Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

accumulation and exacerbates AD-like pathology. Furthermore, SR-B2 interacts with TLR4 and TLR6 to promote the activation of microglia by Aβ, which induces the production of reactive oxygen species, IL-1β and other proinflammatory mediators as well as inflammasome activation. These findings indicate that SRs could be both beneficial and detrimental in the progression of AD — beneficial by promoting clearance of the neurotoxic Aβ peptides, yet detrimental by contributing to disease progression and neurotoxicity through mediating the inflammatory response to Aβ. These dichotomous roles of SRs have led to their description as 'double-edged swords'.

SRs are also associated with atherosclerosis, a chronic inflammatory disease characterized by the accumulation of modified forms of lipoproteins as 'plaques' in the arterial wall. The failure of macrophages to process modified lipoprotein efficiently can lead to the formation of foam cells, thereby contributing to atherosclerosis. SR-A1, SR-A4, SR-B1, SR-B2, SR-D1, SR-E1, and SR-G1 can recognize OxLDL. Furthermore, upon exposure to modified LDL, SR-B2 interacts with TLR4 and TLR6, resulting in NF-κB activation and contributing to the inflammatory response associated with atherosclerosis. The distinct role of each of these SRs in atherosclerosis is not clear; however, it is possible that the role of each SR depends on the level of its expression in a certain tissue or cell type. This interesting area of investigation remains understudied.

Additionally, SRs are critically important in autoimmune diseases, such as SLE. Removal of apoptotic cells is a crucial process in immunity and in maintaining homeostasis in healthy tissues. Many cells, such as macrophages and dendritic cells, have the ability to clear apoptotic cells. A failure in the clearance of apoptotic cells can lead to their accumulation and facilitate the development of an 'anti-self' response to these cells, thereby contributing to autoimmune diseases. SLE is an example of this process, as patients with SLE have high levels of circulating apoptotic cells. SR-F1 binds to and phagocytoses apoptotic cells leading to their clearance, and, in mouse models, SR-F1 deficiency impairs the engulfment of apoptotic cells leading to the development of a syndrome similar to SLE. Because of the limited available options to treat SLE, these findings may have therapeutic implications for this disease.

Conclusions

SRs are phagocytic and innate immune recognition receptors that play a crucial role as regulators of inflammatory signaling. These receptors are involved in multiple physiological and pathological processes, including interactions with TLRs and delivery of ligands to different cellular compartments. Additionally, the roles of these receptors in many degenerative and autoimmune diseases, as well as their potential as targets for therapeutic interventions to treat various disorders, warrant further study.

FURTHER READING

Areschoug, T., and Gordon, S. (2009). Scavenger receptors: role in innate immunity and microbial pathogenesis. Cell. Microbiol. *11*, 1160–1169.

Canton, J., Neculai, D., and Grinstein, S. (2013). Scavenger receptors in homeostasis and immunity. Nat. Rev. Immunol. *13*, 621–634.

Frenkel, D., Wilkinson, K., Zhao, L., Hickman, S.E., Means, T.K., Puckett, L., Farfara, D., Kingery, N.D., Weiner, H.L., and El Khoury, J. (2013). Scara1 deficiency impairs clearance of soluble amyloid-β by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. Nat. Commun. *4*, 2030.

Greaves, D.R., and Gordon, S. (2009). The macrophage scavenger receptor at 30 years of age: current knowledge and future challenges. J. Lipid Res. *50*, S282–S286.

Hickman, S., Izzy, S., Sen, P., Morsett, L., and El Khoury, J. (2018). Microglia in neurodegeneration. Nat. Neurosci. *21*, 1359–1369.

Krieger, M. (1997). The other side of scavenger receptors: pattern recognition for host defense. Curr. Opin. Lipidol. *8*, 275–280.

Means, T.K., Mylonakis, E., Tampakakis, E., Colvin, R.A., Seung, E., Puckett, L., Tai, M.F., Stewart, C.R., Pukkila-Worley, R., Hickman, S.E., *et al*. (2009). Evolutionarily conserved recognition and innate immunity to fungal pathogens by the scavenger receptors SCARF1 and CD36. J. Exp. Med. *206*, 637–653.

PrabhuDas, M.R., Baldwin, C.L., Bollyky, P.L., Bowdish, D.M.E., Drickamer, K., Febbraio, M., Herz, J., Kobzik, L., Krieger, M., Loike, J., *et al*. (2017). A consensus definitive classification of scavenger receptors and their roles in health and disease. J. Immunol. *198*, 3775–3789.

Ramirez-Ortiz, Z.G., Pendergraft, W.F., Prasad, A., Byrne, M.H., Iram, T., Blanchette, C.J., Luster, A.D., Hacohen, N., Khoury, J. El., and Means, T.K. (2013). The scavenger receptor SCARF1 mediates the clearance of apoptotic cells and prevents autoimmunity. Nat. Immunol. *14*, 917–926.

Wilkinson, K., and El Khoury, J. (2012). Microglial scavenger receptors and their roles in the pathogenesis of Alzheimer's disease. Int. J. Alzheimers. Dis. *2012*, 489456.

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Effects of the COVID-19 lockdown on human sleep and rest-activity rhythms

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In modern societies, human rest–activity rhythms and sleep result from the tensions and dynamics between the conflicting poles of external social time (e.g., work hours and leisure activities) and an individual's internal biological time. A mismatch between the two has been suggested to induce 'social jetlag' [1] and 'social sleep restriction', that is, shifts in sleep timing and differences in sleep duration between work days and free days. Social jetlag [2,3] and sleep restrictions [4] have repeatedly been associated with negative consequences on health, mental wellbeing, and performance. In a large-scale quasi-experimental design, we investigated the effects of the phase with the most rigorous COVID-19 restrictions on the relationship between social and biological rhythms as well as sleep during a six-week period (mid-March until end of April 2020) in three European societies (Austria, Germany, Switzerland). We found that, on one hand, the restrictions reduced the mismatch between external (social) and internal (biological) sleep–wake timing, as indexed by significant reductions in social jetlag and social sleep restriction, with a concomitant increase in sleep duration. Sleep quality on the other hand was slightly reduced. The improved individual sleep–wake timing can presumably be attributed to an increased flexibility of social schedules, for instance due to more work being accomplished from home. However, this unprecedented situation also led to a significant increase in self-perceived burden, which was attendant to the decrease in sleep quality. These adverse effects may be alleviated by exposure to natural daylight as well as physical exercise.

Austria entered the strictest form of the COVID-19 'lockdown' on 13 March

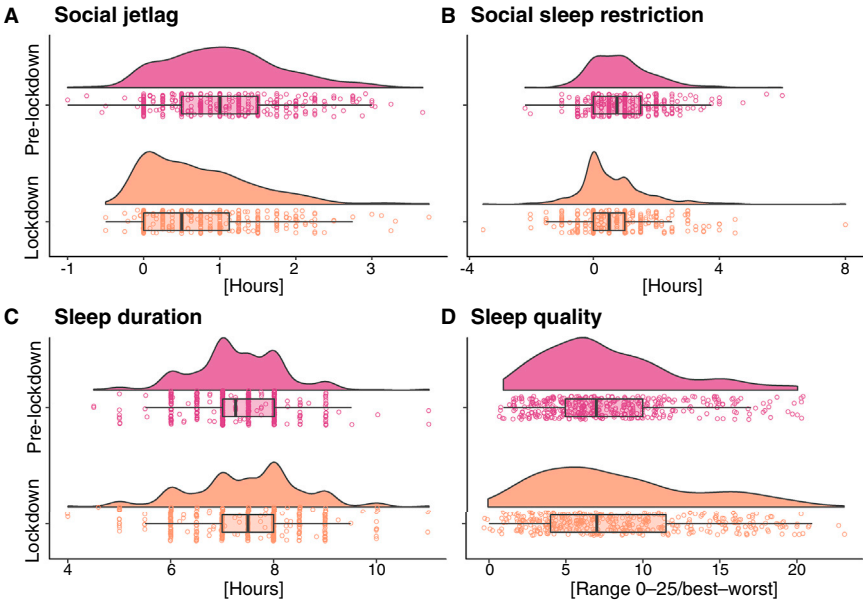

Figure 1. Effects of the 'lockdown' on social jetlag, social sleep restriction, sleep duration, and sleep quality.

Social jetlag (i.e., the difference between mid-sleep on free days and work days) is reduced by 13 minutes (A), and social sleep restriction (i.e., the difference in sleep duration between free days and work days) by 25 minutes (B). Sleep duration is increased by 13 minutes (C) while sleep quality (higher values denote decreased sleep quality) is reduced by 0.25 points on a scale from 0–25 (D). Reported differences are interpolated medians of individual differences. Each plot depicts the probability density of the data on top of a boxplot with overlying individual data points. Boxplots: lower and upper hinges correspond to the first and third quartiles (the 25th and 75th percentiles) and the thick vertical line in the box corresponds to the median. The upper (lower) whisker extends from the hinge to the largest (smallest) value no further than 1.5 * inter-quartile range (IQR, or distance between the first and third quartiles).

2020, Switzerland on 16 March, and in Germany the most rigorous regulations took effect on 23 March (in some federal states even earlier). This meant that all schools and shops, except for stores selling basic supplies (e.g., food shops, drug stores, and pharmacies), were closed. Contact bans were introduced, and freedom to travel was restricted by borders being closed and public transportation being reduced to a minimum. Moreover, public life came to a standstill and a large proportion of employees started working from home. In a one-time online survey addressing people in Switzerland, Germany, and Austria, we studied the effects of the lockdown on social jetlag, social sleep restriction, sleep quality, and sleep duration between 23 March and 26 April 2020. A total of 435 valid datasets were obtained during this period (327 women, four diverse; median age group 26–35 years). The majority of respondents had a rather high socioeconomic status and high educational level (Supplemental Information, published with this article online). The survey included (i) questions to assess volunteers' sleep quality and social sleep restriction (i.e., difference in sleep duration between work days and free days), and (ii) an ultra-short version of the Munich Chronotype Questionnaire [5] to assess social jetlag (i.e., the difference in mid-sleep between work days and free days). Additionally, we assessed (iii) life satisfaction and (iv) collected detailed background information (see Supplemental Information). Importantly, questionnaires i–iii were answered twice in a row, once retrospectively referring to the time before the lockdown and once referring to the time since participants noticed the restrictions.

We preregistered our hypotheses and statistical analyses prior to human data inspection [6]. Advanced non-parametric analyses (see Supplemental Information) revealed that the COVID-19 lockdown reduced the mismatch between external (social) and internal (biological) sleep–wake timing, which was probably due to the responders' increased flexibility of social schedules (i.e., external time). In particular, during the six-week period, median social jetlag was reduced by 13 minutes (inter-quartile range [*IQR*] = –31–17 min; Figure 1A) and median social sleep restriction by 25 minutes (*IQR* = –51–5 min; Figure 1B). The improved alignment was also associated with a median increase in sleep duration by about 13 minutes (*IQR* = –25–51 min; Figure 1C). The reduction in social jetlag was driven by a delay in mid-sleep on work days during the lockdown. One factor that was consistently associated with the ameliorated alignment was an increase in the proportion of work accomplished from home, which in turn was linked to an increased flexibility of working hours. Additionally, a reduction in working hours but not leisure time activities during the lockdown was associated with the 'improved' alignment. In line with previous findings, particularly later chronotypes seemed to benefit from the lockdown in terms of a reduced discrepancy between social and biological sleep–wake timing [1,7].

Beyond this, overall sleep quality slightly decreased during the lockdown by 0.25 points on a scale from 0–25 (higher values indicating decreased sleep quality; *IQR* = –1.6–2.8; Figure 1D). We observed an increase in subjective burden and a decrease in mental and physical wellbeing, which likely resulted from the exceptional situation due to the pandemic and was associated with decreased sleep quality and sleep duration. The strength of these effects may even have masked a link between reduced social jetlag and positive effects on sleep quality, which has previously been reported [8]. On a more positive note, we were also able to identify factors that limited the decline in sleep quality during the lockdown. These included a reduction in social sleep restriction, that is, the harmonisation of sleep duration across work and free days, as well as a reduction in working hours. Moreover, increases in daylight exposure and exercise may have buffered the negative effects of the lockdown and were associated with less decreased sleep quality and increased sleep duration. Possibly, these factors were able to reduce lockdown-induced stress [9].

In sum, in the three European countries included in this study, the COVID-19

lockdown, during which public life came to a standstill and many people experienced increased flexibility regarding social schedules, led to improved individual sleep–wake timing and overall more sleep. At the same time, however, many people suffered from a decrease in sleep quality in this burdening and exceptional situation. Potential strategies to mitigate the adverse effects of the lockdown on sleep quality may include exposure to natural daylight and exercise.

SUPPLEMENTAL INFORMATION

Supplemental Information contains one figure, one table, and experimental procedures, all of which can be found with this article online at https://doi.org/10.1016/j.cub.2020.06.021.

REFERENCES

1. Wittmann, M., Dinich, J., Merrow, M., and Roenneberg, T. (2006). Social jetlag: misalignment of biological and social time. Chronobiol. Int. *23*, 497–509.
2. Wong, P.M., Hasler, B.P., Kamarck, T.W., Muldoon, M.F., and Manuck, S.B. (2015). Social jetlag, chronotype, and cardiometabolic risk. J. Clin. Endocrinol. Metab. *100*, 4612–4620.
3. Levandovski, R., Dantas, G., Fernandes, L.C., Caumo, W., Torres, I., Roenneberg, T., Hidalgo, M.P.L., and Allebrandt, K.V. (2011). Depression scores associate with chronotype and social jetlag in a rural population. Chronobiol. Int. *28*, 771–778.
4. Depner, C.M., Melanson, E.L., Eckel, R.H., Snell-Bergeon, J.K., Perreault, L., Bergman, B.C., Higgins, J.A., Guerin, M.K., Stothard, E.R., Morton, S.J., *et al*. (2019). Ad libitum weekend recovery sleep fails to prevent metabolic dysregulation during a repeating pattern of insufficient sleep and weekend recovery sleep. Curr. Biol. *29*, 957–967.e4.
5. Ghotbi, N., Pilz, L.K., Winnebeck, E.C., Vetter, C., Zerbini, G., Lenssen, D., Frighetto, G., Salamanca, M., Costa, R., Montagnese, S., and Roenneberg, T. (2019). The µMCTQ: an ultra-short version of the Munich ChronoType Questionnaire. J. Biol. Rhythms *35*, 98–110.
6. Blume, C., Schmidt, M., and Cajochen, C. (2020). Sleep and social jetlag during COVID-19. Open Science Framework, http://doi.org/10.17605/osf.io/mhsw8.
7. Roepke, S.E., and Duffy, J.F. (2010). Differential impact of chronotype on weekday and weekend sleep timing and duration. Nat. Sci. Sleep *2010*, 213–220.
8. Raman, S., and Coogan, A.N. (2020). A cross-sectional study of the associations between chronotype, social jetlag and subjective sleep quality in healthy adults. Clocks Sleep *2*, 1–6.
9. de Quervain, D., Aerni, A., Amini, E., Bentz, D., Coynel, D., Gerhards, C., Fehlmann, B., Freytag, V., Papassotiropoulos, A., and Schicktanz, N. *et al.* (2020). The Swiss Corona Stress Study. Open Science Framework, https://doi.org/10.31219/osf.io/jqw6a.

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Sleep in university students prior to and during COVID-19 Stay-at-Home orders

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Sleep health has multiple dimensions including duration, regularity, timing, and quality [1–4]. The Coronavirus 2019 (COVID-19) outbreak led to Stay-at-Home orders and Social Distancing Requirements in countries throughout the world to limit the spread of COVID-19. We investigated sleep behaviors prior to and during Stay-at-Home orders in 139 university students (aged 22.2 ± 1.7 years old [±SD]) while respectively taking the same classes in-person and remotely. During Stay-at-Home, nightly time in bed devoted to sleep (TIB, a proxy for sleep duration with regard to public health recommendations [5]) increased by ~30 min during weekdays and by ~24 mins on weekends and regularity of sleep timing improved by ~12 min. Sleep timing became later by ~50 min during weekdays and ~25 min on weekends, and thus the difference between weekend and weekday sleep timing decreased — hence reducing the amount of social jetlag [6,7]. Further, we find individual differences in the change of TIB devoted to sleep such that students with shorter TIB at baseline before the first COVID-19 cases emerged locally had larger increases in weekday and weekend TIB during Stay-at-Home. The percentage of participants that reported 7 h or more sleep per night, the minimum recommended sleep duration for adults to maintain health [5] — including immune health — increased from 84% to 92% for weekdays during Stay-at-Home versus baseline. Understanding the factors underlying such changes in sleep health behaviors could help inform public health recommendations with the goal of improving sleep health during and following the Stay-at-Home orders of the COVID-19 pandemic.

The COVID-19 pandemic has led to unprecedented changes in human behavior worldwide. We conducted an observational study to investigate changes in multiple dimensions of sleep health behaviors during the COVID-19 pandemic by comparing baseline sleep log data collected from January 29 to February 4, 2020 (before the COVID-19 outbreak spread across North America), to sleep log data collected in the same university students from April 22 to April 29, 2020, when the Stay-at-Home/Safer-at Home order was in effect. We used daily sleep logs to assess bedtimes and waketimes across each study week. Classes at the University of Colorado Boulder officially switched from in-person teaching to remote learning on March 16, 2020. Thirteen participants subsequently moved out of the local Mountain Time Zone (7 moved one time zone west, 5 moved one time zone east, and one moved two time zones east). Because students continued remote learning with classes scheduled according to Mountain Time, the sleep logs for all participants were analyzed according to Mountain Time. Institutional review board approval was obtained.

Outcomes included daily, weekday, and weekend TIB devoted to sleep, bedtimes, waketimes, and sleep midpoints — middle of the reported sleep opportunity — and regularity of sleep timing. Regularity was quantified by the standard deviations of bedtimes, sleep midpoint times and waketimes of each individual with lower scores indicating more regular sleep schedules. We also computed social jetlag — the difference between sleep midpoint on weekends versus weekdays [6] — and the percentage of individuals reporting ≥ 7 h sleep per night.

Three dimensions of sleep health behaviors significantly changed during Stay-at-Home (Table S1, in Supplemental Information, published with this article online): (i) TIB devoted to sleep increased on weekdays (Baseline = 7.9 ± 1.0 h, Stay-at-Home = 8.4 ± 1.1 h, $p < 0.0001$) and weekends (8.4 ± 1.5 h, 8.8 ± 1.2 h, $p < 0.05$) during Stay-at-Home (Figure 1 panel A) — in fact, TIB increased every day of the week ($p < 0.05$) except for Saturday ($p = 0.29$; see Supplemental Information), and more participants reported the recommended 7 h TIB [5] on