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Circadian Rhythm Amplitude, Not Fragmentation, Predicts Adolescent Insulin Sensitivity

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ABSTRACT

Adolescence is a critical period for metabolic development, often characterized by delayed sleep phases and severe circadian disruption. While the link between disrupted circadian rhythms and insulin resistance is established in adults, the specific impact of rhythm fragmentation versus rhythm amplitude in adolescents remains unclear. We analyzed 8.5 million minutes of continuous 80 Hz wrist-worn accelerometry data from 729 adolescents (ages 12–17) in the 2011–2014 National Health and Nutrition Examination Survey (NHANES). Custom signal processing extracted two non-parametric circadian metrics: Intradaily Variability (IV) and Relative Amplitude (RA). Survey-weighted least squares (WLS) regression assessed the independent associations of IV and RA with log-transformed HOMA-IR, adjusting for age, sex, BMI, race/ethnicity, and total physical activity volume. Intradaily Variability showed no statistically significant association with HOMA-IR ($p = 0.664$). Conversely, Relative Amplitude exhibited a highly significant inverse relationship with HOMA-IR ($\beta = -0.578$, $p = 0.003$), independent of total daily activity volume and BMI. The strength of the 24-hour circadian rhythm (RA), rather than day-to-day fragmentation (IV), is a primary independent predictor of adolescent insulin sensitivity. Interventions targeting adolescent metabolic health should prioritize circadian consolidation, maximizing daytime activity and protecting nighttime rest beyond simple exercise volume prescription.

1. INTRODUCTION

The prevalence of adolescent obesity and metabolic syndrome has reached epidemic proportions globally. A primary hallmark of this metabolic dysfunction is insulin resistance, wherein peripheral tissues exhibit a diminished response to insulin, necessitating compensatory hyperinsulinemia [1]. Quantified clinically via the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), early identification is critical, as insulin resistance serves as a direct precursor to type 2 diabetes mellitus and cardiovascular disease [2].

Glucose homeostasis is heavily regulated by the circadian system. Every cell in the human body, including hepatic and skeletal muscle cells responsible for glucose clearance, operates on peripheral circadian clocks governed by core transcription-translation feedback loops involving the genes BMAL1 and CLOCK [3]. These peripheral oscillators rely on strong behavioral cues—specifically the contrast between feeding/fasting and activity/rest—to synchronize with the brain’s master clock in the suprachiasmatic nucleus (SCN). Circadian misalignment dysregulates the timing of cortisol secretion and impairs GLUT4 translocation in muscle cells, directly predisposing the individual to insulin resistance [4, 5].

The advent of continuous wrist-worn accelerometry allows for the objective, mathematical quantification of biological rhythms in free-living populations [6]. Two foundational non-parametric metrics developed by Witting et al. are frequently used to evaluate these actigraphy profiles: Intradaily Variability (IV), which measures the fragmentation of the rhythm, and Relative Amplitude (RA), which measures the robustness or contrast between the most active and least active periods of the day [7].

In adult populations, blunted circadian amplitude and high fragmentation have been consistently linked to metabolic syndrome and diabetes [8, 9]. However, a significant gap exists regarding adolescents. Teenagers experience a natural biological shift toward a delayed sleep phase, compounded by erratic school schedules, evening screen time, and “social jetlag” [10]. We hypothesized that adolescents with more fragmented 24-hour activity rhythms (high IV) would exhibit higher HOMA-IR scores than those with consolidated rhythms, independent of total physical activity volume.

2. MATERIALS AND METHODS

2.1 Study Population

This cross-sectional study utilized data from the 2011–2012 and 2013–2014 cycles of the National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention (CDC). The analytic sample was restricted to adolescents aged 12 to 17 years. Exclusion criteria included missing fasting plasma glucose or insulin data, missing BMI measurements, or insufficient accelerometer data to derive a 24-hour circadian profile (defined as fewer than 1,000 valid wear minutes per 24-hour cycle). The final analytic sample comprised N = 729 participants.

2.2 Accelerometer Signal Processing

Raw accelerometry data were collected via ActiGraph GT3X+ devices worn on the non-dominant wrist for seven consecutive days, sampling at 80 Hz. Monitor-Independent Motion Summary (MIMS) triaxial units were extracted from the NHANES PAXMIN files. Signal processing was conducted using Python 3.13 (pandas, NumPy). Non-wear time and poor sensor quality minutes (flagged by NHANES quality control variable PAXQFM > 0) were systematically removed. Valid minutes were synchronized to a standardized 1,440-minute clock using modulo arithmetic to establish an average 24-hour biological profile for each participant.

2.3 Circadian Feature Extraction

Two primary non-parametric circadian metrics were mathematically derived following the methodologies established by Witting et al. (1990) and Van Someren et al. (1999) [7, 13]. Intradaily Variability (IV) quantified the fragmentation of the rhythm; it was calculated as the ratio of the mean square of the first derivative of the data to the overall variance, utilizing an $(n-1)$ denominator. Relative Amplitude (RA) quantified the robustness of the rhythm using a circular rolling window to identify the most active 10-hour period (M10) and the least active 5-hour period (L5), utilizing the formula: $RA = (M10 - L5) / (M10 + L5)$.

2.4 Clinical Measures and Statistical Analysis

Insulin resistance was quantified using HOMA-IR = (Fasting Glucose [mg/dL] × Fasting Insulin [μU/mL]) / 405. HOMA-IR was log-transformed to satisfy the assumption of normality. Survey-Weighted Least Squares (WLS) regression models were constructed using the statsmodels API to test the independent associations of IV and RA with log-transformed HOMA-IR. Models utilized 4-year MEC weights (WTMEC4YR) to account for the NHANES complex sampling design. Models were adjusted for age, sex, BMI, race/ethnicity, and mean daily total activity volume. Variance Inflation Factors (VIF) were monitored to ensure no significant multicollinearity.

3. RESULTS

3.1 Sample Characteristics

Of the 963 adolescents aged 12–17 selected for the fasting subsample in NHANES 2011–2014, 831 possessed valid fasting glucose, insulin, and BMI data. Following actigraphy processing, 729 met all inclusion criteria, forming the final analytic cohort. Demographic characteristics are summarized in Table 1. The cohort reflects a nationally representative distribution when applying 4-year MEC survey weights.

3.2 Descriptive Statistics of Circadian Metrics

Continuous 80 Hz wrist accelerometry yielded robust non-parametric profiles for the cohort. The mean Intradaily Variability (IV) was 0.42 (SD = 0.13), indicating the average frequency of transitions between rest and activity. The mean Relative Amplitude (RA) was 0.87 (SD = 0.09), demonstrating the baseline strength of the sleep-wake contrast within the adolescent population.

3.3 Regression Analysis

Following adjustment for total daily activity volume, age, sex, BMI, and race/ethnicity using WLS regression, IV demonstrated no statistically significant association with insulin resistance ($p = 0.664$; Table 2, Model 1). This indicates that day-to-day fragmentation of activity is not a primary driver of altered insulin sensitivity (Figure 1A).

In contrast, Relative Amplitude exhibited a highly significant inverse relationship with log-transformed HOMA-IR ($\beta = -0.578$, SE = 0.194, $p = 0.003$; Table 2, Model 2). Adolescents with a more robust circadian rhythm possessed significantly greater insulin sensitivity, independent of their total physical activity volume, BMI, and demographic covariates (Figure 1B).

4. DISCUSSION

This study investigated the impact of circadian rhythm disruptions on adolescent metabolic health. Contrary to our initial hypothesis, IV demonstrated no statistically significant relationship with HOMA-IR. However, RA exhibited a highly significant inverse relationship with insulin resistance. Crucially, this association remained robust after adjusting for total physical activity volume and BMI—isolating the specific metabolic importance of the circadian clock itself.

The null finding regarding IV provides crucial biological context. It suggests that adolescent physiology may be resilient to brief interruptions in daily activity patterns, such as daytime naps or short nocturnal awakenings, but highly sensitive to the overall loss of day-night contrast. Because the molecular mechanisms of circadian-metabolic synchronization (BMAL1/CLOCK transcription and GLUT4 expression) rely on distinct behavioral cues to remain aligned with the SCN, a blunted RA indicates a failure to provide these vital physiological signals [3, 4].

While these findings are robust, several limitations must be acknowledged. The cross-sectional nature of NHANES data precludes causal inference. There is potential for reverse causation: insulin-resistant adolescents may experience systemic fatigue and be less active during the day. Additionally, wrist-worn accelerometers cannot perfectly distinguish between physiological sleep and lying still while awake, and the NHANES protocol captures only seven days of actigraphy, which may not fully represent long-term behavioral patterns [11]. Finally, HOMA-IR is an estimate derived from fasting glucose and insulin, not a direct measurement like the hyperinsulinemic-euglycemic clamp [12].

5. CONCLUSION

The strength of the daily circadian rhythm (Relative Amplitude) is a significant, independent predictor of metabolic health in adolescents. These findings suggest that future clinical interventions for adolescent insulin resistance should expand beyond total exercise volume and weight loss to prioritize “circadian hygiene”—consolidating physical activity to the daytime and fiercely protecting nighttime rest to restore natural biological rhythms.

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Table 1. Sample Characteristics of the Adolescent Cohort (N = 729).

Table 2. Survey-Weighted Least Squares (WLS) Regression Models Predicting Log(HOMA-IR). IV = Intradaily Variability; RA = Relative Amplitude.

Characteristic	Mean (SD) or N (%)
Age (years)	14.4 (1.7)
Sex (Female)	359 (49.2%)
BMI (kg/m²)	23.5 (6.1)
Fasting Glucose (mg/dL)	94.3 (11.1)
Fasting Insulin (µU/mL)	15.2 (12.5)
HOMA-IR	3.6 (3.2)
Total Daily Volume (MIMS/day)	11,695.8 (3,661.7)

Variable	Model 1: IV β (p-value)	Model 2: RA β (p-value)
Circadian Metric (IV or RA)	0.111 (p = 0.664)	−0.578 (p = 0.003)
Total Daily MIMS	-6.18×10^{-6} (p = 0.386)	-6.38×10^{-6} (p = 0.209)
Age (years)	−0.092 (p < 0.001)	−0.094 (p < 0.001)
Sex (Female)	0.082 (p = 0.027)	0.085 (p = 0.021)
BMI (kg/m²)	0.070 (p < 0.001)	0.068 (p < 0.001)
Race/Ethnicity: Other Hispanic	−0.175 (p = 0.043)	−0.184 (p = 0.032)
Race/Ethnicity: Non-Hispanic White	−0.149 (p = 0.005)	−0.154 (p = 0.004)
Race/Ethnicity: Non-Hispanic Black	−0.108 (p = 0.107)	−0.124 (p = 0.065)
Race/Ethnicity: Non-Hispanic Asian	0.058 (p = 0.540)	0.042 (p = 0.658)
Race/Ethnicity: Other/Multi-Racial	−0.204 (p = 0.095)	−0.221 (p = 0.070)
R²	0.213	0.228

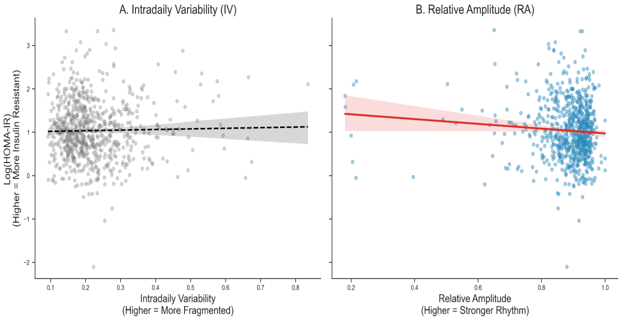

Figure 1. The relationship between Intradaily Variability, Relative Amplitude, and HOMA-IR in adolescents. (A) Scatter plot demonstrating the null association between IV and log-transformed HOMA-IR. (B) Scatter plot demonstrating the statistically significant inverse relationship between RA and log-transformed HOMA-IR, indicating that stronger circadian rhythms are associated with lower insulin resistance. Both models represent N = 729 and account for age, sex, BMI, race/ethnicity, and total physical activity volume. The dashed line (A) represents a non-significant trend; the solid red line (B) indicates a statistically significant trend (p = 0.003) with shaded 95% confidence intervals.