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Review

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Potential bidirectional communication between the liver and the central circadian clock in MASLD

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Most aspects of physiology and behaviour fluctuate every 24 h in mammals. These circadian rhythms are orchestrated by an autonomous central clock located in the suprachiasmatic nuclei that coordinates the timing of cellular clocks in tissues throughout the body. The critical role of this circadian system is emphasized by increasing evidence associating disruption of circadian rhythms with diverse pathologies. Accordingly, mounting evidence suggests a bidirectional relationship where disruption of rhythms by circadian misalignment may contribute to liver diseases while liver diseases alter the central clock and circadian rhythms in other tissues. Therefore, liver pathophysiology may broadly impact the circadian system and may provide a mechanistic framework for understanding and targeting metabolic diseases and adjust metabolic setpoints.

The mammalian liver circadian clock

The mammalian circadian system is a network of cellular clocks that coordinates the timing of internal physiological processes in anticipation of daily recuring environmental changes. Nearly every organ and cell in the body harbours a circadian clock. Together, these clocks are organised to produce coherent, ~24-h tissue-level oscillations. In mammals, the central circadian pacemaker is localised in the bilateral suprachiasmatic nuclei (SCN) of the hypothalamus and receives input about environmental light directly from the retina. The SCN clock entrains to the light-dark cycle and then coordinates the timing, or phases, of tissue clocks located throughout the brain and body[1,2]. Importantly, while the molecular building blocks of the clock are largely preserved across tissues, each tissue clock entrains with a different temporal relationship to the light-dark cycle[3,4]. The putative value of this circadian organisation is that it temporally partitions behaviour and tissue-specific gene expression and biochemistry so that internal processes anticipate predictable changes in the environment, such as food availability and predation, caused by Earth's rotation on its axis[5] (Fig. 1).

The liver is arguably the most well-studied peripheral circadian clock in mammals. It responds dynamically to feeding and fasting cycles and, when nutrients are abundant, it stores energy as glycogen, triglycerides and proteins. Conversely, during periods of fasting or increased energy demand, the liver mobilises energy reserves. Most liver functions have 24-h rhythms to anticipate periods of energy supply and demands. In addition to regulating daily cycles of nutrients, the liver also rhythmically metabolises bile acids, amino acids, toxins and drugs (for reviews see refs. 6,7). Circadian rhythms in liver function are regulated in part by the molecular circadian timekeeping mechanism. The molecular clock in mammals is based on a set of transcriptional-translational negative feedback loop. The circadian protein BMAL1 heterodimerizes with CLOCK (or NPAS2 in some tissues) to drive the transcription of *Period* (*Per1*, *2*, *3*) and *Cryptochrome* (*Cry1*, *2*) genes. As PER and CRY proteins are translated, they dimerise, translocate into the nucleus and feedback on BMAL1/CLOCK to inhibit their own transcription. This cycle takes approximately 24 h to complete and thus sets the pace of cellular circadian clocks. An additional accessory feedback loops contribute to cellular timekeeping. For example, the BMAL1/CLOCK regulated nuclear receptors ROR (α, γ, β) and REV-ERB (α, β) activate and inhibit the expression of *Bmal1* and *Clock*, respectively, and contribute to fine tune the time keeping system[8] (Fig. 1).

Meal timing also regulates circadian rhythms in liver gene expression and function. Consequently, perturbing the daily rhythm of food intake has a strong impact on the organisation of the rhythmic liver clock and physiology[9–14]. When feeding is restricted to the inactive phase, the phases of circadian clocks in peripheral tissues involved in energy metabolism, including the liver, white adipose tissue (WAT), and gut, entrain to feeding time independently of the central circadian clock and other non-metabolic tissues clocks[15,16]. This results in, both,

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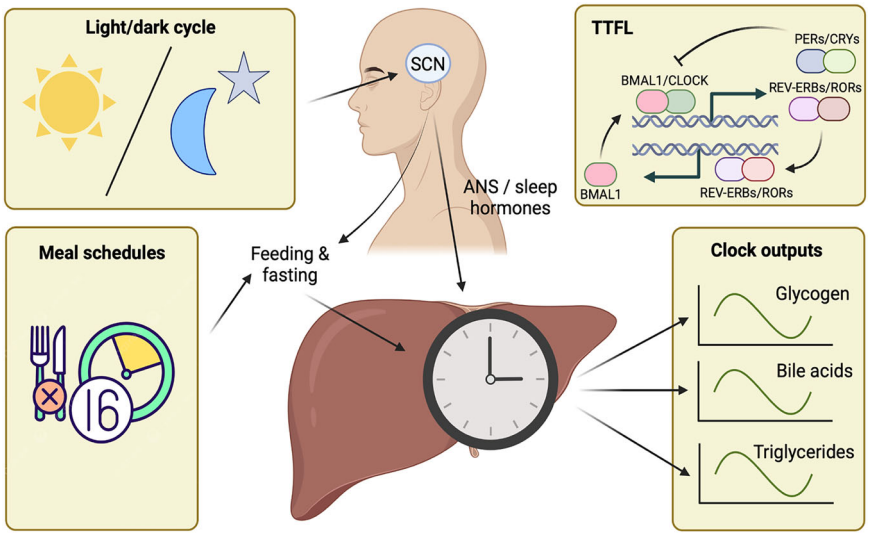

Fig. 1 | Circadian coordination of liver metabolism. A circadian pacemaker in the hypothalamic suprachiasmatic nuclei (SCN) is reset by the external light-dark cycle. Through temporal regulation of behavioural functions such as the sleep-wake cycle or feeding-fasting rhythms, endocrine outputs and the autonomic nervous system (ANS), the SCN clock controls the timing of cellular clocks in hepatocytes (and other central and peripheral tissues). At the molecular level, these clocks are comprised of interlocked transcriptional-translational feedback loops (TTFLs) of clock genes and proteins characterised by marked 24-h rhythms in transcriptional activity and protein abundance. In the liver, local clock rhythms and internal (e.g., hormones) and external circadian inputs (e.g., meal schedules) are integrated to generate metabolic clock outputs such as glycogen storage/release, bile acid and triglyceride biosynthesis.

internal (liver, gut etc. vs. SCN) and external circadian misalignment (liver, gut vs. light-dark cycle)[17].

While mechanisms are still not entirely clear, food-borne metabolites and postprandial hormone signals such as insulin, oxyntomodulin, glucagon-like peptide 1 and leptin can act as "zeitgebers" (German word for "time giver") for circadian clocks in peripheral organs and parts of the brain[18–21]. Other factors more prevalent during fasting phases (e.g., during sleep), such as fatty acids or glucagon, may act as pre-feeding signals to reset peripheral clocks[22,23]. Additionally, feeding is associated with an increase in body movements that contribute to the rhythmic body temperature[15,24,25] that, in turn, may act as a synchroniser of the peripheral circadian clocks[26–29] (Fig. 1).

In sum, ~24-h rhythms of liver functions are controlled by both the molecular circadian timekeeping mechanism in hepatocytes and by systemic factors, particularly those related to food intake. Thus, the liver is perfectly poised to anticipate predictable changes in nutrient availability as well as respond to unpredictable metabolic demands.

Disruption of rhythmic liver function is associated with metabolic dysfunction-associated steatotic liver disease (MASLD)

Metabolic dysfunction-associated steatotic liver disease (MASLD) is defined by an excessive accumulation of lipid in the liver in the presence of at least one cardiometabolic risk factor. MASLD comprises isolated liver steatosis (metabolic dysfunction-associated steatotic liver (MASL)), steatohepatitis (MASH), as well as fibrosis and cirrhosis. The new definition thus highlights the metabolic roots of the disease and its tight association with type 2 diabetes (T2D), obesity and other cardiometabolic risk factors[30,31]. MASLD is the most common chronic liver disease and its prevalence is projected to increase even further. At least one in four patients with MASLD has MASH, which is the second leading cause of liver disease in adults scheduled for liver transplantation in the USA[32]. In patients with obesity and T2D, prevalence of MASLD increase two- to fourfold, depending on age and comorbidities[33,34].

Progression of liver damage in MASLD is extremely variable. Whereas simple steatosis reflects non-progressive dysfunctional metabolism, MASH is a chronic liver disease that may progress undiagnosed for years, before eventually emerging as liver failure and hepatocellular carcinoma (HCC). The earliest event initiating MASLD is absolute or relative calorie excess, as confirmed by the link between MASLD and obesity. Limited physical activity or sedentary behaviours are complementary aspects of calorie imbalance, irrespective of body mass index[35]. As triglyceride synthesis outpaces the capacity for VLDL synthesis and export, triglycerides accumulate within hepatocytes, resulting in steatosis and eventually lipotoxicity[36]. Additional increased de novo lipogenesis from carbohydrates, specifically fructose, may produce similar lipotoxic effects. Moreover, consumption of sugar-sweetened drinks containing either fructose or sucrose, which is converted to fructose and glucose in the gut, may be more potent than dietary lipids in promoting MASH[37,38]. Uncontrolled and incomplete lipid oxidation, oxidative stress and activation of the unfolded protein response are two well characterised pathways that promote cell death in MASH. These multiple insults synergistically drive the development and progression of MASLD, particularly in genetically predisposed people.

Increasing evidence suggests an association between MASLD and the perturbation of the daily rhythms in liver physiology, also called circadian disruption. Liver physiology has been studied in rodent models with circadian disruption including light at night[39,40], forced work during the resting phase mimicking shift work[41], chronic shifts of the light-dark cycle[42–44], and genetic disruption of molecular clock function in hepatocytes[43,45,46]. These animal studies demonstrated that circadian disruption causes fatty liver and MASLD. However, recent studies suggest a more contrasted conclusion. In contrast to hepatocyte-specific circadian clock disruption, disabling the molecular clock in the entire animal[47–49] or in the intestinal epithelium[50] protects mice from MASLD and MASH. While the mechanism is not clear, it likely involves perturbations of circadian clock-dependent endocrine regulation and/or nutrient storage that decrease lipid storage and steatosis in the liver and, consequently, the associated fibrosis and inflammation.

In humans, clinical data are still lacking that document a tight link between disruption of liver circadian rhythms and MASLD/MASH. Recent studies of liver biopsies collected at different times of the daily cycle showed that rhythmic gene expression, including circadian clock gene expression, is disrupted in patients with HCC[51]. Moreover, increased liver fibrosis severity in human was associated with a decreased expression of circadian clock genes[48]. Another recent report shows that while livers from MASH patients do not have altered expression of circadian clock genes, the time-of-day-dependent expression of hundreds of transcripts involved in cell-to-cell communication, intracellular signalling and energy metabolism were altered[52]. Amino acid and lipid metabolome rhythms were also altered suggesting that MASH modulates output rhythms. Similarly, circadian disruption caused by chronic jet lag in a "humanised liver" mouse model in which mouse hepatocytes were partially replaced by human hepatocytes led to MASH and HCC with characteristics similar to the human diseases[44]. Altogether, these studies suggest that perturbation of rhythmic liver physiology is associated with the development of MASLD.

The relationship between circadian disruption and MASLD is further supported by studies of MASLD in shift workers. One study of >8000 shift

Table 1 | Overview of the studies reporting the impact of shift work on MASLD

SHIFT WORK AND MASLD			
Authors - year	**Study design**	**Hypothesis / Aim**	**Outcomes—Remarks**
Balakrishnan et al.[53]	8159 participants from the 2005-2010 NHANES cycles, aged 20–79 years	To investigate the association between shiftwork and the risk of MASLD identified by elevated aminotransferases	MASLD occurred more frequently in shift workers than in non-shift workers, but overall shift work was not associated with the risk of MASLD
Wang et al.[55]	4740 male workers of whom 39.5% were night shift workers	To address the relationship between night shift work and the elevated alanine transaminase level of workers, and analyse the potential mediating effect of MASL by means of liver ultrasound	Night shift workers had a higher risk of elevated alanine transaminase levels, which increased with increasing years of night shifts. It is likely that shift work involving circadian disruption exerts a direct effect on liver dysfunction
Zhang et al.[54]	6881 subjects including night shift workers and those who never worked night shifts	To explore the association between night shift work and MASLD assessed with abdominal ultrasonography in steel workers	Night shift workers had greater odds of MASLD compared to those who never worked night shifts. The duration, cumulative number and cumulative duration of night shifts were positively associated with MASLD
Huang et al.[56]	281,280 UK Biobank participants aged 37–73 years	To explore the association between night shift work and the risk of MASLD diagnosed in the event of hospitalisation or death	Compared to workers who never/rarely worked night shifts, those who worked some or regular/permanent night shifts were more likely to develop MASLD. Longer duration and higher frequency shift work showed a higher risk of incident MASLD, and the association was not modified by genetic predisposition
Maidstone et al.[57]	286,825 UK Biobank participants aged 40–69 years	To study the relationship between shift work and chronotype with liver fat fraction and MASLD defined by Dallas steatosis index, previous hospital admissions and proton density fat fraction (PDFF)	Shift workers were more likely to develop pathological fat content in the liver, predisposing to MASLD, and this effect was mediated by obesity. Extreme late chronotypes had accumulation of liver fat similar to shift workers

workers showed no association with MASLD[53]. However, a more recent study of >6000 rotating and night shift workers in China showed that longer duration of shift work and extended nighttime work hours increased the risk of MASLD by 23%[54]. In a comparable study of male shift workers, night shift work was associated with elevated alanine transaminase levels, which is a marker of hepatic pathology[55]. In a large-scale, retrospective analysis of UK Biobank data, night shift work was associated with MASLD, and the risk increased as years of night shift work increased[56]. Moreover, irregular schedules of shift work and extreme late chronotype were also associated with elevated liver steatosis[57]. These results are summarised in Table 1. Interestingly, there is an association between the risk of HCC (and other types of cancer, even in the absence of cirrhosis) and geographical location in a time zone[58,59]. Those in the Western portion of a time zone have greater HCC risk, possibly because they experience more circadian disruption caused by delayed exposure to sunlight.

Another highly prevalent condition with chronodisruptive potential and an impact on liver steatosis is sleep apnoea. Obstructive sleep apnoea (OSA) is characterised by recurring obstruction of the upper airways during sleep. This results in sub-optimal ventilation and intermittent hypoxia which promotes arousal and reduces overall sleep quality[60] and alters circadian activity rhythms[61]. Mounting evidence suggests OSA and chronic intermittent hypoxia (CIH) are risk factors for MASLD[62–64]. In MASLD patients with OSA, CIH triggers an increase in oxidative stress and generation of reactive oxygen species, release of pro-inflammatory cytokines, and induction of systemic inflammation, which further exacerbate liver steatosis and inflammation[65]. In addition, OSA in a mouse model is associated with tissue-specific transcriptomic changes in circadian rhythmicity and mean 24-h gene expression levels[66]. Moreover, hypoxic events themselves act as synchronising stimuli for some tissue clocks. Such tissue-specific responses to OSA-associated hypoxic intervals may provoke circadian tissue clock misalignment (or internal desynchrony) reminiscent of what is observed in animal models of shift work[67].

These observations support the hypothesis that high amplitude circadian rhythms protect against the development of liver disease. Accordingly, restoring rhythmic feeding in animals during high-fat (HFD) obesogenic regimen with time-restricted feeding[68,69] or synchronising the clock using small molecules targeting the ROR/REV-ERB pathway improves MASLD in mice[70–72]. However, in clinical trials, time-restricted feeding was no more effective than caloric restriction in treating obesity and MASLD[73–76].

MASLD and cirrhosis are related to disrupted circadian physiology and sleep

Research on obesity and MASLD has shown that there are reciprocal connections between metabolic liver disease and circadian physiology. Chronic consumption of HFD, which leads to MASLD in mice[77], alters circadian physiology and global rhythmic metabolism in mice. HFD consumption disrupts daily rhythms of meal intake and the associated humoral signals, as well as rhythmic gene expression in peripheral tissues including the liver in male mice[69,78–81]. During HFD feeding, mice increase their food intake during the light phase, which is the resting phase for nocturnal rodents during which they normally do not eat[79]. A parallel observation was made in mice carrying a mutation in the circadian *Clock* gene, which also promotes overweight and obesity[82]. Genetic animal models of obesity including the mouse *Ob* and *Db* mutations of *Leptin* and its receptor, respectively, also have disrupted eating rhythms[83–85]. The disruption of the eating rhythm by HFD consumption is reversible[86] and dependent on sex and strain since female C57BL/6J mice or mouse strains that are resistant to HFD-induced obesity do not have disrupted eating rhythms during HFD feeding[87,88].

The SCN circadian pacemaker and circadian entrainment are also affected by HFD consumption in mice. The circadian period of locomotor activity, a direct output of the activity of the SCN clock, is increased during HFD feeding[79]. Moreover, the response of circadian activity rhythms to a light pulse, a property of the SCN clock, was also altered[89]. However, these effects are not specific to obesity and metabolic syndrome. Choline-deficient diet, which rapidly induces liver fibrosis with minimum impact on body weight[90], causes wide-spread changes liver transcriptome diurnal rhythms including genes associated with lipid metabolism and inflammatory processes[91,92]. It also advances the phases of the liver and kidney circadian clocks, suggesting an impact on the global circadian physiology[91,92].

In humans, the impact of liver diseases on circadian behaviour has been mainly studied in patients with cirrhosis to identify aetiological strategies to manage the sleep-wake disturbances that are common in these patients[93]

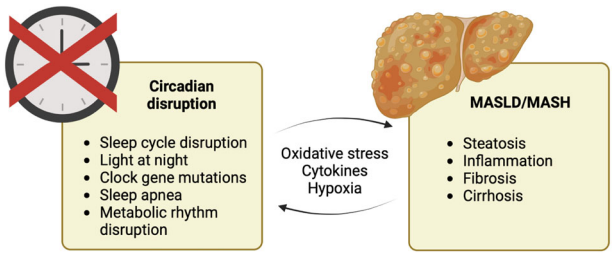

Fig. 2 | Circadian disruption-MASLD/MASH crosstalk. Circadian disruption is a risk factor for the development of fatty liver disease. It can arise from external factors such as light at night or shift work-associated alterations in sleep-wake cycles or internal factors such as sleep apnoea, clock gene modifications or metabolic dysfunction. Through alterations in oxidative stress, cytokine release and hypoxia, circadian disruption promotes the development of all levels of fatty liver disease—from steatosis to cirrhosis. Vice versa, MASLD/MASH can feed back on circadian regulatory functions through the same pathways, thus generating a vicious cycle of chronometabolic dysfunction.

(Fig. 2). Delayed sleep and wake timing, daytime sleepiness, increased sleep latency and interrupted night sleep are more common in patients with cirrhosis than in patients with other chronic diseases (e.g., renal failure requiring dialysis)[94–97]. While sleep-wake abnormalities in patients with cirrhosis have traditionally been ascribed to hepatic encephalopathy, they have recently been linked to excessive daytime sleepiness[98] and, in its more severe forms, sleep–wake inversion[99]. Further, the hepatic metabolism of hypnotic drugs is disturbed in cirrhotic patients[100] and patients are extremely sensitive to these medications. Therefore, special care must be taken when treating their sleep disturbances. However, the increase in daytime sleepiness also impairs night sleep and the sleep–wake cycle, making difficult to separate in patients the influence of the increased daytime sleep and the perturbed nighttime sleep. Homoeostatic[101,102] and circadian abnormalities in sleep–wake regulation have been associated with liver cirrhosis. The latter includes phase delays in the daily rhythms of melatonin[103,104] and cortisol[105], impaired melatonin responses to light[103] and impaired melatonin catabolism[106]. There is also anecdotal evidence that liver transplantation can reverse sleep disturbances[107], suggesting a direct effect of the cirrhotic liver on circadian behaviour. There are other, largely unexplored mechanisms through which cirrhosis, and especially decompensated cirrhosis, might affect the circadian timing system, including endocrine[108] and metabolic[109] disruptions as well as sympathetic denervation[110] potentially affecting the communication with the SCN, abnormal temperature regulation, reduced muscle mass and ability to exercise, and aberrant meal timing (i.e., evening snacking) (reviewed in ref. 7).

Clinically, sleep–wake rhythm disturbances are associated with the onset and the worsening of chronic

liver disease and negatively affect quality of life and health[95]. Observational studies showed that short sleep duration and poor sleep quality were associated with increased risk of MASLD in middle-aged[111] and younger people[112]. A meta-analysis reported increased risk of MASLD in people experiencing insomnia[113]. Additionally, a study comparing 46 patients with histologically diagnosed MASLD to 22 healthy individuals found that MASLD patients had later sleep onset times, worse sleep quality and shorter sleep duration[114]. Furthermore, large cohort longitudinal studies support the relationship between sleep disturbances and duration and MASLD[115,116]. However, it is unknown whether sleep disturbances promote MASLD and how MASLD influences sleep. A recent bidirectional Mendelian randomisation study using genetic and sleep data found that different sleep traits could trigger and foster progression of MASLD, whereas MASLD did not appear to alter sleep traits, thereby rejecting the two-way hypothesis[117].

Poor sleep quality and delayed sleep onset could affect metabolic physiology and thereby promote MASLD. Obesity, a risk factor for MASLD, is associated with fragmented daily temperature and sleep rhythms[118], as well as changes in endocrine oscillations, e.g., of nocturnal melatonin[119,120]. Sleep disturbances can also dysregulate hormones such as ghrelin and leptin and the activity of the endocannabinoid system[121–123]. Studies in healthy individuals showed that sleep restriction increases appetite and calorie intake, decreases insulin sensitivity and alters cortisol levels[124]. MASLD patients are more likely than healthy patients to eat later in the day[114] and go to bed later[114,125]. Furthermore, the combination of late chronotype with poor adherence to a Mediterranean-type diet is associated with advanced liver fibrosis in patients with MASLD[126]. In a study of 295,837 participants who were followed for 15 years, a *U*-shaped relationship between duration of sleep and the incidence of HCC and mortality from chronic liver disease was observed[127]. Excessive daytime sleepiness and longer daytime naps also increases MASLD risk[113,128] (Table 2).

MASLD influences the physiology of peripheral organs and global physiology

Because of its central role in organising metabolism, disruption of the circadian clock is associated with obesity and insulin resistance[129,130]. In a clinical study, only ten days of circadian misalignment were sufficient to reduce insulin sensitivity[131]. Thus, insulin resistance caused by circadian disruption could contribute to the development of MASLD by stimulating adipose tissue to expand and release pro-inflammatory adipokines and free fatty acids, leading to systemic inflammation and ectopic fat accumulation[132,133]. This state of chronic systemic inflammation, also observed in obesity and T2D, is associated with the disruption of the circadian clock in skeletal muscles and WAT[134,135], possibly because of the direct interaction between the inflammation-activated transcription factors NF-κB and BMAL1[136,137]. The relationship between malnutrition or sarcopenia, which is common in decompensated cirrhosis, and circadian disruption has not been well studied. In cirrhosis patients, malnutrition and sarcopenia has been attributed to the combination of abnormalities in nutrients intake, absorption and metabolism[138]. Albeit reasonable (please refer to ref. 7 for a review), the possibility that it may relate, at least to some extent, to liver clock dysfunction and central-peripheral clock desynchrony has remained untested.

Is the liver a hub between central and peripheral clocks?

The liver integrates rhythmic systemic cues to synchronise its physiology with nutrient cycles and food intake and transmits these signals to other tissues, including the central clock in the SCN[2]. Accordingly, and as previously discussed, advanced fibrosis is associated with alterations of the activity/sleep cycle and disturbed metabolism in other tissues, potentially through inter-organ communication. There is other evidence that the liver clock communicates with circadian clocks in other organs. For example, WAT and lung circadian clocks cannot entrain properly to feeding rhythms in mice with *Bmal1* deleted in hepatocytes[139]. The liver clock is also necessary and sufficient to integrate feeding signals and restore rhythmic liver physiology in animals otherwise devoid of functional circadian clocks[140]. Moreover, the reconstituted liver clock in these clock-less mice also communicates with the clocks in skeletal muscles and regulates rhythmic gene expression in muscles[140,141]. However, the restoration of the rhythmic physiology of these tissues is only partial and functional clocks in both liver and skeletal muscles are required to completely restore glucose metabolism in condition of rhythmic feeding[140,141].

The role of the liver in coordinating global physiology in animals with functional circadian systems is less clear. Mice in which mouse hepatocytes were replaced by human hepatocytes were unable to integrate signals from the mouse[142]. Mice with human hepatocytes had advances liver circadian clocks, similar to clock-less animals with functional circadian clocks restored only in hepatocytes[143]. Strikingly, this liver phase advance impacted their global physiology. Additionally, mice with human hepatocytes had altered rhythms of gene expression in the SCN and the arcuate nucleus of the hypothalamus.

Table 2 | Overview of the studies reporting the link between MASLD and sleep disruption.

SLEEP DISRUPTION AND MASLD			
Authors - year	**Study design**	**Hypotesis / Aim**	**Outcomes - Remarks**
Kim et al.[111]	69,463 middle-aged workers and their spouses	To investigate the association between sleep duration and sleep quality with MASLD diagnosed by ultrasound	Short sleep duration and poor sleep quality were significantly associated with increased risk of MASLD
Bernsmeier et al.[114]	46 patients with MASLD assessed by biopsy and 22 healthy controls	To explore the relationship between sleep characteristics, daytime sleepiness, mealtimes and disease severity in patients with MASLD	MASLD patients had longer sleep onset times, shorter sleep duration, poorer sleep quality and meal frequency shifted towards night compared to healthy controls
Peng et al.[128]	8559 Chinese individuals aged ≥ 40 years	To study the associations between MASLD diagnosed by ultrasonography and night and daytime sleep duration	Short sleep duration and long daytime naps were associated with increased risk of MASLD
Okamura et al.[115]	12,306 participants	To study the association between sleep duration and incident MASLD diagnosed by abdominal ultrasonography	Short sleep duration was a significant risk for incident MASLD
Um et al.[116]	143,306 Korean adults without MASLD	To examine the association between sleep duration and quality with the development of MASLD by means of abdominal ultrasound	Short sleep duration was independently associated with increased risk of incident MASLD
Zhou et al.[125]	4572 individuals with a diagnosis of MASLD based on the controlled attenuated parameter score	To examine the association between night rest and MASLD	Later bedtime was positively associated with MASLD
Sun et al.[117]	GWAS data for insomnia of 336,082 participants from European populations obtained from the Neale LABS Open GWAS database in 2017	To investigate the causal relationship between MASLD, described by MASLD diagnosis, alanine transaminase levels, aspartate aminotransferase and liver fat percentage, and changes in sleep traits using Mendelian randomisation	Sleep characteristics may cause the onset and exacerbation of MASLD, but MASLD does not change sleep characteristics
Castelnuovo et al.[126]	126 adult patients with MASLD determined by ultrasound	To investigate the association of chronotype and adherence to the Mediterranean diet with the liver fibrosis risk assessed by transient elastography	Intermediate + late chronotype and low adherence to the mediterranean diet were associated with significant and advanced liver fibrosis in patients with MASLD
Long et al.[127]	295,837 individuals in the National Institutes of Health-American Association of Retired Persons Diet and Health Study	To explore the associations between night and daytime sleep duration with the risk of HCC incidence and CLD mortality, extrapolated from state cancer registries	U-shaped association between night-time sleeping and mortality risk for HCC and CLD. Longer daytime sleep duration was associated with increased risk of death from HCC and CLD

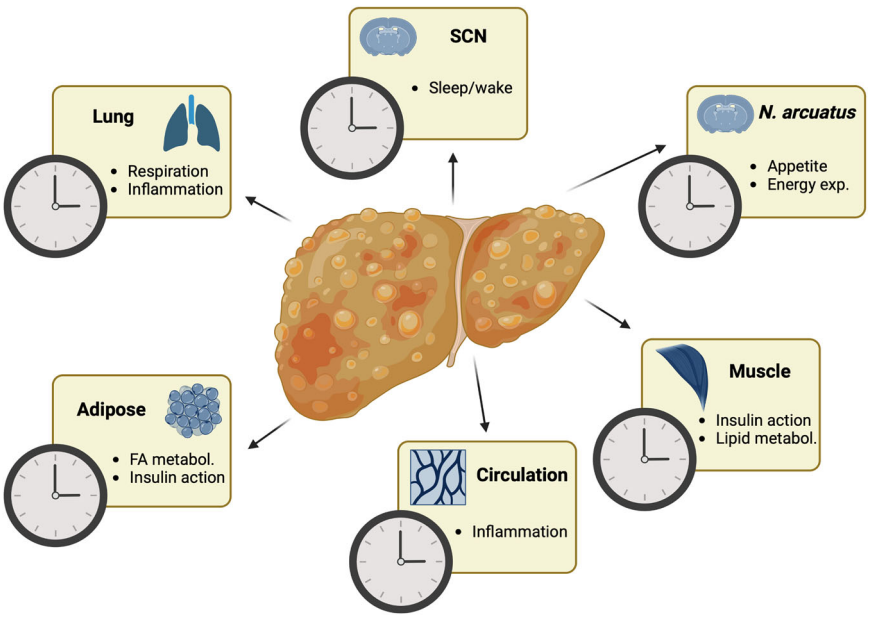

Fig. 3 | Systemic effects of altered circadian regulation in MASH. Disrupted circadian outputs from the diseased liver can affect metabolic and immune rhythms in other tissues. In MASH patients or animal models of fatty liver disease repercussions on rhythmic functions outside the liver have been shown for the SCN (sleep–wake cycle regulation), the arcuate nucleus (appetite regulation), metabolic tissues such as muscle (lipid and carbohydrate metabolism), and inflammatory processes in the lung and circulating immune cells.

Their capacity to synchronise to daytime feeding was impacted. The humanised mice showed a behaviour similar to that of SCN-lesioned animals[142]. Considering the similarities in phenotypes, similar mechanisms could be involved in altering the phases of liver clocks in mouse models of liver fibrosis[91,92] and in humans with liver cirrhosis[93]. Thus, it is possible that in MASH or liver cirrhosis, the liver could transmit signals to the hypothalamus to modulate diurnal activity.

The mechanism that could transmit the signal from the pathogenic liver to the brain and other organs remains elusive. One hypothesis is that abnormal circulating factors originating from the liver and specific to

MASLD impact the rhythmic physiology of other central and peripheral organs. Accordingly, MASLD leads to perturbed profiles of circulating proteins and metabolites[144,145]. A recent study shows that disrupting the liver circadian clock by simultaneously deleting *Rev-erbα* and *Rev-erbβ* or *Bmal1* specifically in hepatocytes of adult mice disrupted their feeding rhythm[146]. Because deletion of *Rev-erbα/β* or *Bmal1* is associated with disrupted liver physiology[139,147–149], this condition could recapitulate models of MASLD and mice with "humanised" livers. Surprisingly, the perturbation of the feeding rhythm was lost after vagotomy or ablation of liver vagal afferent neurons, implying a role of the autonomous nervous system (ANS). In addition, the perturbation of the feeding rhythm and body weight gain caused by HFD feeding were mitigated by liver vagotomy[146]. Together, these data highlight a potential critical role of the ANS in the modulation of SCN activity by the cirrhotic liver, exemplified by the fact that lipid liver accumulation modulates the activity of the ANS *via* the alteration of direct GABAergic connections[150,151]. However, this result is at odds with previous publications showing a normal feeding rhythm in hepatocyte *Bmal1*[149,152] and *Rev-erbs*[153] knockout mice. Moreover, this finding must be considered relative to numerous studies that showed that severing the neuronal connection between the liver and the SCN through vagotomy or liver transplantation was sufficient to induce a global loss of the diurnal feeding pattern in rodents[154–157], a phenomenon not observed in this study.

Conclusion

Mounting evidence suggests there may be bidirectional connections between the liver and the central clock that regulate circadian behaviour. Circadian disruption leads to liver steatosis and MASLD with liver fibrosis is associated with alterations of circadian rhythms and sleep (Fig. 3). Accordingly, restoring a rhythmic liver physiology through dietary intervention of small molecules targeting the circadian clock appears like an interesting strategy that was successful in animal models. Reciprocally, anecdotical evidence tends to show that eliminating liver fibrosis can restore circadian rhythmicity and sleep in patients with liver cirrhosis. Recent experimental evidence suggests a role of the ANS in this inter-organ communication. Accordingly, degeneration of sympathetic liver innervation observed in MASLD could play a role in both the pathophysiology of the disease and the associated alterations of circadian behaviour[110]. Therefore, the liver–brain connection would deserve more attention in future research.

Data Availability

No datasets were generated or analysed during the current study.

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Competing interests

The authors declare no competing interests.

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