Original Article

autism

Autism
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DOI: 10.1177/13623613241258546
journals.sagepub.com/home/aut
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The role of circadian rhythms and sleep in the aetiology of autism spectrum disorder and attention-deficit/hyperactivity disorder: New evidence from bidirectional two-sample Mendelian randomization analysis

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Abstract

Increasing evidence highlights the role of disrupted circadian rhythms in the neural dysfunctions and sleep disturbances observed in autism spectrum disorder and attention-deficit/hyperactivity disorder. However, the causality and directionality of these associations remain unclear. In this study, we employed a bidirectional two-sample Mendelian randomization framework, leveraging genome-wide association study data from the UK Biobank ($n = 85{,}670$) and FinnGen ($n = 377{,}277$). Genetic variants served as instrumental variables to infer causation, and objective accelerometer-derived metrics identified circadian rhythm and sleep genetic instruments. The results showed that the timing of the most active 10 h was significantly linked to higher odds of autism spectrum disorder and attention-deficit/hyperactivity disorder. Independently, higher sleep efficiency predicted a lower risk of autism spectrum disorder, while attention-deficit/hyperactivity disorder was linked to an increase in nocturnal sleep episodes. Heterogeneity and sensitivity analyses confirmed these findings. Our study establishes causal links between circadian alterations and autism spectrum disorder and attention-deficit/hyperactivity disorder, distinguishing the independent and protective role of sleep efficiency in autism spectrum disorder from circadian rhythms. In attention-deficit/hyperactivity disorder, however, disrupted sleep appears as a consequence, not a cause. These insights highlight divergent interactions with sleep factors in autism spectrum disorder and attention-deficit/hyperactivity disorder, laying the groundwork for tailored therapeutic strategies that recognize the distinct influences of sleep quality and circadian rhythms in each disorder.

Lay abstract

Research shows that people with autism spectrum disorder and attention-deficit/hyperactivity disorder often have sleep issues and problems with the body's natural daily rhythms, known as circadian rhythms. By exploring the genetic variants associated with these rhythms and the conditions, this study reveals that these rhythm changes and sleep patterns are directly linked to autism spectrum disorder and attention-deficit/hyperactivity disorder. It found that the timing of one's most active hours can increase the likelihood of having both autism spectrum disorder and attention-deficit/hyperactivity disorder. Importantly, it also shows that good sleep quality might protect against autism spectrum disorder, while disturbed sleep in people with attention-deficit/hyperactivity disorder seems to be a result rather than the cause of the condition. This understanding can help doctors and researchers develop better treatment approaches that focus on the specific ways sleep and body rhythms affect those with autism spectrum disorder and attention-deficit/hyperactivity

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disorder, considering their unique associations with circadian rhythms and sleep patterns. Understanding these unique links can lead to more effective, personalized care for those affected by these conditions.

Keywords
attention-deficit/hyperactivity disorder, autism spectrum disorder, chronotype, circadian rhythm, Mendelian randomization, sleep disorder

Introduction

Autism spectrum disorder (ASD) and attention-deficit hyperactivity disorder (ADHD) are prevalent lifelong neurodevelopmental disorders with distinctive yet overlapping symptoms. ASD, affecting approximately one in 100 individuals, is characterized by challenges in social interaction, communication and repetitive behaviours (Zeidan et al., 2022). ADHD, impacting about 5%–7% of children, is defined by persistent symptoms of impulsivity, inattention and hyperactivity (Polanczyk et al., 2007). Typically identified in early childhood, the implications of these disorders extend into adulthood, influencing overall functioning.

Recent studies suggest a substantial link between circadian rhythm (CR) alternations and psychiatric disorders (Levandovski et al., 2011; Takahashi et al., 2008), with increasing evidence highlighting the role of disrupted CRs in the neural dysfunctions and sleep disturbances observed in ASD (Carmassi et al., 2019; Geoffray et al., 2016) and ADHD (Bijlenga et al., 2019; Coogan & McGowan, 2017). CRs which encompass the body's natural 24-h cycles of physiological, behavioural and psychological processes are crucial for regulating hormones and sleep-wake patterns. Chronotype, an individual's tendency towards earlier or later sleep times, reflects the alignment of internal circadian cycles with sleep requirements, and is considered a valuable tool in studying CRs (Jones et al., 2016; Jones, Lane, et al., 2019). This CR disorders hypothesis (Bijlenga et al., 2019; Geoffray et al., 2016; Wimpory et al., 2002) explains certain observations related to ASD and ADHD. For instance, consistent evidence links ADHD to a late chronotype and phase delays in circadian markers, such as the onset of melatonin production under dim light conditions and delayed sleep onset (Coogan & McGowan, 2017). In addition, sleep disturbances, abnormal melatonin profiles and circadian sleep dysfunctions (e.g. irregular sleep-wake patterns and delayed sleep phase) have been linked to the severity of symptoms in ASD (Carmassi et al., 2019; Tordjman et al., 2013). Moreover, both ASD and ADHD exhibit a similar sleep impairment profiles, marked by longer sleep onset latency, reduced sleep efficiency, more frequent awakenings during sleep, and poorer self-reported sleep quality (Lugo et al., 2020; Ming & Walters, 2009), suggesting a circadian component as the underlying mechanism in these sleep disturbances (Bijlenga et al., 2019). However, it is also important to note that certain sleep disturbances found in ASD and ADHD, such as sleep-related movement and breathing disorders, insomnia and hypersomnia, cannot solely be attributed to CR dysfunctions (Mehta et al., 2019; Ming & Walters, 2009).

Despite the evidence, the exact mechanisms by which CRs and sleep contribute to the pathophysiology of disorders such as ASD and ADHD remain unclear. Current research, which is largely observational, has not definitively established a causal link between these factors. However, interventions targeting CRs, including light therapy and melatonin supplementation, have proven effective in alleviating sleep disturbances in ASD and ADHD, yet their impact on cognitive and behavioural outcomes in these disorders presents inconsistent findings (der Heijden et al., 2007; Esposito et al., 2019; Parvataneni et al., 2020; Rzepka-Migut & Paprocka, 2020). In addition, this gap in research methodology also highlights the potential for reverse causality or the influence of confounding factors. Recent developments in this field suggest a potentially bidirectional relationship between circadian disturbances and the behavioural and cognitive symptoms typical of ASD and ADHD. For example, circadian dysfunction might aggravate core symptoms such as stereotypical behaviours and attention deficits (Cortese et al., 2009). In contrast, the intrinsic challenges of ASD and ADHD, like difficulties in social interaction and sensory processing, may in turn exacerbate disruptions in circadian and sleep patterns (Geoffray et al., 2016; Imeraj et al., 2012).

This complex interplay necessitates a comprehensive understanding of CR's role in these disorders, pivotal for both pathogenesis comprehension and chronotherapeutic strategy development. Genetic analyses identifying variants robustly associated with putative risk factors, such as circadian timing and sleep, can improve causal understanding by providing genetic instruments for use in Mendelian randomization (MR) analyses, which can minimize the effect of both reverse causality and confounding bias (Lawlor et al., 2008). MR calculates the proportion of the change explained by genetics in the exposure (e.g. chronotype and sleep) and the change explained by the same genetic factors on the outcome (e.g. ASD and ADHD). It is possible to calculate how changes in the exposure influence the outcome. This approach is useful to avoid reverse causality or confounding issues and can provide a more robust understanding of the associations of

CRs, sleep disturbances and these disorders and may offer insights into novel therapeutic targets for managing their comorbidities (Burgess et al., 2023).

A recent genome-wide association study (GWAS) using objective accelerometer data from 85,670 UK Biobank participants has advanced our understanding of the genetic basis of sleep (Jones, van Hees, et al., 2019). This study uncovered 47 independent genetic associations (single-nucleotide polymorphisms, SNPs) with eight distinct sleep traits, falling into three different categories: circadian timing, sleep quality and duration. Accelerometers, aligning closely with polysomnography and sleep diaries (van Hees et al., 2015, 2018), are crucial for accurately measuring sleep patterns (Van de Water et al., 2011) and CR activity levels (Vitale et al., 2015) outside laboratory settings. This approach is particularly beneficial in large epidemiological studies, overcoming biases often present in self-reported chronotype and sleep assessments (Bianchi et al., 2013; Lauderdale et al., 2008). In addition, a subsequent comparison with self-reported chronotype measures and a GWAS meta-analysis, excluding UK Biobank participants with prior accelerometer data (Jones, Lane, et al., 2019; Jones, van Hees, et al., 2019), confirmed the impact of chronotype SNPs on sleep timing and circadian metrics. These analyses validate these genetic variants for MR analysis, facilitating the exploration into the intricate connections between CRs and sleep, and its implications for ASD and ADHD.

Therefore, in this study, using the SNPs identified from the GWAS study mentioned above, we conducted a bidirectional two-sample MR analysis to clarify the role of CRs in the aetiology of ASD and ADHD. By analysing genetic variants derived from objective, accelerometer-based measurements, we explored the associations between various circadian timing, along with sleep quality and quantity traits, and ASD and ADHD, focusing on establishing causality and directionality in these relationships.

Method

This two-sample bidirectional MR investigation was based on publicly available genome-wide association studies. Figure 1 shows the overview design of the study.

CRs and sleep data source

Genetic associations with eight measures of chronotype and sleep were derived from the large-scale GWAS of multiple sleep traits, which estimated objective, accelerometer data from 85,670 UK Biobank participants (Jones, van Hees, et al., 2019), who wore research-grade activity monitors (accelerometers) continuously for up to 7 days.

A total of eight accelerometer-based measures of circadian timing and sleep included measures representative of (1) circadian timing, including sleep midpoint ($N = 84{,}810$), timing of the least-active 5 h (L5) ($N = 85{,}205$) and timing of the most active 10 h (M10) ($N = 85{,}670$); (2) sleep quality, including sleep efficiency (sleep duration divided by the time between the start and end of the first and last nocturnal inactivity period, respectively) ($N = 84{,}810$) and the number of nocturnal sleep episodes ($N = 84{,}810$); and (3) sleep duration, including diurnal inactivity ($N = 84{,}757$), nocturnal sleep duration ($N = 85{,}449$) and variability ($N = 84{,}441$). Phenotypes were rank-normalized and adjusted for age, sex, location and season when activity-monitor worn and genotyping chip (Jones, van Hees, et al., 2019). It should also be noted that the indicators of sleep quality and sleep duration are uncorrelated with circadian timing indicators (Jones, van Hees, et al., 2019). Detailed information on circadian timing and sleep data is available in Supplementary Table 1.

ASD and ADHD data source

Summary-level genetic data on ASD with 564 cases and ADHD with 2340 cases were sourced from the most recent release (Release 9) of FinnGen data (Kurki et al., 2023). We used independent sources for exposure and outcome to avoid biases caused by sample overlap (Burgess et al., 2016). The FinnGen research project represents a collaborative effort between the public and private sectors, amalgamating genotype data from Finnish biobanks and digital health record information from Finnish health registries to establish a cohort of 500,000 participants. Genome-wide association analyses with FinnGen were adjusted for sex, age, genetic components and genotyping batch. As of May 2023 (Release 9), 2272 endpoints and 377,277 samples have been analysed (Kurki et al., 2023). The endpoints of ASD and ADHD were defined by *International Classification of Diseases, Ninth revision* (*ICD-9*) and *Tenth revision* (*ICD-10*) codes. Detailed diagnostic codes in FinnGen are listed in Supplementary Table 2.

Instrumental variable selection

Genetic instrumental variables (IVs) for circadian timing and sleep were identified based on the genome-wide significance threshold ($p < 5 \times 10^{-8}$) and criteria excluding linkage disequilibrium (defined as $r^2 < 0.01$). As for the reversed direction of MR, no SNPs associated with ASD and ADHD reached the conventional threshold. For instrument selection, we opted for variants with $p < 5 \times 10^{-6}$ and $r^2 < 0.01$. It is crucial to emphasize that all these SNPs underwent verification to confirm non-proximity, and any palindrome SNPs were deliberately excluded from consideration.

Statistical analysis

The two-sample MR analysis was conducted by the inverse-variance weighted (IVW) method. Using a

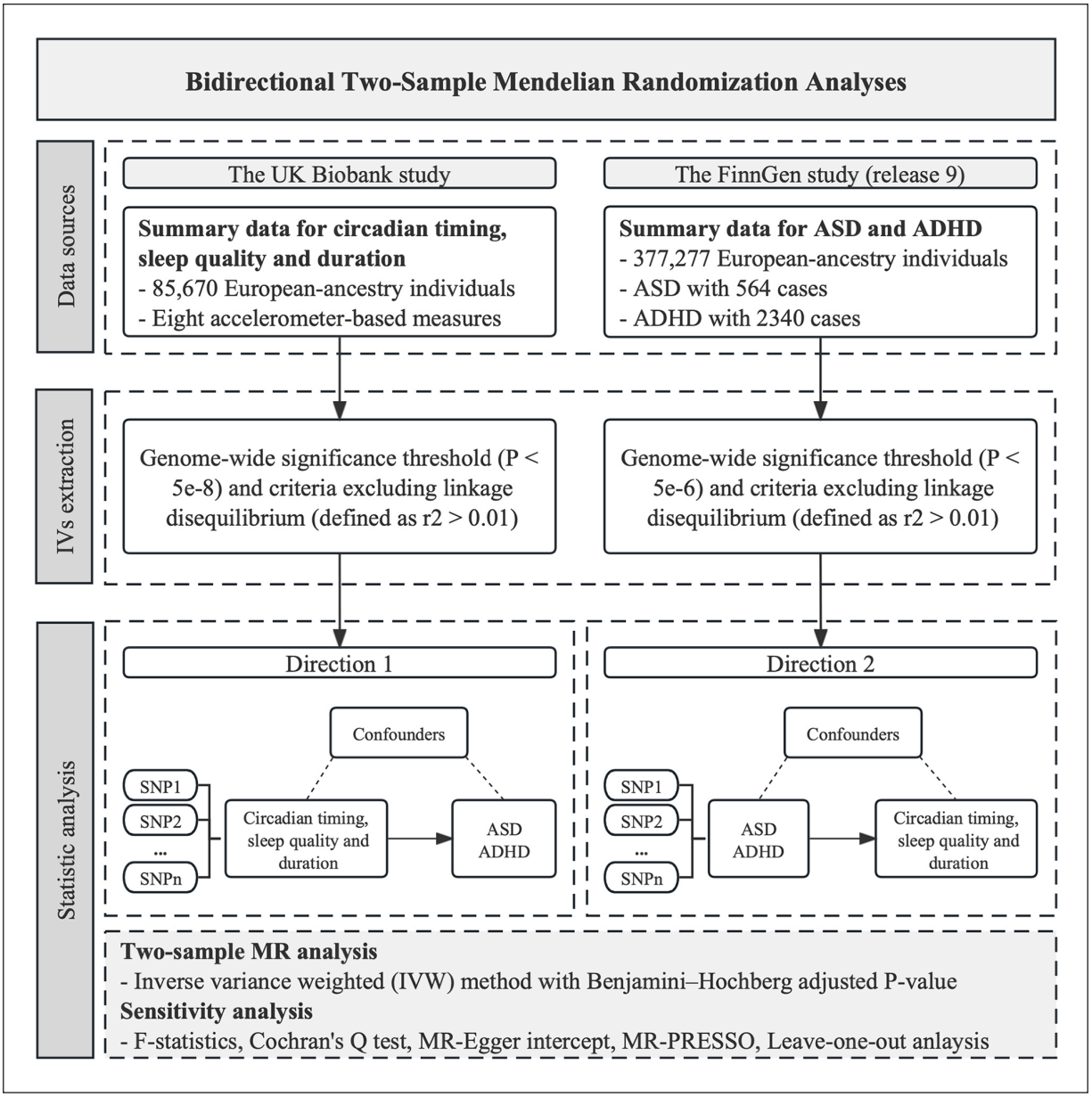

Figure 1. The flowchart illustrates the study design methodology. Rectangles represent key steps or processes.

weighted average, the IVW method is the most powerful estimator under the assumption of all the IVs being valid (Burgess et al., 2023), and its significance can be interpreted as evidence of a causal association. In this analysis, a Benjamini–Hochberg (BH)-adjusted $p < 0.05$ was considered indicative of a significant causal exposure-outcome relationship (Benjamini & Hochberg, 1995), while a nominal $p < 0.05$ but BH-adjusted $p > 0.05$ suggested a potential relationship. To assess the robustness of the IVW results, four sensitivity analyses were conducted. These included *F*-statistics (Burgess & Thompson, 2011), MR-Egger intercept test (Bowden et al., 2017), MR-PRESSO (global and outlier test) (Verbanck et al., 2018), and leave-one-out (LOO) analysis (Hemani et al., 2018), with the aim of identifying insufficient instruments and potential horizontal pleiotropy that could compromise the MR assumptions. Heterogeneity tests for IVW method were performed to estimate the variability in the effect estimated by each variant using Cochran's Q test (Greco et al., 2015). All analyses were performed using R version 4.3.1 with the R packages 'TwoSampleMR' and 'MR-PRESSO' (R Core Team, 2023).

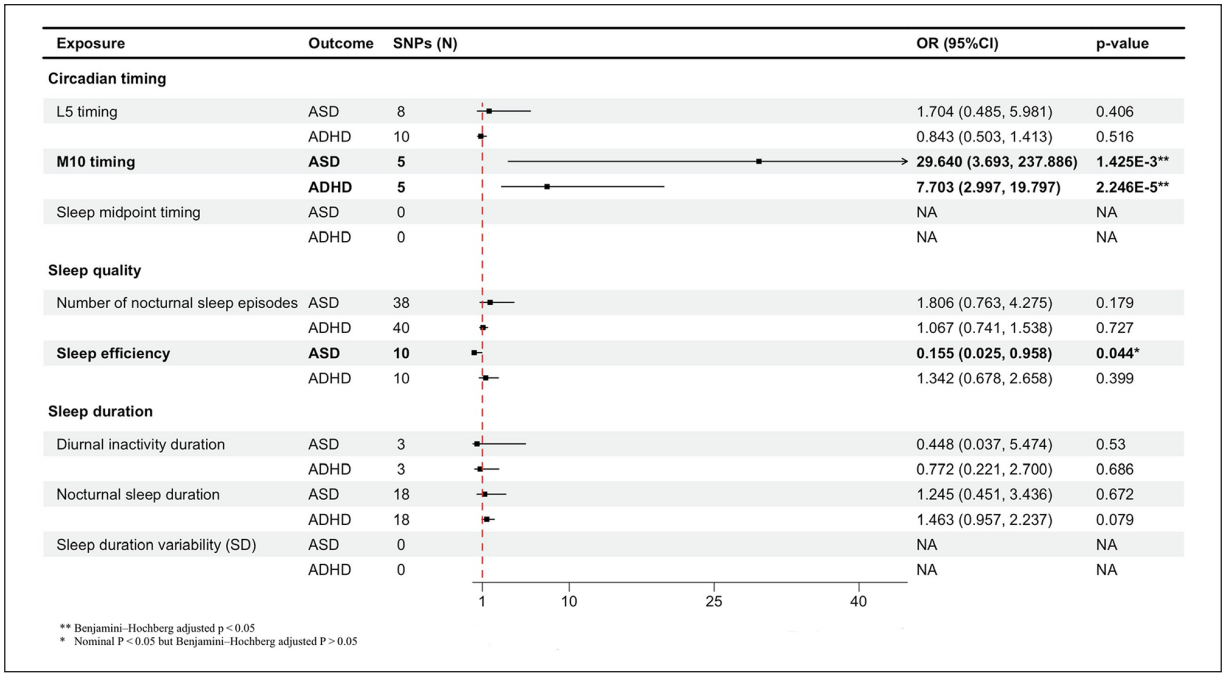

Figure 2. The forest plot visually represents the associations between genetic liability to circadian timing and sleep traits measured by accelerometers and the risks of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD), expressed as odds ratios.

Community involvement

This study was conceptualized by the authors who have extensive clinical experience in providing behavioural assessment and intervention services to children with autism. Recognizing the vital importance of community engagement, efforts were made to incorporate insights and perspectives from the autistic community and their advocates to ensure that the research aligns with the needs and values of those it aims to serve. We acknowledge the diversity within the autistic community and strive to contribute to a body of knowledge that supports inclusive and respectful practices.

Results

From circadian timing and sleep traits to ASD and ADHD

This set of analyses investigated the causal role of eight accelerometer-based measures of circadian timing and sleep (exposure) on ASD and ADHD (outcome). In the final analysis, 10 SNPs strongly associated with L5 timing, five with M10 timing, 40 with number of nocturnal sleep episodes, 10 with sleep efficiency, three with diurnal inactivity duration, and 18 with nocturnal sleep duration met the recruitment threshold. The *F*-statistics for each IV exceeded 10, indicating a robust association between CR and sleep exposure (Supplementary Table 3).

Genetically predicted M10 timing was linked to higher odds of ASD (odds ratio (OR) = 29.640, 95% confidence interval (CI) = [3.693, 237.886]; $p = 1.425 \times 10^{-3}$, BH adjusted $p < 0.01$) and ADHD (OR = 7.703, 95% CI = [2.997, 19.797]; $p = 2.246 \times 10^{-5}$, BH-adjusted $p < 0.001$). In the case of using sleep efficiency as the exposure, a potentially protective effect on ASD (OR = 0.155, 95% CI = [0.025, 0.958]; $p < 0.05$, BH-adjusted $p > 0.05$) was identified. The results of the sensitivity analysis for these significant associations were consistent, with no heterogeneity, horizontal pleiotropy, or outlier SNP detected (Supplementary Table 4). MR-PRESSO detected 2 outliers in the analysis from L5 timing and number of nocturnal sleep episodes to ASD; however, the association remained insignificant after the removal of these SNPs (Figure 2).

From ASD and ADHD to circadian timing and sleep traits

We inverted the direction of MR in this set of analysis. Table 1 displays the β estimates for ASD and ADHD exposure with sleep and activity as the outcome. As outlined in the 'Methods' section, we used a reduced $p < 5 \times 10^{-6}$ threshold and identified 10 instruments with ASD and 18 with ADHD after clumping and harmonization with the summary data for circadian timing and sleep. All *F*-statistics suggested IVs were strongly associated with ASD and ADHD exposure ($F > 100$, see Supplementary Table 3). Genetic liability to ADHD was associated with

Table 1. Associations of genetic liability to ASD and ADHD with eight accelerometer-based measures of circadian timing and sleep quality and duration traits.

Exposure	Outcome	No. of used SNPs	β	p value
ASD	L5 timing	10	–0.006 (–0.020, 0.009)	0.440
	M10 timing	10	–0.001 (–0.013, 0.010)	0.807
	Sleep midpoint timing	10	–0.005 (–0.017, 0.007)	0.416
	Number of nocturnal sleep episodes	10	0.004 (–0.008, 0.015)	0.533
	Sleep efficiency	10	–0.004 (–0.016, 0.008)	0.486
	Diurnal inactivity duration	10	0.003 (–0.009, 0.016)	0.624
	Nocturnal sleep duration	10	–0.003 (–0.013, 0.008)	0.597
	Sleep duration variability (SD)	10	0.002 (–0.008, 0.013)	0.663
ADHD	L5 timing	18	–0.013 (–0.029, 0.003)	0.114
	M10 timing	18	0.001 (–0.014, 0.017)	0.857
	Sleep midpoint timing	18	0.003 (–0.013, 0.019)	0.735
	Number of nocturnal sleep episodes	**18**	**0.017 (0.001, 0.033)**	**0.036***
	Sleep efficiency	18	–0.013 (–0.029, 0.003)	0.101
	Diurnal inactivity duration	18	0.009 (–0.007, 0.024)	0.268
	Nocturnal sleep duration	18	0.007 (–0.009, 0.023)	0.374
	Sleep duration variability (SD)	18	0.002 (–0.014, 0.018)	0.816

*Nominal $p < 0.05$ but Benjamini–Hochberg-adjusted $p > 0.05$.

the number of nocturnal sleep episodes ($\beta = 0.017$, 95% CI = [0.001, 0.033]; $p < 0.05$, BH-adjusted $p > 0.05$), suggesting a potential causal influence from ADHD to poorer sleep quality. No heterogeneity, horizontal pleiotropy, or outlier was detected (Supplementary Table 5).

Discussion

In this study, we conducted a comprehensive bidirectional MR analysis to investigate the causal relationship between various CRs along with sleep quality and quantity traits, and both ASD and ADHD. Our findings reveal significant evidence supporting a causal link between certain CR patterns and these disorders. Notably, using GWAS data derived from objective, accelerometer-based estimates of circadian timing and sleep measures, we established a causal relationship between genetically predicted M10 timing and both ASD and ADHD. M10 timing serves as a key indicator of chronotype, with higher values corresponding to a late chronotype preference. This finding suggests a potential causal impact of late chronotype preference in the development of ASD and ADHD. Moreover, our study offers new insights into the role of sleep efficiency, revealing a potential protective effect independently from circadian timing against ASD but not ADHD. In a novel observation, our bidirectional MR analyses indicated that ADHD led to an increased number of sleep episodes, highlighting a potential one-way causal relationship. However, the reverse scenario, where sleep disruptions cause ADHD, was not supported by our data. This distinction underlines the unique pathways through which the genetically predicted alterations in CRs and sleep interact with ASD and ADHD. To our knowledge, this investigation is the first to robustly demonstrate these specific causal relationships and their directions. Our findings imply that circadian alternation is causally linked with both ASD and ADHD. Interestingly, while sleep quality appears to play a causally independent role exclusively in ASD, it emerges as a consequence rather than a cause in ADHD (Figure 3).

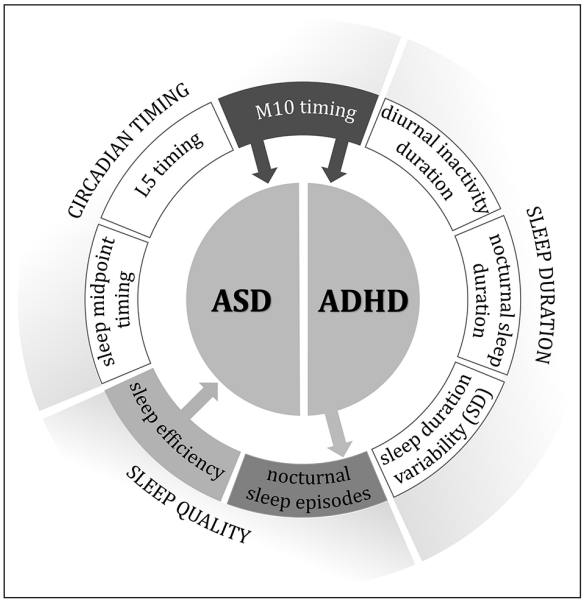

Figure 3. This figure summarizes the key causal associations identified in the study between genetic liability to circadian timing and sleep traits, and the risks of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Each arrow signifies a causal pathway.

Our research offers important supporting evidence for the CR disorder hypothesis, demonstrating that certain CR patterns, particularly a late chronotype preference as

indicated by M10 timing, are causally linked to both ASD and ADHD. This finding is in line with previous studies that reported an atypical CR pattern in these populations (Arns et al., 2021; Carmassi et al., 2019; Coogan & McGowan, 2017). Our study, using objective measures, expands upon these findings by establishing a causal relationship. There is growing evidence from epidemiological studies suggesting that circadian traits are linked with a range of psychiatric disorders, both general and specific (Arns et al., 2021; Schuch et al., 2018; von Schantz et al., 2021). This circadian alteration may explain certain sleep disturbances commonly observed in ASD and ADHD, such as prolonged sleep onset, nocturnal awakenings and early morning arousal (Cortese et al., 2009; Cortesi et al., 2010; Glickman, 2010; Lugo et al., 2020). These sleep challenges might be indicative of broader neurobehavioral and endocrine dysfunctions, as evidenced by abnormal cortisol and melatonin profiles in children with these disorders (Tordjman et al., 2005). Despite these insights, interventions like bright light therapy and melatonin supplementation have shown inconsistent results in improving behaviours and functions in children with ASD and ADHD (Coogan & McGowan, 2017; Rzepka-Migut & Paprocka, 2020), which may be attributable to variations in intervention duration or melatonin dosage (Rzepka-Migut & Paprocka, 2020). Under the assumption of an MR approach, we found that genetically predicted M10 timing is linked to an increased risk of ASD and ADHD. This contrasts with a prior MR study (Sun et al., 2022), which reported no association between chronotype and psychiatric disorders. Notably, the SNPs for morning chronotype in the previous study were based on self-reported data, whereas our study used SNPs calculated from objective accelerometer data, potentially providing a more accurate chronotype assessment.

In contrast to earlier research suggesting a bidirectional relationship between CR patterns and ASD (Geoffray et al., 2016) and ADHD (Imeraj et al., 2012), our findings indicate a unidirectional causal relationship. This primarily emphasizes the role of a consistently late chronotype in the onset and aggravation of these disorders, rather than the reverse. More importantly, our research provides a strong mechanistic basis for treatments aimed at modifying CRs, highlighting their potential not only in managing circadian sleep issues but also in directly influencing the disorders themselves. Therefore, promoting such interventions could be crucial in addressing complex sleep-related challenges and the broader symptoms of ASD and ADHD. The underlying mechanistic basis through which the circadian pathways influence the risk and progression of ASD and ADHD can be multifaceted. For instance, alterations in CRs can disrupt neurodevelopment and affect immune-inflammatory, metabolic, nitro-oxidative stress and neurotransmitter pathways, potentially through epistatic interactions or epigenetic modifications (Abdul et al., 2022), thereby contributing to the neurobiological changes associated with ASD. CR disruptions might affect the expression of key molecules like neurexins and neuroligins, known to play a role in the aetiology of these disorders. These disruptions are likely to occur during critical periods of brain development and plasticity (Zafeiriou et al., 2013). Evidence suggests that ASD and ADHD may be linked to CR disorders during critical periods of brain development (Geoffray et al., 2016), which could also include foetal and postnatal periods. Given the significant interplay between maternal and child CRs during these periods (Serón-Ferré et al., 2001), further research is essential to control for maternal and postnatal CRs and sleep patterns of the mothers, and to clarify the precise role of disrupted CRs in the onset and progression of these conditions. Future research should include longitudinal studies tracking circadian patterns from early foetal development into later life stages, and investigations into genetic and epigenetic markers associated with CR dysregulation in individuals with ASD and ADHD to further clarify the pathway. By enhancing our understanding of how CR disruptions impact neurodevelopment and behaviour, we can better design interventions to mitigate the effects of these disorders.

Our study suggests that sleep quality measures appear to independently influence ASD, differing from its role in ADHD, where it primarily acts as a consequence rather than a cause. This distinction contributes a new perspective to our understanding of these disorders, challenging previous notions of bidirectional interactions between sleep disturbances and ASD/ADHD (Owens et al., 2013; Whelan et al., 2022). While CRs affect sleep phenotypes and sleep-wake disorders, and the genetic determinants of these tend to emerge (Dijk & Archer, 2010), it is important to note that our measures of sleep quality and duration are proven to be independent of CR indicators as shown in the previous GWAS study (Jones, van Hees, et al., 2019). This underscores that sleep quality's protective role in ASD does not stem from shared mechanisms with CRs, highlighting sleep quality's unique contribution to ASD. Conversely, in ADHD, impaired sleep quality appears to be a result rather than a contributing factor. This, however, does not diminish the relevance of sleep disturbances in ADHD; rather, it suggests that non-circadian aspects of sleep disruption such as sleep quality and duration, as measured in our study, do not directly lead to ADHD. The circadian sleep disturbances can still act as the mediators from CRs to these disorders. A meta-analysis of 42 studies (Wagner et al., 2004) investigating sleep disturbances in adults with ASD and ADHD reveals similar patterns of sleep impairment in both groups, including longer sleep onset latency, reduced sleep efficiency, more frequent awakenings and lower self-perceived sleep quality compared to healthy controls. In ASD, poor sleep quality and insomnia, not linked to CR dysfunction, may exacerbate

specific symptoms. In ADHD, hyperactivity might intensify sleep fragmentation. These insights underscore the necessity for disorder-specific interventions: enhancing sleep quality could benefit individuals with ASD, whereas in ADHD, addressing the core symptoms may mitigate sleep issues.

The relationship between psychiatric disorders and both short and long sleep duration is well-documented (Lugo et al., 2020; Mayes et al., 2009; Parvataneni et al., 2020; Singh & Zimmerman, 2015). However, our study suggested that in ASD, it is sleep quality, as measured by sleep efficiency, rather than sleep duration, which plays a crucial contributing role. In ADHD, the increased number of sleep episodes, indicative of fragmented sleep, also reflects sleep quality issues. Therefore, sleep quality emerges as a more comprehensive aspect than sleep duration alone. While total sleep hours (duration) are important, the restfulness of sleep is more critical in disorders like ASD and ADHD. Focusing solely on sleep duration may overlook the complexities of sleep disturbances in these disorders.

Strengths and limitations

A major strength of our study lies in the MR design, using GWAS data leveraging objective accelerometer-based estimates of circadian timing and sleep measures. The use of MR design minimizes the residual confounding and reverse causality inherent in observational studies, and has allowed us to explore potential pathways of CRs, sleep disturbances and these disorders with greater accuracy. Moreover, unlike most other MR studies that rely on subjective self-reported sleep measures, our approach utilizes accelerometer data from the UK Biobank to provide a more precise and comprehensive picture of sleep patterns. Previous large-scale genetic studies of sleep traits have depended heavily on self-reported measures, often constrained to a limited set of questions that can only approximate a few sleep traits and are prone to biases like misperception and recall errors. These biases, including social desirability bias and the influence of current mood on recall, can significantly skew the accuracy of self-reported sleep data. Our method, by contrast, offers a more objective and nuanced understanding of sleep and CRs, free from such subjective biases. Our comprehensive GWAS analysis, the largest scale to date using accelerometer data, identified numerous genetic associations across circadian timing, sleep duration and quality, offering novel insights into sleep biology that were not detectable in larger studies relying on self-reported sleep traits.

Despite its strengths, our study has limitations. First, the genetic analyses were confined to individuals of European ancestry, restricting the generalizability of the findings and leaving unexplored associations on individuals of non-European ancestry who might be at risk. In addition, due to the absence of sex-stratified GWAS, we could not examine potential causal differences by sex, a significant factor commonly associated with psychiatric disorders. Second, the associations identified reflect cumulative lifetime exposure effects. However, it is plausible that personal CR, sleep quality and duration may vary with age. Unfortunately, the current analyses lack the capability to stratify MR effects by age, raising the possibility that causal effects may differ for younger and older adults. Notably, our study does not consider potential nonlinear effects of sleep-associated traits on psychiatric disorders due to the summary-data-level nature of MR analyses. Future research could investigate sleep-associated traits at different life stages to understand the impact of sleep changes on psychiatric disorder risk. Furthermore, chronotype measured as the most active 10 h period in the study, influenced by an interplay of CRs, innate sleep homeostatic mechanisms and societal pressures (Jones, Lane, et al., 2019), may not fully capture the complexities of circadian misalignment. Future research should focus on discerning whether it is circadian misalignment, rather than chronotype per se, that exhibits a stronger association with ASD and ADHD.

Conclusion

Using bidirectional MR analysis and GWAS data derived from objective accelerometer-based measures, our study provides solid evidence to reveal a causal link between late chronotype and both ASD and ADHD. Notably, we find that sleep quality independently influences ASD but emerges as a consequence rather than cause in ADHD, highlighting distinct interactions between CRs and sleep disturbances with each disorder. These findings emphasize the need for tailored approaches in studying and managing ASD and ADHD, considering their unique associations with sleep patterns and CRs. Our research, by identifying specific causal relationships, lays the groundwork for more focused therapeutic strategies.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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