  
47 449 [published Online First: 2019/12/25]  
48  
49 450 31. Crowley SK, Rebellon J, Huber C, et al. Cardiorespiratory fitness, sleep, and physiological responses  
50 451 to stress in women. *Eur J Sport Sci* 2020;20(10):1368-77. doi:  
51 452 10.1080/17461391.2020.1716855 [published Online First: 2020/01/16]  
52  
53 453 32. Ross RM. ATS/ACCP statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med*  
54 454 2003;167(10):1451; author reply 51. doi: 10.1164/ajrccm.167.10.950 [published Online First:  
55 455 2003/05/10]  
56  
57 456 33. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*  
58 457 2002;166(1):111-7. doi: 10.1164/ajrccm.166.1.at1102 [published Online First: 2002/07/02]  
59  
60

- 1  
2  
3 458 34. Buysse DJ, Reynolds CF, 3rd, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument  
4 459 for psychiatric practice and research. *Psychiatry Res* 1989;28(2):193-213. doi: 10.1016/0165-  
5 460 1781(89)90047-4 [published Online First: 1989/05/01]  
6  
7 461 35. Tsai PS, Wang SY, Wang MY, et al. Psychometric evaluation of the Chinese version of the  
8 462 Pittsburgh Sleep Quality Index (CPSQI) in primary insomnia and control subjects. *Qual Life*  
9 463 *Res* 2005;14(8):1943-52. doi: 10.1007/s11136-005-4346-x [published Online First:  
10 464 2005/09/13]  
11  
12 465 36. Levis B, Benedetti A, Thombs BD. Accuracy of Patient Health Questionnaire-9 (PHQ-9) for  
13 466 screening to detect major depression: individual participant data meta-analysis. *Bmj*  
14 467 2019;365:l1476. doi: 10.1136/bmj.l1476 [published Online First: 2019/04/11]  
15  
16 468 37. Lin Q, Bonkano O, Wu K, et al. The Value of Chinese Version GAD-7 and PHQ-9 to Screen Anxiety  
17 469 and Depression in Chinese Outpatients with Atypical Chest Pain. *Ther Clin Risk Manag*  
18 470 2021;17:423-31. doi: 10.2147/tcrm.S305623 [published Online First: 2021/05/28]  
19  
20 471 38. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety  
21 472 disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-7. doi:  
22 473 10.1001/archinte.166.10.1092 [published Online First: 2006/05/24]  
23  
24 474 39. Gilthorpe MS, Dahly DL, Tu YK, et al. Challenges in modelling the random structure correctly in  
25 475 growth mixture models and the impact this has on model mixtures. *J Dev Orig Health Dis*  
26 476 2014;5(3):197-205. doi: 10.1017/s2040174414000130 [published Online First: 2014/06/06]  
27  
28 477 40. Muthén B, Asparouhov T. Growth mixture modeling with non-normal distributions. *Stat Med*  
29 478 2015;34(6):1041-58. doi: 10.1002/sim.6388 [published Online First: 2014/12/17]  
30  
31 479 41. Kolansky DM. Acute coronary syndromes: morbidity, mortality, and pharmaco-economic burden.  
32 480 *Am J Manag Care* 2009;15(2 Suppl):S36-41. [published Online First: 2009/04/16]  
33  
34 481 42. Haghayegh S, Khoshnevis S, Smolensky MH, et al. Accuracy of Wristband Fitbit Models in  
35 482 Assessing Sleep: Systematic Review and Meta-Analysis. *J Med Internet Res*  
36 483 2019;21(11):e16273. doi: 10.2196/16273 [published Online First: 2019/11/30]  
37  
38 484 43. Chinoy ED, Cuellar JA, Huwa KE, et al. Performance of seven consumer sleep-tracking devices  
39 485 compared with polysomnography. *Sleep* 2021;44(5) doi: 10.1093/sleep/zsaa291 [published  
40 486 Online First: 2020/12/31]  
41  
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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					√

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505 **Notes:** T1: Baseline assessment and enrolment; T2: one month after the beginning of CR

506 program; T3: three months after the beginning of CR program; T4: six months after the beginning

507 of CR program; T5: twelve months after the beginning of CR program. Physical examination: Body

508 mass index (BMI) , Waist circumference (WC), blood pressure (BP); Blood sampling: fasting

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4 509 plasma glucose (FPG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), B-type  
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6 510 natriuretic peptide (BNP), serum high-sensitivity C-reactive protein (hsCRP), Homocysteine  
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8 511 (HCY); Echocardiography: left ventricular ejection fraction (LVEF), left atrium diameter (LAD), left  
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10 512 ventricular internal diameter at end-diastole (LVIDd), interventricular septal thickness (IVST), left  
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12 513 ventricular posterior wall thickness (LVPWT)

13 514 **Abbreviations:** CPET: cardiopulmonary exercise testing; 6MWT: six-minute walk test; PSQI:  
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15 515 Pittsburgh Sleep Quality Index; PHQ-9: Patient Health Questionnaire; GAD-7: General anxiety  
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17 516 disorder scale; MACEs: major adverse cardiovascular events

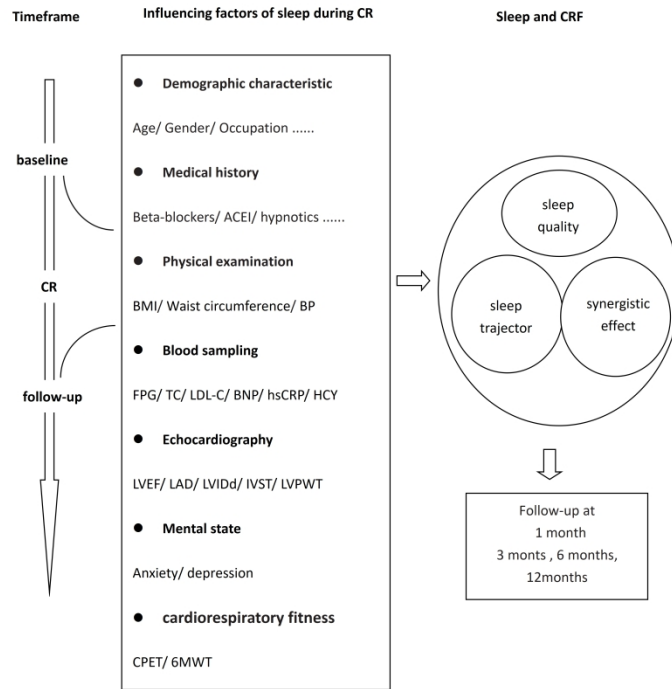
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### 20 518 **FIGURE 1 Study framework**

21 519 **Abbreviations:** BMI: Body mass index; BP: blood pressure; FPG: fasting plasma glucose; TC: total  
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23 520 cholesterol; LDL-C: low-density lipoprotein cholesterol; BNP: B-type natriuretic peptide; hsCRP:  
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25 521 serum high-sensitivity C-reactive protein; HCY: Homocysteine; LVEF: left ventricular ejection  
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27 522 fraction; LAD: left atrium diameter; LVIDd: left ventricular internal diameter at end-diastole;  
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29 523 IVST: interventricular septal thickness; LVPWT: left ventricular posterior wall thickness; CPET:  
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31 524 cardiopulmonary exercise testing; 6MWT: six-minute walk test

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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
<b>Title and abstract</b>	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
<b>Introduction</b>			
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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	5
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> —If applicable, describe analytical methods taking account of sampling strategy	n/a
		(e) Describe any sensitivity analyses	n/a

Continued on next page

<b>Results</b>			
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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	n/a
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	n/a
		<i>Cross-sectional study</i> —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
<b>Discussion</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).