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Accelerometry-assessed sleep clusters and cardiometabolic risk factors in adolescents

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Abstract

Objective: This study aimed to identify sleep clusters based on objective multidimensional sleep characteristics and test their associations with adolescent cardiometabolic health.

Methods: The authors included 1090 participants aged 14.3 to 16.4 years (mean = 15.2 years) who wore 7-day accelerometers during the 15-year follow-up of the German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus) and the Influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany (LISA) birth cohorts. K-means cluster analysis was performed across 12 sleep characteristics reflecting sleep quantity, quality, schedule, variability, and regularity. Cardiometabolic risk factors included fat mass index (FMI), blood pressure, triglycerides, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and insulin resistance ($n = 505$). Linear and logistic regression models were examined.

Results: Five sleep clusters were identified: good sleep ($n = 337$); delayed sleep phase ($n = 244$); sleep irregularity and variability ($n = 108$); fragmented sleep ($n = 313$); and

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prolonged sleep latency ($n = 88$). The "prolonged sleep latency" cluster was associated with increased sex-scaled FMI ($\beta = 0.39$, 95% CI: 0.15–0.62) compared with the "good sleep" cluster. The "sleep irregularity and variability" cluster was associated with increased odds of high triglycerides only in male individuals (odds ratio: 9.50, 95% CI: 3.22–28.07), but this finding was not confirmed in linear models.

Conclusions: The prolonged sleep latency cluster was associated with higher FMI in adolescents, whereas the sleep irregularity and variability cluster was specifically linked to elevated triglycerides (≥1.7 mmol/L) in male individuals.

INTRODUCTION

Cardiometabolic risk factors may appear as early as childhood and track into adulthood, increasing cardiovascular disease risk [1]. Accumulating evidence has linked short sleep to increased cardiometabolic risk in children and adolescents [2, 3]. Recently, the American Heart Association added sleep duration as the eighth metric to cardiovascular health's definition (Life's Essential 8) [4]. Besides sleep duration, other sleep characteristics, including sleep efficiency, timing, variability, regularity, and wake time, have also been associated with adolescent cardiometabolic health [5–8]. These sleep characteristics within an individual were mainly assessed independently; however, they tend to be correlated with each other [9].

Cluster analysis provides the ability to consider multidimensional sleep characteristics from a holistic perspective [9]. To date, only one study has applied this approach to identify sleep patterns and explored their relationships with cardiometabolic health in children and adults using accelerometry-measured sleep data [10]. Four patterns were identified, and the "overall good sleepers" pattern was associated with more favorable body mass index (BMI) and metabolic syndrome severity score. However, associations among sleep patterns and other cardiometabolic risk factors such as fat mass index (FMI), high-sensitivity C-reactive protein (hs-CRP), or insulin resistance have not been investigated [2, 3]. For instance, several studies have linked short sleep to higher CRP in children and adolescents [2]. Additionally, earlier objective sleep midpoint timing was associated with increased 1-year fat mass in youth [5]. However, adolescents with late objective sleep midpoint timing had increased odds of developing insulin resistance within 2 years [6].

Therefore, we applied cluster analysis to identify sleep clusters across 12 accelerometry-assessed sleep characteristics in 1090 adolescents and investigated their associations with cardiometabolic risk factors, including FMI, blood pressure (BP), lipids, hs-CRP, and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR).

Study Importance

What is already known?

- Multiple objective sleep characteristics, including sleep duration, efficiency, timing, variability, regularity, and wake time, are associated with cardiometabolic risk in children and adolescents.
- These sleep characteristics within an individual are often assessed independently, although they tend to be correlated with each other.

What does this study add?

- Five sleep clusters were identified in adolescents by cluster analysis across 12 accelerometry-derived sleep characteristics, i.e., "good sleep," "delayed sleep phase," "sleep irregularity and variability," "fragmented sleep," and "prolonged sleep latency."
- The prolonged sleep latency cluster was associated with increased fat mass index, and male individuals within the sleep irregularity and variability cluster had higher odds of having high triglycerides.

How might these results change the direction of research or the focus of clinical practice?

- Considering the relationships among multidimensional sleep characteristics and health from a holistic perspective deserves further investigation.
- Our results suggest that improvements in sleep latency, variability, and regularity may enrich existing sleep-targeted intervention strategies for cardiometabolic health that mainly focus on improving adequate sleep.

METHODS

Study participants

We used data from the 15-year follow-up of two ongoing German birth cohorts, the German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development (GINIplus) and the Influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany (LISA). More details of both studies have been published [11]. Briefly, the GINIplus study recruited 5991 healthy

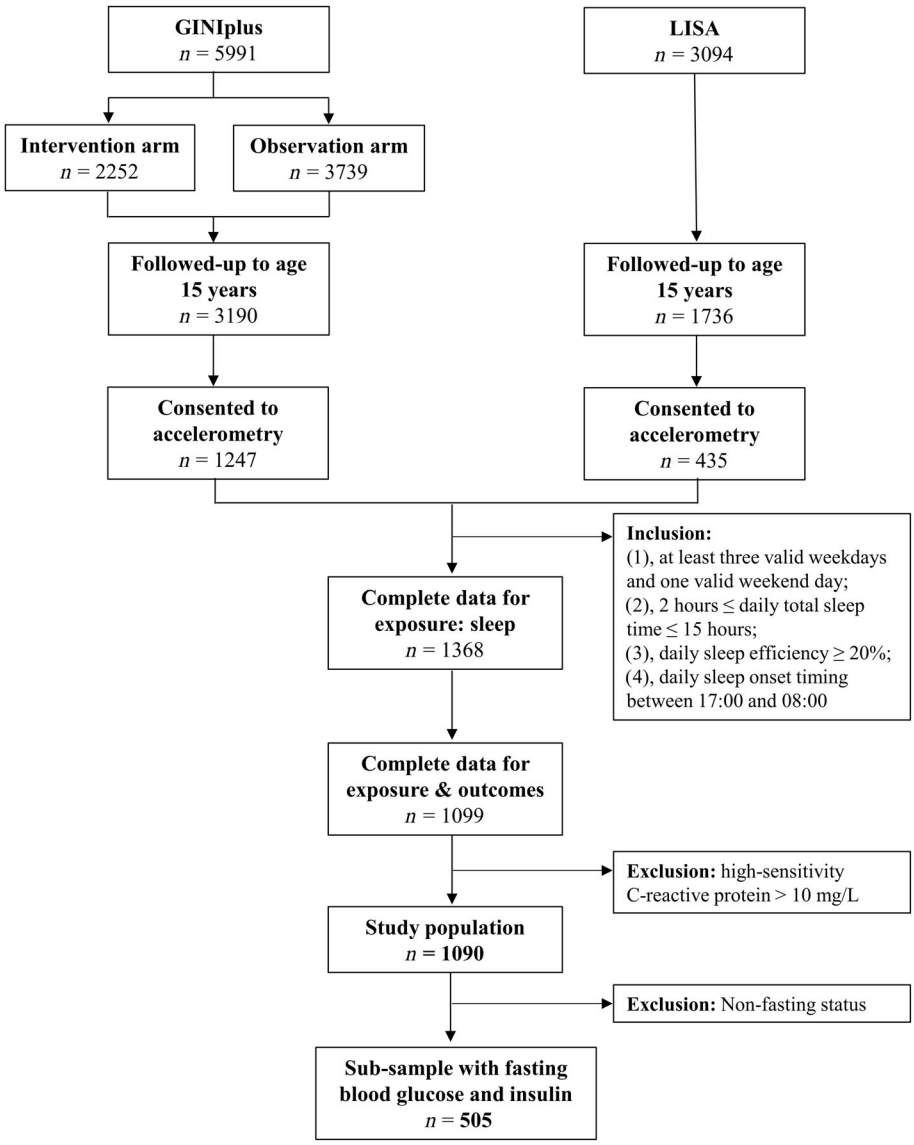

FIGURE 1 Flowchart of participants. GINIplus, German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development; LISA, Influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany.

newborns in Munich and Wesel from 1995 to 1998, comprising an intervention arm, which aimed to investigate the hydrolyzed formulae effects for allergy prevention in infants with a family history of allergy, and an observation arm, including newborns without a family history of allergy and those whose parents declined to participate in the intervention. The LISA study recruited 3094 healthy neonates in Munich, Wesel, Leipzig, and Bad Honnef between 1997 and 1999. At the 15-year follow-up between May 2011 and July 2014, a subset of participants (1247 in GINIplus and 435 in LISA) consented to wear accelerometers to measure sleep and physical activity (PA) in Munich and Wesel. Finally, a total of 1090 participants with valid accelerometry-measured sleep data and complete information on cardiometabolic outcomes (except for HOMA-IR in a subsample, $n = 505$) were included in the analyses. Participants were included only with at least 3 weekdays and 1 weekend day of valid accelerometry recording for ≥10 h/day [12]. More details are described in Figure 1. Both studies were approved by the respective local ethics committees, and written consents were provided by all participants and their families.

Sleep assessment and characteristics

Accelerometry

Nighttime sleep and daytime PA were measured by a triaxial accelerometer (ActiGraph GT3X, Pensacola, Florida) during a regular school week, the validity of which has been demonstrated in adolescents [13]. Participants wore accelerometers for 7 consecutive days and nights, with

accelerometers worn on the nondominant wrists at night, and kept sleep diaries. Accelerometry protocol details have been provided elsewhere [12].

Sleep characteristics

Accelerometry-measured sleep data were analyzed with the ActiLife software (version 5.5.5, firmware 4.4.0) using the Sadeh algorithm [14]. The sampling rate was set to 30 Hz, and measured accelerations were stored at 1 Hz after conversion into proprietary "activity counts," which were summed over 60-s epochs. The "probability of sleep" was computed as a score centered around zero for each minute participants indicated as time-in-bed in their diary (time between going to bed and getting up). The minute was identified as "asleep" if the score was equal to or greater than zero, and the minute was identified as "awake" if the score was less than zero [14]. The following six sleep characteristics were derived for each valid night:

1. Total sleep time (hours): the total number of minutes scored as asleep by the algorithm, divided by 60;
2. Sleep efficiency (percentage): the ratio of algorithm-scored asleep minutes to the total diary-recorded minutes in bed;
3. Sleep midpoint timing (24-h clock): the first minute algorithm-scored as asleep, adding half of the total sleep time, then converted to 24-h clock;
4. Sleep latency (minutes): the total number of minutes between diary-recorded time of going to bed and the first minute algorithm-scored as asleep;
5. Time awake per hour after sleep onset (minutes per hour): the total number of algorithm-scored awake minutes after sleep onset (WASO), divided by the hours in bed after sleep onset (total sleep time + WASO/60);
6. Awakenings per hour after sleep onset: the number of algorithm-scored different awakening episodes after sleep onset, divided by the hours in bed after sleep onset.

For each of six daily sleep characteristics, the daily average was calculated as mean value across all valid days, and the day-to-day variability was calculated as standard deviation (SD) across all valid days. In total, 12 sleep characteristics reflecting sleep quantity (total sleep time), quality (sleep efficiency), schedule (sleep midpoint timing, sleep latency, time awake per hour after sleep onset, and awakenings per hour after sleep onset), variability (SD in total sleep time, SD in sleep efficiency, SD in sleep latency, SD in time awake per hour after sleep onset, and SD in awakenings per hour after sleep onset), and regularity (SD in sleep midpoint timing) were used in subsequent cluster analysis.

Cardiometabolic risk factors

Participants' body weight (kilograms), height (meters), systolic BP (SBP, millimeters of mercury), and diastolic BP (DBP, millimeters of mercury) were measured. Fat-free mass (kilograms) was assessed by means of phase sensitive bioelectrical impedance (NutriBox, Data Input GmbH, Pöcking, Germany), and fat mass (kilograms) was calculated by subtracting fat-free mass from body weight. FMI was calculated as fat mass (kilograms) per height squared (meters squared). Serum total cholesterol (TC, millimoles per liter), triglycerides (TG, millimoles per liter), high-density lipoprotein cholesterol (HDL, millimoles per liter), low-density lipoprotein cholesterol (LDL, millimoles per liter), and hs-CRP (milligrams per liter) were measured. Fasting glucose (millimoles per liter) and fasting insulin (picomoles per liter) were measured, and HOMA-IR was calculated as follows: (glucose $\times$ insulin)/(22.5 $\times$ 6.945) [15]. Details on the measurements are provided in online Supporting Information Methods.

Cardiometabolic risk factors were dichotomized based on established cutoffs or sex-specific percentiles. According to three components of metabolic syndrome definitions in children and adolescents by the International Diabetes Federation (IDF) [16], high BP was defined as SBP ≥ 130 mm Hg or DBP ≥ 85 mm Hg; high TG was defined as TG ≥ 1.7 mmol/L; and low HDL was defined as HDL < 1.03 mmol/L at ages 10 to 16 years and, at ages ≥16 years, <1.03 mmol/L in male individuals and <1.29 mmol/L in female individuals. High hs-CRP was defined as hs-CRP ≥ 75% sex-specific percentile of the current population with hs-CRP ≥ 0.2 mg/L (0.91 mg/L in male and 0.87 mg/L in female individuals) [17]. High FMI was defined as FMI ≥ 75% sex-specific percentile (5.01 kg/m^2 in male and 6.68 kg/m^2 in female individuals), and high HOMA-IR was defined as HOMA-IR ≥ 75% sex-specific percentile (2.59 in male and 2.74 in female individuals).

Confounders

Sex, age at blood sampling, study (GINIplus observation arm, GINIplus intervention arm, and LISA study), study center (Munich and Wesel), season of sleep measurement (spring, summer, autumn, and winter), parental highest education (low/medium: ≤10th grade; high: >10th grade), and fasting status at blood sampling (yes, no) were collected by questionnaires. Pubertal stage was categorized into two groups: pre-, early, or midpubertal and late or postpubertal stage based on a self-rated questionnaire [18]. Accelerometry-measured PA was classified into sedentary, light, moderate, and vigorous PA according to published triaxial cutoffs by Aguilar-Farías [19] (for sedentary) and Romanzini [20], and then moderate and vigorous PA were merged into moderate-to-vigorous PA (MVPA) [12]. Average sedentary (hours) and MVPA (minutes) across all valid days were included. Depressive symptoms were evaluated by the Depression Screener for Teenagers and defined as a score ≥ 12 [21]. Dietary information was assessed by a self-administered food frequency questionnaire [22]. Total energy intake (EI, kilocalories) was calculated [23], and carbohydrate intake was expressed as its percentage in total EI (%EI).

Statistical analysis

All statistical analyses were performed in R (version 4.1.2, R Center for Statistical Computing, Vienna, Austria). A total of 12 sleep

TABLE 1 Participant characteristics in total population and stratified by sex

	Total	Male	Female	*p* value
n	1090	489	601	
Age (y)	15.2 ± 0.3	15.2 ± 0.3	15.2 ± 0.3	0.230
Weight (kg)	61.2 ± 11.0	64.1 ± 11.7	58.8 ± 9.9	**<0.001**
Height (cm)	171.4 ± 8.0	176.2 ± 7.4	167.5 ± 6.1	**<0.001**
FMI (kg/m^2)	5.1 ± 2.1	4.1 ± 1.9	5.9 ± 1.9	**<0.001**
High FMI, *n* (%)	272 (25.0)	122 (24.9)	150 (25.0)	1.000
SBP (mm Hg)	118.5 ± 11.7	121.2 ± 12.3	116.3 ± 10.8	**<0.001**
DBP (mm Hg)	69.4 ± 8.9	68.7 ± 8.9	70.1 ± 9.0	**0.010**
High BP, *n* (%)	206 (18.9)	124 (25.4)	82 (13.6)	**<0.001**
TC (mmol/L)	4.3 (3.8, 4.8)	4.1 (3.6, 4.6)	4.4 (3.9, 5.0)	**<0.001**
TG (mmol/L)	1.0 (0.7, 1.3)	1.0 (0.7, 1.4)	1.0 (0.7, 1.3)	0.561
High TG, *n* (%)	130 (11.9)	70 (14.3)	60 (10.0)	**0.036**
HDL (mmol/L)	1.5 ± 0.4	1.4 ± 0.4	1.6 ± 0.4	**<0.001**
Low HDL, *n* (%)	84 (7.7)	56 (11.5)	28 (4.7)	**<0.001**
LDL (mmol/L)	2.3 (1.9, 2.7)	2.2 (1.8, 2.6)	2.4 (2.0, 2.8)	**<0.001**
hs-CRP (mg/L)	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	0.4 (0.2, 0.7)	0.305
High hs-CRP, *n* (%)	218 (20.0)	96 (19.6)	122 (20.3)	0.843
HOMA-IR	2.1 (1.5, 2.6)	2.0 (1.4, 2.6)	2.1 (1.6, 2.7)	0.095
High HOMA-IR, *n* (%)	128 (25.3)	61 (25.4)	67 (25.3)	1.000
Total EI (kcal/day)	2093.9 ± 645.2	2406.4 ± 643.4	1868.0 ± 544.9	**<0.001**
Carbohydrate intake (%EI)	53.0 ± 7.3	52.5 ± 7.2	53.4 ± 7.4	0.095
Sedentary (h)	8.2 ± 1.4	8.0 ± 1.5	8.4 ± 1.3	**<0.001**
MVPA (min)	50.4 ± 26.5	57.3 ± 25.4	44.7 ± 26.2	**<0.001**
Depression, *n* (%)	141 (13.9)	48 (10.6)	93 (16.5)	**0.010**
Fasting status (yes), *n* (%)	511 (46.9)	241 (49.3)	270 (44.9)	0.170
Sleep clusters, *n* (%)				**<0.001**
Good sleep	337 (30.9)	109 (22.3)	228 (37.9)	
Delayed sleep phase	244 (22.4)	103 (21.1)	141 (23.5)	
Sleep irregularity and variability	108 (9.9)	43 (8.8)	65 (10.8)	
Fragmented sleep	313 (28.7)	193 (39.5)	120 (20.0)	
Prolonged sleep latency	88 (8.1)	41 (8.4)	47 (7.8)	
Study, *n* (%)				0.278
GINIplus observation	414 (38.0)	179 (36.6)	235 (39.1)	
GINIplus intervention	437 (40.1)	192 (39.3)	245 (40.8)	
LISA	239 (21.9)	118 (24.1)	121 (20.1)	
Study center, *n* (%)				0.136
Munich	625 (57.3)	293 (59.9)	332 (55.2)	
Wesel	465 (42.7)	196 (40.1)	269 (44.8)	
Season, *n* (%)				0.357
Spring	281 (25.8)	133 (27.2)	148 (24.6)	
Summer	167 (15.3)	65 (13.3)	102 (17.0)	
Autumn	353 (32.4)	158 (32.3)	195 (32.4)	
Winter	289 (26.5)	133 (27.2)	156 (26.0)	
Parental highest education, *n* (%)				0.824
Low/medium	337 (30.9)	149 (30.5)	188 (31.3)	
High	753 (69.1)	340 (69.5)	413 (68.7)	

TABLE 1 (Continued)

	Total	Male	Female	*p* value
Pubertal stage, *n* (%)				**<0.001**
Pre-, early, or midpubertal	202 (21.7)	178 (43.8)	24 (4.6)	
Late or postpubertal	729 (78.3)	228 (56.2)	501 (95.4)	

Note: The results are presented as mean ± SD, median (first quartile, third quartile), or *n* (percentage). The number of participants with available information was as follows: HOMA-IR (505); total EI (865); carbohydrate intake (865); sedentary (1082); MVPA (1082); depression (1017); and pubertal stage (931). $P < 0.05$ are highlighted in bold.

Abbreviations: BP, blood pressure; carbohydrate intake (%EI), carbohydrate as percentage of total energy intake; DBP, diastolic blood pressure; EI, energy intake; FMI, fat mass index; GINIplus, German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein cholesterol; LISA, Influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany; MVPA, moderate-to-vigorous physical activity; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

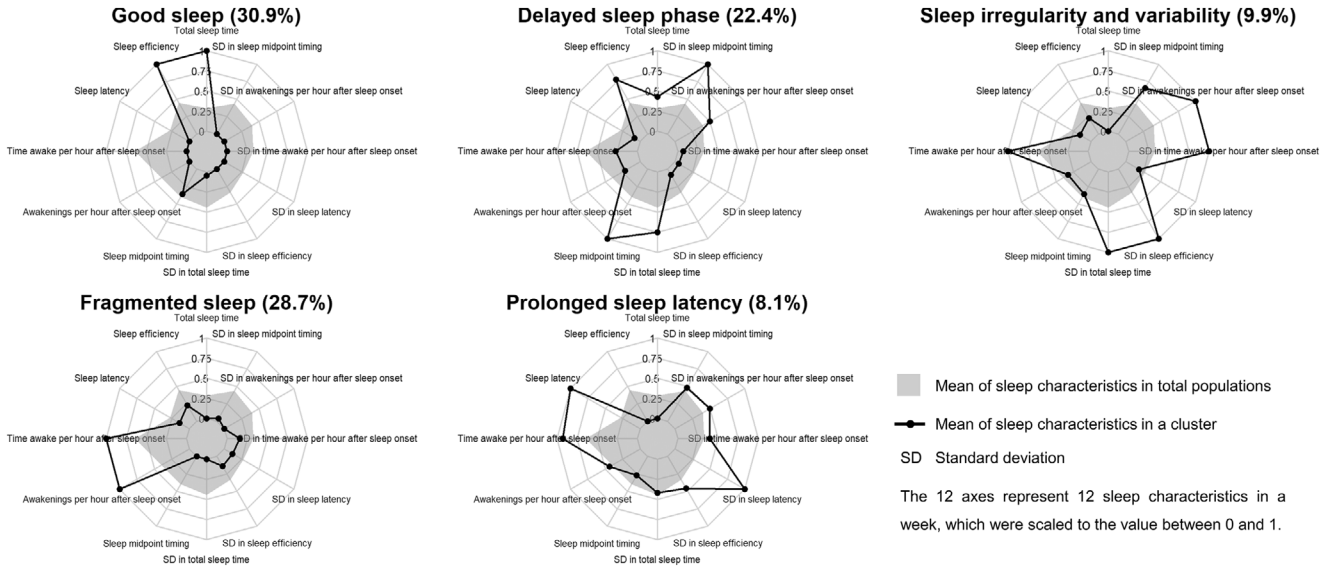

FIGURE 2 Distributions of sleep characteristics in a week in five sleep clusters.

characteristics were standardized, and their Spearman correlation was examined (Figure S1). Hierarchical cluster analysis was conducted using Euclidean distance and Ward's linkage (Ward.D2). K-means cluster analysis was applied testing three, four, five, and six clusters. The final number of sleep clusters was set to five, considering the combination of the following methods: 1) interpretability of k-means results; 2) hierarchical cluster dendrogram (Figure S2); 3) results of principal component analysis (Table S1; 5 components account for 80% cumulative percentage of variance); and 4) sum of squares method (Figure S3, by minimizing the within-cluster sum of squares and maximizing the between-cluster sum of squares). More details are provided in online Supporting Information Methods. In final k-means cluster analysis, the number of clusters was specified as five, with 50 random initial centroids. One-way ANOVA and Kruskal–Wallis rank sum test for continuous variables and χ^2 test for categorical variables were used to explore differences among sexes and sleep clusters, followed by Bonferroni-adjusted post hoc tests.

Linear regression models were conducted to evaluate associations among sleep clusters and continuous cardiometabolic markers, which were examined for normality and naturally log-transformed as appropriate. Outliers were detected visually using box plots (median ± 3 interquartile range, outliers were not excluded). Three models were performed: Model 1 was adjusted for sex, age, study, study center, and parental highest education; Model 2 was additionally adjusted for season, pubertal stage, sedentary, MVPA, depression, fasting status (except for HOMA-IR), total EI, and carbohydrate intake; and Model 3 was Model 2 plus adjustment for FMI. For comparability, FMI (sex-specific), SBP, DBP, and HDL (inverse) were scaled, and results were described as β with 95% confidence intervals (CI). TC, TG, LDL, and HOMA-IR were log-transformed, and the β estimate of linear models were then back-transformed to means ratio (MR = exp[β]) with 95% CI. MR represents the ratio of the mean of the outcome variable in one group versus the reference group. Considering the correlation among outcomes, the number of independent tests was calculated as seven according to Nyholt [24] using the R package "poolr" [25], yielding a Bonferroni-

TABLE 2 Associations among sleep clusters and continuous cardiometabolic risk factors in adolescents

Total (1090)	Good sleep (337)	Delayed sleep phase (244)		Sleep irregularity and variability (108)		Fragmented sleep (313)		Prolonged sleep latency (88)	
Outcomes	**β (95% CI)**	**β (95% CI)**	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***	**β (95% CI)**	***p***
FMI sex-scaled									
Model 1	Ref.	0.06 (−0.11 to 0.22)	0.500	0.14 (−0.07 to 0.36)	0.195	0.11 (−0.05 to 0.27)	0.167	0.28 (0.04 to 0.51)	0.020
Model 2	Ref.	0.01 (−0.15 to 0.17)	0.888	0.16 (−0.05 to 0.37)	0.139	0.16 (0.00 to 0.31)	0.050	0.39 (0.15 to 0.62)	**0.001**
SBP scaled									
Model 1	Ref.	−0.01 (−0.17 to 0.15)	0.885	0.04 (−0.17 to 0.25)	0.727	0.00 (−0.16 to 0.15)	0.960	0.11 (−0.13 to 0.34)	0.372
Model 2	Ref.	0.01 (−0.15 to 0.16)	0.950	0.03 (−0.18 to 0.24)	0.779	0.02 (−0.14 to 0.17)	0.843	0.12 (−0.12 to 0.35)	0.327
Model 3	Ref	0.00 (−0.15 to 0.16)	0.974	0.00 (−0.21 to 0.20)	0.965	−0.02 (−0.17 to 0.13)	0.814	0.03 (−0.19 to 0.26)	0.781
DBP scaled									
Model 1	Ref.	0.04 (−0.12 to 0.21)	0.605	0.19 (−0.03 to 0.40)	0.087	−0.04 (−0.20 to 0.12)	0.616	0.00 (−0.24 to 0.23)	0.987
Model 2	Ref.	0.06 (−0.11 to 0.22)	0.500	0.21 (−0.01 to 0.42)	0.058	0.00 (−0.16 to 0.15)	0.971	−0.01 (−0.25 to 0.22)	0.905
Model 3	Ref.	0.05 (−0.11 to 0.22)	0.509	0.18 (−0.03 to 0.40)	0.093	−0.03 (−0.18 to 0.13)	0.729	−0.08 (−0.31 to 0.16)	0.528
HDL inversely scaled									
Model 1	Ref.	−0.05 (−0.21 to 0.11)	0.561	−0.16 (−0.37 to 0.06)	0.147	0.08 (−0.08 to 0.23)	0.336	0.01 (−0.22 to 0.24)	0.913
Model 2	Ref.	−0.05 (−0.21 to 0.11)	0.549	−0.16 (−0.37 to 0.06)	0.150	0.10 (−0.06 to 0.26)	0.205	0.04 (−0.20 to 0.27)	0.763
Model 3	Ref.	−0.05 (−0.21 to 0.11)	0.523	−0.19 (−0.40 to 0.02)	0.080	0.07 (−0.08 to 0.22)	0.366	−0.04 (−0.27 to 0.19)	0.743
	MR (95% CI)	**MR (95% CI)**	***p***	**MR (95% CI)**	***p***	**MR (95% CI)**	***p***	**MR (95% CI)**	***p***
TC									
Model 1	Ref.	1.01 (0.98 to 1.04)	0.500	1.02 (0.98 to 1.06)	0.269	1.01 (0.98 to 1.04)	0.674	1.02 (0.97 to 1.06)	0.453
Model 2	Ref.	1.01 (0.98 to 1.04)	0.431	1.02 (0.98 to 1.07)	0.241	1.01 (0.98 to 1.04)	0.677	1.01 (0.97 to 1.06)	0.591
Model 3	Ref.	1.01 (0.98 to 1.04)	0.438	1.02 (0.98 to 1.06)	0.313	1.00 (0.97 to 1.03)	0.847	1.00 (0.96 to 1.05)	0.868
TG									
Model 1	Ref.	1.00 (0.93 to 1.08)	0.951	1.03 (0.93 to 1.13)	0.551	1.05 (0.98 to 1.13)	0.178	1.00 (0.90 to 1.11)	0.982
Model 2	Ref.	1.01 (0.94 to 1.09)	0.726	1.02 (0.93 to 1.12)	0.659	1.05 (0.98 to 1.13)	0.137	1.01 (0.92 to 1.12)	0.775
Model 3	Ref.	1.01 (0.94 to 1.08)	0.743	1.01 (0.92 to 1.10)	0.893	1.04 (0.97 to 1.11)	0.272	0.98 (0.89 to 1.08)	0.690
LDL									
Model 1	Ref.	1.01 (0.97 to 1.06)	0.595	1.02 (0.95 to 1.08)	0.616	1.03 (0.98 to 1.08)	0.253	1.04 (0.97 to 1.12)	0.271
Model 2	Ref.	1.02 (0.97 to 1.07)	0.525	1.02 (0.96 to 1.09)	0.533	1.03 (0.98 to 1.08)	0.221	1.03 (0.96 to 1.11)	0.411
Model 3	Ref.	1.02 (0.97 to 1.07)	0.535	1.01 (0.95 to 1.08)	0.691	1.02 (0.98 to 1.07)	0.354	1.01 (0.94 to 1.09)	0.749

TABLE 2 (Continued)

	MR (95% CI)	MR (95% CI)	*p*	MR (95% CI)	*p*	MR (95% CI)	*p*	MR (95% CI)	*p*
HOMA-IR[a]									
Model 1	Ref.	1.04 (0.93 to 1.17)	0.466	1.18 (1.01 to 1.39)	0.041	1.05 (0.93 to 1.17)	0.442	1.09 (0.92 to 1.29)	0.307
Model 2	Ref.	1.03 (0.92 to 1.15)	0.604	1.19 (1.01 to 1.40)	0.039	1.07 (0.95 to 1.20)	0.249	1.15 (0.97 to 1.36)	0.120
Model 3	Ref.	1.04 (0.94 to 1.16)	0.472	1.14 (0.98 to 1.33)	0.084	1.04 (0.93 to 1.15)	0.505	1.08 (0.92 to 1.27)	0.367

Note: Model 1: Adjusted for sex, age, study, study center, and parental highest education; Model 2: Model 1 + season, pubertal stage, sedentary, MVPA, depression, fasting status (except for HOMA-IR), total EI, and carbohydrate intake; and Model 3: Model 2 + FMI. $P < 0.007$ are highlighted in bold, which remained significant after Bonferroni correction using the Nyholt method.

Abbreviations: DBP, diastolic blood pressure; EI, energy intake; FMI, fat mass index; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; LDL, low-density lipoprotein cholesterol; MR, means ratio; MVPA, moderate-to-vigorous physical activity; Ref., reference; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

[a]HOMA-IR available for 505 participants.

corrected, two-sided α level of 0.007 (0.05/7; online Supporting Information Methods). Given the highly skewed distribution of hs-CRP, it was not tested in linear models.

To explore the vulnerable/extreme subgroups of cardiometabolic outcomes, logistic regression models were used to assess associations among sleep clusters and dichotomous cardiometabolic markers (high FMI, high BP, high TG, low HDL, high hs-CRP, and high HOMA-IR), with the same adjustment levels as in linear models. Results were described as odds ratios (OR) with 95% CI. Bonferroni correction was applied with the Nyholt method [24], yielding a two-sided α level of 0.010 (0.05/5).

Additionally, the interaction effects among sleep clusters and sex were tested, followed by sex-stratified analyses. The following two sensitivity analyses were performed: 1) restricted to only fasting participants; and 2) sleep clusters were identified by sleep characteristics only on weekdays. Multiple imputation by sex was applied to some confounders with missing values (pubertal stage, sedentary, MVPA, depression, total EI, and carbohydrate intake) using the R package "mice" [26].

RESULTS

The overall prevalence of high BP, high TG, low HDL, and high hs-CRP was 18.9%, 11.9%, 7.7%, and 20.0%, respectively (Table 1). Male individuals had a higher prevalence of high BP, high TG, and low HDL than female individuals, but female individuals had higher FMI, TC, and LDL than male individuals ($p < 0.05$).

Five sleep clusters were identified and named by their characteristics: "good sleep" ($n = 337$; average total sleep time = 7.6 h); "delayed sleep phase" ($n = 244$; 7.2 h); "sleep irregularity and variability" ($n = 108$; 6.9 h); "fragmented sleep" ($n = 313$; 6.9 h); and "prolonged sleep latency" ($n = 88$; 6.9 h; Table 1, Table S2). Figure 2 displays the distributions of sleep characteristics in a week in each sleep cluster. The good sleep cluster was characterized by higher total sleep time and sleep efficiency. The delayed sleep phase cluster was characterized by higher sleep midpoint timing, SD in sleep midpoint timing, and sleep efficiency. The sleep irregularity and variability cluster exhibited higher SD in most sleep characteristics such as total sleep time, sleep midpoint timing, and higher time awake per hour after sleep onset. Furthermore, the fragmented sleep cluster had higher time awake and awakenings per hour after sleep onset, whereas the prolonged sleep latency cluster had higher sleep latency, SD in sleep latency, and time awake per hour after sleep onset. Figure S4 demonstrates the stability and robustness of the identified sleep clusters in the present study by demonstrating that the distributions of sleep characteristics only during weekdays were similar to those of the entire week (Figure 2). Table S3 shows the participant characteristics in five sleep clusters.

In linear analyses, compared with the good sleep cluster, the prolonged sleep latency cluster was significantly associated with increased sex-scaled FMI (β = 0.39, 95% CI: 0.15–0.62; Model 2, Table 2). The sleep irregularity and variability cluster was associated

TABLE 3 Associations among sleep clusters and dichotomous cardiometabolic risk factors in adolescents

Total (1090)	Good sleep (337)	Delayed sleep phase (244)		Sleep irregularity and variability (108)		Fragmented sleep (313)		Prolonged sleep latency (88)	
Outcomes	**OR (95% CI)**	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
High FMI									
No. of cases (%)	72 (21.4)	63 (25.8)		27 (25.0)		82 (26.2)		28 (31.8)	
Model 1	Ref.	1.22 (0.83–1.81)	0.312	1.13 (0.68–1.89)	0.644	1.32 (0.90–1.92)	0.153	1.60 (0.95–2.72)	0.080
Model 2	Ref.	1.13 (0.75–1.68)	0.565	1.22 (0.72–2.07)	0.468	1.46 (0.99–2.15)	0.059	1.98 (1.14–3.45)	0.016
High BP									
No. of cases (%)	59 (17.5)	48 (19.7)		19 (17.6)		65 (20.8)		15 (17.0)	
Model 1	Ref.	1.03 (0.67–1.59)	0.877	0.89 (0.50–1.59)	0.686	0.97 (0.65–1.47)	0.903	0.79 (0.42–1.50)	0.469
Model 2	Ref.	1.09 (0.70–1.69)	0.708	0.86 (0.47–1.56)	0.616	1.00 (0.66–1.53)	0.999	0.77 (0.40–1.49)	0.440
Model 3	Ref.	1.09 (0.70–1.71)	0.699	0.79 (0.43–1.46)	0.453	0.92 (0.60–1.42)	0.716	0.64 (0.33–1.25)	0.192
High TG									
No. of cases (%)	31 (9.2)	23 (9.4)		21 (19.4)		42 (13.4)		13 (14.8)	
Model 1	Ref.	0.98 (0.55–1.73)	0.932	2.29 (1.24–4.22)	**0.008**	1.32 (0.79–2.20)	0.282	1.59 (0.79–3.24)	0.197
Model 2	Ref.	1.07 (0.59–1.93)	0.827	2.35 (1.24–4.48)	**0.009**	1.35 (0.79–2.29)	0.271	1.61 (0.76–3.39)	0.212
Model 3	Ref.	1.04 (0.57–1.90)	0.890	2.26 (1.18–4.34)	0.014	1.27 (0.74–2.16)	0.386	1.41 (0.67–3.00)	0.368
Low HDL									
No. of cases (%)	22 (6.5)	18 (7.4)		8 (7.4)		29 (9.3)		7 (8.0)	
Model 1	Ref.	0.96 (0.50–1.85)	0.897	0.99 (0.42–2.33)	0.986	1.07 (0.59–1.95)	0.828	1.03 (0.41–2.55)	0.954
Model 2	Ref.	0.98 (0.50–1.92)	0.950	1.00 (0.42–2.40)	0.999	1.12 (0.60–2.09)	0.711	1.00 (0.39–2.55)	0.996
Model 3	Ref.	0.97 (0.49–1.94)	0.939	0.88 (0.36–2.16)	0.783	1.01 (0.54–1.90)	0.978	0.79 (0.30–2.06)	0.627
High hs-CRP									
No. of cases (%)	62 (18.4)	53 (21.7)		27 (25.0)		63 (20.1)		13 (14.8)	
Model 1	Ref.	1.19 (0.78–1.80)	0.420	1.42 (0.84–2.40)	0.187	1.16 (0.77–1.73)	0.482	0.74 (0.38–1.43)	0.367
Model 2	Ref.	1.18 (0.77–1.80)	0.445	1.39 (0.82–2.38)	0.225	1.15 (0.76–1.74)	0.520	0.71 (0.36–1.40)	0.321
Model 3	Ref.	1.17 (0.76–1.82)	0.471	1.29 (0.74–2.25)	0.367	1.03 (0.67–1.59)	0.883	0.53 (0.26–1.08)	0.080
High HOMA-IR[a]									
No. of cases (%)	37 (23.3)	28 (22.4)		13 (29.5)		37 (27.2)		13 (31.7)	
Model 1	Ref.	0.99 (0.56–1.75)	0.966	1.41 (0.66–3.01)	0.373	1.23 (0.71–2.12)	0.457	1.64 (0.76–3.55)	0.212
Model 2	Ref.	0.90 (0.50–1.62)	0.721	1.59 (0.72–3.48)	0.251	1.48 (0.83–2.61)	0.182	2.70 (1.17–6.25)	0.021
Model 3	Ref.	0.92 (0.49–1.72)	0.801	1.45 (0.64–3.28)	0.367	1.34 (0.73–2.46)	0.339	2.32 (0.96–5.63)	0.064

Note: Model 1: Adjusted for sex, age, study, study center, and parental highest education; Model 2: Model 1 + season, pubertal stage, sedentary, MVPA, depression, fasting status (except for HOMA-IR), total EI, and carbohydrate intake; and Model 3: Model 2 + FMI. $P < 0.01$ are highlighted in bold, which remained significant after Bonferroni correction using the Nyholt method.

Abbreviations: BP, blood pressure; EI, energy intake; FMI, fat mass index; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; MVPA, moderate-to-vigorous physical activity; OR, odds ratio; Ref., reference; TG, triglycerides.

[a]High HOMA-IR in 505 participants.

with higher HOMA-IR (MR = 1.19, 95% CI: 1.01–1.40, Model 2); however, it was nonsignificant after adjustment for FMI. No significant interaction with sex was found. Male and female individuals within the prolonged sleep latency cluster had higher FMI (β = 0.38, 95% CI: 0.01–0.75; β = 0.41, 95% CI: 0.10–0.72), respectively, but these associations were not significant after multiple testing correction (Table S4).

In logistic analyses, the sleep irregularity and variability cluster was associated with increased odds of high TG (OR = 2.35, 95% CI: 1.24–4.48, Model 2); however, it was not significant after adjustment for FMI and multiple testing correction (Table 3). The association of the prolonged sleep latency cluster with high FMI (OR = 1.98, 95% CI: 1.14–3.45; Model 2, Table 3) was detected, but it did not reach the significance threshold after multiple testing correction. Additionally, the prolonged sleep latency cluster was associated with high HOMA-IR (OR = 2.70, 95% CI = 1.17–6.25; Model 2, Table 3), but it was nonsignificant after adjustment for FMI. A significant interaction effect between sex and the sleep irregularity and variability cluster on high TG was observed ($p = 0.002$), restricting this association only to male individuals (OR = 9.50, 95% CI: 3.22–28.07; Figure 3, Table S5). In female individuals, the association between the prolonged sleep latency cluster and high FMI (OR = 2.23, 95% CI: 1.05–4.72), as well as the association between sleep irregularity and variability cluster and high hs-CRP (OR = 2.05, 95% CI: 1.02–4.14), were observed, but they were nonsignificant after multiple testing correction (Figure 3, Table S5).

In sensitivity analyses, the overall findings did not change substantially when considering only fasting adolescents (Tables S6 and S7) and when sleep clusters were limited to being defined based on sleep characteristics on weekdays only (Tables S8 and S9).

DISCUSSION

Based on 1090 adolescents, five sleep clusters, i.e., "good sleep," "delayed sleep phase," "sleep irregularity and variability," "fragmented sleep," and "prolonged sleep latency," were identified by applying cluster analysis across 12 accelerometry-derived sleep characteristics. The prolonged sleep latency cluster was associated with increased FMI. Furthermore, the sleep irregularity and variability cluster was associated with high TG (≥1.7 mmol/L) only in male individuals, but this finding was not replicated in linear models.

We identified five sleep clusters using 12 sleep characteristics reflecting sleep quantity, quality, schedule, variability, and regularity. Several studies have identified sleep patterns by comprehensively considering multiple objectively assessed sleep characteristics, including cluster analysis [10, 27], latent class analysis [28, 29], and composite sleep scores considering self-reported sleep behaviors [30], but only a few studies have been conducted in children and adolescents. Matricciani et al. used cluster analysis to identify four sleep clusters (overall good sleepers, short sleepers, late to bed, and long sleepers) in

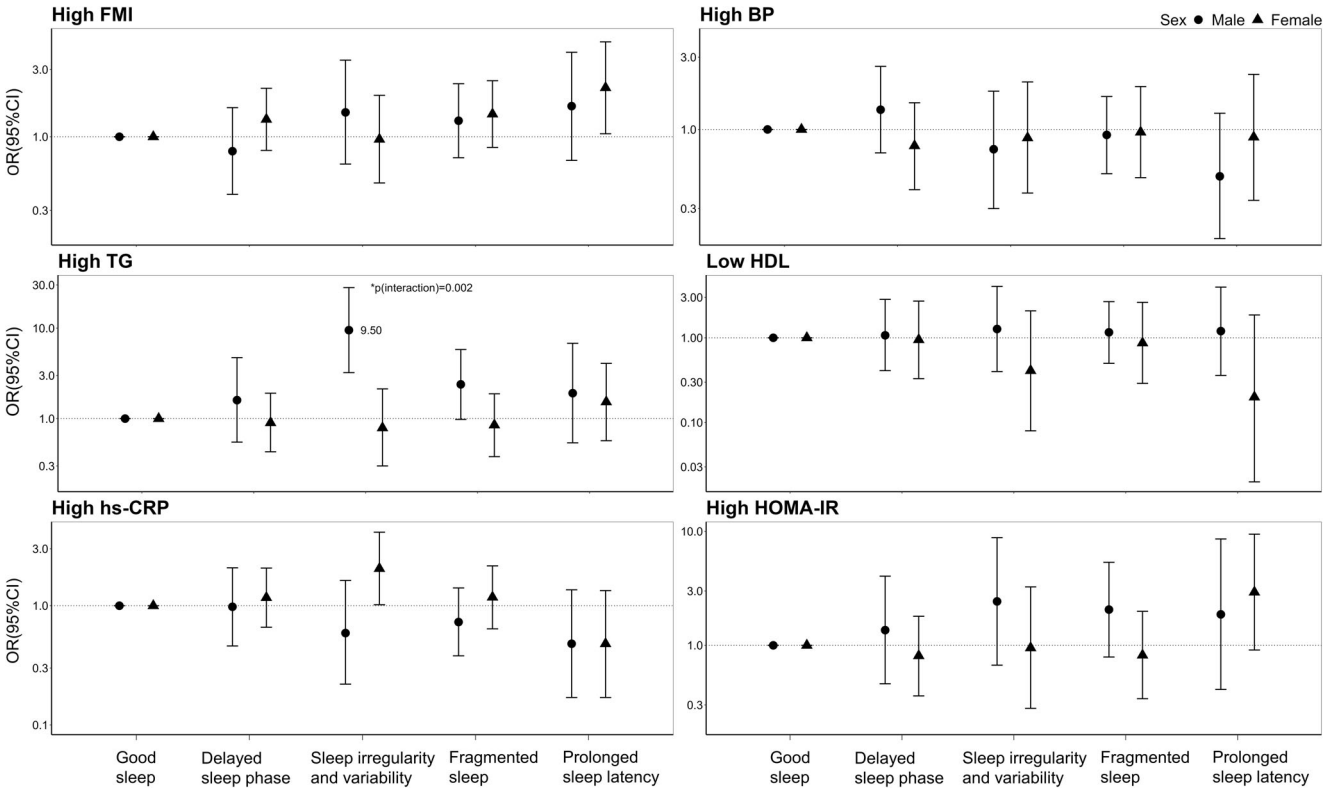

FIGURE 3 Associations among sleep clusters and dichotomous cardiometabolic risk factors in adolescents by sex. BP, blood pressure; FMI, fat mass index; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; hs-CRP, high-sensitivity C-reactive protein; OR, odds ratio; TG, triglycerides.

1043 Australian children aged 11 to 12 years, using four accelerometry-measured sleep characteristics (period, efficiency, midpoint timing, and sleep period variability) [10]. Furthermore, Thumann et al. applied latent class analysis to classify four sleep subtypes (optimal sleep, early birds, short sleep duration, and poor sleep quality) among 559 European children aged 9 to 16 years, using five sleep characteristics (duration, efficiency, latency, reported wake-up time, and reported lights-off time) [29]. Other studies have detected various sleep patterns in adults, but they all identified a cluster or group named good sleep or healthy sleep [28, 30]. Our findings provided further insights into more diverse sleep patterns by additionally including time awake, awakenings, sleep latency, and their variabilities because we were able to classify sleep profiles labeled fragmented sleep, prolonged sleep latency, and sleep irregularity and variability. Notably, the identified delayed sleep phase cluster clearly presented the common phenotype of delayed sleep phase disorder in adolescents [31]. Furthermore, to enhance comparability among participants with varying total sleep time and effectively capture distinct sleep patterns, we used the time awake per hour after sleep onset (ratio of WASO to (total sleep time + WASO/60)) [12] rather than relying solely on WASO. This standardized assessment approach was also applied to the awakenings per hour after sleep onset.

The prolonged sleep latency cluster was significantly associated with increased FMI in linear models, which was also observed in logistic models but was nonsignificant after multiple testing correction, possibly due to lower power. Previous studies have demonstrated an association between short sleep and childhood obesity, but only a few studies have examined the impact of objective sleep latency, an aspect leading to sleep loss, on obesity [8]. One study showed no association of accelerometry-measured long sleep latency with BMI *z* scores among 107 Swedish children aged 2 to 6 years [32]. Moreover, Thumann et al. reported that accelerometry-measured sleep latency was not associated with BMI *z* scores among 559 European children aged 9 to 16 years [29]. However, in our study, the prolonged sleep latency cluster ($n = 88$) was characterized by extremely high sleep latency (46.4 min; Table S2) compared with the other four sleep clusters (13.8–18.9 min). Possible mechanisms for this association may include the following: 1) prolonged sleep latency can cause frustration, anxiety, or stress, leading to emotional eating, preference for energy-dense foods, and increased calorie intake [3, 33]; 2) prolonged sleep latency may delay the onset of the first sleep stage and reduce time spent in deep sleep (third sleep stage), impacting physical restoration and leading to fatigue and decreased motivation for PA [34]; and 3) disruption of hormonal balance such as cortisol due to prolonged sleep latency can impact EI and expenditure [3].

Male individuals within the sleep irregularity and variability pattern were at increased odds of high TG. Similarly, Spruyt et al. found that accelerometry-determined sleep duration variability during school days was correlated with TG among 47 children with obesity aged 4 to 10 years [35]. Duan et al. also observed a relationship between short sleep and high TG (≥1.24 mmol/L) only in adolescent boys [36]. Furthermore, a recent review supported associations of greater sleep variability and irregularity with obesity and adverse cardiometabolic health in adolescence [7]. The underlying mechanism may involve sociocultural and biological influences. Adolescents within the sleep irregularity and variability cluster may have irregular breakfast behaviors, which were associated with higher TG [7, 37]. Additionally, it may be explained by increased absorption of dietary lipids with increased *de novo* synthesis of TG in the liver or decreased ability to catabolize absorbed dietary fat in male individuals with sleep deprivation [38]. Moreover, in our study, male individuals with a sleep irregularity and variability pattern were more likely to be in late or postpuberty (70.6% compared with 55.9% in the good sleep cluster), whereas no difference in female individuals was found. This suggests that, in male individuals with a sleep irregularity and variability pattern, puberty may start earlier, leading to increased testosterone and decreased sex hormone-binding globulin, and may potentially affect TG level [39]. However, the causality needs to be verified to determine whether pubertal hormonal changes drive sleep behaviors changes [40].

Although we found a significant association of sleep irregularity and variability cluster with high TG (≥1.7 mmol/L) in male individuals, this was not confirmed in linear analyses. We further explored potential reasons. The median TG values were similar across five sleep clusters, but the prevalence of high TG in the sleep irregularity and variability cluster (19.4%; Table S3) was higher than in other sleep clusters (9.2%–14.8%). Additionally, this finding was only found in male individuals and was consistent in fasting male individuals (Figure S5). Regarding the cutoff for TG, the IDF recommended that elevated TG (≥1.7 mmol/L) was most commonly observed in adults with metabolic syndrome, and using adult levels was a wise, easy-to-apply definition to identify children and adolescents at increased risk [16]. Because linear models can only discover differences in the mean TG, logistic models suggested a higher prevalence of extreme values of TG, which could point toward vulnerable subgroups at risk.

Notably, the prolonged sleep latency cluster and the sleep irregularity and variability cluster seemed to be associated with higher insulin resistance, possibly due to increased adiposity, because associations were nonsignificant after adjustment for FMI. The relationship among sleep, adiposity, and insulin resistance may be bidirectional and potentially causal [41]. Sleep disturbance affects metabolic pathways, increasing insulin resistance, potentially reducing energy expenditure, and boosting appetite. Conversely, psychological and endocrine abnormalities in individuals with obesity and/or diabetes disrupt sleep, creating a harmful cycle.

This study investigated associations among sleep patterns identified by cluster analysis and cardiometabolic health in a large adolescent population, with accelerometry-measured sleep data and a comprehensive assessment of cardiometabolic risk factors. However, some limitations should be noted. First, our cross-sectional, observational study was unable to infer causality. Notably, our previous study found a bidirectional association between reported sleep difficulty and overweight/obesity from adolescence to young adulthood [42]. Second, we used sex-specific upper quartiles to dichotomize FMI, HOMA-IR, and hs-CRP to improve comparability across outcomes because no standard thresholds are available in adolescents, which

may limit comparability with other studies. Third, although the accelerometer is a practical approach to measure sleep in epidemiological research [43], it differs from polysomnography (gold standard) [44]. Fourth, daytime sleep data were unavailable. Fifth, we assumed that 1-week sleep measurements estimated habitual sleep patterns over a longer period [43], although the measurements of cardiometabolic risk factors preceded sleep assessments in our study, with a mean age difference of 0.36 years. Sixth, caution should be exercised when generalizing our findings to other age groups or cultures because our participants are German adolescents aged 14 to 16 years.

CONCLUSION

We identified five distinctive sleep patterns by cluster analysis and found that the cluster describing "prolonged sleep latency" pattern was associated with higher fat mass in adolescents. Additionally, the cluster describing "sleep irregularity and variability" pattern seemed to be associated with high TG in male individuals. Our results suggest that improvements in sleep latency, variability, and regularity may enrich existing sleep-targeted intervention strategies for cardiometabolic health that mainly focus on improving adequate sleep.O

AUTHOR CONTRIBUTIONS

Mingming Wang conceptualized and designed the study, conducted the statistical analyses, drafted the initial manuscript, and revised and finalized the manuscript. Claudia Flexeder conceptualized and designed the study, contributed to data acquisition and interpretation, supervised the statistical analyses, and critically reviewed and revised the manuscript. Carla P Harris contributed to data interpretation, supervised the statistical analyses, and critically reviewed and revised the manuscript. Elisabeth Thiering, Sibylle Koletzko, Carl-Peter Bauer, Gerd Schulte-Körne, Andrea von Berg, Dietrich Berdel, Joachim Heinrich, Holger Schulz, and Tamara Schikowski contributed to data acquisition and interpretation and critically reviewed and revised the manuscript. Annette Peters contributed to study design and data interpretation and critically reviewed and revised the manuscript. Marie Standl conceptualized and designed the study, contributed to data acquisition and interpretation, supervised the statistical analyses and the manuscript process, and critically reviewed and revised the manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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CONFLICT OF INTEREST STATEMENT

The authors declared no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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