

Association between Circadian Syndrome and Incident Chronic Lung Disease: A Dual-Cohort Prospective Study

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Article

Keywords: Circadian syndrome, Chronic lung disease, Chronomedicine, Epidemiology, Cohort study, Sleep quality

Posted Date: March 4th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-8947745/v1>

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Additional Declarations: No competing interests reported.

Version of Record: A version of this preprint was published at Scientific Reports on May 16th, 2026. See the published version at <https://doi.org/10.1038/s41598-026-50994-1>.

Abstract

Background

Circadian syndrome (CircS) is a novel clinical issue integrating systemic circadian disruption with cardiometabolic risk factors. Although isolated rhythm disturbances are associated with respiratory pathology, the longitudinal effect of CircS on the incidence of chronic lung disease (CLD) remains undescribed. We investigated this association and validated its universality across distinct genetic and environmental contexts.

Methods

We conducted a prospective dual-cohort study using data from the China Health and Retirement Longitudinal Study (CHARLS, $n = 7,553$) as the discovery cohort and data from the English Longitudinal Study of Ageing (ELSA, $n = 4,957$) as the validation cohort. CircS was defined by the clustering of at least four of the seven circadian-metabolic components, including central obesity, high blood pressure, glucose, and triglycerides, low HDL-C levels, short duration of sleep, and depression. Multivariate Cox proportional hazards models were constructed to estimate hazard ratios (HRs) for incident CLD over a follow-up of seven years, adjusting for sociodemographic and lifestyle confounders.

Results

We found that in the discovery cohort (CHARLS), CircS was independently associated with an increased risk of incident CLD (fully adjusted $HR = 1.16$, 95% $CI = 1.01–1.33$). This association was confirmed in the validation cohort (ELSA), with a stronger effect size ($HR = 1.53$, 95% $CI = 1.20–1.95$). Phenotypic comparison revealed that while the association was consistent across subgroups in the Chinese population, it was significantly modulated by alcohol consumption in the British population ($P < 0.05$). The risk was disproportionately higher among drinkers, supporting a synergistic “double hit” mechanism between circadian misalignment and lifestyle stressors.

Conclusion

Circadian syndrome serves as a robust and independent predictor of respiratory decline across various populations. These findings challenge traditional organ-centric prevention models and emphasize that circadian integrity is a reliable indicator of respiratory vulnerability. Public health strategies that integrate holistic chronomedicine approaches, focusing on sleep hygiene and moderate alcohol consumption, may reveal novel pathways to mitigate the global burden of CLD.

Introduction

Chronic lung diseases (CLDs) are a leading cause of morbidity and mortality globally; traditional preventive strategies that focus solely on the cessation of smoking and avoidance of pollutants cannot further decrease morbidity and mortality(1). New physiological evidence suggests that pulmonary

homeostasis is not autonomous but is orchestrated by the central circadian clock. The molecular clockwork regulates important lung defense mechanisms, including the inflammation of airways, redox balance via the Nrf2 pathway, and mucus secretion(2–4). Consequently, circadian syndrome (CircS) has emerged as a novel clinical issue and represents the pathological convergence of systemic circadian disruption and metabolic stress(5). Unlike isolated risk factors, CircS captures the cumulative burden of disturbances in the sleep-wake cycle and cardiometabolic dysregulation, offering a holistic metric of physiological desynchrony(6).

Although researchers have established a link between circadian genes and lung immunity in experimental models, the epidemiological translation of these findings is incomplete and fragmented(7). Previous studies largely adopted an organ-centric perspective, focusing on single variables such as sleep duration or shift work; however, they ignored the synergistic effect of clustered metabolic and rhythm disturbances(8). Whether CircS, as a composite phenotype, serves as a prodromal driver for respiratory decline remains unknown. Given the distinct environmental and lifestyle patterns in the East and West, whether the effect of CircS on lung health is a universal biological phenomenon or a context-dependent risk is not clear(9).

To fill this knowledge gap, we conducted a prospective dual-cohort study using data from the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA). By adopting this study design, we could perform rigorous cross-cultural validation. We aimed to (1) characterize the longitudinal trajectory of the risk of CLD associated with baseline CircS; (2) separate the contribution of CircS from traditional lifestyle confounders; and (3) determine whether this association is modified by environmental stressors, such as obesity and alcohol consumption, to identify vulnerable subpopulations.

Method

Study Population

To conduct this prospective dual-cohort study, we used data from CHARLS(10) as the discovery cohort and ELSA(11) as the validation cohort. Both surveys are harmonized longitudinal studies of adults who are at least 45 years old, designed to represent the Chinese and English populations, respectively. In CHARLS, the baseline data were collected in 2011 (Wave 1), with follow-up extending to 2018 (Wave 4). In ELSA, Wave 6 (2012) served as the baseline data, with outcomes assessed through Wave 9 (2019). Participants were excluded if they (1) were < 45 years old; (2) had a self-reported diagnosis of CLD (including chronic bronchitis, emphysema, or asthma) at baseline; or (3) had missing data on key components or covariates of CircS. The final analytic samples comprised 7,553 participants in CHARLS and 4,957 participants in ELSA.

Assessment of CircS

Circadian syndrome (CircS) was operationalized as a composite phenotype reflecting systemic circadian misalignment(5, 12). As reported in other studies, we defined CircS based on the presence of at least four of the following seven components(13): (1) Central obesity: High waist circumference or BMI (population-specific cutoffs applied); (2) High blood pressure: Systolic pressure ≥ 130 mmHg, diastolic pressure ≥ 85 mmHg, or use of antihypertensives; (3) High triglyceride levels: ≥ 150 mg/dL or specific treatment; (4) Low HDL-C levels: < 40 mg/dL (men) or < 50 mg/dL (women), or specific treatment; (5) High fasting glucose levels: ≥ 100 mg/dL, HbA1c $\geq 5.7\%$, or diagnosed diabetes; (6) Short sleep duration: < 6 h/day; (7) Depression: High depressive symptoms assessed by the CES-D 10 (CHARLS) or CES-D 8 (ELSA)(14).

Determination of Incident CLD

The primary outcome was incident CLD, defined as a self-reported physician diagnosis of CLDs (including chronic bronchitis or emphysema) during the follow-up period. Participants who reported CLD at baseline were excluded. The follow-up time was calculated from the date on which the baseline data were collected to the date of first reported diagnosis of CLD, death, or the end of the follow-up, whichever occurred first(15).

Covariates and Data Harmonization

To ensure rigorous comparability between the cohorts, data harmonization was conducted following a validated protocol established in other studies. Sociodemographic covariates included age, sex, and marital status(12). The level of education was standardized into three levels: low (illiterate or primary school), medium (middle or high school), and high (college, university, or above)(12). Regarding lifestyle behaviors, smoking status was classified as non-smoker, former smoker, or current smoker, while alcohol consumption was classified as drinkers and non-drinkers. Body mass index (BMI) was derived from height and weight measurements and treated as a continuous variable or categorized based on population-specific criteria(16, 17).

Statistical Analysis

The baseline characteristics were compared between participants with and without CircS by conducting Student's t-tests for continuous variables and Chi-square tests for categorical variables. To evaluate the longitudinal association between CircS and incident CLD, we constructed three sequential Cox proportional hazards regression models as follows: (1) Model 1 (unadjusted) assessed the crude association; (2) Model 2 (demographic-adjusted) adjusted for age, sex, marital status, and level of education; (3) Model 3 (fully adjusted) further adjusted for lifestyle factors (smoking status and alcohol consumption) to control for behavioral confounding.

The proportional hazards assumption was verified using Schoenfeld residuals. For subgroup analyses, the data were stratified by sex, smoking status, alcohol consumption, and obesity; statistical interactions were tested by entering a product term into the fully adjusted models(18). To rigorously assess the robustness of our findings against potential bias from missing data, we performed multiple imputation by chained equations (MICE)(19). Five imputed datasets were generated for each cohort, assuming that the data were missing at random (MAR). Cox regression estimates were pooled according to Rubin's rules. All statistical analyses were performed using Stata (Version 17.0) and R (Version 4.2.0). All results were considered to be statistically significant at $P < 0.05$ (two-tailed).

Results

Study Population and Selection of Participants

The selection process for the study population is illustrated in Figure 1. In the discovery cohort (CHARLS), 17,705 participants were initially enrolled at baseline (Wave 1). Based on the exclusion criteria, we excluded individuals who were <45 years old, those with missing data on CircS components, and those with invalid baseline or follow-up data on CLD. A total of 7,553 eligible participants were retained for the final analysis. In the validation cohort (ELSA), from an initial pool of 19,802 participants identified at Wave 6, 14,845 individuals were excluded as the data were incomplete or the inclusion criteria were not met. Finally, 4,957 participants were included to validate the associations. The detailed exclusion pathways and sample sizes for both cohorts are presented in Figures 1A and 1B, respectively.

Figure 1. Selection process of the study population in the discovery and validation cohorts. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; CircS, Circadian syndrome; CLD, chronic lung disease.

Baseline Characteristics and Phenotypic Heterogeneity

In the discovery cohort (CHARLS), 7,553 participants were included in the final analysis. The prevalence of CircS was 38.5%. Individuals with CircS were significantly older ($P < 0.001$), predominantly female, and had a lower level of education compared to those without CircS (Table 1). CircS was more prevalent in urban residents ($P < 0.001$), potentially reflecting the circadian disruption associated with urbanization in China.

In contrast, the validation cohort (ELSA, $n = 4,957$) showed a considerably lower prevalence of CircS (17.8%). Unlike the pattern observed in the Chinese population, no significant differences in age or sex distribution were found between groups ($P > 0.05$). However, the CircS phenotype in the British population was strongly driven by metabolic factors, characterized by a substantially higher BMI and a clustering of social isolation (Table 2).

	level	Overall	No	Yes	p
n		7553	4646	2907	
Age (mean (SD))		58.26 (8.79)	57.76 (8.75)	59.07 (8.79)	<0.001
Sex (%)	Female	4173 (55.2)	2476 (53.3)	1697 (58.4)	<0.001
	Male	3380 (44.8)	2170 (46.7)	1210 (41.6)	
Marital (%)	Married and living with a spouse	6465 (85.6)	3998 (86.1)	2467 (84.9)	0.004
	Married but living without a spouse	288 (3.8)	193 (4.2)	95 (3.3)	
	Single, divorced, and windowed	800 (10.6)	455 (9.8)	345 (11.9)	
Education (%)	Elementary school or below	5258 (69.6)	3177 (68.4)	2081 (71.6)	0.003
	Middle school or above	2295 (30.4)	1469 (31.6)	826 (28.4)	
Smoking (%)	Non-smoker	4712 (62.4)	2815 (60.6)	1897 (65.3)	<0.001
	Smoker	2840 (37.6)	1830 (39.4)	1010 (34.7)	
Drinking (%)	Drinker	2085 (29.0)	1337 (30.5)	748 (26.7)	0.001
	Non-drinker	5095 (71.0)	3046 (69.5)	2049 (73.3)	
Annual Household Expenditure (mean (SD))		6852.63 (8636.27)	6845.56 (9114.78)	6863.82 (7819.39)	0.934
Number of chronic conditions (%)	Yes	1962 (26.0)	1023 (22.0)	939 (32.3)	<0.001
	No	3126 (41.4)	2075 (44.7)	1051 (36.2)	
	Yes	2465 (32.6)	1548 (33.3)	917 (31.5)	
event (%)	No	6306 (83.5)	3924 (84.5)	2382 (81.9)	0.005
	Yes	1247 (16.5)	722 (15.5)	525 (18.1)	
Survival time (mean (SD))		6.76 (0.91)	6.77 (0.90)	6.74 (0.94)	0.271

Table 1. Baseline characteristics of the discovery cohort (CHARLS) stratified by the CircS status.

	level	Overall	No	Yes	p
n		4957	4076	881	
Age (mean (SD))		65.84 (8.42)	65.75 (8.38)	66.24 (8.59)	0.12
Sex (%)	Female	2764 (55.8)	2273 (55.8)	491 (55.7)	1
	Male	2193 (44.2)	1803 (44.2)	390 (44.3)	
Marital (%)	Married	3419 (71.6)	2885 (73.6)	534 (62.5)	<0.001
	Single	1353 (28.4)	1033 (26.4)	320 (37.5)	
Education (%)	Elementary school or below	1274 (27.8)	944 (25.0)	330 (40.8)	<0.001
	Middle school or above	3304 (72.2)	2826 (75.0)	478 (59.2)	
Smoking (%)	Smoker	2952 (59.6)	2365 (58.0)	587 (66.6)	<0.001
	Non-smokers	2005 (40.4)	1711 (42.0)	294 (33.4)	
Drinking (%)	Drinkers	4128 (89.5)	3470 (90.9)	658 (83.1)	<0.001
	Non-drinkers	482 (10.5)	348 (9.1)	134 (16.9)	
Annual Household Expenditure (mean (SD))		6438.12 (35747.92)	6754.49 (34340.86)	4981.23 (41609.48)	0.185
Number of chronic conditions (%)	No	1204 (24.3)	1077 (26.4)	127 (14.4)	<0.001
	Yes	3753 (75.7)	2999 (73.6)	754 (85.6)	
event (%)	No	4793 (96.7)	3957 (97.1)	836 (94.9)	0.001
	Yes	164 (3.3)	119 (2.9)	45 (5.1)	
Survival time (mean (SD))		7.92 (0.57)	7.93 (0.53)	7.86 (0.73)	0.002

Table 2. Baseline characteristics of the validation cohort (ELSA) stratified by the CircS status.

Incidence and Survival Analysis

During the seven-year follow-up period, 1,247 and 164 incident CLD cases were identified in CHARLS and ELSA, respectively. The results of the Kaplan-Meier survival analysis demonstrated a prominent divergence in respiratory trajectories. In the discovery and validation cohorts, participants with CircS had a significantly higher cumulative incidence of CLD compared to those without CircS (log-rank test $P < 0.001$; Figure 2).

Figure 2. Kaplan-Meier cumulative incidence estimates of CLD stratified by the CircS status; (A) Discovery cohort (CHARLS), and (B) Validation cohort (ELSA).

Association between CircS and Incident CLD

We quantified this risk using Cox proportional hazards models. In the discovery cohort (Table 3), CircS was significantly associated with an increased risk of incident CLD. The unadjusted hazard ratio (HR) was 1.173 (95% CI: 1.042–1.320). In the fully adjusted model, in which sociodemographic and lifestyle factors were adjusted for (Model 3), CircS was an independent predictor of respiratory decline (*HR* = 1.155, 95% CI: 1.005–1.327, *P* = 0.042).

In the validation cohort (Table 3), the effect of CircS was even greater. Although the effect sizes were attenuated after adjustment, the association remained robust. In the fully adjusted model, CircS was associated with a 52.6% higher risk of incident CLD (*HR* = 1.526, 95% CI: 1.197-1.946, *P* < 0.001). The replication of this signal in two different populations confirms that CircS is a universal risk factor.

	CHARLS		ELSA	
	<i>HR (95%CI)</i>	<i>P</i>	<i>HR (95%CI)</i>	<i>P</i>
Model 1	1.173 (1.042-1.320)	0.008	1.677 (1.351-2.082)	<0.001
Model 2	1.172 (1.033-1.331)	0.014	1.569 (1.247-1.975)	<0.001
Model 3	1.155 (1.005-1.327)	0.042	1.526 (1.197-1.946)	<0.001

Table 3. Cox proportional hazards regression analysis of the association between CircS and incident CLD in the CHARLS and ELSA cohorts. Model 1: Unadjusted model; Model 2: Adjusted for sociodemographic factors (including age, sex, marital status, and education level); Model 3: Fully adjusted model, adjusted for sociodemographic factors and lifestyle factors (smoking status and alcohol consumption).

Subgroup Analyses

To investigate potential effect modifiers, we performed stratified analyses based on sex, smoking status, alcohol consumption, and obesity (Figure 3). In CHARLS, the positive association between CircS and the risk of CLD was highly consistent across all subgroups, with no significant multiplicative interactions observed (*P* > 0.05).

In ELSA, while the direction of association was mostly consistent, alcohol consumption showed a significant association (Figure 3). The risk of CLD associated with CircS was greater among current drinkers, whereas the association was not significant among non-drinkers, suggesting a potential synergistic “double hit” mechanism.

Figure 3. Forest plots of subgroup analyses for the association between CircS and incident CLD. Hazard ratios (HRs) were estimated using fully adjusted Cox proportional hazards models stratified by sex, smoking status, alcohol consumption, and obesity. (A) Discovery cohort (CHARLS), and (B) Validation cohort (ELSA).

Sensitivity Analyses

To assess whether missing covariate data did not introduce bias into our results, we conducted sensitivity analyses using MICE. The results reinforced the primary findings (Table 4). In the CHARLS cohort, the fully adjusted HR derived from the imputed dataset was 1.213 (95% CI: 1.080–1.363, $P = 0.001$). Similarly, in the ELSA cohort, the association remained robust after imputation ($HR = 1.627$, 95% CI: 1.108–2.388, $P = 0.013$).

	CHARLS		ELSA	
	<i>HR (95%CI)</i>	<i>P</i>	<i>HR (95%CI)</i>	<i>P</i>
Model 1	1.176 (1.051-1.316)	0.005	1.772 (1.258-2.497)	0.001
Model 2	1.211 (1.079-1.360)	0.001	1.695 (1.157-2.484)	0.007
Model 3	1.213 (1.080-1.363)	0.001	1.627 (1.108-2.388)	0.013

Table 4. Sensitivity analysis of the association between CircS and incident CLD was conducted using multiple imputation. Model 1: Unadjusted model. Model 2: Adjusted for sociodemographic factors (including age, sex, marital status, and education level). Model 3: Fully adjusted model, adjusted for sociodemographic factors and lifestyle factors (smoking status and alcohol consumption).

Discussion

This is the first prospective study to characterize the longitudinal trajectory of the risk of CLD associated with CircS across distinct genetic and cultural contexts. Using harmonized data from the CHARLS and ELSA cohorts(10, 11), we provided strong evidence that CircS is not merely a cluster of comorbidities but a distinct, independent driver of respiratory decline. Our findings showed that systemic circadian-metabolic disruption precedes the onset of CLD, with a risk magnitude that remains robust even after rigorously adjusting for traditional lifestyle confounders(20). While the association is universal, its phenotypic expression is context-dependent; the effect was amplified in the British population, driven by a synergistic interaction with alcohol consumption and obesity, which supported a “double hit” pathophysiological mechanism(21, 22).

Previous studies have mostly examined circadian markers (e.g., sleep duration, shift work) and metabolic dysfunction in isolation, often adopting an organ-centric perspective of respiratory health(23, 24). While the LUNG SAFE study and other studies have established the role of individual metabolic components in the decline of lung function, they failed to capture the cumulative physiological burden of desynchrony(25, 26). Our study advances this paradigm by confirming that CircS is a composite “sentinel indicator”(27). The consistency of our findings with recent experimental models, which showed that clock gene mutations compromise lung immunity, bridges the gap between molecular chronobiology and clinical epidemiology(28).

The association between CircS and incident CLD is biologically plausible and probably mediated through the dysregulation of the “clock-lung axis.” The molecular clockwork orchestrates important pulmonary

defense mechanisms, including resolution of airway inflammation, secretion of mucus, and redox balance(3).

First, circadian misalignment decreases the expression of Nrf2 (Nuclear factor erythroid 2-related factor 2), the master regulator of antioxidant responses(3). In the CircS state, the rhythmic activation of Nrf2 is weakened, increasing the susceptibility of lung tissue to oxidative stress caused by environmental factors(29).

Second, systemic metabolic stress promotes a chronic low-grade inflammatory state (“meta-inflammation”)(30). The increase in visceral adiposity and insulin resistance drives the secretion of pro-inflammatory cytokines (IL-6 and TNF- α), which can spill over into the pulmonary circulation, priming the lung for exaggerated inflammatory responses and tissue remodeling(31, 32).

A key finding of our study is the stronger effect size observed in the ELSA cohort compared to the CHARLS cohort. We proposed a “double hit” hypothesis to explain this divergence. The ELSA cohort exhibited a significantly higher baseline BMI and prevalence of alcohol consumption. Alcohol is a potent chronodisruptor that uncouples the central pacemaker in the suprachiasmatic nucleus from peripheral clocks in the liver and lung(33, 34). When CircS (the first hit) compromises the baseline circadian integrity, alcohol consumption or severe obesity (the second hit) may overwhelm the residual compensatory mechanisms of the lung(35, 36). This is supported by our subgroup analysis involving the ELSA cohort, where the risk was disproportionately concentrated among alcohol consumers, suggesting that lifestyle stressors can synergistically amplify the pathogenicity of circadian misalignment.

The primary strength of this study is its dual-cohort design, which validates findings across East Asian and Western European populations, increasing the generalizability of our findings. The rigorous control for lifestyle factors and the application of sensitivity analyses with multiple imputation further strengthened the robustness of our conclusions. However, our study had several limitations. First, the diagnosis of CLD relied on self-reported physician diagnoses, which may have introduced recall bias, although this method has been validated in large epidemiological surveys(37). Second, although we adjusted for smoking and indoor fuel use (in CHARLS), residual confounding from environmental pollutants cannot be ruled out. Finally, as this was an observational study, we can infer temporal precedence but cannot establish causal relationships(38, 39).

Clinically, these results challenge the traditional isolation of lung health from systemic rhythmicity. Our findings showed that CircS is a reliable indicator of respiratory vulnerability. The presence of clustered circadian-metabolic disturbances should encourage clinicians to perform early respiratory screening, particularly in patients with co-existing obesity or alcohol consumption. From a public health perspective, interventions must shift from simple smoking cessation to embracing a holistic chronomedicine approach. Strategies aiming to resynchronize the biological clock through optimized sleep hygiene(40), time-restricted eating(41), and restricting alcohol consumption to moderate levels may represent novel, modifiable pathways to reduce the growing global burden of CLDs(42).

Conclusion

To summarize, in this study, we found that CircS is a distinct and independent determinant of incident CLD in the aging population. The robustness of this association across genetically and culturally diverse cohorts highlights that systemic circadian dysregulation is a universal driver of respiratory pathology. The synergistic interaction observed between circadian misalignment and alcohol consumption supports a “double hit” mechanism, revealing that a specific subpopulation is at a higher risk. From a clinical perspective, these findings support a paradigm shift in preventive medicine, shifting from organ-centric models to recognizing circadian integrity as a critical target. Consequently, public health strategies that prioritize circadian alignment, specifically through the optimization of sleep hygiene, metabolic correction, and alcohol moderation, are a promising prophylactic approach to mitigate the growing global burden of CLDs.

Abbreviations

Abbreviation	Full Term
BMI	Body Mass Index
CES-D	Center for Epidemiologic Studies Depression Scale
CHARLS	China Health and Retirement Longitudinal Study
CI	Confidence Interval
CircS	Circadian Syndrome
CLD	Chronic Lung Disease
ELSA	English Longitudinal Study of Ageing
HbA1c	Hemoglobin A1c (Glycated Hemoglobin)
HDL-C	High-Density Lipoprotein Cholesterol
HR	Hazard Ratio
IL-6	Interleukin-6
MAR	Missing at Random
MICE	Multiple Imputation by Chained Equations
Nrf2	Nuclear Factor Erythroid 2-Related Factor 2
SD	Standard Deviation
TNF-α	Tumor Necrosis Factor-alpha

Declarations

Ethics approval and consent to participate

This study involves the secondary analysis of publicly available, de-identified data from the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA). The CHARLS study received ethical approval from the Biomedical Ethics Review Committee of Peking University (approval number: IRB00001052-11015). The ELSA study was approved by the London Multicentre Research Ethics Committee (MREC/01/2/91). All participants in both cohorts provided written informed consent at the time of recruitment. As the current study utilized anonymized data, no further ethical approval or participant consent was required.

Consent for publication

Not applicable. This manuscript does not contain any individual person's data in any form (including individual details, images, or videos).

Competing interests

The authors declare that they have no competing interests.

Clinical trial number

Not applicable.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Author Contribution

[Boheng Liu]: Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. [Shurui Wu]: Data curation, Methodology, Supervision, Writing – original draft, Writing – review & editing. [Yan Xu]: Formal Analysis, Project administration, Validation, Writing – original draft, Writing – review & editing. [Jipeng Jiang]: Funding acquisition, Resources, Visualization, Writing – original draft, Writing – review & editing. [Yang Liu]: Funding acquisition, Resources, Visualization, Writing – original draft, Writing – review & editing.

Acknowledgement

We gratefully acknowledge the China Health and Retirement Longitudinal Study (CHARLS) and the English Longitudinal Study of Ageing (ELSA) teams for providing data access. We also thank the UK Data Service and the National School of Development at Peking University, as well as all study participants, for their essential contributions.

Data Availability

The datasets generated and/or analyzed during the current study are available in public repositories. Data from the China Health and Retirement Longitudinal Study (CHARLS) are publicly available at <http://charls.pku.edu.cn/en>. Data from the English Longitudinal Study of Ageing (ELSA) are available through the UK Data Service at <https://ukdataservice.ac.uk/> or the ELSA project website at <https://www.elsa-project.ac.uk/>. Access to these datasets requires registration with the respective repositories.

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Figures

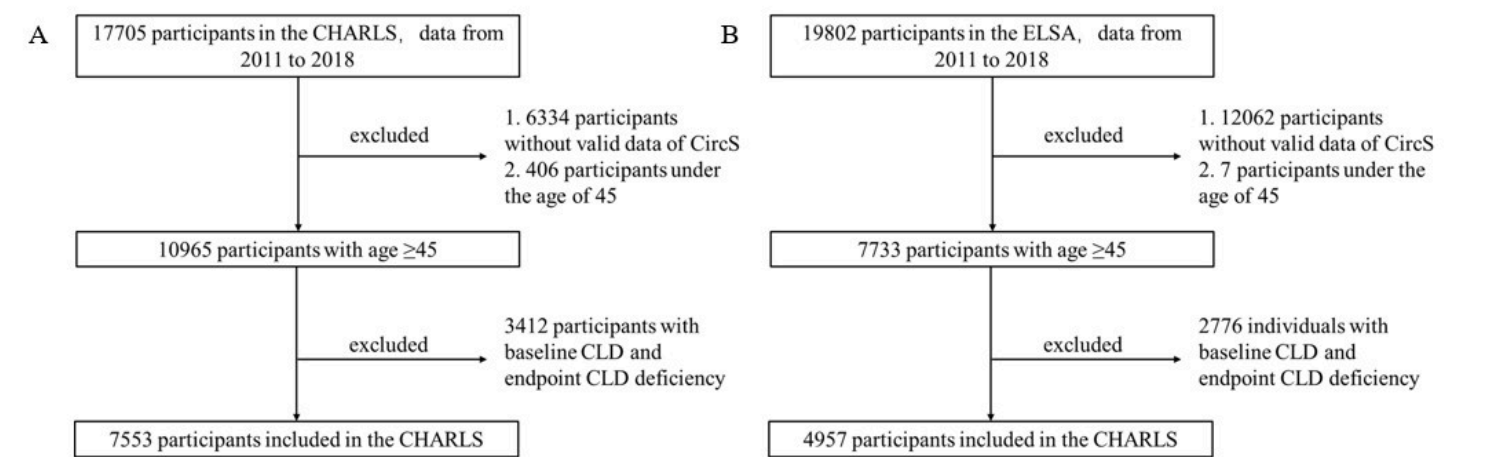


Figure 1

Selection process of the study population in the discovery and validation cohorts. CHARLS, China Health and Retirement Longitudinal Study; ELSA, English Longitudinal Study of Ageing; CircS, Circadian syndrome; CLD, chronic lung disease.

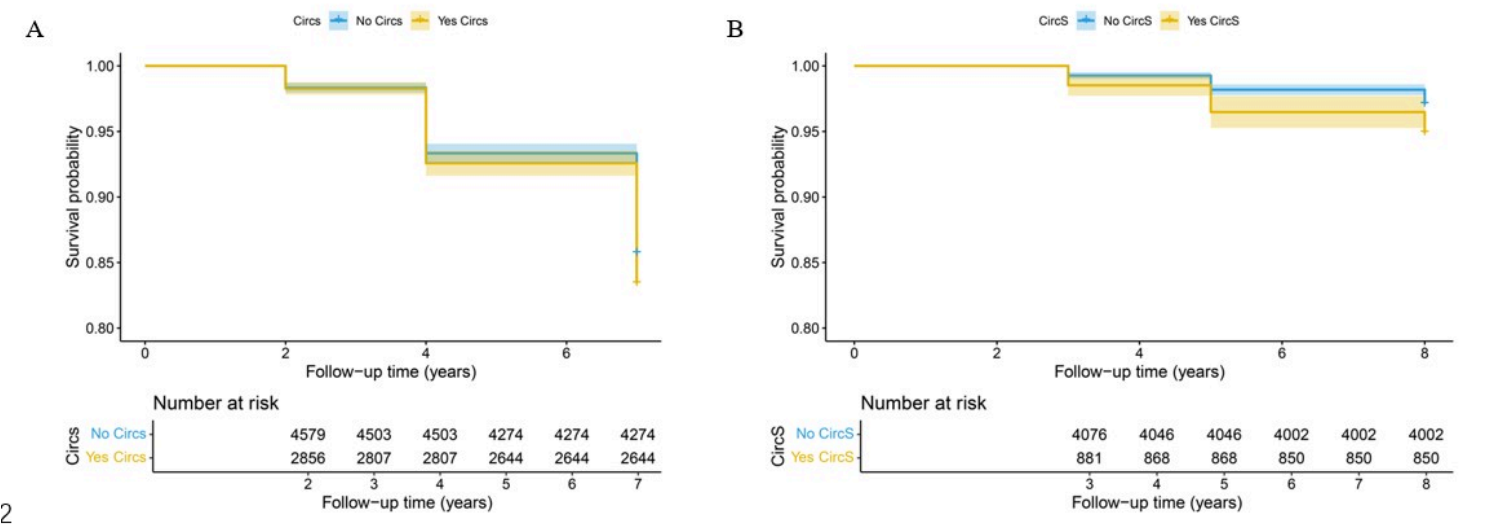


Figure 2

Kaplan-Meier cumulative incidence estimates of CLD stratified by the CircS status; (A) Discovery cohort (CHARLS), and (B) Validation cohort (ELSA).

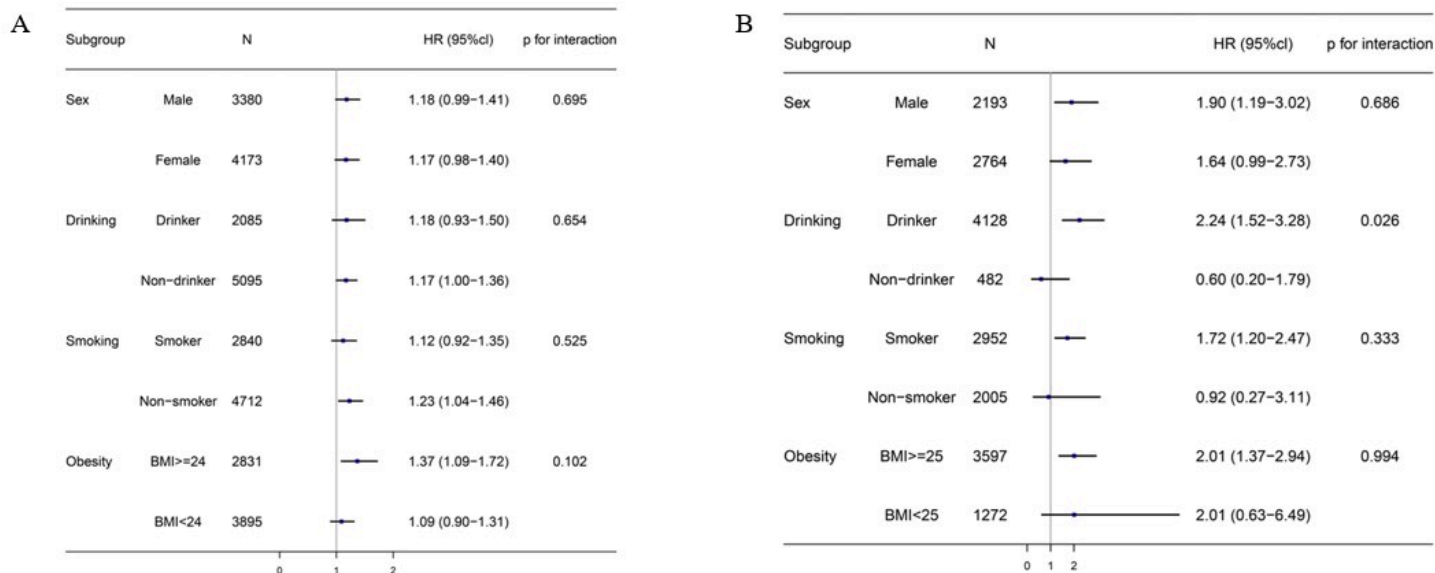


Figure 3

Forest plots of subgroup analyses for the association between CircS and incident CLD. Hazard ratios (HRs) were estimated using fully adjusted Cox proportional hazards models stratified by sex, smoking status, alcohol consumption, and obesity. (A) Discovery cohort (CHARLS), and (B) Validation cohort (ELSA).