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Impact of cumulative sleep duration on cardiac structural remodeling in asymptomatic adolescents

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Abbreviations

AUC: Area Under the Curve

BP: Blood Pressure

EnIGMA: Early ImaginG Markers of unhealthy lifestyles in Adolescents

LV: Left ventricle

MR: Magnetic Resonance

MVPA: Moderate-to-Vigorous Physical Activity

Text

Insufficient sleep is common and has been associated with cardiovascular events, such as myocardial infarction and stroke, in adults, as well as with adverse adiposity markers in pediatric populations(1). However, its possible effect on early cardiac remodeling is not well documented. Our aim was to assess the cumulative impact of objectively-measured sleep health on early cardiac and liver subclinical imaging features assessed by magnetic resonance (MR).

This work included adolescents without cardiovascular disease who were enrolled in the Early ImaginG Markers of unhealthy lifestyles in Adolescents (EnIGMA) study, with previously reported inclusion and exclusion criteria(2). Cardiovascular health metrics (including sleep health) were assessed longitudinally at approximately 12, 14 and 16 years of age(3). MR examinations were conducted coinciding with the final assessment period at the *Centro Nacional de Investigaciones Cardiovasculares* (CNIC) using a Philips 3-T Elition X whole-body scanner (Philips Healthcare, The Netherlands). The study was approved by the ethics committee of the *Instituto de Salud Carlos III* (CEI PI 63_2020).

Sleep duration was assessed with a wrist-worn triaxial accelerometer (Actigraph wGT3X-BT) for seven consecutive days, 24 hours a day, at each assessment period(1). Participant body-mass-index (BMI), blood pressure (BP) and moderate-to-vigorous physical activity (MVPA) were obtained as described previously(1,3). The cardiac imaging protocol included a balanced segmented cine steady-state free-precession sequence, and T2 and native T1 mapping sequences(2). Cardiac size parameters were indexed by height with an allometric exponent (height$^{2.7}$) to approximate lean body mass and to adjust for the impact of growth during childhood. Left ventricle (LV) mass-to-volume ratio and concentricity were calculated as (*LV mass/LV end-diastolic volume*

[LVEDV]) and (*LV mass/LVEDV*)$^{0.67}$, respectively. Liver fat content was quantified using a 3-dimensional multi-echo gradient echo sequence with spectral analysis (mDixonQuant). The technical details of the imaging acquisition and analysis are described elsewhere(2).

Cumulative exposure to sleep and other cardiovascular health metrics over time was analyzed using the area under the curve (AUC) method. AUC values were divided by the years of follow-up (AUCi), so that the interpretation is similar to an average value. Furthermore, adolescents were grouped based on their adherence to current sleep guidelines (8-10 h/day)(1) over the study period; they were categorized as either never following the sleep recommendations, or following them during 1 or 2-3 assessment periods. Multivariable linear regression analyses were conducted to examine the independent associations between sleep health and MR parameters adjusting for age, sex, and the AUCis of MVPA, BMI percentile, and systolic and diastolic BP percentiles(1,3). All statistical analyses were performed with Stata.

Among 123 participants included in the EnIGMA study(2), 14 had missing sleep data; the final study population thus included 109 adolescents (56.0% girls) with a mean age of 12.4±0.4 years at cohort entry and 16.0±0.5 years at the time of MR scan (**Table**). None of them reported having clinical sleep disorder or taking sleep medications.

Indexed LV mass, LV mass-to-volume ratio and concentricity increased as adherence to sleep recommendations declined (**Table**). Moreover, there was a significant inverse association between the AUCi of sleep duration (h/day) and indexed LV mass (adjusted β-coefficient: -1.03 g/m$^{2.7}$, 95% confidence interval [CI]: -1.92 to -0.13, p-value=0.025), LV mass-to-volume ratio, (adjusted β-coefficient: -0.03 g/ml, 95%CI: -0.05 to -0.01, p-value=0.005), LV concentricity (adjusted β-coefficient: -0.14 g/ml$^{0.67}$, 95%CI: -0.25 to -0.03, p-value=0.012), and liver fat content (adjusted β-coefficient: -

0.42%, 95%CI: -0.77 to -0.07, p-value=0.018; β-coefficient after further adjusting for the AUCi of energy intake : -0.32%, 95%CI: -0.58 to -0.06, p=0.016). Sleep duration was not significantly associated with any other MR-based parameter evaluated. Results were similar when indexing cardiac size parameters by body surface area with the DuBois formula (data not shown).

In this longitudinal study, shorter sleep duration was independently associated with adverse markers of LV wall remodeling and increased liver fat accumulation in adolescence; and this effect was cumulative. Few cross-sectional studies have examined the relationship between sleep health and subclinical cardiac features(4,5); most relied on self-reported questionnaires, lacked reference MR imaging, and focused mainly on adults. Overall, these studies concur on reporting an inverse association between sleep duration and LV mass. Our study adds valuable insights by demonstrating not only higher LV mass in adolescents with objectively-measured shorter sleep duration but also increased MR-based markers of concentric remodeling. These findings highlight sleep's distinct influence on health and suggest that the consequences of inadequate sleep may emerge as early as adolescence.

The mechanisms underlying the association between insufficient sleep and LV remodeling are not well understood. Short sleep duration is an independent risk factor for hypertension, a key trigger for LV hypertrophy. Although the present study included healthy adolescents and the associations found were maintained after adjustment for BP, insufficient sleep may provoke global sympathetic overactivity that can induce LV hypertrophy even in normotensive persons(5). Sleep deprivation has been also linked to a decrease in plasma leptin, which has been related to greater LV mass(4). However, the association between insufficient sleep and increased LV mass previously reported was maintained after adjustment for leptin(5), and future research should explore other

possible mechanisms. Regardless of the pathways, LV remodeling is a well-established independent risk factor for cardiovascular events, and the present study supports the need for public policies that promote sleep health from an early age.

Study limitations include the possibility of residual confounding, the absence of mechanistic evidence, and the potential that the analyzed population may not fully represent other adolescent populations. Strengths include the longitudinal approach, objective sleep health assessment, use of reference imaging methods, and consistent results whether sleep duration was analyzed continuously (h/day) or by adherence to current sleep recommendations, enhancing robustness and clinical relevance.

In conclusion, shorter sleep duration is independently associated with adverse markers of LV wall remodeling and liver fat accumulation in adolescence, with a suggested cumulative effect. These findings underscore the importance of sleep health from an early age and support its consideration as a key target in public health policies.

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Table. Demographic, cardiovascular health, and magnetic resonance parameters stratified by adherence to current sleep guidelines (8-10 hours per day)

	Total **N=109**	**Never following sleep recommendations** **n=49**	**Following sleep recommendations in 1 assessment period** **n=32**	**Following sleep recommendations in 2-3 assessment periods** **n=28**	**p-value for linear trend**
Female sex, n (%)	61 (56.0%)	25 (51.0%)	18 (56.3%)	18 (64.3%)	0.264
Age*, years	16.0 ± 0.5	16.1 ± 0.6	15.9 ± 0.3	16.1 ± 0.4	0.398
AUCi measures					
Sleep duration, h/day	7.6 ± 0.7	7.1 ± 0.6	7.8 ± 0.5	8.2 ± 0.4	<0.001
Body-mass-index, percentile	59.1 ± 24.2	60.1 ± 23.3	61.8 ± 23.5	54.2 ± 26.6	0.375
Systolic blood pressure, percentile	53.7 ± 22.5	52.8 ± 22.6	53.2 ± 23.4	56.0 ± 21.8	0.575
Diastolic blood pressure, percentile	44.5 ± 17.0	42.3 ± 16.7	45.0 ± 16.4	47.8 ± 18.1	0.172
Moderate-vigorous PA, min/day	65.3 ± 19.2	67.7 ± 17.9	68.9 ± 20.7	56.9 ± 18.0	0.029
Magnetic resonance parameters					
LVEDVi, $ml/m^{2.7}$	34.9 ± 4.8	35.8 ± 6.0	34.4 ± 3.8	33.9 ± 2.6	0.473
LVESVi, $ml/m^{2.7}$	13.1 ± 2.4	13.3 ± 3.0	13.1 ± 1.9	12.8 ± 1.8	0.949
LV indexed mass, $g/m^{2.7}$	17.4 ± 3.9	18.8 ± 4.5	16.7 ± 3.1	15.6 ± 2.6	0.002
Mass-to-volume ratio, g/ml	0.50 ± 0.08	0.53 ± 0.08	0.49 ± 0.08	0.46 ± 0.08	0.001
Concentricity, $g/ml^{0.67}$	2.55 ± 0.49	2.71 ± 0.51	2.50 ± 0.45	2.34 ± 0.41	0.002
LVEF, %	62.4 ± 4.2	62.9 ± 4.3	62.0 ± 4.1	62.1 ± 4.3	0.448
LV longitudinal strain, %	-19.0 ± 2.0	-18.9 ± 2.2	-18.8 ± 1.7	-19.5 ± 2.0	0.330

RVEDVi, ml/m$^{2.7}$	38.0 ± 5.6	39.3 ± 7.0	37.7 ± 4.3	36.1 ± 3.6	0.149
RVESVi, ml/m$^{2.7}$	16.8 ± 3.5	17.4 ± 4.2	16.8 ± 2.7	15.8 ± 2.6	0.198
RVEF, %	56.0 ± 4.5	56.0 ± 4.5	55.5 ± 4.5	56.4 ± 4.7	0.675
RV longitudinal strain, %	-22.4 ± 3.3	-22.2 ± 3.4	-22.0 ± 2.9	-23.3 ± 3.5	0.503
Native T1 relaxation time, ms	1235.0 ± 31.3	1233.6 ± 32.8	1229.9 ± 24.5	1243.3 ± 34.9	0.764
T2 relaxation time, ms	44.3 ± 2.3	44.8 ± 2.2	44.0 ± 2.1	43.7 ± 2.5	0.066
LA maximum volume, ml/m$^{2.7}$	15.6 ± 3.1	16.0 ± 3.3	15.0 ± 3.4	15.5 ± 2.4	0.840
LA ejection fraction, %	62.4 ± 8.0	61.7 ± 7.8	64.3 ± 8.4	61.4 ± 7.7	0.608
Liver fat fraction, %	2.04 ± 1.33	2.17 ± 1.71	2.08 ± 1.20	1.77 ± 0.45	0.161

Continuous variables are presented as mean ± standard deviation. P-values for linear trends are derived from a post-estimation test of the linear hypothesis across sleep recommendation categories using coefficients of orthogonal polynomials run after simple unadjusted (demographic, AUCi measures of cardiovascular health metrics) and multivariable adjusted (magnetic resonance parameters) linear regression models. *On the magnetic resonance scan day. AUCi, area under the curve; PA, physical activity; i, indexed; LV, left ventricle; RV, right ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LA, left atrium.