RESEARCH PAPER

Delayed Sleep Timing and Left Ventricular Global Longitudinal Strain in Young Adults: A Cross-Sectional Speckle-Tracking Echocardiography Study

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Abstract
Background: Sleep timing may affect cardiovascular health independently of sleep duration.
Objective: To evaluate whether habitual delayed sleep timing ("sleep inversion") is associated with subclinical LV systolic dysfunction in apparently healthy young adults using speckle-tracking echocardiography (STE).
Methods: This cross-sectional comparative investigation included 200 healthy adults aged 18–35 years. Group A included 100 participants with habitual sleep onset outside the 10:00PM-5:00 AM sleep window on at least 3 nights/week, while Group B included 100 controls with usual sleep timing between 10:00 PM and 5:00 AM on ≥5 nights/week, with no more than one night/week outside this window. All participants underwent clinical and lifestyle assessment, fasting laboratory tests, conventional echocardiography, and 2D STE. LV global longitudinal strain (GLS) was analysed as a continuous outcome. To address confounding because of non-randomization, a multivariable linear regression was performed, adjusting for age, sex, smoking, exercise, social media use, junk food intake, blood pressure, glucose, and lipids. BSA and BMI, calculated from measured height and weight, were added as additional covariates.
Results: Group A had more males (87% vs. 56%, $p < 0.001$), smokers (52% vs. 25%, $p < 0.001$), social media users (92% vs. 72%, $p < 0.001$), junk food consumers (65% vs. 38%, $p < 0.001$), and fewer regular exercisers (39% vs. 63%, $p = 0.001$). Conventional echocardiographic parameters did not differ significantly between groups. However, LV GLS was significantly less negative (i.e. worse systolic deformation) in Group A than in Group B (-20.90 ± 3.45 vs. -22.87 ± 3.67, $p < 0.001$). BMI was not significantly associated with GLS (β=-0.01, 95% CI -0.20 to 0.17, p=0.886) and did not differ between groups (24.80 ± 2.94 vs. 24.46 ± 2.83 kg/m^2, p=0.41). On multivariable linear regression, sleep inversion remained independently associated with lower GLS after adjustment for 13 covariates (β=-1.84, 95% CI -3.01 to -0.66, p=0.002; standardized β=-0.25) –only modest attenuation from the unadjusted effect (β=-1.97, 95% CI -2.96 to -0.98, p<0.001). This association persisted after excluding smokers (β=-1.83, 95% CI -3.31 to -0.36, p=0.015, n=123) and in a males-only subgroup (β=-2.05, 95% CI -3.40 to -0.70, p=0.003, n=143); results in the smaller females-only subgroup (13 sleep inversion cases) were directionally consistent but not independently significant (p=0.12).
Conclusions: In this cross-sectional sample, delayed sleep timing was independently associated with lower LV GLS despite normal conventional echocardiographic indices, even after adjustment for measured confounders in a multivariable linear regression model. Because of the cross-sectional design and the substantial baseline imbalance between groups, a causal relationship cannot be established, and residual confounding cannot be excluded.
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Introduction

Sleep timing is a core dimension of sleep health, distinct from sleep duration and sleep quality. In free-living populations, preferred sleep timing shows wide interindividual variation and follows an approximately normal distribution, reflecting both endogenous circadian preference and social constraints such as work and study schedules(1). Over the past few years, research has moved beyond sleep quantity alone and has shown that circadian disruption, irregular sleep timing, and late chronotype are linked to adverse cardiometabolic profiles and poorer cardiovascular (CV) health(2,3). In large cohort data, later bedtime and delayed sleep midpoint have also been correlated with higher all-cause and CV mortality, which supports the clinical relevance of sleep timing as more than a behavioural habit(4).

Several mechanisms may explain this relationship. Misalignment between behavioural sleep timing and the endogenous circadian system alters autonomic balance, blood pressure regulation, inflammatory signalling, glucose homeostasis, and lipid metabolism, all of which are relevant to CV risk(3). Prospective population data further suggest that evening chronotype is correlated with a modestly higher incidence of CV disease, an effect that appears to be partly mediated by less favourable health behaviours, including smoking, lower physical activity, and poorer diet quality. These findings are important, but most available studies have focused on middle-aged or older populations and on clinical outcomes or risk-factor profiles rather than on early myocardial functional changes in otherwise healthy young adults(5).

Detecting such early changes requires tools that are more sensitive than conventional LVEF. Speckle-tracking echocardiography (STE) provides angle-independent assessment of myocardial deformation, and LV global longitudinal strain (GLS) has become a robust measure of subtle systolic impairment that may be present despite preserved LVEF. Contemporary guidance from the American Society of Echocardiography recognizes strain imaging as clinically valuable when conventional measures appear normal or only mildly abnormal, and recent work in healthy subjects has refined reference ranges for LV GLS and highlighted the importance of biological and technical factors in its interpretation. This makes GLS a suitable parameter for investigating whether altered sleep timing is accompanied by early subclinical ventricular dysfunction(6,7).

Therefore, this study aimed to determine whether habitually delayed sleep timing ("sleep inversion") in young, otherwise healthy adults is associated with subtle alterations in LV systolic function, as assessed by GLS using STE. Given the cross-sectional design, this study was designed to test association rather than causation.

Patients and methods

Study design and setting

This cross-sectional comparative investigation enrolled 200 apparently healthy young adults aged 18 to 35 years. Participants were stratified into two equal groups according to their habitual sleep timing. The sleep-inversion group (Group A) included 100 individuals who reported usual sleep onset outside the 10:00 PM- 5:00 AM window, in practice after approximately 1:00-3:00 AM, on at least three nights per week, whereas the control group (Group B) included 100 individuals with a usual sleep schedule between 10:00 PM and 5:00 AM on at least five nights per week. Participants were recruited during pre-employment medical evaluation and from healthy volunteers of the same age range. Recruitment and group assignment were blinded to the echocardiographer performing or analysing the strain studies. The study was reviewed by the REC of Cairo University Faculty of Medicine and received approval under number N-33-2019. All participants provided informed consent before enrolment. A sample-size power calculation was not performed prospectively; a post-hoc power calculation is reported in the Statistical Methods and revisited in the Limitations sections.

Eligibility criteria

Eligible participants were apparently healthy adults with no cardiac symptoms and no known CV disease. Sleep inversion (Group A) was defined as habitual sleep occurring outside the interval between 10:00 PM and 5:00 AM, and for the study group this pattern had to be present on at least three nights per week. Regular sleep (Group B) was defined as sleep onset occurring within 10:00 PM - 5:00 AM on ≥ 5 nights per week. Individuals were excluded if they had any structural heart disease or a history of substance abuse. Participants with hypertension, diabetes mellitus, dyslipidemia, or other clinically evident systemic disease were not included.

Clinical and lifestyle assessment

All participants underwent standardized clinical evaluation. Demographic data were recorded. Blood pressure was measured in all participants, and a detailed history was obtained with special attention to CV risk factors and lifestyle habits. Height and weight were recorded and body surface area (BSA) and body mass index (BMI) calculated.

Sleep timing, smoking, exercise, dietary habits, social media use at night, ad substance abuse were assessed using a structured, non-validated, self-administered questionnaire developed for this study. Relevant sleep behaviour data included usual sleep timing, frequency of late sleep per week, possible reasons for delayed sleep, and sleep consistency as reflected by nighttime awakenings. Smoking data included smoking status, number of cigarettes smoked per day, exercise type and frequency, dietary pattern including junk food, fried food, fruits, vegetables, and salt intake, and duration of social media use at night.

Laboratory evaluation

Fasting blood samples were obtained from all participants for measurement of FBG and lipid profile. Serum total cholesterol, TG, and LDL cholesterol were assessed to exclude dyslipidemia and to compare metabolic status between the two groups.

Conventional echocardiography

All participants underwent TTE according to ASE recommendations. Standard measurements included LVEDD, LVESD, LVPWTd, IVSTd, and LAD. LVEF was calculated using the biplane Simpson method. LV diastolic function was assessed by

measuring transmitral early diastolic flow velocity (E), tissue Doppler-derived septal e′ and lateral e′, and calculating the E/e′ ratio.

Speckle-tracking echocardiography

2D STE was performed with a General Electric Vivid-5S system using a 3-MHz transducer. Apical four-chamber, three-chamber, and two-chamber views were recorded across more than three cardiac cycles while maintaining optimal image quality and frame rate. The acquisition frame rate ranged from 60 to 110 frames per second. Cycles containing extra systolic beats, post-extra systolic beats, or rhythm disturbances were excluded from analysis.

Acceptable images from three cardiac cycles were digitally stored in cine-loop format and then analysed offline using EchoPAC software version 11. The LV myocardium was automatically divided into standard segments from the apical views, and strain analysis was performed on a 17-segment model. Both segmental and GLS were obtained. GLS, calculated as the average peak systolic longitudinal strain of the 17 LV segments, was used as the principal index of subtle LV systolic dysfunction. The echocardiographer performing image acquisition and offline strain analysis was blinded to group assignment.

Study outcome

The main outcome of this study was LV GLS, analysed as a continuous variable, as a marker of subclinical LV systolic dysfunction. Conventional echocardiographic parameters, blood pressure, and laboratory variables were also assessed to determine whether any observed difference in GLS occurred despite otherwise normal clinical, metabolic, and echocardiographic findings.

Statistical methods

The collected data were analysed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was evaluated using the Shapiro–Wilk test. Quantitative data were summarized as mean ± standard deviation, whereas qualitative data were presented as frequency and percentage. Comparisons between groups were performed using the independent t test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables, as appropriate. Effect sizes (Cohen's d for continuous variables; odds ratio with 95% CI for categorical variables) were calculated for all between-group comparisons. Mann-Whitney U testing was performed as a sensitivity analysis for all continuous variables with meaningful skewness or kurtosis on Shapiro-Wilk testing.

To directly address any between-group baseline imbalance because of non-randomization, multivariable linear regression was performed with GLS as a continuous outcome, adjusting for age, sex, BSA, BMI, smoking, irregular exercise, social media use, junk food intake, systolic blood pressure, fasting glucose, and lipid profile. Model assumptions were checked, including residual normality, homoscedasticity (Breusch-Pagan test), and multicollinearity (variance inflation factors, VIF), the latter specifically to check for redundancy between BSA and BMI. Sensitivity analyses repeated this model after excluding smokers and within sex-stratified subgroups.

A prospective sample-size calculation was not performed because of constraints dictated by the available numbers coming for pre-employment checkup, but a post-hoc power calculation for the primary GLS comparison, based on the observed effect size (Cohen's d = 0.55, n=100/group), indicated >95% power at a two-sided α=0.05. Statistical significance was set at a two-sided p value < 0.05.

Results

Group A had a significantly higher proportion of males than Group B (87% vs. 56%, respectively, $p < 0.001$). Smoking was also substantially more frequent in Group A than in Group B (52% vs. 25%, respectively, $p < 0.001$). Irregular exercise was more frequent in Group A than in Group B (61% vs. 37%, respectively, $p = 0.001$). Moreover, social media use and junk food intake were notably more frequent in Group A than in Group B, with social media use reported in 92% versus 72% ($p < 0.001$) and junk food intake in 65% versus 38% ($p < 0.001$), respectively. BMI did not differ significantly between groups; the proportion of participants classified as overweight or obese (BMI ≥ 25 kg/m^2) was similar between groups (44% vs. 48%). **Table 1**

Table 1. Demographic and lifestyle characteristics of the studied groups.

Variable	Group A (n = 100)	Group B (n = 100)	*p* value	Effect size
Age (years)	28.61 ± 7.24	30.32 ± 7.16	0.095	d=-0.24
Sex				
Males	87 (87)	56 (56)	<0.001*	OR 5.26 (2.60-10.63)
Females	13 (13)	44 (44)		

BSA (m^2)	1.81 ± 0.22	1.82 ± 0.21	0.775	d=-0.04
BMI (kg/m^2)	24.80 ± 2.94	24.46 ± 2.83	0.407	d= 0.12
Smoking	52 (52)	25 (25)	<0.001*	OR 3.25 (1.79-5.92)
Irregular exercise	61 (61)	37 (37)	0.001*	OR 2.66 (1.50-4.71)
Social media use	92 (92)	72 (72)	<0.001*	OR 4.47 (1.92-10.40)
Junk food intake	65 (65)	38 (38)	<0.001*	OR 3.03 (1.70-5.39)

*: Significant P-value. Continuous variables: independent-samples t-test, Cohen's d. Categorical variables: chi-square test, odds ratio (95% CI).

No marked variations were detected between both groups regarding blood pressure, FBG or lipid profile. **Table 2**

Table 2. Laboratory and blood pressure parameters.

Variable	Group A (n = 100)	Group B (n = 100)	*p* value	Cohen's d
Cholesterol (mg/dL)	169.28 ± 21.08	168.50 ± 22.15	0.799	0.04
TG (mg/dL)	108.71 ± 20.98	108.83 ± 20.62	0.967	-0.01
LDL (mg/dL)	83.04 ± 10.50	82.95 ± 10.74	0.954	0.01
FBG (mg/dL)	83.45 ± 8.69	85.72 ± 10.69	0.101	-0.23
SBP (mmHg)	115.74 ± 9.95	116.27 ± 10.03	0.708	-0.05
DBP (mmHg)	68.50 ± 7.47	69.55 ± 7.72	0.330	-0.14

Data were presented as mean ±SD, n: number, TG: triglycerides, LDL: low-density lipoprotein, FBG: fasting blood glucose.

No conventional echocardiographic parameter differed between groups; LV GLS was the only significant discriminator –substantially lower in Group A than in Group B (-20.90 ± 3.45 vs. -22.87 ± 3.67, respectively, $p < 0.001$). **Table 3**

Table 3. Conventional echocardiographic and strain parameters.

	Group A (n = 100)	Group B (n = 100)	*p* value	Cohen's d
FS (%)	36.39 ± 5.98	36.70 ± 6.09	0.717	-0.05
EF (%)	65.59 ± 7.23	65.98 ± 7.36	0.706	-0.05
LVEDD (mm)	47.08 ± 4.41	46.99 ± 4.39	0.885	0.02
LVESD (mm)	29.89 ± 3.84	29.70 ± 3.77	0.724	0.05
IVS thickness (mm)	9.06 ± 1.43	8.94 ± 1.33	0.539	0.09
PW thickness (mm)	9.22 ± 1.52	9.11 ± 1.40	0.595	0.08
LA diameter (mm)	33.13 ± 4.66	33.11 ± 4.66	0.976	0.00
E′ septal, cm/s	11.47 ± 2.02	11.41 ± 1.96	0.831	0.03
E′ lateral, cm/s	14.10 ± 2.84	14.19 ± 2.92	0.825	-0.03
E/E′	6.57 ± 1.33	6.55 ± 1.35	0.92	0.01
GLS (%)	-20.90 ± 3.45	-22.87 ± 3.67	**<0.001**	**-0.55 ***

Data were presented as mean ±SD, Significant P-value and Cohen's d in bold. * Cohen's d was calculated on GLS magnitude (Group A- Group B); the sign therefore reflects the direction of the magnitude comparison, not the displayed strain-convention (negative) means directly.

Mann-Whitney U testing confirmed the primary GLS comparison (p=0.004) and all other between-group comparisons for variables with non-normal distributions (BSA, FS, EF, E' septal, E' lateral, cholesterol, TG, LDL; all p>0.65), consistent with the t-test results above. No conclusion changed between parametric and non-parametric testing.

On univariate correlation across the whole sample, BMI was not significantly associated with GLS (Spearman r= -0.061, p=0.388).

To address potential confounding from the substantial baseline imbalance between groups, multiple linear regression was performed with LV GLS as a continuous outcome and sleep-inversion status, age, sex, BSA, BMI, smoking, irregular exercise, social media use, junk food intake, SBP, fasting glucose, and lipid profile as covariates (Table 4). Sleep inversion remained independently associated with lower GLS after adjustment (β=-1.84, 95% CI -3.01 to -0.66, p= 0.002; standardized β = -0.25), representing only modest attenuation from the unadjusted estimate (β = -1.97, 95% CI -2.96 to -0.98, p<0.001). Model residuals were normally distributed (Shapiro-Wilk p=0.16) with no evidence of heteroscedasticity (Breusch-Pagan p=0.84) or multicollinearity (all VIF <1.5, specifically no collinearity between BMI and BSA although correlated, r=0.37). This association persisted after excluding smokers (β = -1.83, 95% CI -3.31 to -0.35, p=0.016, n= 123) and in a males-only subgroup (β= -2.14, 95% CI -3.51 to -0.77, p=0.002, n=143); the corresponding female subgroup (13 sleep-inversion cases) showed the same direction of effect but was not independently significant (p=0.12) and is underpowered for reliable inference (Table 5).

Table 4. Multivariable linear regression –GLS as a continuous outcome.

Predictor	β (unstandardized)	95% CI	*p* value
Sleep inversion	-1.84	-3.01 to -0.66	**0.002**
Age	+0.06	-0.01 to 0.13	0.110
Male sex	-0.37	-1.57 to 0.84	0.548
BSA	-1.88	-4.23 to 0.47	0.115
BMI	-0.01	-0.20 to 0.17	0.886
Smoker	-0.86	-1.94 to 0.22	0.118
Irregular exercise	-0.73	-1.76 to 0.29	0.160
Social media use	+0.36	-0.97 to 1.70	0.593
Junk food	+1.27	+0.23 to 2.31	**0.017**
Systolic BP	-0.02	-0.07 to 0.03	0.373
Fasting glucose	-0.03	-0.08 to 0.02	0.278
Cholesterol	-0.01	-0.03 to 0.02	0.543
Triglycerides	-0.01	-0.04 to 0.01	0.319
LDL	-0.02	-0.07 to 0.03	0.448

This model had R^2=0.175, adjusted R^2=0.113, p<0.001, n=200.

Table 5. Sensitivity analyses (same mode, same 13 covariates unless otherwise noted).

Analysis	n	Sleep-inversion β	95% CI	P-value
Full sample	200	-1.84	-3.01 to -0.66	0.002
Excluding smokers	123	-1.83	-3.31 to -0.35	0.016
Males only	143	-2.14	-3.51 to	0.002

			-0.77	
Females only (descriptive – 13 sleep inversion cases, underpowered)	57	-	-	0.12*

*Females-only comparison is a crude between-group t-test (Cases 21.46 ± 3.51 vs. Control 23.31 ± 3.71), not an adjusted regression – sample too small for reliable multivariable inference.

Discussion

Sleep inversion, or sleep–wake inversion, refers to excessive sleepiness during the day and wakefulness at night; that is, a reversal of the usual sleep pattern(8). For the purposes of this study, the normal sleep interval was defined as the period from 10:00 PM to 5:00 AM. In this cross-sectional sample, delayed sleep timing was associated with lower GLS, as assessed by STE. This association was robust to a multivariable linear regression that treated GLS as a continuous outcome rather than relying on any dichotomized threshold: adjustment for the measured baseline imbalances between groups produced only limited attenuation of the sleep-inversion effect, and the association held after excluding smokers and in a males-only subgroup. To our knowledge, this study is the first to evaluate the influence of sleep pattern, particularly sleep onset and wake-up time, on LV systolic function.

Emerging evidence has increasingly highlighted the potential impact of sleep timing on cardiometabolic health. Sleep timing is regarded as a behavioural characteristic that differs substantially among individuals and is shaped by both biological influences and social factors. At the population level, this trait tends to follow an approximately normal distribution, although a subgroup of individuals demonstrates a preference for markedly delayed sleep schedules(9). Data derived from more than 55,000 online survey responses showed that, in the absence of occupational and social constraints, the most preferred sleep period was approximately from midnight to 8:00 AM. Notably, 8.3% of respondents reported a preferred sleep onset time of 3:00 AM or later, indicating that delayed sleep timing is not uncommon. Sleep timing also varies across the lifespan, with earlier timing typically seen in childhood, delayed timing during adolescence, and a return toward earlier sleep timing in older adulthood(10).

SOLID-TIMI 52(11) was conducted as a multinational, double-blind trial enrolling 13,026 cases within 30 days following an ACS. At baseline, participants completed the Berlin Questionnaire in addition to a sleep and shift-work survey. Cases who reported sleeping less than 6 hours per night exhibited a 29% increased risk of MACE—defined as CAD death, MI, or urgent revascularization—relative to those with longer sleep duration. Overnight shift work, defined as at least 3 night shifts per week for at least 1 year, was correlated with a 15% greater risk of MACE.

This investigation tested the hypothesis that sleep inversion is correlated with an adverse effect on LV systolic function. The study included 100 completely healthy individuals aged 18 to 35 years with sleep inversion, who constituted Group A. All participants demonstrated normal LV systolic function on conventional 2D echocardiography. Comparison was made with 100 age-matched healthy volunteers with normal sleep timing (i.e., from 10:00 PM to 5:00 AM), who comprised Group B. Although we attempted to recruit age-matched volunteers, it was difficult to identify many healthy individuals with normal sleep timing. Mean GLS was lower in Group A than in Group B (-20.90% ± 3.45 vs -22.87% ± 3.67). In addition, males were markedly more prevalent in Group A than in Group B (87% vs. 56%). Smoking, social media use, lower levels of exercise, and junk food intake were also markedly more common among participants with sleep inversion.

In line with our findings, a previous review suggested that three principal pathways related to shift work may contribute to coronary heart disease: social disruption, behavioural changes, and disturbed circadian rhythm. Social problems correlated with shift work may increase psychological stress. Important shift work–related behavioural changes include smoking and unhealthy dietary habits. Disturbance of the circadian rhythm may also lead to sleep deprivation. In addition, the unphysiological timing of food intake and physical activity relative to circadian rhythms may further explain the adverse CV effects of shift work(12).

In the present study, sleep inversion was independently associated with lower LV GLS on multivariable linear regression, despite preserved EF. This finding may indicate a subclinical, long-term adverse association with LV systolic function that is not detected by conventional 2D echocardiography.

Mechanistic studies in both animals and humans have increasingly supported a close relationship between sleep timing and cardiovascular physiology. Alibhai et al.(13) reported that circadian control is directly involved in the recruitment of immune cells into infarcted myocardial tissue, and that interruption of this rhythmic regulation leads to worse outcomes after myocardial infarction. In another experimental model, Turek et al.(14) found that chronic disturbances of the light–dark cycle adversely

affected survival in hamsters with cardiomyopathy. Likewise, Martino et al.(15) demonstrated that loss of normal diurnal organization exacerbated cardiac remodeling in mice with pressure overload–related hypertrophy, whereas recovery toward a normal remodeling pattern was observed only after re-establishment of the usual light–dark rhythm. Consistent with these findings, work from the Sole and Ralph laboratories identified circadian disorganization in FL/tau hamsters as a direct contributor to the pathogenesis of dilated cardiomyopathy(16).

Experimental work by Scheer et al.(17) showed that circadian misalignment in healthy adults adversely influences metabolic, hormonal, and autonomic markers linked to cardiovascular risk as well as other adverse health outcomes. Supporting this observation, longitudinal data from 504 Swedish paper-mill shift workers demonstrated an elevated risk of IHD(18). Similar findings were reported among female nurses in the United States, where shift work was associated with a greater risk of CAD(19). Moreover, a meta-analysis including 34 studies on shift work and cardiovascular disease identified an increased risk of myocardial infarction among shift workers(20).

Sleep characteristics may also play a role in the development of atherosclerosis. This possibility was supported by a cross-sectional study conducted among 2,510 shift workers in Germany(21). Similarly, a longitudinal study of 6,495 Japanese male shift workers documented a higher occurrence of severe hypertension(22). Beyond vascular disease, accumulating evidence suggests that circadian regulation may directly influence myofilament behaviour and thereby affect overall cardiac performance(23).

Experimental findings support this mechanistic link. In Langendorff preparations, ex vivo rat hearts exhibited peak contractile function during the animals' usual wake phase compared with their sleep phase. However, this time-dependent variation was no longer observed in hearts obtained from mice exposed to diurnal disruption(24). In addition, recent data have shown that murine cardiac titin-cap expression (Tcap, telethonin), an essential modulator of sarcomeric structure and function, is under the control of the circadian transcription factors CLOCK and BMAL1(25). Alibhai et al. (13) further reported that diurnal disruption following myocardial infarction in mice reduces protein kinase A-mediated phosphorylation of myofilaments.

Clinical and epidemiologic studies have also linked disturbed sleep with cardiovascular abnormalities. Gangwisch et al.(26) proposed that short sleep duration may contribute to the development of hypertension in certain individuals, while Matthew et al.(27) demonstrated a consistent association between sleep disruption and both prevalent and incident AF.

Considering that global and regional LV myocardial function correlates with the number of normally functioning myocytes, conventional echocardiographic parameters may lack sensitivity for identifying subclinical LV systolic dysfunction. By contrast, recent progress in 2D strain and strain-rate imaging allows detection of subclinical myocardial dysfunction(28,29) through the provision of complementary data on global and regional myocardial performance(30).

Strain derived from TDI is markedly angle dependent and provides assessment of deformation in a single dimension. Conversely, 2D strain analysis is not limited by angle dependency, permits evaluation of deformation in two dimensions, exhibits reduced intraobserver and interobserver variability, and requires less time. Accordingly, 2D strain imaging has the potential to identify subclinical heart disease and true wall-motion abnormalities that cannot be detected using TDI-derived strain analysis(31). Accordingly, in the present study, we used the 2D strain imaging technique.

Interpretation of effect size. The absolute between-group difference in GLS was approximately 1.97 percentage points. While statistically significant, whether this exceeds published inter- and intra-observer variability for GLS measurement (typically reported in the range of 1-2 percentage points) could not be assessed in this study, since reproducibility was not formally tested. Both groups' mean GLS values remained within, or close to, commonly cited normal reference ranges. In the absence of longitudinal follow-up, it cannot be determined whether this difference constitutes a clinically meaningful early marker of disease or reflects a statistically significant but not yet clinically actionable finding.

The role of BMI. Adiposity is a candidate confounder because of its established links to both sleep behaviour(32,33) and myocardial deformation(34). In this study, BMI did not differ between the sleep-inversion and control groups, so it was not a source of the baseline imbalance driving concern about confounding. Moreover, BMI was not independently associated with GLS in this cohort. This suggests that, at least within the BMI range represented in this healthy young cohort, adiposity is not a meaningful confounder of the observed association –though this should not be over-generalized to populations with a wider BMI distribution or higher obesity prevalence.

A note on the junk-food finding. After adjustment, junk food intake was unexpectedly associated with numerically better, not worse, GLS.

Given that multiple covariates were tested without correction for multiplicity, this is most plausibly a chance finding or a marker of an unmeasured factor rather than a genuine protective effect; yet it is reported for completeness and transparency.

This study has several important limitations. *First,* the cross-sectional design precludes any causal inference between delayed sleep timing and reduced GLS; reverse causation (e.g., subclinical cardiac or metabolic disease influencing sleep behaviour) and confounding by shared lifestyle or psychosocial factors cannot be excluded. A confounder-adjusted continuous-outcome regression and cross-validated predictor-selection analysis supported the robustness of the association to the confounders that were measured, but this addresses confounding, not the fundamental limits on causal inference imposed by a cross-sectional design. *Second,* the two groups differed substantially at baseline in sex distribution, smoking, exercise, social media use, and dietary habits; the association persisted after multivariable adjustment, exclusion of smokers, and in a males-only subgroup, but residual confounding from unmeasured variables (including thyroid function, psychological stress, caffeine/energy-drink intake, and objective sleep quality – none of which were assessed in this study) cannot be ruled out. *Third,* sleep timing was assessed by a non-validated, self-reported questionnaire rather than a validated chronotype instrument or objective measure such as actigraphy, which may have introduced misclassification, particularly given the narrow and potentially overlapping boundary between the two groups' sleep-timing definitions. *Fourth,* a formal a priori sample-size calculation was not performed; a post-hoc calculation based on the observed effect indicates the study was well powered (>95%) to detect the primary GLS difference, but this does not substitute for prospective justification and is a just a description of precision rather than proof the study was appropriately sized in advance. *Fifth,* the inter-/intra-observer reproducibility of GLS was not formally assessed. *Sixth,* no longitudinal follow-up was performed, so the reversibility of the observed changes after correction of sleep timing, and their prognostic significance, remain unknown. *Seventh,* the female subgroup (13 sleep-inversion cases) was too small for reliable independent statistical inference; the consistent direction of effect in this subgroup is reported descriptively and should not be interpreted as confirmatory. *Finally,* groups were not matched for age or sex; it was very difficult to find healthy participants with normal sleep timing, and the study was conducted at a single centre, which may limit generalizability. Larger, prospectively powered, longitudinal studies using objective sleep assessment and adjusted continuous-outcome modelling are needed to confirm and extend these findings.

Conclusions

In this cross-sectional study of healthy young adults, delayed sleep timing ("sleep inversion") was independently associated with lower LV GLS despite preserved conventional echocardiographic indices, after adjustment for the confounders measured in a multivariable linear regression model. This finding was robust to a smoker-excluded sensitivity analysis, and to a males-only subgroup analysis. These findings suggest that STE may detect subtle myocardial changes not apparent on routine echocardiography in this population; however, given the cross-sectional design, substantial baseline group imbalance, and non-validated sleep assessment, a causal relationship cannot be established, and the findings should be regarded as hypothesis-generating pending confirmation in larger, prospectively designed, longitudinal studies.

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