Nature and Science of Sleep

Open Access Full Text Article

HYPOTHESIS

Bidirectional Communication Between Circadian Rhythm Disruption and Frailty: A Hypothesis From Gut Microbiota Metabolites

Yu Pan[1],*, Yan Yuan[1],*, Juan Yang[2],*, Zhu Qing Feng[1], Xue Yin Tang[1], Yi Jiang[1], Gui Ming Hu[1], Dong Li Luo[1], Yang Jiang[1], Jiang Chuan Dong[3]

[1]Department of Geriatrics, The Second Affiliated Hospital of Chongqing Medical University, Chongqing, 400010, People's Republic of China; [2]Department of Integrated of Chinese and Western Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, 400016, People's Republic of China; [3]Oncology Treatment Center of Traditional Chinese Medicine, Affiliated Cancer Hospital of Chongqing University, Chongqing, 400900, People's Republic of China

*These authors contributed equally to this work

Correspondence: Jiang Chuan Dong, Email dongjiangchuan2023@163.com

---

Abstract: Disruption of circadian rhythms and the condition of frailty are believed to be interrelated. Various manifestations of sleep disturbances, including insomnia, disrupted sleep-wake cycles, and alterations in sleep timing, are considered integral components of circadian rhythm disruption, which are also observed in individuals with frailty. Extensive research has established a connection between gut microbiota and both frailty and circadian rhythm disruption. However, prior studies have predominantly focused on investigating isolated links between gut microbiota and its metabolites with either frailty or circadian rhythm disruption, often neglecting the significant role that gut microbiota and its metabolites may play in the bidirectional relationship between circadian rhythms and frailty. Consequently, we propose the hypothesis that circadian rhythm disruption may induce frailty by altering the composition and structure of gut microbiota metabolites, and conversely, frailty may influence circadian rhythm disruption through similar mechanisms. The aim of our hypothesis is to emphasize the important role of gut microbiota metabolites in the bidirectional communication between circadian disruption and frailty and to speculate on the relevant mechanisms by which gut microbiota metabolites mediate the bidirectional communication between circadian disruption and frailty, rather than being solely related to frailty or circadian disorders.

Keywords: circadian rhythm, frailty, gut microbiota metabolites

---

Introduction

Circadian rhythmicity constitutes a critical physiological phenomenon essential for sustaining metabolic homeostasis and normal biological processes within organisms.[1] In mammals, the circadian rhythm operates as a self-sustaining, interlocking transcriptional-translational feedback loop, comprising a network of genes such as BMAL1, CLOCK, the period genes (PER1/2/3), and the cryptochrome genes (CRY1/2).[2] While light signals serve as the primary cues for synchronizing the master clock with the external environment, other factors, including diet, feeding behaviors, hormones, and short-chain fatty acids (SCFAs) produced by the gut microbiota, also play significant roles.[3,4] Notably, the gut microbiota exhibits circadian rhythms analogous to those of the host, and the rhythmicity of microbial metabolites is disrupted in mice deficient in the BMAL1 gene.[5,6] This interplay and coexistence between the rhythmicity of the gut microbiota and host circadian rhythms are pivotal in maintaining regular rhythms and biological processes within the organism.

Once the circadian system of an organism becomes disrupted, these mechanisms of communication and coexistence are compromised, leading to alterations in the metabolites of the intestinal microbiota. This disruption results in the dysregulation of the organism's intestinal ecology and the accumulation of chronic low-grade inflammation throughout the body. Consequently, this can initiate or exacerbate frailty, a geriatric syndrome characterized by a decline in physiological reserves and increased susceptibility to stressors.[7] The clinical phenotype and pathophysiology of frailty are complex, involving multiple physiological systems and their interactions throughout the body. A commonly employed tool for assessing frailty in

Received: 23 February 2025
Accepted: 7 April 2025
Published: 29 April 2025

clinical practice is the Frailty Phenotype Score, as proposed by Fried et al.[8] By examining clinical data from more than 5000 cases of frail individuals aged≥ 65 years, Fried's team proposed a definition of frailty characterized by five primary manifestations. They established five diagnostic criteria: weight loss, slow gait, poor grip strength, low physical activity, and a sense of fatigue. Individuals meeting three or more of these criteria were diagnosed with frailty, those meeting one or two criteria were classified as pre-frail, and those meeting none were considered non-frail. Although several epidemiological studies have validated this model's ability to predict adverse clinical outcomes, its primary limitation lies in its exclusive focus on somatic functioning, neglecting important aspects of daily life such as emotional and psychological well-being, sleep, and socialization. The frailty index model developed by Rockwood's team addresses these limitations and has become another widely used tool for assessing frailty.[9] The frailty index model was developed based on the theory of health deficits, also known as the cumulative assessment of deficits. This theory refers to the proportion of potentially unhealthy measures of an individual relative to all measures at a given point in time. The model is capable of simultaneously considering a wide range of health variables that influence changes in frailty, including somatic functioning, mental state, psychological, and social factors. Interestingly, frailty and circadian rhythm disruption are intersecting "shadows" of these considered health variables and their downstream pathophysiological mechanisms, suggesting a bidirectional relationship exists.[10] Logically, it can be hypothesized that the gut microbiota, which has been confirmed to be correlated with both circadian disruption and frailty, can provide a rational explanation for this correlation as well as the bidirectional relationship.

In recent years, the "microbiota-gut-brain axis" and "microbiota-gut-muscle axis" doctrines have established two bidirectional homeostatic systems connecting the gastrointestinal tract, the central nervous system, and the muscular system,[11,12] and various pathways involved, such as the hypothalamic-pituitary-adrenal axis,[13] the endocrine system,[14] and muscle mass control,[12] have been implicated in the pathology of frailty and circadian disorders, suggesting that it is highly likely that the gut microbiota may play a mediating role between frailty and circadian disruption through dietary modalities. For instance, a single-arm, two-sample clinical trial involving 19 participants with metabolic syndrome and a baseline mean daily eating window of ≥14 hours demonstrated that a 10-hour time-restricted diet enhanced cardiometabolic health in patients with metabolic syndrome who were receiving standard medical care, including high utilization of statins and antihypertensives. This finding suggests that time-restricted diets represent a potent lifestyle intervention that may be pertinent to the restoration of normal circadian rhythms in individuals.[15] Additionally, an animal study employing multiple lung cancer cell lines, two xenograft mouse models, and a chemically-induced mouse lung cancer model revealed that an intermittent 6-hour time-restricted diet inhibited lung cancer progression and reprogrammed circadian gene expression in the host, in contrast to normal ad libitum feeding.[16] Correspondingly, while there is no specific treatment option for frailty, the necessity for nutritional support is well recognized. A cohort study involving the oldest participants demonstrated a dose-dependent negative correlation between improvements in diet quality and the incidence of frailty.[17] Another prospective cohort study analyzing a total of 180 older adults demonstrated that significant increases in energy, protein, vitamin D, vitamin C, and folate intake were associated with significant improvements in individual frailty and subsequent reductions in malnutrition rates.[18] However, although the single link between gut microbiota metabolites and frailty or circadian rhythm disruption has been well established in previous studies, however, the role of gut microbiota metabolites in the bidirectional communication between circadian rhythm and frailty has not been addressed. Based on this, we propose hypotheses to emphasize the important role of gut microbiota metabolites in the bidirectional relationship between circadian rhythm disruption and frailty in the organism and to speculate on the possible mechanisms.

Hypothesis

Here we hypothesize that circadian disruption can induce individual frailty by disrupting gut microbiota composition and metabolites. Correspondingly, alterations in gut microbiota composition and metabolites in the frail status will also induce or exacerbate a state of circadian imbalance. When frailty occurs or when circadian rhythms produce abnormal oscillations, the gut microbiota and its metabolites respond, leading to abnormalities in a variety of important physiological pathways in the body, such as neuroendocrine, metabolic, and skeletal muscle mass. Rather than merely asserting the involvement of gut microbiota in frailty or circadian rhythm disorders, our hypothesis seeks to highlight the critical role of gut microbiota metabolites in mediating the bidirectional relationship between these conditions.

Discussion

The bidirectional relationship between circadian rhythm disruption and frailty encompasses numerous intriguing features and mechanisms. Sleep disorders, including insomnia, poor sleep quality, and reduced sleep duration, represent significant phenotypes of circadian disruption that both predict and directly influence frailty.[19,20] Furthermore, circadian rhythm disruption can induce oxidative damage to the brain, accelerate brain aging, and cause neuronal damage, all of which may impact frailty and contribute to the onset of cognitive frailty.[21,22] Consequently, frail older adults frequently exhibit psychological disorders such as anxiety and depression, which in turn exacerbate sleep-wake disturbances, disrupt normal eating patterns, and ultimately lead to the development of circadian disorders.[23]

Although the precise mechanisms underlying this bidirectional relationship between circadian rhythm disruption and frailty have yet to be systematically elucidated, it can be speculated that metabolic function is one of the significant answers (Figure 1). Circadian rhythms are believed to regulate metabolic function, with many metabolic processes demonstrating circadian rhythmicity, suggesting they are subject to direct or intermittent circadian control. Moreover, individuals possessing variants and polymorphisms in the CRY2 and PER2 genes demonstrate metabolic dysfunction, evidenced by elevated blood glucose levels.[24] A study assessing the body's circadian rhythm through melatonin level monitoring has revealed that disruptions in the central circadian rhythm, indicated by reduced melatonin levels, are linked to insulin resistance, diabetes and obesity.[25] Another study corroborated that metabolic syndrome, characterized by insulin resistance, is significantly associated with frailty,[26] suggesting that impaired metabolic function and the development of metabolic syndrome, potentially due to reduced melatonin levels during disruptions of the circadian rhythm, may constitute a mechanism through which such disruptions promote frailty. Cohort studies involving community-dwelling older adults have further substantiated the validity of this hypothesis.[27,28] Moreover, research on rodent

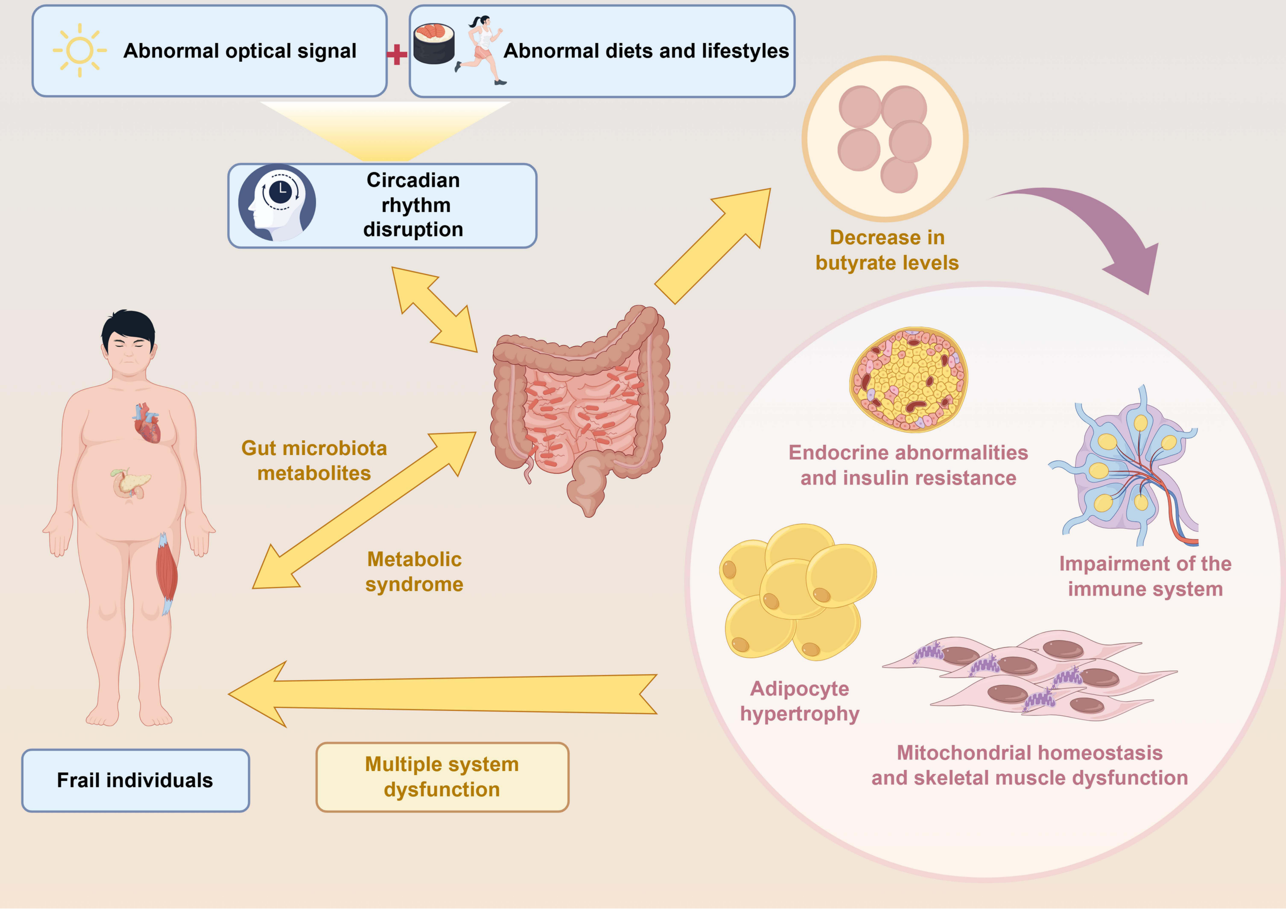

Figure 1 Brief introduction of mechanisms for the role of gut microbiota metabolites (eg, butyrate) in circadian rhythm disruption mediating frailty onset.

https://doi.org/10.2147/NSS.S524570

models has shown that genetic disruption of circadian genes leads to abnormalities in both central and peripheral clocks, resulting in a range of symptoms indicative of metabolic syndrome, such as adipocyte hypertrophy, fatty liver, dyslipidemia, hypoglycemia, hyperglycemia, and obesity.[29,30] These alterations may accelerate the decline in muscle function and overall fitness, thereby contributing to the onset of frailty.[31]

Gut microbial metabolites represented by SCFAs imply another significant answer (Figure 1). SCFAs, as endocrine mediators of the gut microbiota, are not only capable of influencing skeletal muscle metabolism and function, but also have a circadian rhythm.[32,33] During the circadian rhythm disruption, such as insomnia or fragmented sleep, there is a consequent decrease in butyrate levels, a compound recognized for its anti-inflammatory properties and its role in maintaining mitochondrial function and which itself follows a circadian pattern.[34,35] This decrease is accompanied by an increased production of acetate and propionate.[36] This distinct process directly contributes to elevated levels of reactive oxygen species and dysregulated mitochondrial homeostasis. The ensuing upregulation of oxidative stress and mitochondrial dysfunction disrupts the microbiota-gut-muscle axis, ultimately altering the composition and structure of the gut microbiota. Such alterations facilitate an inappropriate increase in bacterial-derived material, leading to the accumulation of skeletal muscle hypoplasia. In conjunction with systemic chronic low-grade inflammation, these changes contribute to the onset of frailty.[37–39] Moreover, the decline in butyrate levels due to disruptions in circadian rhythms also specifically leads to impaired intestinal barrier function. This impairment facilitates the translocation of bacteria and their byproducts, such as lipopolysaccharides, into the circulatory system through a "leaky gut", allowing their migration to the mesenteric lymph nodes, liver, and brain.[40,41] This process triggers a systemic inflammatory response that ultimately contribute to the development of frailty. Furthermore, both in vitro and in vivo studies have shown that butyrate can enhance the levels of regulatory T cells in the intestinal tract and promote the T cells' polarization in the immune organs.[42] This action helps prevent the accumulation of chronic inflammation in the intestinal tract, thereby reducing the risk of frailty. Additionally, butyrate has been shown to activate the PI3K/Akt/mTOR signaling pathway, which inhibits oxidative stress and autophagy in skeletal muscle cells, and promotes macrophage polarization towards the M2 phenotype, thereby preventing the onset of myasthenia gravis, which can reduce the incidence of sarcopenia and frailty.[32,43] In a separate animal study, butyrate was demonstrated to function as a histone deacetylase inhibitor, markedly enhancing histone acetylation at the corticotropin-releasing hormone receptor 2 (CRHR2) promoter in vitro.[44] This action normalized corticosterone levels and CRHR2 expression in vivo, resulting in improvements in brain function and behavior, potentially preventing cognitive frailty and exerting beneficial effects on the circadian system. Furthermore, SCFAs, exemplified by butyrate, can also modulate satiety through G-protein-coupled receptors (GPCR) 41 and 43, thereby interacting with the circadian system. Specifically, SCFAs decrease appetite by promoting the secretion of satiety peptides, such as peptide YY and glucagon-like peptide 1, from enteroendocrine cells via GPCRs.[45,46] This targeted regulatory influence of the circadian system on dietary rhythms, mediated by gut microbiota metabolites, effectively mitigates the decline in somatic function due to undernutrition or the development of metabolic syndrome due to overnutrition, both of which impact the state of frailty.

In summary, while existing research has identified a unidirectional relationship between gut microbiota and disruptions in circadian rhythm or frailty, the critical role of gut microbiota metabolites in the bidirectional interaction between circadian rhythm disruption and frailty remains unexplored. We hypothesize, based on a body of evidence and established pathophysiological mechanisms, that disruptions in circadian rhythm or the presence of frailty can alter normal physiological processes and functional pathways by impacting the composition and structure of gut microbiota metabolites. Notably, butyrate may play a pivotal role in this process.

Expectations

We suggest that subsequent research examining this hypothesis should comprehensively account for the potential impacts of significant covariates, including various circadian rhythm disorders such as insomnia, sleep-wake cycle disorders and sleep-wake delay, as well as other critical factors like age, physical activity, smoking habits, medication use, and comorbidities on the gut microbiota metabolites. This consideration is essential to minimize errors that may arise. In managing confounding variables, future studies should initially employ a stratified randomized grouping method to ensure baseline equilibrium. Furthermore, given that confounding variables may encompass both categorical and continuous types, it is crucial to utilize multifactor regression analysis techniques and propensity score analyses, the latter of which can effectively reduce the number of independent variables and address the limitations associated with the number of independent variables in both stratified and multifactor analyses by consolidating multiple confounders into a single composite score.

Research models, such as the recently proposed zebrafish model, are of significant interest due to their skeletal muscles exhibiting remarkable histological and molecular similarities to human muscles, which makes them an invaluable model for studying the gut-muscle-brain axis. Furthermore, zebrafish possess the unique ability to absorb substances from water through their skin and gills, which facilitates the use of drug-induced disease models and the subsequent testing of newly developed drugs.[47] In addition, assessing the concentrations of gut microbiota metabolites, such as butyrate, is also crucial for validating this hypothesis. It is recommended that future research employ more robust methodologies for sequencing gut microbiota metabolites. Techniques such as microbial metabolomics analysis based on gas chromatography-time-of-flight mass spectrometry (GC-TOF-MS) technology,[48] which facilitates high-throughput absolute quantification of over 150 significant gut flora metabolites, should be considered to enhance the identification and detection of specific gut microbial metabolites associated with circadian rhythm disorders and frailty, thereby fully substantiating the significance of butyrate. Additionally, future studies should also focus on polyamines, a class of metabolites produced by both the mammalian host and gut microbiota, which exhibit circadian characteristics. As versatile signaling molecules, polyamines participate in numerous physiological and pathological processes, and their levels exhibit significant fluctuations in frailty mouse models,[49] indicating that polyamines may play an equally critical role in frailty. Unfortunately, the currently available evidence does not allow for conclusions or speculation regarding the relationship between polyamines and the bidirectional connection between frailty and circadian disturbances. Further research is needed to elucidate these relationships.

In considering interventions, the most direct approach involves supplementation with exogenous butyrate or gavage therapy with Clostridium butyrate to evaluate its effects on the host's circadian system or frailty status. Oral supplementation with exogenous probiotics, such as Lactobacillus casei, is believed to maintain intestinal ecological balance and stabilize the intestinal barrier, and should also be considered as a potential therapeutic intervention.[37] Furthermore, when designing the study, researchers should consider using clinical assessment scales, wearable devices, somatic function tests, and melatonin levels to assess changes in circadian rhythm disturbance and frailty following reductions in gut microbiota products such as butyrate. Subsequently, it should also be evaluated whether gut microbiota metabolite levels similarly improve after nutritional support and exercise therapy to improve a frail state or exogenous melatonin supplementation to improve circadian disorders. Equally important is the consideration of the study population. When designing studies, it is crucial to assess whether individuals in the "advanced stages of frailty" (high or very high frailty index scores) and those who develop frailty at a younger or middle age exhibit improved responses to interventions. Additionally, centenarians represent another valuable study population, often regarded as a model of healthy aging. It is important to acknowledge that the status of being a centenarian does not automatically equate to optimal health; rather, centenarians often exhibit higher morbidity rates and endure prolonged periods of illness compared to younger adults. Future research is advised to thoroughly examine the significance of this distinct population to enhance understanding of the critical role that gut microbiota metabolites play in the bidirectional relationship between circadian rhythm disruption and frailty. In this context, meticulous consideration of healthy aging populations is crucial, as it can significantly aid in eliminating potential confounding factors arising from the natural effects of aging on the circadian system, frailty, and gut microbiota metabolites. Additionally, given the reversible nature of frailty and the dynamic characteristics of circadian rhythms, it is imperative for future studies to incorporate extended follow-up periods and longitudinal data. This approach will facilitate the observation of changes in the composition and structure of gut microbiota and its metabolites throughout disease progression, thereby enabling a more robust establishment of causal relationships between gut microbiota metabolites, frailty, and circadian rhythm disruption. Such studies hold the potential to provide compelling evidence to test these hypotheses and may contribute to enabling frail individuals to reverse their frail status, thereby improving their quality of life.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Acknowledgments

Figure 1 was accomplished with the help of the Figdraw platform, and the authors would like to sincerely thank the staff for their assistance.

Author Contributions

Yu P: Conception, Study design, Execution, Investigation, Visualization, Writing-original draft. Yan Y: Acquisition of data, Analysis and interpretation, Investigation, Writing-review & editing. Juan Y: Analysis and interpretation, Investigation, Writing-review & editing. Zhu Q.F: Execution, Visualization, Writing-review & editing. Yi J: Analysis and interpretation, Visualization, Writing-review & editing. Xue Y.T: Acquisition of data, Writing-review & editing. Gui M.H: Acquisition of data, Writing-review & editing. Dong L.L: Analysis and interpretation, Writing-review & editing. Yang J: Execution, Writing-review & editing. Jiang C.D: Conception, Study design, Funding acquisition, Project administration, Resources, Supervision, Writing-review & editing.

All Authors have agreed on the article submitted to this journal. They reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage. All of them agree to take responsibility and be accountable for the contents of the article.

Funding

This work was supported by the 2021 Future Medical Innovation Team Support Program of Chongqing Medical University (Project No.W0070), 2024 Chongqing Municipal Health Commission, Chongqing Municipal Bureau of Science and Technology jointly funded project (2024ZYYB002) and Chongqing Natural Science Foundation (Project No.CSTB2022NSCQ-MSX0125).

Disclosure

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.

References

1. Ruan W, Yuan X, Eltzschig HK. Circadian rhythm as a therapeutic target. *Nat Rev Drug Discov*. 2021;20(4):287–307. doi:10.1038/s41573-020-00109-w
2. Reppert SM, Weaver DR. Molecular analysis of mammalian circadian rhythms. *Annu Rev Physiol*. 2001;63:647–676. doi:10.1146/annurev.physiol.63.1.647
3. Adafer R, Messaadi W, Meddahi M, et al. Food timing, circadian rhythm and chrononutrition: a systematic review of time-restricted eating's effects on human health. *Nutrients*. 2020;12(12). doi:10.3390/nu12123770.
4. Montaruli A, Castelli L, Mulè A, et al. Biological rhythm and chronotype: new perspectives in health. *Biomolecules*. 2021;11(4):487. doi:10.3390/biom11040487
5. Segers A, Desmet L, Thijs T, Verbeke K, Tack J, Depoortere I. The circadian clock regulates the diurnal levels of microbial short-chain fatty acids and their rhythmic effects on colon contractility in mice. *Acta Physiol*. 2019;225(3):e13193. doi:10.1111/apha.13193
6. Segers A, Desmet L, Sun S, Verbeke K, Tack J, Depoortere I. Night-time feeding of Bmal1-/- mice restores SCFA rhythms and their effect on ghrelin. *J Endocrinol*. 2020;245(1):155–164. doi:10.1530/JOE-20-0011
7. Hoogendijk EO, Afilalo J, Ensrud KE, Kowal P, Onder G, Fried LP. Frailty: implications for clinical practice and public health. *Lancet*. 2019;394(10206):1365–1375. doi:10.1016/S0140-6736(19)31786-6
8. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol a Biol Sci Med Sci*. 2001;56(3):M146–156. doi:10.1093/gerona/56.3.M146
9. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol a Biol Sci Med Sci*. 2007;62(7):722–727. doi:10.1093/gerona/62.7.722
10. Pan Y, Feng ZQ, Yuan Y, Hu GM, Jiang Y, Dong JC. Bidirectional relationship between circadian rhythm and frailty. *Nat Sci Sleep*. 2023;15:949–953. doi:10.2147/NSS.S436488
11. Honarpisheh P, Bryan RM, McCullough LD. Aging microbiota-gut-brain axis in stroke risk and outcome. *Circ Res*. 2022;130(8):1112–1144. doi:10.1161/CIRCRESAHA.122.319983
12. Ticinesi A, Lauretani F, Milani C, et al. Aging gut microbiota at the cross-road between nutrition, physical frailty, and sarcopenia: is there a gut-muscle axis? *Nutrients*. 2017;9(12):1303. doi:10.3390/nu9121303
13. Rusch JA, Layden BT, Dugas LR. Signalling cognition: the gut microbiota and hypothalamic-pituitary-adrenal axis. *Front Endocrinol*. 2023;14:1130689. doi:10.3389/fendo.2023.1130689
14. Qi X, Yun C, Pang Y, Qiao J. The impact of the gut microbiota on the reproductive and metabolic endocrine system. *Gut Microbes*. 2021;13(1):1–21. doi:10.1080/19490976.2021.1894070

15. Wilkinson MJ, Manoogian ENC, Zadourian A, et al. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. *Cell Metab*. 2020;31(1):92–104.e105. doi:10.1016/j.cmet.2019.11.004
16. Shi D, Fang G, Chen Q, Li J, Ruan X, Lian X. Six-hour time-restricted feeding inhibits lung cancer progression and reshapes circadian metabolism. *BMC Med*. 2023;21(1):417. doi:10.1186/s12916-023-03131-y
17. Goshen A, Goldbourt U, Benyamini Y, Shimony T, Keinan-Boker L, Gerber Y. Diet quality and incident frailty in adults 65 years or older: the Israeli longitudinal study on aging. *Mayo Clin Proc*. 2023;98(12):1774–1784. doi:10.1016/j.mayocp.2023.08.015
18. Shin HR, Kim YS, Park YK, et al. Nutritional status and frailty improvement through senior-friendly diet among community-dwelling older adults in South Korea. *Nutrients*. 2023;15(6). doi:10.3390/nu15061381.
19. Moreno-Tamayo K, Manrique-Espinoza B, Ortiz-Barrios LB, Cárdenas-Bahena Á, Ramírez-García E, Sánchez-García S. Insomnia, low sleep quality, and sleeping little are associated with frailty in Mexican women. *Maturitas*. 2020;136:7–12. doi:10.1016/j.maturitas.2020.03.005
20. Wai JL, Yu DS. The relationship between sleep-wake disturbances and frailty among older adults: a systematic review. *J Adv Nurs*. 2020;76 (1):96–108. doi:10.1111/jan.14231
21. Latha Laxmi IP, Tamizhselvi R. Epigenetic events influencing the biological clock: panacea for neurodegeneration. *Heliyon*. 2024;10(19):e38836. doi:10.1016/j.heliyon.2024.e38836
22. Hastings MH, Brancaccio M, Gonzalez-Aponte MF, Herzog ED. Circadian rhythms and astrocytes: the good, the bad, and the ugly. *Annu Rev Neurosci*. 2023;46:123–143. doi:10.1146/annurev-neuro-100322-112249
23. Soysal P, Veronese N, Thompson T, et al. Relationship between depression and frailty in older adults: a systematic review and meta-analysis. *Ageing Res Rev*. 2017;36:78–87. doi:10.1016/j.arr.2017.03.005
24. Garcia-Rios A, Gomez-Delgado FJ, Garaulet M, et al. Beneficial effect of CLOCK gene polymorphism rs1801260 in combination with low-fat diet on insulin metabolism in the patients with metabolic syndrome. *Chronobiol Int*. 2014;31(3):401–408. doi:10.3109/07420528.2013.864300
25. McMullan CJ, Curhan GC, Schernhammer ES, Forman JP. Association of nocturnal melatonin secretion with insulin resistance in nondiabetic young women. *Am J Epidemiol*. 2013;178(2):231–238. doi:10.1093/aje/kws470
26. Zeng P, Li M, Cao J, Zeng L, Jiang C, Lin F. Association of metabolic syndrome severity with frailty progression among Chinese middle and old-aged adults: a longitudinal study. *Cardiovasc Diabetol*. 2024;23(1):302. doi:10.1186/s12933-024-02379-9
27. McCarthy K, Laird E, O'Halloran AM, Fallon P, Ortuño RR, Kenny RA. Association between metabolic syndrome and risk of both prevalent and incident frailty in older adults: findings from The Irish longitudinal study on ageing (TILDA). *Exp Gerontol*. 2023;172:112056. doi:10.1016/j.exger.2022.112056
28. Saifuddin Ekram ARM, Espinoza SE, Ernst ME, et al. The association between metabolic syndrome, frailty and disability-free survival in healthy community-dwelling older adults. *J Nutr Health Aging*. 2023;27(1):1–9. doi:10.1007/s12603-022-1860-2
29. Turek FW, Joshu C, Kohsaka A, et al. Obesity and metabolic syndrome in circadian clock mutant mice. *Science*. 2005;308(5724):1043–1045. doi:10.1126/science.1108750
30. Marcheva B, Ramsey KM, Buhr ED, et al. Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature*. 2010;466(7306):627–631. doi:10.1038/nature09253
31. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. *Lancet Diabetes Endocrinol*. 2018;6(9):743–752. doi:10.1016/S2213-8587(18)30110-4
32. Liu H, Xi Q, Tan S, et al. The metabolite butyrate produced by gut microbiota inhibits cachexia-associated skeletal muscle atrophy by regulating intestinal barrier function and macrophage polarization. *Int Immunopharmacol*. 2023;124(Pt B):111001. doi:10.1016/j.intimp.2023.111001
33. Zhang Y, Zhang S, Yuan Y, et al. Metagenomic assembly reveals the circadian oscillations of the microbiome and antibiotic resistance genes in a model of laying hens. *Sci Total Environ*. 2022;836:155692. doi:10.1016/j.scitotenv.2022.155692
34. Anderson G, Rodriguez M, Reiter RJ. Multiple sclerosis: melatonin, orexin, and ceramide interact with platelet activation coagulation factors and gut-microbiome-derived butyrate in the circadian dysregulation of mitochondria in glia and immune cells. *Int J mol Sci*. 2019;20(21):5500. doi:10.3390/ijms20215500
35. Liu H, Wang J, He T, et al. Butyrate: a double-edged sword for health? *Adv Nutr*. 2018;9(1):21–29. doi:10.1093/advances/nmx009
36. Hays KE, Pfaffinger JM, Ryznar R. The interplay between gut microbiota, short-chain fatty acids, and implications for host health and disease. *Gut Microbes*. 2024;16(1):2393270. doi:10.1080/19490976.2024.2393270
37. Chen LH, Chang SS, Chang HY, et al. Probiotic supplementation attenuates age-related sarcopenia via the gut-muscle axis in SAMP8 mice. *J Cachexia Sarcopenia Muscle*. 2022;13(1):515–531. doi:10.1002/jcsm.12849
38. Li X, Wang C, Zhu J, et al. Sodium butyrate ameliorates oxidative stress-induced intestinal epithelium barrier injury and mitochondrial damage through AMPK-mitophagy pathway. *Oxid Med Cell Longev*. 2022;2022:3745135. doi:10.1155/2022/3745135
39. Hu S, Kuwabara R, de Haan BJ, Smink AM, de Vos P. Acetate and butyrate improve β-cell metabolism and mitochondrial respiration under oxidative stress. *Int J Mol Sci*. 2020;21(4):1542. doi:10.3390/ijms21041542
40. Everson CA, Toth LA. Systemic bacterial invasion induced by sleep deprivation. *Am J Physiol Regul Integr Comp Physiol*. 2000;278(4):R905–916. doi:10.1152/ajpregu.2000.278.4.R905
41. Matenchuk BA, Mandhane PJ, Kozyrskyj AL. Sleep, circadian rhythm, and gut microbiota. *Sleep Med Rev*. 2020;53:101340. doi:10.1016/j.smrv.2020.101340
42. Furusawa Y, Obata Y, Fukuda S, et al. Commensal microbe-derived butyrate induces the differentiation of colonic regulatory T cells. *Nature*. 2013;504(7480):446–450. doi:10.1038/nature12721
43. Tang G, Du Y, Guan H, et al. Butyrate ameliorates skeletal muscle atrophy in diabetic nephropathy by enhancing gut barrier function and FFA2-mediated PI3K/Akt/mTOR signals. *Br J Pharmacol*. 2022;179(1):159–178. doi:10.1111/bph.15693
44. Wang X, Sun Z, Yang T, et al. Sodium butyrate facilitates CRHR2 expression to alleviate HPA axis hyperactivity in autism-like rats induced by prenatal lipopolysaccharides through histone deacetylase inhibition. *mSystems*. 2023;8(4):e0041523. doi:10.1128/msystems.00415-23
45. Portincasa P, Bonfrate L, Vacca M, et al. Gut microbiota and short chain fatty acids: implications in glucose homeostasis. *Int J Mol Sci*. 2022;23 (3):1105. doi:10.3390/ijms23031105
46. Byrne CS, Chambers ES, Morrison DJ, Frost G. The role of short chain fatty acids in appetite regulation and energy homeostasis. *Int J Obes Lond*. 2015;39(9):1331–1338. doi:10.1038/ijo.2015.84
47. Aranda-Martínez P, Sayed RKA, Fernández-Martínez J, et al. Zebrafish as a human muscle model for studying age-dependent sarcopenia and frailty. *Int J Mol Sci*. 2024;25(11):6166. doi:10.3390/ijms25116166

48. Cai S, Lin J, Li Z, et al. Alterations in intestinal microbiota and metabolites in individuals with Down syndrome and their correlation with inflammation and behavior disorders in mice. *Front Microbiol*. 2023;14:1016872. doi:10.3389/fmicb.2023.1016872
49. Kato Y, Hoshino T, Ogawa Y, Sugahara K, Katakura A. Aging-related metabolome analysis of the masseter muscle in senescence-accelerated mouse-prone 8. *Int J Mol Sci*. 2024;25(17):9684. doi:10.3390/ijms25179684