




## Accelerometry-assessed sleep and liver health in adolescents and adults: Links to liver enzymes, MASLD, and MRI-derived liver fat

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### ABSTRACT

**Background:** To investigate associations of accelerometry-assessed sleep characteristics with liver enzymes and liver fat in adolescents and adults.

**Methods:** We analyzed data from four German cohorts: GINIplus and LISA (n = 1132, 14–16 years), KORA-Fit (n = 1318, 53–74 years), and KORA-MRI (n = 108, 48–67 years). Eleven accelerometry-assessed sleep characteristics captured sleep quantity, efficiency, fragmentation, latency, and timing. Liver enzymes included alanine aminotransferase (ALT), aspartate aminotransferase, and gamma-glutamyl transferase (GGT). Adult liver fat markers were steatotic liver disease (SLD) and metabolic dysfunction-associated SLD (MASLD, plus  $\geq 1$  cardiometabolic risk factor and without excessive alcohol intake), defined by fatty liver index (FLI,  $\geq 60$ ) or 3T-Magnetic Resonance Imaging (MRI) derived proton density fat fraction (PDFF,  $\geq 5\%$ ). Linear and logistic regression models were evaluated.

**Results:** Time awake per hour after sleep onset (WASO/h) was associated with higher ALT both in adolescents (percentage change [95 % confidence interval, CI] per interquartile range [IQR]: 3.82 [0.86, 6.87]) and adults (3.05 [0.38, 5.78]). In adults, WASO/h was associated with increased odds of SLD-FLI (odds ratio [95 %CI] per IQR: 1.47 [1.26, 1.71]), MASLD-FLI (1.61 [1.34, 1.94]), SLD-PDFF (2.10 [1.16, 3.78]), and MASLD-PDFF (3.32 [1.47, 7.52]). Similar results were observed for poor sleep efficiency and sleep fragmentation index. However, these associations lost significance after body mass index (BMI) adjustment. Significant interactions between WASO/h and BMI groups were observed for ALT, GGT, and SLD-FLI.

**Conclusions:** Objectively measured sleep fragmentation was associated with increased liver enzymes in adolescents and hepatic steatosis in adults, with BMI potentially mediating or modifying these associations.

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## 1. Introduction

Steatotic liver disease (SLD), a new term covering various forms of hepatic steatosis, is increasingly recognized as a significant public health challenge, with the global prevalence of 37.5 % [1]. Metabolic dysfunction-associated steatotic liver disease (MASLD), a major subtype of SLD, expands the definition of nonalcoholic fatty liver disease (NAFLD) by including at least one of five cardiometabolic risk factors [2]. A recent study reported that MASLD and NAFLD were similar, with no observed differences in mortality, suggesting the interchangeable use of the two terms [3]. Elevated liver enzymes, such as alanine and aspartate aminotransferase (ALT, AST), and  $\gamma$ -glutamyl transferase (GGT), indicate liver injury, fatty liver, and impaired oxidative stress processes, and are commonly used as surrogate measures of SLD in clinical research [4]. Additionally, cost-effective markers like the fatty liver index (FLI) are well-validated for large-scale studies [5], and magnetic resonance imaging (MRI) provides a precise and non-invasive, yet expensive measure of liver fat content [6].

Liver is a highly rhythmic organ, regulating daily functions through its circadian clock [7]. Sleep-wake problems disrupt the circadian system, increasingly recognized as a risk factor for cardiovascular disease [8] and chronic liver diseases [9]. Sleep health is a multidimensional construct including duration, efficiency, timing, and wake time, and can be objectively measured using accelerometry, which has been validated in large population studies [10]. Existing research has shown that short sleep duration and poor sleep quality were significantly associated with MASLD in adults, yet these sleep variables were all assessed through reported questionnaires [11,12]. Regarding the objectively measured sleep characteristics, several papers only examined their associations with cardiometabolic risk factors in general population, but not with liver related markers [13,14]. One study found that cirrhosis patients had objectively measured lower sleep efficiency and higher wake time after sleep onset, compared to healthy controls [15]. Furthermore, obstructive sleep apnea (OSA), characterized by intermittent airway obstruction and sleep fragmentation, was linked to elevated liver enzymes in both children and adults [16,17].

To the best of our knowledge, no study has investigated the associations between objectively assessed multidimensional sleep characteristics and SLD-related markers among general populations of children, adolescents, and adults. This study aimed to evaluate cross-sectional associations of accelerometry-assessed sleep characteristics: (1) with liver enzymes in 1132 adolescents from the GINIplus and LISA birth cohorts; (2) with liver enzymes, SLD and MASLD defined by FLI in 1318 adults from the KORA-Fit cohort; and (3) with SLD and MASLD defined by MRI-derived liver fat in 108 adults from the KORA-MRI cohort.

## 2. Methods

### 2.1. Study population

We obtained data from the 15-year follow-up of two ongoing birth cohorts GINIplus and LISA, as well as two adult cohorts, KORA-Fit and KORA-MRI. GINIplus is the German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development birth cohort, which recruited 5991 healthy newborns in Munich and Wesel during 1995–1998 [18]. LISA is the Influence of Lifestyle factors on the development of the Immune System and Allergies in East and West Germany birth cohort, which included 3094 healthy newborns in Munich, Wesel, Leipzig, and Bad Honnef in 1997–1999 [18]. During the 15-year follow-up, a total of 1682 participants completed accelerometry for sleep and physical activity (PA) assessments. KORA-Fit is a follow-up examination conducted in 2018–2019, building on four cross-sectional baseline surveys (S1: 1984–1985, S2:1989–1990, S3: 1994–1995, and S4: 1999–2001) from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study [19]. Of the recruited 3059 participants in KORA-Fit, 1589

participants completed accelerometry measurements. KORA-MRI is a sub-study where participants underwent whole-body 3T- MRI conducted in 2013–2014, shortly after the second follow-up examination (FF4) of the KORA S4 survey [20]. Since a key objective of the KORA-MRI study was to evaluate subclinical disease across the glycemic spectrum, it included a large proportion of participants with prediabetes (26 %) and diabetes (14 %). Of the recruited 400 participants in KORA-MRI, 119 participants had complete accelerometry measurements at FF4.

Finally, we included 1132 adolescents from the GINIplus and LISA cohorts, 1318 adults from the KORA-Fit cohort, and 108 adults from the KORA-MRI cohort, all with complete information on accelerometry-assessed sleep, liver health markers, and confounders. More details about inclusion and exclusion criteria are provided in Fig. S1. All studies received approvals from the respective local ethics committees, and all participants (and families for birth cohorts) provided written informed consent. Minimum detectable effect analyses were performed for each dataset to assess the smallest effect size that could be reliably detected (see Method S1).

### 2.2. Accelerometry-assessed sleep characteristics

#### 2.2.1. Accelerometry

All four cohorts used the triaxial accelerometer (ActiGraph GT3X or wGT3XBT only for KORA-Fit, Pensacola, Florida) to measure participants' nighttime sleep and daytime PA, over seven consecutive days during a typical school or work week. Participants wore accelerometers on their non-dominant wrist at night to assess sleep and on their dominant hip during the day to measure PA, with maintaining activity and sleep diaries. The accelerometry protocol in GINIplus and LISA cohorts has been thoroughly detailed in previous publications [21], and the accelerometry procedure in KORA-Fit was the same as that in KORA-FF4 [22]. Notably, the specific accelerometers and analysis software were described in Method S2.

#### 2.2.2. Sleep characteristics

The accelerometry-measured sleep data were analyzed using the ActiLife software with the Sadeh algorithm [23] for adolescents in GINIplus and LISA cohorts, and with the Cole-Kripke algorithm [24] for adults in KORA-Fit and KORA-MRI cohorts. Measured accelerations were sampled at 30 Hz, converted to proprietary "activity count units", and stored at 1 Hz, then aggregated into 1-min epochs for analysis. The "probability of sleep" was calculated as a score centered around zero for each minute that participants recorded as time-in-bed in their diary. A minute was classified as "asleep" if the score was zero or greater, and as "awake" if the score was below zero [23,24].

The following sleep characteristics averaged across all valid days were used in the current study:

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

8. Awakenings per hour after sleep onset (Awakenings/h), num/h: Awakenings divided by the hours in bed after sleep onset (total sleep time + WASO/60).
9. Movement index: the total of algorithm-scored epochs with one or more activity counts, divided by diary-recorded total time in bed in hours, then multiply by 100 [25].
10. Fragmentation index: the algorithm-scored 1-min periods of sleep divided by all periods of sleep during the sleep period, then multiply by 100 [25].
11. Sleep fragmentation index: the sum of movement index and fragmentation index [25].

Movement index, fragmentation index and sleep fragmentation index were only available in the KORA-Fit cohort. Note that in the GINIplus, LISA, and KORA-MRI cohorts, the diary-recorded “starts in bed” referred to the time participants reported they went to bed, and “starts out bed” to when they got up. In the KORA-Fit cohort, “starts in bed” referred to the time participants reported they fell asleep, and “starts out bed” to when they woke up.

### 2.3. Liver health markers

#### 2.3.1. Liver enzymes

Liver enzymes are continuous ALT, AST, and GGT, as well as dichotomous variables, elevated ALT, elevated AST, and elevated GGT. In adolescents from GINIplus and LISA cohorts, serum ALT (U/L), AST (U/L), and GGT (U/L) were measured using homogenous enzymatic colorimetric methods on a Modular Analytics System (Roche, Mannheim, Germany). They were dichotomized as elevated liver enzymes, based on the published 90th age- and sex-specific percentiles of liver enzyme serum levels in German pediatric population [4]. In adults, serum ALT (U/L), AST (U/L), and GGT (U/L) were measured using a Cobas c702 clinical chemistry analyzer (Roche, Rotkreuz, Switzerland) in KORA-Fit cohort, and using the Roche/Hitachi Cobas® system (Roche, Mannheim, Germany) in KORA-MRI cohort. They were dichotomized as elevated liver enzymes, according to the published cutoffs: ALT: male  $\geq 40$  U/L, female  $\geq 31$  U/L; AST: male  $\geq 37$  U/L, female  $\geq 31$  U/L; GGT: male  $\geq 50$  U/L, female  $\geq 35$  U/L [26].

#### 2.3.2. Fatty liver index (FLI)

The FLI in KORA-Fit and KORA-MRI cohorts was calculated using the formula developed by Bedogni et al. [5].

$$FLI = \left( \frac{e^{0.953 \cdot \log(\text{triglycerides}) + 0.139 \cdot BMI + 0.718 \cdot \log(GGT) + 0.053 \cdot WC - 15.745}}{1 + e^{0.953 \cdot \log(\text{triglycerides}) + 0.139 \cdot BMI + 0.718 \cdot \log(GGT) + 0.053 \cdot WC - 15.745}} \right) \cdot 100$$
 where triglyceride was measured in mg/dL and GGT in U/L, body mass index (BMI) was calculated using weight divided by squared height ( $\text{kg/m}^2$ ), and waist circumference (WC) in cm. The FLI ranges from 0 to 100, with the value  $< 30$  ruling out and the value  $\geq 60$  ruling in fatty liver [5]. The detailed laboratory measurements can be found in previous papers [27,28].

SLD-FLI was defined as  $FLI \geq 60$  in KORA-Fit and KORA-MRI cohorts. MASLD-FLI in KORA-Fit was defined as  $FLI \geq 60$  with at least one of five metabolic risk factors among participants without excessive alcohol intake ( $\geq 30\text{g/day}$  in males and  $\geq 20\text{g/day}$  in females), human immunodeficiency virus (HIV) or hepatitis, systemic corticosteroids or antiarrhythmic drugs ( $N = 1002$ ). MASLD-FLI in the KORA-MRI cohort was defined similarly to that in the KORA-Fit cohort, except that participants with HIV or hepatitis were not excluded due to unavailable information ( $N = 80$ ). The metabolic risk factors included: (1) adiposity:  $BMI \geq 25 \text{ kg/m}^2$  or  $WC > 94/80 \text{ cm}$  (male/female); (2) high blood glucose: fasting serum glucose  $\geq 5.6 \text{ mmol/L}$  or diagnosed diabetes; (3) high blood pressure: systolic/diastolic blood pressure  $\geq 130/85 \text{ mmHg}$  or antihypertensive use; (4) high triglycerides: triglycerides  $\geq 1.70 \text{ mmol/L}$  or intake of lipid-lowering medication; (5) low high-density lipoprotein (HDL) cholesterol: HDL cholesterol  $\leq 1.0/1.3 \text{ mmol/L}$  (male/female) or intake of lipid-lowering medication [2].

#### 2.3.3. MRI-derived liver fat

Participants from the KORA-MRI cohort underwent whole-body MRI using a 3-T MRI scanner (Magnetom Skyra; Siemens AG, Siemens Healthineers, Erlangen, Germany) [20]. Liver fat content, expressed as the proton density fat fraction (PDFF), was measured in the left and right liver lobes applying the high-speed T2-corrected multi-echo sequence [29]. In the current study, we used the arithmetic mean of PDFF in left and right liver lobes as continuous outcome, and defined SLD-PDFF as  $PDFF \geq 5\%$  [6]. MASLD-PDFF was defined as  $PDFF \geq 5\%$  with at least one of five metabolic risk factors among participants without excessive alcohol intake, systemic corticosteroids or antiarrhythmic drugs.

### 2.4. Confounders

In adolescents from GINIplus and LISA cohorts, sex, age, study (GINIplus observation arm, GINIplus intervention arm, and LISA study), study center (Munich, Wesel), season of sleep assessment (spring, summer, autumn, and winter), parental highest education ( $\leq 10$  years,  $> 10$  years), fasting status at blood sampling (yes, no), pubertal stage (pre-, early, or mid-pubertal; late or post-pubertal stage), and total energy intake were collected by questionnaires. Sedentary behavior (hours) and moderate-to-vigorous physical activity (MVPA, minutes) were assessed by the same accelerometry as sleep and averaged over the recording period. The specific definitions have been published previously [13]. Body weight (kilograms) and height (meters) were measured objectively during physical examinations, and BMI was calculated. Overweight or obesity (overweight/obesity) was defined as BMI z-scores  $> 1$  [30].

In adults from KORA-Fit and KORA-MRI cohorts, sex, age, season of sleep assessment (spring, summer, autumn, and winter), education ( $\leq 10$  years,  $> 10$  years), current smoking (non, yes), and alcohol consumption (g/day) were collected by questionnaires. Daytime PA was measured by the same accelerometry as sleep, was categorized into sedentary, light, moderate, and vigorous PA according to triaxial cutoffs by Sasaki [31], then the latter two were merged into MVPA. Weekly averages of sedentary behavior (hours) and MVPA (minutes) were used in the current study. The PA classification details in KORA-MRI have been reported previously [22]. Body weight (kilograms) and height (meters) were measured objectively, with BMI ( $\text{kg/m}^2$ ) calculated to define obesity as  $BMI \geq 30$  [32]. Relevant medical history (only available in KORA-Fit), including liver disease, HIV or hepatitis, as well as medication use, including lipid-lowering, systemic corticosteroids, or antiarrhythmic drugs, were collected by questionnaires with the answer (yes or no).

### 2.5. Statistical analysis

We conducted all statistical analyses using R (version 4.3.1). We presented continuous characteristics as mean  $\pm$  standard deviation, or median [first quartile, third quartile], and categorical characteristics as number (percentage). We used Spearman's rank correlation test to assess correlations within sleep characteristics and within liver enzymes in adolescents (GINIplus and LISA) and adults (KORA-Fit), as well as between FLI and MRI-derived PDFF in adults (KORA-MRI).

To explore associations of sleep characteristics with liver enzymes and elevated liver enzymes in adolescents (GINIplus and LISA) and adults (KORA-Fit), we applied linear and logistic regression models. Percentage (%) change and 95 % confidence interval (CI) from linear models, and odds ratio (OR) and 95 % CI from logistic models were reported for an interquartile range (IQR) increase in sleep characteristics. Since liver enzymes were log-transformed, % change was calculated by the formula:  $(\exp[\beta] - 1) \cdot 100$ , reflecting the mean change in outcomes per unit (IQR) increase in exposures. In adolescents (GINIplus and LISA), two models were performed: Model 1 (main model) was adjusted for sex, age, study, study center, season, parental highest education, sedentary behavior, MVPA, and fasting status; Model 2 was additionally adjusted

for BMI. Two sensitivity analyses were conducted: (1) Model 1 plus adjustment for pubertal stage and total energy intake; (2) excluding non-fasting participants. Interaction effects of sleep characteristics with sex and overweight/obesity status were further tested, followed by stratified analyses. In adults (KORA-Fit cohort), two models were used: Model 1 (main model) was adjusted for sex, age, season, education, sedentary behavior, MVPA, smoking, and alcohol consumption; Model 2 was additionally adjusted for BMI. Two sensitivity analyses were conducted: (1) excluding participants with excessive alcohol; (2) excluding participants with liver disease, HIV or hepatitis, and with lipid-lowering, systemic corticosteroids, or antiarrhythmic drugs. Interaction and stratified analyses by sex, age, and obesity status were further examined.

To investigate associations of sleep characteristics with SLD-FLI and MASLD-FLI in adults (KORA-Fit), we used logistic regression models, presenting results as OR (95 %CI) per IQR increase in sleep characteristics. Since FLI remained non-normally distributed after log-transformation, linear models were not applied. One model was used, with the same adjustments as Model 1 in logistic regression analysis for associations with liver enzymes, as FLI calculation already included BMI. We also used logistic regression models to assess associations of categorical sleep characteristics with SLD-FLI and MASLD-FLI in adults (KORA-Fit). The categorizations of total sleep time, sleep efficiency, time awake after sleep onset were based on the National Sleep Foundation's sleep quality recommendations: first report [33]. The sensitivity analysis was conducted excluding participants with liver disease, HIV or hepatitis, lipid-lowering, systemic corticosteroids, or antiarrhythmic drugs. Interaction and stratified analyses by sex, age, and obesity status were further examined.

To assess associations of sleep characteristics with MRI-derived liver fat in adults (KORA-MRI), we performed linear models on log-transformed PDFF and logistic models on SLD-PDFF and MASLD-PDFF, presenting results as % change (95 %CI) and OR (95 %CI) per IQR increase in sleep characteristics, respectively. Logistic models were also used to examine associations between sleep characteristics and SLD-FLI and MASLD-FLI, for comparison with results on SLD-PDFF and MASLD-PDFF. Two models were applied, with the same adjustments as in logistic regression analysis for associations with liver enzymes in KORA-Fit cohort. The sensitivity analysis was conducted excluding participants with lipid-lowering, systemic corticosteroids, or antiarrhythmic drugs. *P*-values <0.05 were considered statistically significant.

### 3. Results

#### 3.1. Participants characteristics

Table 1 summarizes the characteristics for 1132 adolescents from the GINIplus and LISA birth cohorts, 1318 adults from the KORA-Fit cohort, and 108 adults from the KORA-MRI cohort. Adolescents had lower ALT and GGT levels, with medians of 11.5 U/L and 12.1 U/L, respectively, compared to adults, whose medians were 23.7 U/L and 23.0 U/L in KORA-Fit, and 28.5 U/L and 29.0 U/L in KORA-MRI. AST values were similar between adolescents and adults. In KORA-Fit, the prevalence of SLD-FLI and MASLD-FLI was 36.8 % and 35.3 %, respectively, while in KORA-MRI, the prevalence of SLD-PDFF and MASLD-PDFF was 64.8 % and 62.5 %, respectively.

Adolescents had longer total sleep time (median 7.2 h) than adults (6.7 h in KORA-Fit and 6.9 h in KORA-MRI), but lower sleep efficiency (median 79.9 % vs. 90.3 % and 85.4 %, respectively). Additionally, adolescents experienced longer sleep latency (median 16 min) and WASO (median 89.3 min) compared to adults in KORA-Fit (3.0 and 39.1 min) and in KORA-MRI (7.9 and 62.2 min). Moreover, KORA-Fit included three additional variables related to sleep fragmentation: movement index (median 12.5), fragmentation index (10.6), and sleep fragmentation index (23.6). Fig. S2 illustrates correlations within various sleep characteristics and within three liver enzymes in adolescents (GINIplus and LISA) and adults (KORA-Fit).

**Table 1**

Participants characteristics in adolescents from GINIplus and LISA, and adults from KORA-Fit and KORA-MRI cohorts.

Characteristics	GINIplus and LISA	KORA-Fit	KORA-MRI
N	1132	1318	108
Sex, n(%)			
Male	511 (45.1)	606 (46.0)	59 (54.6)
Female	621 (54.9)	712 (54.0)	49 (45.4)
Age range, years	14.3–16.4	53.0–74.0	48.0–67.0
Age, years	15.2 ± 0.3	62.8 ± 5.5	57.8 ± 5.7
Weight, kg	61.3 ± 11.1	79.2 ± 16.6	82.9 ± 16.1
Height, cm	171.5 ± 8.0	168.4 ± 9.3	170.5 ± 10.6
BMI, kg/m <sup>2</sup>	20.8 ± 3.0	27.9 ± 5.0	28.5 ± 4.7
BMI z-score	0.07 ± 0.98		
Overweight/obesity, n (%)	198 (17.5)	924 (70.1)	86 (79.6)
Obesity, n(%)	32 (2.8)	361 (27.4)	34 (31.5)
Sedentary behavior, hours	8.3 ± 1.4	8.0 ± 1.7	7.9 ± 1.8
MVPA, mins	50.5 ± 26.6	55.4 ± 37.1	54.1 ± 32.1
ALT, U/L	11.5 [9.0, 13.9]	23.7 [18.5, 30.4]	28.5 [19.8, 38.0]
AST, U/L	24.1 [21.1, 27.7]	23.3 [20.1, 27.7]	24.0 [20.0, 31.0]
GGT, U/L	12.1 [10.2, 15.1]	23.0 [16.0, 37.0]	29.0 [17.9, 52.5]
Elevated ALT, n(%)	45 (4.0)	206 (15.6)	31 (28.7)
Elevated AST, n(%)	100 (8.8)	134 (10.1)	21 (19.4)
Elevated GGT, n(%)	149 (13.2)	263 (20.0)	35 (32.4)
FLI		43.5 [19.4, 74.3]	66.87 [34.40, 85.81]
SLD-FLI (≥60), n(%)		485 (36.8)	62 (57.4)
MASLD-FLI (≥60), n(%)		354 (35.3)	44 (55.0)
MRI-derived PDFF, %			7.26 [3.58, 14.19]
SLD-PDFF (≥5 %), n(%)			70 (64.8)
MASLD-PDFF (≥5 %), n (%)			50 (62.5)
Fasting blood, n(%)	529 (46.7)	1318 (100)	108 (100)
Season, n(%)			
Spring	292 (25.8)	449 (34.1)	26 (24.1)
Summer	169 (14.9)	235 (17.8)	30 (27.8)
Autumn	370 (32.7)	297 (22.5)	27 (25.0)
Winter	301 (26.6)	337 (25.6)	25 (23.1)
Parental highest education, n(%)			
≤10 years	353 (31.2)		
>10 years	779 (68.8)		
Study, n(%)			
GINIplus observation	430 (38.0)		
GINIplus intervention	451 (39.8)		
LISA	251 (22.2)		
Study center, n(%)			
Munich	650 (57.4)		
Wesel	482 (42.6)		
Alcohol consumption, g/day		5.7 [0.0, 21.7]	12.3 [2.9, 26.6]
Current smoking, n (%)			
No		1171 (88.8)	91 (84.3)
Yes		147 (11.2)	17 (15.7)
Education, n (%)			
≤10 years		527 (40.0)	44 (40.7)
>10 years		791 (60.0)	64 (59.3)
Total sleep time, hours	7.2 [6.7, 7.6]	6.7 [6.1, 7.2]	6.9 [6.3, 7.3]
Sleep efficiency, %	79.9 [75.7, 83.8]	90.3 [87.0, 92.9]	85.4 [81.9, 87.8]
Sleep latency, mins	16.0 [10.7, 24.2]	3.0 [1.2, 5.0]	7.9 [5.2, 11.3]
Sleep onset timing, 24-h clock	22:56 [22:26, 23:27]	23:23 [22:49, 00:03]	23:28 [22:39, 00:02]
WASO, mins	89.3 [70.4, 114.9]	39.1 [27.6, 54.8]	62.2 [48.1, 79.5]
WASO/h, mins/h	10.1 [8.2, 12.7]	5.4 [3.9, 7.3]	8.0 [6.3, 9.5]
Awakenings, num	25.0 [21.0, 29.0]	14.1 [10.6, 18.0]	18.5 [15.1, 23.3]
Awakenings/h, num/h	2.9 [2.5, 3.3]	1.9 [1.5, 2.4]	2.4 [2.0, 2.8]
Movement index		12.5 [9.9, 15.8]	

(continued on next page)



Table 1 (continued)

Characteristics	GINIplus and LISA	KORA-Fit	KORA-MRI
Fragmentation index		10.6 [7.6, 13.9]	
Sleep fragmentation index		23.6 [18.2, 29.2]	

The results are presented as mean ± standard deviation, median [first quartile, third quartile], or number (percentage). Abbreviation: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FLI, fatty liver index; GGT, γ-glutamyl transferase; GINIplus, German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development; KORA-Fit, a follow-up examination of participants conducted in 2018–2019, building on four cross-sectional baseline surveys (S1: 1984–1985, S2:1989–1990, S3: 1994–1995, and S4: 1999–2001) from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study. KORA-MRI, a sub-study where participants underwent whole-body 3T-Magnetic Resonance Imaging (MRI) conducted in 2013–2014, shortly after second follow-up examination of the KORA S4 survey; 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; MASLD, metabolic dysfunction-associated steatotic liver disease; PDFF, proton density fat fraction; SLD, steatotic liver disease; WASO, time awake after sleep onset; WASO/h, time awake per hour after sleep onset.

Elevated ALT, AST, GGT in adolescents were categorized by a published 90th age- and sex-specific percentiles of liver enzyme serum levels in German pediatric population. Elevated liver enzymes in adults were categorized by published cutoffs: ALT: male ≥40 U/L; female ≥31 U/L; AST: male ≥37 U/L; female ≥31 U/L; GGT: male ≥50 U/L; female ≥35 U/L. SLD-FLI was defined as FLI ≥60. MASLD-FLI was defined as FLI ≥60 with at least one of five cardiometabolic risk factors among participants without excessive alcohol intake, human immunodeficiency virus (HIV) or hepatitis, systemic corticosteroids or antiarrhythmic drugs. MASLD-PDFF was defined as PDFF ≥5 % with at least one of five cardiometabolic risk factors among participants without excessive alcohol intake, systemic corticosteroids or antiarrhythmic drugs. SLD-FLI was defined as FLI ≥60. SLD-PDFF was defined as PDFF ≥5 %.

3.2. Associations of sleep characteristics with liver enzymes in adolescents and adults

Fig. 1 shows associations between multiple sleep characteristics and three liver enzymes in adolescents (GINIplus and LISA) and adults (KORA-Fit). Among adolescents, an IQR increase in WASO and WASO/h was significantly associated with higher ALT (% change [95 % CI]: 3.12 [0.27, 6.04] and 3.82 [0.86, 6.87]), while sleep efficiency was inversely associated with ALT (−3.33 [−6.08, −0.49], Model 1). However, these associations were no longer significant after adjustment for BMI (Model 2). Among adults, an IQR increase in WASO and WASO/h was significantly associated with higher ALT (% change [95 % CI]: 4.27 [1.54, 7.08] and 3.05 [0.38, 5.78]), but also with higher GGT (6.54 [2.39, 10.85] and 5.45 [1.41, 9.65], Model 1). An IQR increase in sleep efficiency was inversely associated with ALT (% change [95 % CI]: −2.97 [−5.54, −0.34]) and GGT (−4.85 [−8.58, −0.97] Model 1). These associations became non-significant after BMI adjustment (Model 2). Additionally, an IQR increase in movement index and sleep fragmentation index was associated with higher ALT and GGT, remaining significantly linked to higher GGT even after adjustment for BMI (% change [95 % CI]: 5.67 [1.64, 9.86] and 4.99 [0.68, 9.49], Model 2). Notably, higher total sleep time in adults was associated with higher ALT (% change [95 % CI]: 3.28 [0.50, 6.13], Model 2). When examining the dichotomized liver enzymes (Table S1) and sensitivity analyses (Table S2, Table S3), the main findings remained almost similar.

The results of the interaction and stratified analysis are visually presented in Figure S3 (sex), Fig. S4 (BMI groups), and Fig. S5 (age groups only in adults). It is worth noting that several sleep variables related to sleep fragmentation had significant interaction effect with overweight/obesity status on ALT and GGT in adolescents (Fig. S4). Fig. 2 illustrates that adolescents with overweight/obesity had stronger

associations of increased WASO/h with higher ALT and GGT, compared to those without overweight/obesity (*P*-interaction <0.05).

3.3. Associations of sleep characteristics with SLD-FLI and MASLD-FLI in adults

Fragmented sleep characteristics were significantly associated with higher odds of SLD-FLI and MASLD-FLI in adults from KORA-Fit study (Table 2). For example, for each IQR increase, the OR (95 % CI) of SLD-FLI was 1.54 (1.32, 1.80) for WASO, 1.47 (1.26, 1.71) for WASO/h, and 1.41 (1.20, 1.66) for sleep fragmentation index. Similarly, the OR (95 % CI) per IQR increase of MASLD-FLI was 1.69 (1.41, 2.02) for WASO, 1.61 (1.34, 1.94) for WASO/h, and 1.58 (1.30, 1.92) for sleep fragmentation index. An IQR increase in sleep latency was also significantly associated with higher odds of SLD-FLI in adults (OR [95 % CI]: 1.18 [1.02, 1.36]). Conversely, an IQR increase in sleep efficiency was linked to lower odds of SLD-FLI (OR [95 % CI]: 0.67 [0.57, 0.78]) and MASLD-FLI (OR [95 % CI]: 0.61 [0.51, 0.74]) in adults. Similar results were observed when examining categorical sleep characteristics (Fig. 3). Compared to ≤20 min of WASO, more than 40 min was significantly associated with higher odds of SLD-FLI (OR [95 % CI]: 1.84 [1.23, 2.79]) and MASLD-FLI [2.09 (1.31, 3.41)] in adults. Likewise, adults in the highest quartile (Q4) of the sleep fragmentation index had higher odds of SLD-FLI (OR [95 % CI]: 1.79 [1.27, 2.52]) and MASLD-FLI (2.00 [1.35, 2.96]) compared to those in the lowest quartile (Q1).

These associations remained largely unchanged in the sensitivity analyses (Table S4), after excluding those with liver-related conditions and with relevant medication use. In the interaction and stratified analysis (Table S5), the direct association between WASO/h and SLD-FLI, as well as the inverse association between sleep efficiency and SLD-FLI, were significant only among participants with obesity (both *P*-interaction <0.05). In adults with obesity, higher WASO/h was associated with increased odds of SLD-FLI (OR [95 % CI]: 1.83 [1.08, 3.09]), whereas it was not significant in those with non-obesity (1.06 [0.85, 1.31]).

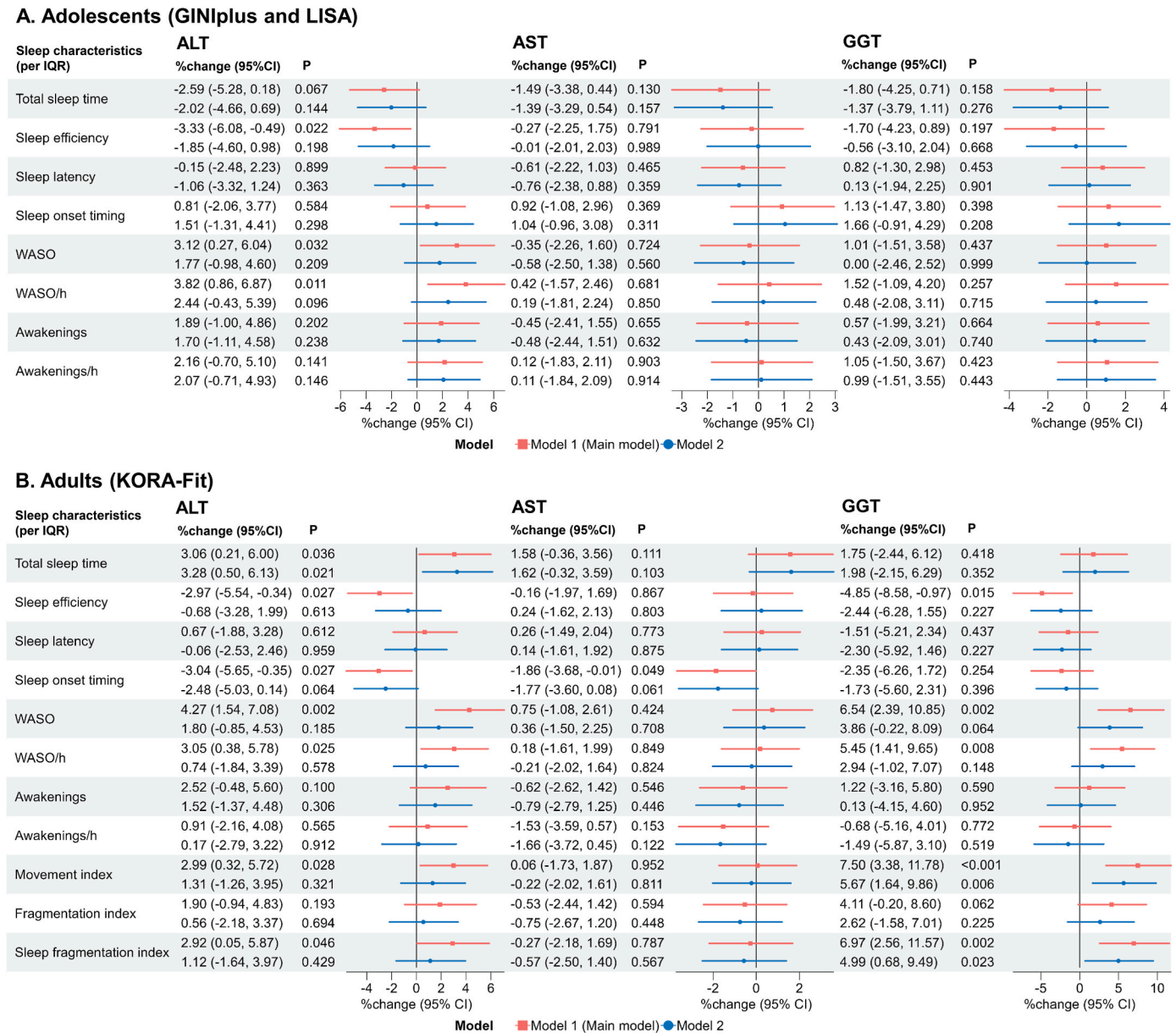
3.4. Associations of sleep characteristics with SLD-PDFF and MASLD-PDFF in adults

Table 3 presents the associations between sleep characteristics and SLD-PDFF and MASLD-PDFF in 108 adults (KORA-MRI). WASO and WASO/h were significantly associated with increased odds of SLD-PDFF (OR [95 % CI] per IQR increase: 2.01 [1.10, 3.69] and 2.10 [1.16, 3.78], Model 1). Similar associations with MASLD-PDFF were observed for both WASO (3.36 [1.40, 8.04]) and WASO/h (3.32 [1.47, 7.52], Model 1). Additionally, an IQR increase in sleep efficiency was linked to lower odds of SLD-PDFF (OR [95 % CI]: 0.43 [0.23, 0.81]) and MASLD-PDFF (0.27 [0.11, 0.65], Model 1). However, these associations were not significant after adjustment for BMI (Model 2).

Notably, sleep latency was significantly associated with higher MRI-derived PDFF (%change (95 % CI) per IQR increase: 20.08 (4.71, 37.72), Model 2, Table S6) in linear models, even after adjusting for BMI, but not in logistic models. Table S7 presented the consistent findings between sleep characteristics and SLD-FLI and MASLD-FLI in KORA-MRI cohort. There was a strong correlation between MRI-derived PDFF and FLI (Spearman's coefficient = 0.76), and the agreement between SLD-PDFF and SLD-FLI was moderate (Cohen's Kappa = 0.69). These associations of WASO/h and sleep efficiency with SLD-PDFF remained robust in the sensitivity analyses (Table S8).

4. Discussion

Using objectively measured sleep data and various liver health markers across four German cohorts, we found that fragmented sleep characteristics and lower sleep efficiency were associated with increased ALT levels in adolescents, and with higher ALT, GGT, and odds of SLD-



**Fig. 1. Associations between sleep characteristics and liver enzymes in adolescents (GINIplus and LISA cohorts) and adults (KORA-Fit cohort).** In Fig. 1A: Model 1: Adjusted for sex, age, study, study center, season, parental highest education, sedentary behavior, moderate-to-vigorous physical activity, and fasting status; Model 2: Model 1 + BMI. In Fig. 1B: Model 1: Adjusted for sex, age, season, education, sedentary behavior, moderate-to-vigorous physical activity, smoking, and alcohol consumption; Model 2: Model 1 + BMI. Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; CI, confidence interval; IQR, interquartile range; GGT, Gamma-Glutamyl Transferase; 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; KORA-Fit, a follow-up examination of participants conducted in 2018–2019, building on four cross-sectional baseline surveys from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study; WASO, time awake after sleep onset; WASO/h, time awake per hour after sleep onset.

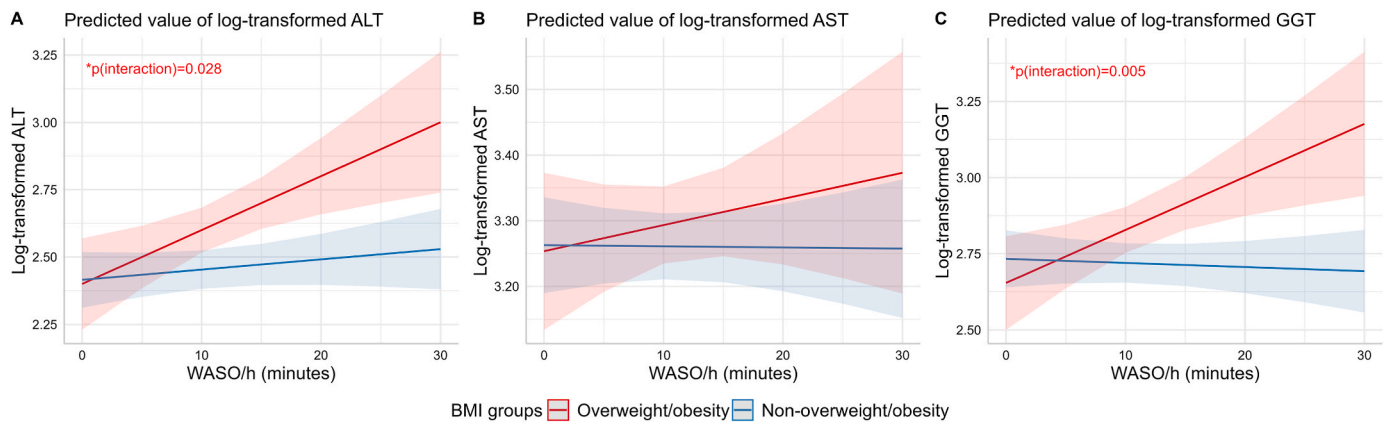
FLI, MASLD-FLI, SLD-PDFF and MASLD-PDFF in adults. Additionally, prolonged sleep latency was linked to SLD-FLI and increased PDFF in adults. However, these associations were attenuated and became non-significant after adjustment for BMI. Furthermore, significant interactions were observed between WASO/h and BMI groups on ALT and GGT levels in adolescents, as well as on SLD-FLI in adults.

Accelerometry-assessed fragmented sleep and poor sleep efficiency were associated with higher ALT in adolescents, and both higher ALT and GGT in adults, reflecting their potential link between disrupted sleep patterns and liver injury. Additional fragmented sleep characteristics, such as sleep fragmentation index, were also linked to increased ALT and GGT in adults. These findings were consistent with previous research showing that reported insomnia or OSA were associated with

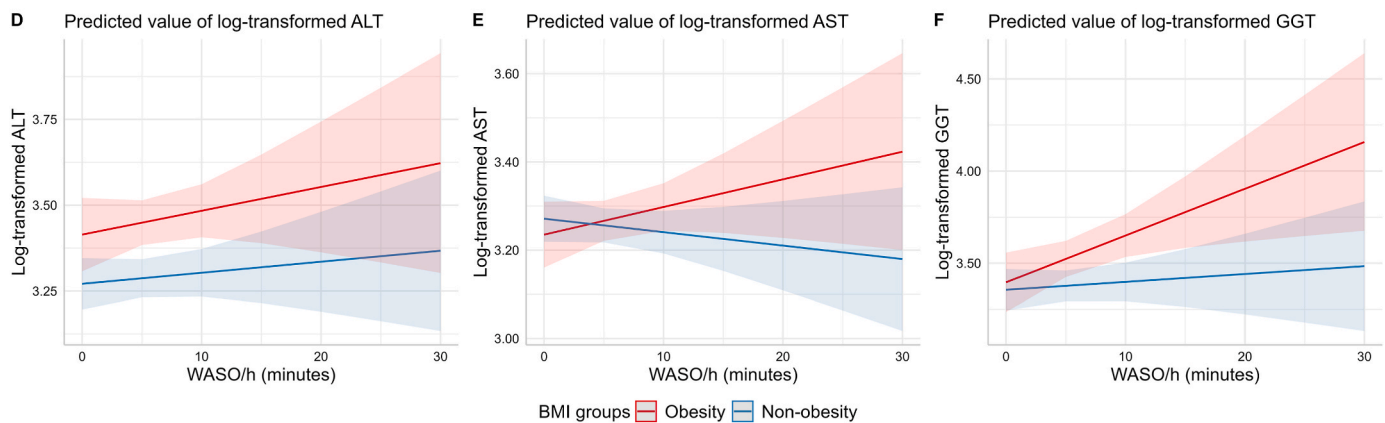
elevated liver enzymes in both children and adults [16,17,34]. However, evidence on the impact of objectively fragmented sleep remains lacking. The association between fragmented sleep and ALT elevation, rather than AST, maybe due to ALT's liver-specific nature and its sensitivity to hepatocellular damage [35]. Fragmented sleep may impact hepatocellular damage through oxidative stress, inflammation, and metabolic disruptions [36,37]. In adults, fragmented sleep was also linked to increased GGT, likely due to accumulated oxidative stress, liver burden from aging, and chronic intermittent hypoxia, which often co-occurs as part of OSA [38–40]. While GGT elevation is sensitive to biliary injury and alcohol intake [26,35], our sensitivity analysis excluding participants with excessive alcohol intake still found significant associations.

In adults, we also observed that accelerometry-assessed fragmented

### Interaction effects among adolescents from the GINIplus and LISA cohorts



### Interaction effects among adults from the KORA-Fit cohort



**Fig. 2.** Interaction effects of WASO/h with BMI groups on liver enzymes among adolescents (GINIplus and LISA cohorts) and adults (KORA-Fit cohort). Abbreviations: ALT, Alanine Aminotransferase; AST, Aspartate Aminotransferase; BMI, body mass index; GGT, Gamma-Glutamyl Transferase; 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; KORA-Fit, a follow-up examination of participants conducted in 2018–2019, building on four cross-sectional baseline surveys from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study; WASO/h, time awake per hour after sleep onset.

sleep and poor sleep efficiency were consistently associated with elevated liver fat, as measured by SLD-FLI, MASLD-FLI, SLD-PDFF and MASLD-PDFF, suggesting their potential role in liver fat accumulation. Notably, while the FLI has been validated in children aged 5–15 years [41], the absence of WC data in our adolescents prevented its calculation. Our findings in adults align with previous research indicating that reported insomnia or poor sleep quality were associated with percent liver fat or NAFLD or MASLD [12,34]. Similarly, several studies have revealed significant associations of objectively assessed fragmented sleep characteristics (WASO or sleep fragmentation index) with obesity [14,42]. However, to our knowledge, no prior studies have reported significant associations of objectively assessed fragmented sleep and liver fat. The underlying mechanism remains unclear, but it might be suggested that fragmented sleep may lead to disruptions in metabolic pathways, including impaired insulin sensitivity [43], altered lipid metabolism [40], and systemic inflammation [37], all contributing to liver fat accumulation [9].

Prolonged sleep latency, another contributing factor to poor sleep efficiency, was also linked to elevated liver fat in adults, as indicated by SLD-FLI and higher MRI-derived PDFF. While a few studies have identified significant associations between subjective sleep latency and NAFLD, evidence based on objective assessments remains scarce. A study found that reported sleep latency score was associated with higher odds of NAFLD in 1864 Japanese male adults [44]. Additionally, one study discovered that accelerometry-assessed longer sleep latency was linked

to higher BMI and body fat percent in 430 adults aged 21–35 years [42]. Prolonged sleep latency may lead to elevated liver fat through mechanisms such as disruption of circadian rhythms, metabolic dysregulation, and systemic inflammation, affecting liver metabolism [7].

Our study also found that after adjusting for BMI, the associations between sleep characteristics and liver health were attenuated and became non-significant. This suggests that BMI, a determinant of metabolic health, may mediate the relationship between sleep disturbances and liver dysfunction. A study using UK Biobank suggested BMI as a significant mediator between shift work and NAFLD [45]. Additionally, in adolescents, the interaction between WASO/h and overweight/obesity status was significant, showing that adolescents with overweight/obesity had stronger associations between WASO/h and increased ALT and GGT. Similarly, adults with obesity exhibited more pronounced associations between WASO/h and SLD-FLI, compared to those with non-obesity. These findings suggest that individuals with overweight/obesity may be more vulnerable to the liver-related effects of sleep fragmentation. While the underlying mechanisms remain unclear, prior research reported that in individuals with obesity, OSA may exacerbate liver injury in NAFLD via insulin resistance and systemic inflammation [46]. Future research is needed to explore the role of obesity in the association between sleep and liver fat accumulation, with a particular focus on fragmented sleep.

It is worth noting that longer total sleep time in adults was significantly associated with higher ALT in our study, but not with elevated



**Table 2**

Associations of sleep characteristics with SLD-FLI and MASLD-FLI in adults (KORA-Fit cohort).

Sleep characteristics (per IQR)	SLD-FLI (N = 1318)		MASLD-FLI (N = 1002)	
	OR (95 %CI)	P	OR (95 %CI)	P
Total sleep time, hours	1.04 (0.89, 1.22)	0.626	1.07 (0.90, 1.28)	0.454
Sleep efficiency, %	0.67 (0.57, 0.78)	<b>&lt;0.001</b>	0.61 (0.51, 0.74)	<b>&lt;0.001</b>
Sleep latency, mins	1.18 (1.02, 1.36)	<b>0.028</b>	1.17 (0.99, 1.38)	0.062
Sleep onset timing, hours	0.95 (0.82, 1.11)	0.514	0.93 (0.78, 1.11)	0.402
WASO, mins	1.54 (1.32, 1.80)	<b>&lt;0.001</b>	1.69 (1.41, 2.02)	<b>&lt;0.001</b>
WASO/h, mins/h	1.47 (1.26, 1.71)	<b>&lt;0.001</b>	1.61 (1.34, 1.94)	<b>&lt;0.001</b>
Awakenings, num	1.15 (0.98, 1.36)	0.088	1.21 (0.99, 1.47)	0.062
Awakenings/h, num/h	1.07 (0.90, 1.27)	0.418	1.11 (0.90, 1.36)	0.336
Movement index	1.39 (1.20, 1.62)	<b>&lt;0.001</b>	1.50 (1.25, 1.80)	<b>&lt;0.001</b>
Fragmentation index	1.29 (1.10, 1.51)	<b>0.002</b>	1.42 (1.18, 1.71)	<b>&lt;0.001</b>
Sleep fragmentation index	1.41 (1.20, 1.66)	<b>&lt;0.001</b>	1.58 (1.30, 1.92)	<b>&lt;0.001</b>

Adjusted for sex, age, season, education, sedentary behavior, moderate-to-vigorous physical activity, smoking, and alcohol consumption.

Abbreviations: CI, confidence interval; FLI: fatty liver index; IQR, interquartile range; KORA-Fit, a follow-up examination of participants conducted in 2018–2019, building on four cross-sectional baseline surveys from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study; MASLD: metabolic dysfunction-associated steatotic liver disease; OR, odds ratio; SLD, steatotic liver disease; WASO, time awake after sleep onset; WASO/h, time awake per hour after sleep onset.

SLD-FLI was defined as FLI  $\geq 60$ . MASLD-FLI was defined as FLI  $\geq 60$  with at least one of five cardiometabolic risk factors among participants without excessive alcohol intake, HIV or hepatitis, systemic corticosteroids or antiarrhythmic drugs (N = 1002).  $P < 0.05$  are highlighted in bold.

liver fat, which was contradictory with most studies [11]. Similarly, one study comprising 5427 Korean adults also reported a link between reported long sleep duration (greater than or equal to 7 h) and higher incidence of NAFLD, compared to sleep duration less than 6 h [47]. Another study in 5011 Chinese adults revealed that neither reported short nor long sleep duration was observed to be linked to metabolic dysfunction-associated fatty liver disease [48]. Consistent with our findings linking increased liver fat to poor sleep efficiency (fragmentation and prolonged latency) but not total sleep time, a US study found that reported circadian misalignment (mistimed, late, or irregular sleep) was independently associated with MASLD, but not short sleep duration ( $< 6$  h) [49]. Collectively, our study and others suggest that poor sleep quality, driven by fragmented sleep and sleep latency, may have a more significant impact on liver health than total sleep time. Further research using objective measurements and additional sleep dimensions is needed to confirm these findings.

To the best of our knowledge, this is the first study to examine sleep-liver health associations in the general population, using objective sleep characteristics assessed by accelerometry, reducing bias from self-reports. The inclusion of multiple liver health markers, particularly MRI-derived liver fat, and large sample sizes in both adolescents and adults across various age groups, strengthened the generalizability of our findings. However, some limitations should be noted. First, the cross-sectional design limits our ability to infer causal relationships. Second, the lack of WC data in our adolescents limited FLI calculation to explore associations between sleep and liver fat in adolescents. Third, as described in Methods, differences in diary-recorded “starts in bed” and “starts out bed” between KORA-Fit cohort and the other three cohorts,

led to slight variations in calculating sleep latency, WASO and WASO/h. Fourth, due to the high prevalence of OSA in the general adult population with the concurrent occurrence of fragmented sleep and chronic intermittent hypoxia [50], we cannot distinguish their independent effects on liver health. Fifth, due to the high correlations among sleep characteristics (Fig. S2), we did not apply multiple testing correction. Sixth, the small KORA-MRI subsample ( $n = 108$ ) limits statistical power and the precision of estimates. A minimum detectable effect analysis indicates that only moderate associations could be reliably detected, and therefore these findings should be interpreted as exploratory and confirmed in larger imaging cohorts.

## 5. Conclusions

Our study revealed significant associations between objectively assessed poor sleep quality and liver health markers in both adolescents and adults, with fragmented sleep and lower sleep efficiency linked to increased liver enzymes and liver fat. Notably, these associations became non-significant after adjustment for BMI, with interactions between fragmented sleep and BMI groups observed on liver enzymes and fat, underscoring the mediating or modifying role of BMI. These findings highlight the importance of multidimensional sleep health in liver dysfunction across different age groups. Future research should explore the underlying mechanisms and assess the impacts of sleep interventions targeting fragmentation on liver health. Additional longitudinal studies are warranted to further elucidate a potential causal link between sleep fragmentation and liver health.

## CRedit authorship contribution statement

**Mingming Wang:** Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Claudia Flexeder:** Writing – review & editing, Supervision, Data curation, Conceptualization. **Daniel Teupser:** Writing – review & editing, Data curation. **Carla P. Harris:** Writing – review & editing, Data curation. **Roberto Lorbeer:** Writing – review & editing, Data curation. **Fabian Bamberg:** Writing – review & editing, Data curation. **Susanne Rospleszcz:** Writing – review & editing, Data curation. **Jana Nano:** Writing – review & editing, Data curation. **Tamara Schikowski:** Writing – review & editing, Data curation. **Barbara Thorand:** Writing – review & editing, Data curation. **Annette Peters:** Writing – review & editing, Data curation. **Marie Standl:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Data curation, Conceptualization.

## Ethics approval and consent to participate

The GINIplus, LISA, and KORA studies were approved by the local ethics committees, and all participants gave written informed consents.

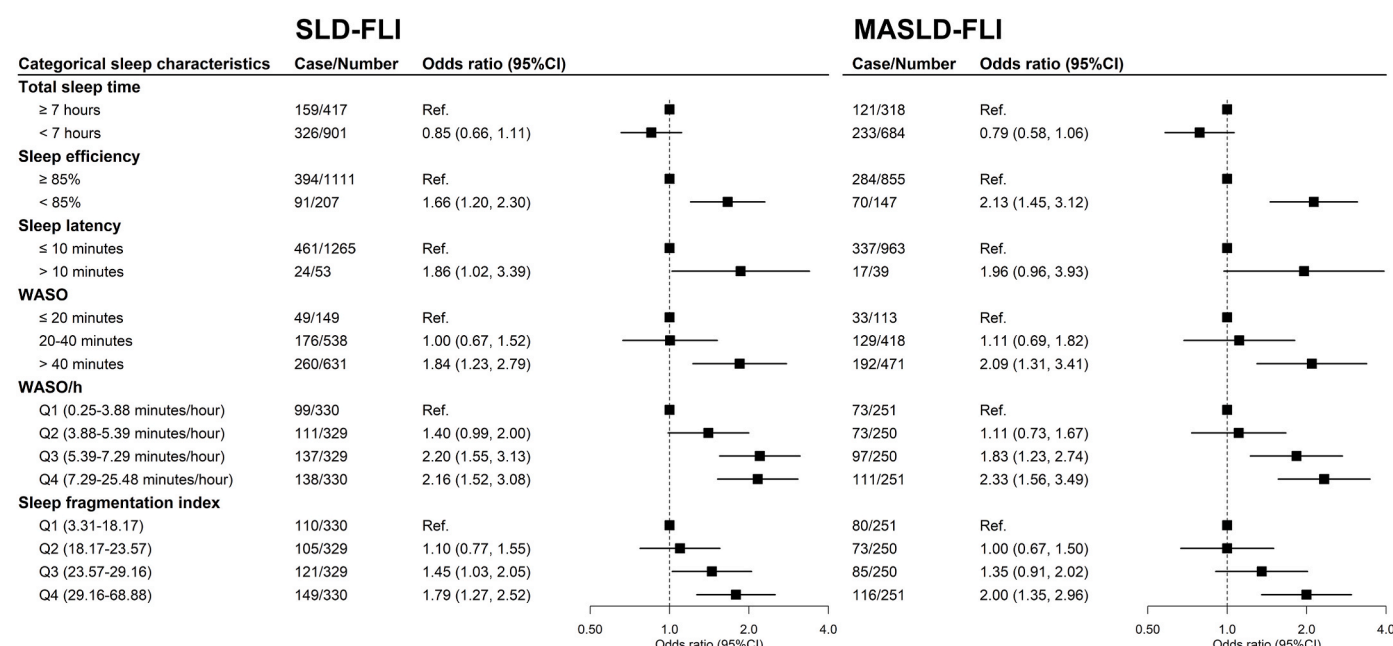
## Consent for publication

All authors consent to the publication of this manuscript.

## Data availability statement

Due to data protection reasons, the datasets generated and/or analyzed during the current study cannot be made publicly available. The datasets are available to interested researchers from the corresponding author on reasonable request (e.g. reproducibility), provided the release is consistent with the consent given by the GINIplus and LISA study participants. Ethical approval might be obtained for the release and a data transfer agreement from the legal department of Helmholtz Munich must be accepted. The informed consent given by KORA study participants does not cover data posting in public databases. However, data are available upon request by means of a project agreement.





**Fig. 3.** The associations of categorized sleep characteristics with SLD-FLI and MASLD-FLI in adults (KORA-Fit cohort). Abbreviations: CI, confidence interval; FLI, fatty liver index; KORA-Fit, a follow-up examination of participants conducted in 2018–2019, building on four cross-sectional baseline surveys from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study; MASLD, Metabolic Dysfunction-Associated Steatotic Liver Disease; Q1, first quartile; Q2, second quartile; Q3, third quartile; Q4, fourth quartile; SLD, steatotic liver disease; WASO, time awake after sleep onset; WASO/h, time awake per hour after sleep onset. The categorizations of total sleep time, sleep efficiency, WASO were based on the National Sleep Foundation's sleep quality recommendations: first report. SLD-FLI was defined as FLI  $\geq 60$ . MASLD-FLI was defined as FLI  $\geq 60$  with at least one of five metabolic risk factors among participants without excessive alcohol intake, HIV or hepatitis, systemic corticosteroids or antiarrhythmic drugs (N = 1002).

**Table 3**

Associations of sleep characteristics with SLD-PDFF and MASLD-PDFF in adults (KORA-MRI cohort).

Sleep characteristics (per IQR)	SLD-PDFF (N = 108)				MASLD-PDFF (N = 80)			
	Model 1 (Main model)		Model 2		Model 1 (Main model)		Model 2	
	OR (95 %CI)	P	OR (95 %CI)	P	OR (95 %CI)	P	OR (95 %CI)	P
Total sleep time, hours	0.72 (0.37, 1.40)	0.326	0.72 (0.23, 2.21)	0.561	0.70 (0.35, 1.41)	0.316	0.51 (0.13, 2.01)	0.337
Sleep efficiency, %	0.43 (0.23, 0.81)	<b>0.009</b>	0.66 (0.30, 1.45)	0.303	0.27 (0.11, 0.65)	<b>0.003</b>	0.56 (0.19, 1.64)	0.292
Sleep latency, mins	1.58 (0.95, 2.63)	0.076	1.70 (0.76, 3.77)	0.196	1.71 (0.92, 3.16)	0.087	2.21 (0.82, 5.97)	0.117
Sleep onset timing, hours	0.97 (0.49, 1.89)	0.918	1.32 (0.46, 3.75)	0.603	1.15 (0.48, 2.73)	0.755	3.25 (0.69, 15.2)	0.135
WASO, mins	2.01 (1.10, 3.69)	<b>0.024</b>	1.31 (0.60, 2.88)	0.498	3.36 (1.40, 8.04)	<b>0.007</b>	1.42 (0.47, 4.28)	0.533
WASO/h, mins/h	2.10 (1.16, 3.78)	<b>0.014</b>	1.37 (0.64, 2.90)	0.415	3.32 (1.47, 7.52)	<b>0.004</b>	1.57 (0.56, 4.41)	0.395
Awakenings, num	1.28 (0.68, 2.42)	0.439	1.06 (0.40, 2.87)	0.901	1.76 (0.84, 3.66)	0.134	1.28 (0.42, 3.88)	0.668
Awakenings/h, num/h	1.16 (0.68, 1.97)	0.584	1.04 (0.45, 2.41)	0.931	1.49 (0.82, 2.69)	0.190	1.32 (0.52, 3.35)	0.555

Model 1: Adjusted for sex, age, season, education, sedentary behavior, moderate-to-vigorous physical activity, smoking, and alcohol consumption.

Model 2: Model 1 + BMI.

Abbreviations: BMI, body mass index; CI, confidence interval; IQR, interquartile range; OR, odds ratio; MASLD, metabolic dysfunction-associated steatotic liver disease; MRI, Magnetic Resonance Imaging; PDFF, proton density fat fraction; SLD, steatotic liver disease; WASO, time awake after sleep onset; WASO/h, time awake per hour after sleep onset; KORA-MRI, a sub-study where participants underwent whole-body 3T-Magnetic Resonance Imaging (MRI) conducted in 2013–2014, shortly after second follow-up examination of the KORA S4 survey (1999–2001).

SLD-PDFF was defined as PDFF  $\geq 5\%$ ; MASLD-PDFF was defined as PDFF  $\geq 5\%$  with at least one of five cardiometabolic risk factors among participants without excessive alcohol intake, systemic corticosteroids or antiarrhythmic drugs.  $P < 0.05$  are highlighted in bold.

Requests should be sent to [kora.passt@helmholtz-muenchen.de](mailto:kora.passt@helmholtz-muenchen.de) and are subject to approval by the KORA Board.

### Financial support statement

The GINIplus study was mainly supported for the first 3 years of the Federal Ministry for Education, Science, Research and Technology (intervention arm) and Helmholtz Zentrum München (former GSF) (observation arm). The 4-year, 6-year, 10-year, and 15-year follow-up examinations of the GINIplus study were covered from the respective budgets of the 5 study centres (Helmholtz Zentrum München (former GSF), Research Institute at Marien-Hospital Wesel/EVK Düsseldorf,

LMU Munich, TU Munich and from 6 years onwards also from IUF – Leibniz Research-Institute for Environmental Medicine at the University of Düsseldorf) and a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Further, the 15-year follow-up examination of the GINIplus study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project and the companies Mead Johnson and Nestlé.

The LISA study was mainly supported by grants from the Federal Ministry for Education, Science, Research and Technology and in addition from Helmholtz Zentrum München (former GSF), Helmholtz Centre for Environmental Research – UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef for the first 2

years. The 4-year, 6-year, 10-year, and 15-year follow-up examinations of the LISA study were covered from the respective budgets of the involved partners (Helmholtz Zentrum München (former GSF), Helmholtz Centre for Environmental Research – UFZ, Leipzig, Research Institute at Marien-Hospital Wesel, Pediatric Practice, Bad Honnef, IUF – Leibniz-Research Institute for Environmental Medicine at the University of Düsseldorf) and in addition by a grant from the Federal Ministry for Environment (IUF Düsseldorf, FKZ 20462296). Further, the 15-year follow-up examination of the LISA study was supported by the Commission of the European Communities, the 7th Framework Program: MeDALL project.

The KORA study was initiated and financed by the Helmholtz Zentrum München – German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education and Research (BMBF) and by the State of Bavaria. Data collection in the KORA study is done in cooperation with the University Hospital of Augsburg. The KORA MRI sub-study received funding by the German Research Foundation, the Centre for Diabetes Research (DZD e. V., Neuherberg, Germany) and the German Centre for Cardiovascular Disease Research. The KORA-MRI sub-study was supported by an unrestricted research grant from Siemens Healthcare.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2025.108686>.

Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
FLI	Fatty liver index;
GGT	γ glutamyltransferase
GINIplus	German Infant Study on the influence of Nutrition Intervention PLUS environmental and genetic influences on allergy development
KORA-Fit	A follow-up examination of participants conducted in 2018–2019, building on four cross-sectional baseline surveys (S1: 1984–1985, S2: 1989–1990, S3: 1994–1995, and S4: 1999–2001) from the Cooperative Health Research in the Region of Augsburg (KORA) cohort study
KORA-MRI	A sub-study where participants underwent whole-body 3T-Magnetic Resonance Imaging (MRI) conducted in 2013–2014, shortly after second follow-up examination of the KORA S4 survey
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
MASLD	Metabolic dysfunction-associated steatotic liver disease
PDFF	Proton density fat fraction
SLD	Steatotic liver disease
WASO	Time awake after sleep onset
WASO/h	Time awake per hour after sleep onset.

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