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Circadian Alignment Through Time-Restricted Feeding: Implications for Health and Longevity

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circadian rhythms, circadian disruption/desynchrony, time-restricted feeding/eating, metabolism, disease, circadian medicine

Abstract

Time-restricted feeding (TRF), which confines food intake to a defined daily window, has emerged as a promising nonpharmacological strategy to improve health by aligning behavior and physiology with the endogenous circadian clock. Preclinical research has expanded substantially, now spanning both nocturnal and diurnal species, diverse dietary regimens, varying intervention durations, and examinations of sex-specific responses. These consistently show that synchronizing feeding-fasting cycles with the natural active phase of an organism's circadian rhythm enhances rhythmic gene expression across tissues. Concomitantly, this mitigates metabolic dysfunction, reduces inflammation, and lowers disease risk, often without reducing caloric intake. While findings in animal models are robust, human outcomes have been more modest and variable, influenced by the timing and duration of feeding window, metabolic state, and sex. This review synthesizes current insights into the relationship between TRF and circadian rhythms, highlighting recent discoveries and the challenges that remain for translation to humans.

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1. INTRODUCTION

The 24-h rotation of the Earth has shaped the evolution of circadian rhythms, daily oscillations in physiology and behavior, which confer adaptive advantages by enabling organisms to anticipate, rather than merely react to, changes in light, food availability, and activity demands (36, 83, 107). These rhythms are driven by endogenous clocks generating near-24-h cycles of gene expression that coordinate sleep-wake behavior, feeding-fasting cycles, and metabolic homeostasis (122, 128). High amplitude and synchronized oscillations between clocks across tissues of the body are known to correlate with improved health (2), whereas misalignment, arising from shift work, jet lag, irregular eating patterns, and the natural decline of aging are linked to metabolic disease, inflammation, and neurodegeneration (10, 11, 40, 45, 93, 113). As feeding has been found to be a powerful cue for entraining peripheral clocks, interventions such as time-restricted feeding (TRF), or time-restricted eating (TRE) in humans, which consolidates food intake into consistent daily windows of 12 h or less without necessarily altering total caloric intake, has been rising in popularity as a way to enhance circadian rhythms and improve health (18, 81, 85).

Within the past decade, TRF has been shown to confer significant health benefits in preclinical models. In classic model species such as mice, rats, and *Drosophila melanogaster*, TRF improves metabolic flexibility, reduces obesity and hepatic steatosis, preserves cardiovascular function, and promotes healthy aging, even when total food intake and body weight are unchanged (85). Recent studies in species such as chickens and pigs also show enhanced circadian alignment, metabolism, and fertility, expanding translational relevance (79, 86, 110, 132, 133). In humans, TRE shows similar promise, although outcomes vary due to differences in timing, duration, and population characteristics, and women remain underrepresented (86).

Here in this review, we discuss the current evidence linking TRF/TRE and circadian rhythms and their impacts on health and longevity across model organisms and clinical studies, as well as highlight data gaps and future directions of study.

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2. CIRCADIAN RHYTHMS ARE ESSENTIAL FOR HEALTH

2.1. Molecular Clocks Drive Daily Rhythms in Behavior and Physiology

Since the mid-20th century, studies in fruit flies and mice have defined the molecular basis of circadian rhythms, revealing transcriptional-translational feedback loops (TTFLs) that generate ~24-h cycles of gene expression (64). In mammals, circadian organization is orchestrated by the suprachiasmatic nucleus (SCN) of the hypothalamus, which synchronizes physiology and behavior to the light–dark cycle (91, 135). Light input from intrinsically photosensitive retinal ganglion cells entrains the SCN via the retinohypothalamic tract (12, 77). At the molecular level, heterodimers of activators CLOCK and BMAL1 drive transcription of period (*Per1*, *Per2*) and cryptochrome (*Cry1*, *Cry2*) genes via binding at E-box elements (122). As PER and CRY proteins accumulate, they inhibit CLOCK–BMAL1 activity, thereby closing the loop with ~24-h periodicity. Additional stabilizing loops involving nuclear receptors REV-ERBs and RORs fine-tune oscillations, creating robust cycles of gene expression. The SCN relays temporal signals to the rest of the brain and body, coordinating feeding–fasting, sleep–wake, and neuroendocrine rhythms (53), which in turn help synchronize clocks in peripheral tissues (92).

Molecular clocks are present in nearly every tissue, including the liver, heart, pancreas, adipose tissue, kidney, lung, and skeletal muscle (92, 144, 149). As in the SCN, these clocks operate via TTFLs to generate tissue-specific rhythmic expression of genes and pathways for bodily functions. For example, in the liver, the tissue with the most cycling genes, hepatic clocks regulate rhythms in glucose homeostasis, lipid metabolism, and detoxification (105), while in skeletal muscle, clocks drive rhythms in energy utilization and contractile function (49, 118).

While mammals depend on the SCN for central coordination, other taxa exhibit alternative organizational strategies. In birds, pacemaking is distributed across the SCN, pineal gland, and retina (15), whereas in invertebrates such as *Drosophila melanogaster*, pacemaker neurons reside in discrete brain regions, yet peripheral tissues can also be directly light-entrained (52). Despite these species-specific architectures, the evolution of circadian systems across taxa provides a shared adaptive advantage, allowing organisms to anticipate and align physiology and behavior with the daily environmental cycle.

2.2. Circadian Decline, Desynchrony, and Disruption

Functional molecular clocks and synchronized circadian rhythms are essential for health and longevity (10, 11, 40, 45, 93, 113). With age, the numbers of rhythmic genes and rhythmic amplitudes decline, and the coherence in the phase of gene expression (e.g., synchronized expression of genes in metabolic pathways) across tissues weakens, leading to desynchronized outputs in humans and animal models (1, 2, 38, 59, 111, 138) (**Figure 1**). This circadian decay contributes to irregular sleep–wake cycles, reduced metabolic resilience, and greater vulnerability to diseases such as Alzheimer's, cardiovascular dysfunction, and type 2 diabetes mellitus (T2DM) (21, 112, 126). Genetic ablation of core clock components further accelerates these outcomes (145). For instance, mice lacking BMAL1 exhibit premature aging phenotypes, including sarcopenia, cataracts, and shortened lifespan (72), while CLOCK mutant mice develop metabolic syndrome-like features, heightened obesity risk, and similar reduced longevity (35).

Disease itself can also disrupt circadian rhythms. In obese mice fed a high-fat diet (HFD), food intake extends into the inactive phase, damping oscillations of hepatic and adipose clock genes and disrupting cross-tissue coherence (37, 71). Similarly, cancers can reprogram cellular metabolism and alter the rhythmic expression of clock-controlled genes (58, 90). Thus, circadian disruption



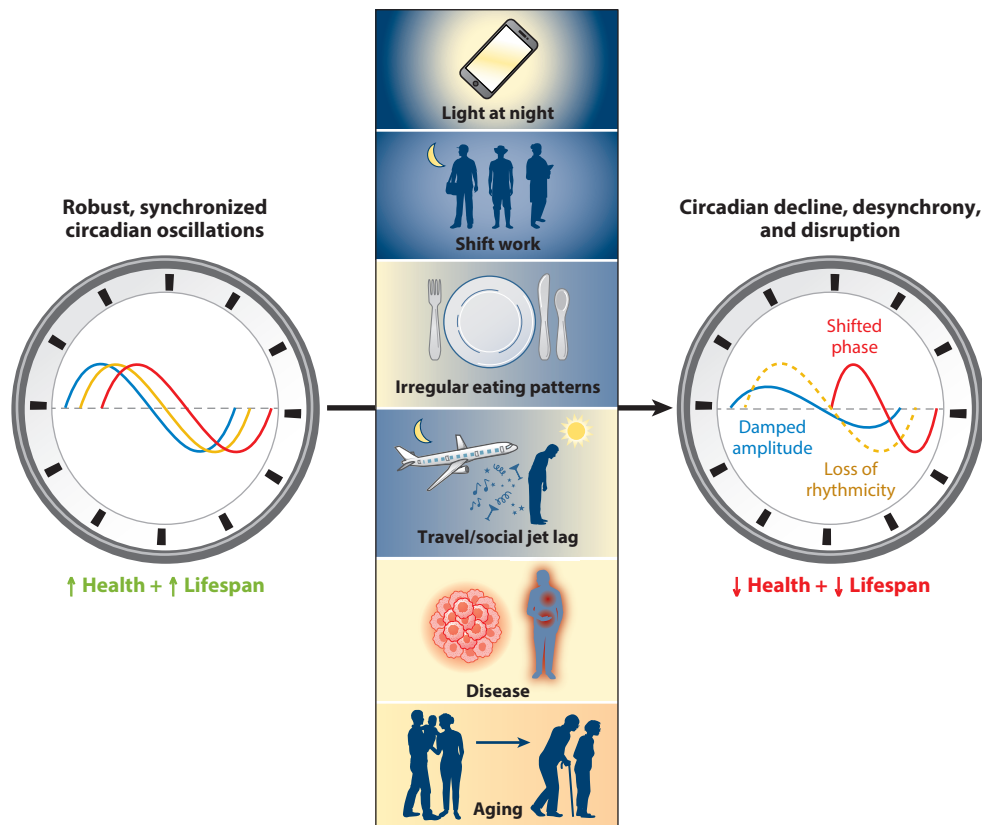


Figure 1

Robust and synchronized circadian rhythms are associated with improved health outcomes. Schematic showing various environmental, lifestyle, and biological factors that contribute to damped, desynchronized, or loss of rhythmicity in circadian rhythms.

is both a driver and a consequence of disease, underscoring the bidirectional link between clocks and health.

Modern lifestyles further compound these effects. Acute circadian disruption from jet lag induces insomnia, daytime fatigue, and cognitive impairment as the SCN rapidly adjusts but peripheral clocks lag behind, creating internal misalignment (130). Chronic jet lag, such as that experienced by frequent international travelers, has even been linked to increased mortality in rodents (28).

Other chronic circadian disruptions such as shift work, where workers remain active during the night while still often being forced into daytime social obligations, result in persistent misalignment between light cues, sleep–wake cycles, and feeding behavior (**Figure 1**). This is strongly associated with obesity, T2DM, cardiovascular disease, gastrointestinal disorders, depression, and certain cancers (139). Even subtle disruptions such as social jet lag (a difference in middle sleep time between working days and days off), nighttime light exposure (e.g., streetlamps, using electronic devices at night), or irregular eating patterns (e.g., late-night snacking, meal skipping) can impair cognition, mood, and metabolic health (14).

3. TARGETING CIRCADIAN RHYTHMS TO IMPROVE HEALTH IN MODEL ORGANISMS

3.1. Timed Feeding Entrain Peripheral Clocks and Enhances Circadian Rhythms

While light is the dominant synchronizer of the SCN, food intake is a major temporal cue for entraining circadian clocks in peripheral organs (3, 47, 75, 106, 129). In rodents, restricting food availability to specific times of day shifts the phase of clock gene expression in the liver, pancreas, kidney, and heart, independently of the SCN, which remains locked to the light–dark cycle (25, 51, 119). The liver appears to play the central role in integrating and relaying feeding signals, as disruption of hepatic clocks alters the rhythmic transcription of clock-controlled genes in other peripheral organs (84). Importantly, food-induced oscillations in metabolites such as NAD⁺, acetyl-CoA, and AMP also feed back onto the core clock, modulating rhythmicity through chromatin remodeling and energy-sensing pathways (95, 112).

3.2. Time-Restricted Feeding as a Circadian Enhancing Intervention to Improve Health in Model Organisms

Given this powerful role of timed food intake, various dietary strategies have been developed to harness feeding as an intervention to improve health and aging, the most notable of which is TRF, a form of intermittent fasting (IF), in which food intake is consolidated into a 12-h or shorter feeding window without a forced reduction in caloric intake (81, 85). Unlike other IF protocols, such as alternate-day fasting, periodic fasting, or fasting-mimicking diets, which involve prolonged fasting intervals of 24 h or more, TRF involves daily cycles of feeding–fasting that align feeding with the organism's active phase. In doing so, TRF reshapes gene expression patterns and strengthens rhythmic oscillations in clock-controlled genes and rhythms in their downstream functions (13, 18, 19, 33, 39, 43, 54, 60, 73, 104, 115, 116, 132, 133). This makes TRF a particularly promising intervention for strengthening metabolic rhythms, enhancing circadian coherence across tissues, and promoting overall health.

3.2.1. Strong evidence for metabolic and cardiovascular benefits. The metabolic benefits of TRF are among the most thoroughly characterized in preclinical models (**Figure 2**; **Table 1**). In mice fed an HFD, restricting food intake to the night, the natural feeding phase for nocturnal animals, mitigates symptoms of metabolic syndrome including obesity, fatty liver, insulin resistance, and hyperlipidemia, even when food intake and body weight remain similar to ad libitum (free-fed) controls (7, 19, 54, 120). These benefits can be further amplified by narrower feeding windows or when combined with resistance training, which modestly reduces caloric intake and enhances metabolic efficiency (24, 120). Notably, metabolic health improvements persist even in clock-deficient mice, indicating that feeding–fasting cycles alone are sufficient to drive metabolic oscillations (17). In nutritionally challenged rats or hypertensive mice models, TRF also improves atherogenic indices, lowers blood pressure (BP), and restores heart rate rhythms, reflecting its broader cardiometabolic protective effects (6, 61, 117).

Mechanistically, TRF appears to enhance cardiometabolic health by reestablishing rhythmic transcriptional and metabolic programs within the liver, adipose tissue, skeletal muscle, and vasculature that are otherwise blunted by HFDs, including pathways regulating lipid and glucose metabolism, nutrient transport, mitochondrial function, and redox homeostasis (99). In adipose tissue, TRF further promotes thermogenic remodeling by enhancing creatine-driven substrate cycling and energy dissipation (55).



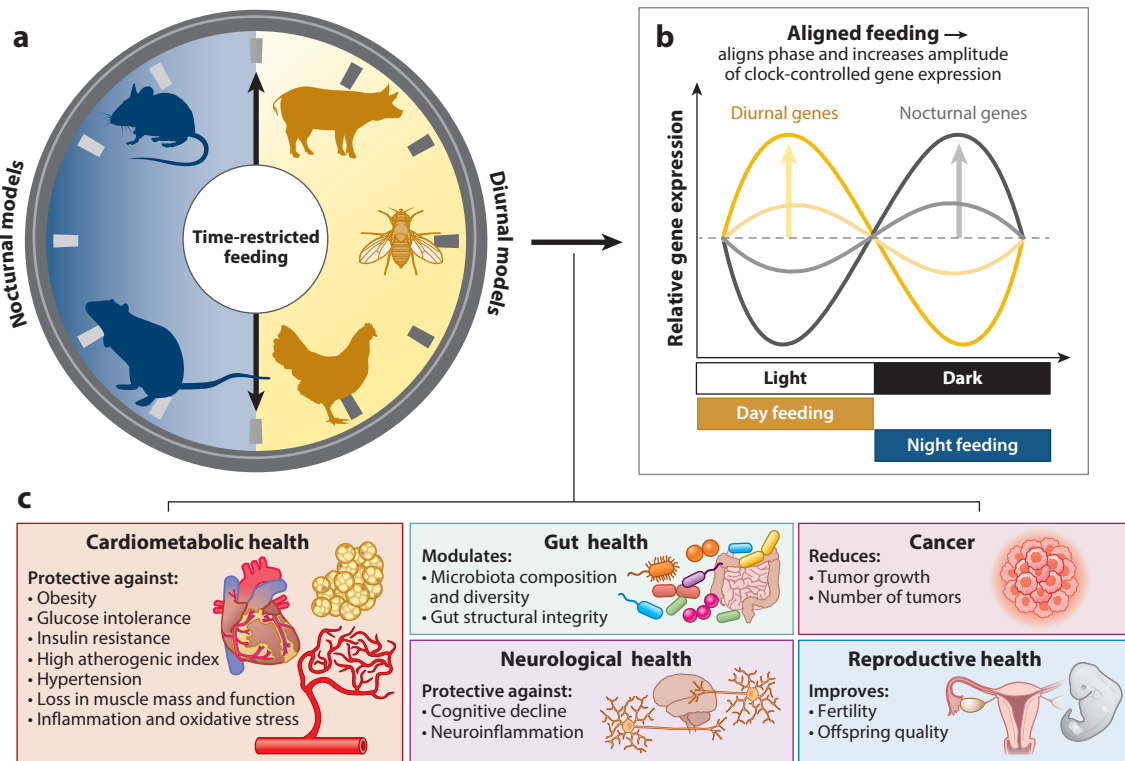


Figure 2

Circadian aligned time-restricted feeding improves circadian rhythms and health in model organisms. (a) Schematic of key nocturnal and diurnal animal models used to study the impacts of time-restricted feeding. (b) Representation of appropriate temporal alignment and enhanced amplitude in clock gene expression between diurnal and nocturnal species. (c) Types of health improvements conferred by time-restricted feeding.

3.2.2. Expanding evidence for improved gut rhythms, cognition, and cancer. A growing body of evidence indicates that TRF not only reorganizes host metabolism but also profoundly reshapes the gut environment (Figure 2; Table 1). In addition to enhancing gut integrity (57), TRF reestablishes diurnal oscillations in microbial community composition and metabolite production, thereby restoring host–microbe synchrony and the rhythmic partitioning of nutrient handling across the day–night cycle (26, 39, 132, 133). In diurnal pigs, TRF induced reprogramming of hypothalamic aromatic amino acid metabolism (133) alongside altered colonic nutrient flux and microbial rhythmicity (132), highlighting coordinated central–peripheral adjustments in a species with human-like activity patterns and physiology. Similar work in rats has found that specific bacterial genera become upregulated by TRF, including *Lactobacillus* and *Akkermansia*, which are associated with mucosal integrity, metabolism, and anti-inflammatory signaling (97). In models of chronodisruption, including jet lag and cancer, TRF also restored rhythmicity in intestinal metabolism and microbiota-linked pathways, effectively counteracting circadian misalignment at the gut level.

In the nervous system, TRF has been found to modulate neuroinflammation and cognitive function (Figure 2; Table 1). In mouse models of Alzheimer’s disease, TRF reduced amyloid deposition, improved sleep–activity rhythms, and rescued spatial memory performance through

Table 1 Key TRF studies in model organisms

Model strain (context)	TRF diet(s)	TRF versus control	TRF onset duration	Intake versus control	Significant health outcomes	Reference
♂ Mice: C57BL/6j (obesity)	HFD	12 h night versus day	9 weeks: 6 weeks	=	Night TRF: ↓ fat, ↓ BW	7
♂ Mice: C57BL/6 (obesity)	SD/ HFD	8 h night versus AL	12 wks: 18 wks	=	Both diets: ↑ VO2 HFD: ↓ fat, ↓ BW, ↓ insulin, ↓ inflammation, ↓ fatty liver; ↑ motor coordination, ↑ amplitude of liver clock, ↑ CREB/mTOR/AMPK pathway function, ↑ glucose homeostasis, ↑ FAO	54
♂ Mice: C57BL/6 (obesity, post-TRF effects, aging)	SD/ HFD/ HSD	9/12/15 h night versus AL	12 or 26 weeks: 12 or 25 weeks/ weekends off/ 12 weeks AL post-TRF	=	↓ Fat, ↓ BW, ↓ leptin, ↓ TG, ↓ fatty liver, ↓ TC, ↓ inflammation, ↓ IR, ↓ oxidative stress; ↑ glucose homeostasis, ↑ motor coordination, ↑ endurance, ↑ metabolic rhythms All enhanced under HFD	19
♂/♀ Flies: <i>Drosophila melanogaster</i> (obesity, clock-KO, aging)	SD/ HFD	12 h day versus AL	2 or 5 weeks: 3–5 weeks	=	↓ BW, ↓ DEGs in mitochondrial electron transport chain; ↑ sleep, ↑ cardiac function, ↑ rhythmic transcripts, ↑ DEGs in TCP1-ring complex	43
♂ Mice: C57BL/6 (obesity)	HFD	8/12 h night versus AL	6 weeks: 9 weeks	12 h: = 8 h: ↓8%	Both windows: ↓ fat, ↓ BW, ↓ insulin, ↓ leptin, ↓ MCP-1, ↓ TIMP-1, ↓ EE ^a ; ↑ VO2, ↑ ghrelin ^a 8 h: ↑ adiponectin	120
♂ Mice: C57BL/6 (obesity, clock-KO)	HFD	10 h night versus AL	8–12 weeks: 12 weeks	=	↓ Fat, ↓ BW, ↓ fatty liver, ↓ IR; ↑ RER, ↑ metabolic/ nutrient sensing rhythms, ↑ glucose homeostasis, ↑ cellular homeostasis	17
♂ Rats: Fisher (liver cancer, aging)	SD	8 h night versus AL	8 weeks: 18 months	=	↓ BW, ↓ fatty liver, ↓ neoplastic cell clusters, ↓ SA-β-Gal, ↓ IGF-1, ↓ TG, ↓ LDL/HDL-C; ↑ BDNF	114
♂/♀ Flies: <i>D. melanogaster</i> (obesity, aging)	SD/ HFD/ HSD	12 h day versus AL	4 days: 3 weeks	♂: = ♀: ↑↑↑; ↓	↓ Fat, ↓ BW, ↓ glucose, ↓ trehalose, ↓ TC, ↓ intramuscular lipids, ↓ IR; ↑ muscle performance	127
♂ Rats: Wistar (misaligned TRF)	SD	10 h day/ night versus AL	?: 4 weeks	=	Night TRF: ↓ IR, ↑ glucose homeostasis	31
♂ Rats: Wistar (obesity, thermoneutrality)	SD/ CAF	8 h night versus AL	?: 16 weeks	=	↓ Fat, ↓ BW, ↓ LDL-C levels, ↓ atherogenic indices, ↓ TG, ↓ TC; ↑ UCP1, ↑ PGC1α, ↑ beiging of white fat	6

(Continued)



Table 1 (Continued)

Model: strain (context)	TRF diet(s)	TRF versus control	TRF onset: duration	Intake versus control	Significant health outcomes	Reference
♀ Mice: C57BL/6 (obesity, fertility)	SD/ HFD	10 h night versus AL	8 weeks: 22–24 weeks	=	↓ BW; ↑ glucose homeostasis, ↑ fertility, ↑ estrous cycling, ↑ ovarian reserve, ↑ FGF21	62
♂ Rats: DPP-IV-Fischer (gut)	SD	8 h night versus AL	8 weeks: 48 weeks	=	↑ <i>Akkermansia</i> and <i>Lactobacillus</i> composition, ↑ carbohydrate/protein metabolism	97
♂ Mice: C57BL/6j (clock disruption-LL)	SD	8 h LL versus AL	5 months: 8 weeks	=	↓ Fat; ↑ feeding/fasting rhythms, ↑ glucose homeostasis, ↑ pancreatic β cell function, ↑ islet clock rhythms	13
♂/♀ Mice: C57BL/6j (obesity, aging)	WD	9 h night versus AL	3 or 12 months: 12–13 weeks	=	Both sexes: ↓ fatty liver, ↓ IR; ↑ glucose homeostasis, ↑ sepsis survival ♂: ↓ BW, ↓ inflammation, ↓ TC; ↑ lean mass, ↑ muscle performance, ↑ motor coordination	16
♀ Mice: C57BL/6j (early versus late TRF)	SD	4 h night early/late versus AL	8 weeks: 2 weeks	?	Shifts phase of uterine clock with onset of feeding	60
♂ Mice: C57BL/6j (obesity, early versus late TRF)	SD/ HFD	10 h night early/late versus AL	8 weeks: 4 weeks	SD: = HFD: ↓	Both: ↓ BW ^b , ↓ fat ^b , ↓ IR; ↑ glucose homeostasis, ↑ amplitude of liver clock, ↑ nutrient utilization/NAD metabolism rhythms Late TRF: delayed peak phase of liver clock	104
♀ Chickens: Leghorn (fertility)	SD	6 h day versus AL	25 weeks: 86 weeks	↓	Fat: ↓ BW, ↓ egg weight; ↑ aged egg quality, ↑ laying efficiency	110
♂ Mice: <i>Dfb/dlb</i> (diabetes, hypertension)	SD	8/12 h night versus AL	≥6 weeks: 10–12 weeks	12 h: = WT 8 h: = <i>Dfb</i> 8 h: ↓	Both genotypes: ↑ RER, ↑ HR rhythms <i>Dfb/dlb</i> : ↑ BP, ↑ EE rhythms	61
♂ Mice: C57BL/6 (obesity)	HFD	8/9 h night versus AL	8 or 12 weeks: 8 weeks	=	↑ Microbial rhythmicity, ↑ GLP-1 rhythms, ↑ amplitude of gut clock, ↑ bile acid signaling	26
♂ Mice: C57BL/6j (obesity, clock- KO, thermoneutrality)	HFD/ HFD + creatine	12 h day/night versus AL	2–3 months: 6–10 weeks	WT day + night: ↓	↓ BW; ↑ VO ₂ , ↑ glycolysis, ↑ citric acid cycle metabolites, ↑ creatine cycling, ↑ thermogenesis All enhanced under TRF night versus day	55

(Continued)



Table 1 (Continued)

Model: strain (context)	TRF diet(s)	TRF versus control	TRF onset: duration	Intake versus control	Significant health outcomes	Reference
♀ Mice: C57BL/6j (obesity, fertility)	SD/ HFD	8 h night versus AL	6 weeks: 11 weeks	=	Both diets: ↑ ovarian follicle counts, ↑ amplitude of liver/fat/ovarian clocks; ↓ LDL-C SD: ↑ ROS, ↑ mitochondrial function, ↑ apoptotic marker in ovaries; ↓ embryo development HFD: ↑ TC, ↓ HDL-C	73
♂/♀ Mice: C57BL/6j (hypertension)	SD/ salt diet	12 h night versus AL	10–12 weeks: 4 weeks	=	↓ BP; ↓ renal immune cells; ↓ IL-6, ↓ IL-1β; ↑ kidney function	117
♂/♀ Mice: APP23 (Alzheimer's disease)	SD	6 h night versus AL	4.5 months: 3 months	=	Both sexes: ↓ glucose, ↓ neuroinflammation; ↑ ketones, ↑ autophagy, ↑ cognition ♀: ↑ sleep	136
♂ Mice: C57BL/6 (obesity, early versus late TRF)	HFD	8 h night early/late versus AL	14 weeks: 5 weeks	↓	Both: ↓ fat, ↓ BW, ↓ insulin, ↓ TC, ↓ LDL/HDL-C, ↓ TNFα, ↓ fatty liver, ↓ leptin, ↓ ALT, ↓ inflammation, ↓ glucose, ↓ IR; ↑ RER rhythms, ↑ adiponectin, ↑ fat/muscle metabolism Early TRF: ↓ TG; ↑ amplitude of liver clock	125
Pigs: crossbred (translational, gut)	SD	11 h day versus AL	110 days: 15 days	=	↓ Cellulose, ↓ alpha diversity richness; ↑ microbial cross-talk; shifts microbial composition and rhythms	132
Pigs: crossbred (translational, gut)	SD	12 h day versus AL	?: 21–22 days	=	↓ Ghrelin, ↓ gastrin, ↓ GLP-1, ↓ cholecystokinin, ↓ peptide YY, ↓ DEGs in amino acid metabolism/drug addiction in brain; ↑ digestive enzymes, ↑ nutrient absorption, ↑ BW	133
♂ Mice: BALB/c; C57BL/6j (cancer, gut)	SD	6 h night versus AL	5–6 weeks: 40 days or 15 weeks	=	↓ BW, ↓ tumor growth; ↑ gut microbial rhythms; shifts metabolome/microbiome composition and gut clock	39
♂ Mice: Swiss (obesity, resistance training)	SD/ HFD	8 h night versus AL	6 weeks: 8 weeks	↓	Fat, ↓ BW, ↓ fatty liver, ↓ lipogenesis, ↓ IR, ↓ inflammation; ↑ glucose homeostasis, ↑ EE, ↑ FAO, ↑ mitochondrial function All enhanced with TRF + resistance training	24

(Continued)



Table 1 (Continued)

Model: strain (context)	TRF diet(s)	TRF versus control	TRF onset: duration	Intake versus control	Significant health outcomes	Reference
♂ Mice: C57BL/6j (obesity)	WD	9 h night versus AL	12 weeks: 7 weeks	1-2 weeks: ↓ >2 weeks: =	↓ BW, ↓ inflammation, ↓ oxidative stress; ↑ intertissue coordination, ↑ RNA and protein processing/ribosome biogenesis/cell cycle regulation/mitochondrial functions rhythms	33
♂ Mice: C57BL/6j (obesity)	SD/ HFD	9 h night versus AL	8 weeks: 16 weeks	=	Both diets: ↓ fatty liver, ↓ TG; ↑ <i>Fgf21</i> , ↑ FAO HFD: ↓ BW, ↓ lipogenesis, ↓ inflammation, ↓ fibrogenesis; ↑ glucose homeostasis	63
♂ Mice: BALB/c (cancer, chemotherapy)	SD	6 h night +/- chemo versus AL	≥5 weeks: 27-33 days	=	↓ BW, ↓ weight/proliferation of tumors; ↑ RER/VO2 rhythms; shifts phase of TIM/metabolic pathways	115
♂ Mice: C57BL/6j (obesity, post-TRF effects)	SD/ HFD	10 h night versus AL	6 weeks: 6 weeks/ 4 weeks TRF + 2 weeks AL, post-TRF	TRF: ↓ Post-TRF: ↑	Both regimens: ↓ adipocyte size, ↓ IR ^a , ↓ insulin ^d TRF 6 weeks: ↓ fat, ↓ BW, ↓ inflammation, ↓ glucose Post-TRF: ↑ BW	147
♂ Mice: C57BL/6 (obesity, aging)	HFD	8 h night versus AL	54/91 weeks: 8 weeks	54 weeks: ↓ 91 weeks: =	Both ages: ↓ lean mass, ↓ inflammation, ↓ fatty liver, ↓ glucose, ↓ IR; ↑ glucose homeostasis 54 weeks: ↓ insulin; ↑ thermogenesis 91 weeks: ↓ BW	141
♂ Rats: Wistar (misaligned TRF, restricted wheel)	SD	10 h day/night versus AL	11 weeks: 4 weeks	Day: = night: ↑	Both day/night: ↓ fat ^e , ↓ BW ^e Day TRF: ↓ amplitude/phase of muscle clock Night TRF: ↑ amplitude of muscle clock	116
♂ Mice: C57BL/6j (obesity, cancer)	WD	8 h night versus AL	8 or 18 weeks: 10-24 weeks	=	↓ Fat, ↓ BW, ↓ glucose, ↓ IR, ↓ fatty liver, ↓ fibrosis, ↓ inflammation, ↓ number/weight of tumors; ↑ glucose homeostasis	27

(Continued)

Table 1 (Continued)

Model: strain (context)	TRF diet(s)	TRF versus control	TRF onset: duration	Intake versus control	Significant health outcomes	Reference
♀ Chickens: Leghorn (fertility, aging)	SD	12 h day versus AL	12 months: life	=	↑ Reproductive longevity	79
♀ Flies: <i>D. melanogaster</i> (fertility, aging)	SD	8 h day versus AL	3–5 days: 4 weeks (1 day AL)/ Life (1 day AL)	↓	↑ Median lifespan, ↑ fecundity, ↑ intestinal stem cell proliferation, ↑ epithelial barrier integrity, ↑ gram-negative microbiota composition	57
♂ Mice: C57BL/6j (8 h jet lag, gut)	SD	12 h night from first LD versus AL	12 weeks: 4 weeks	?	↑ Amplitude of gut clock & nutrient transport/lipid metabolism/ketogenesis/cellular organization rhythms	78
♂/♀ Mice: C57BL/6j (aging)	SD	8/12 h night versus AL	4 months: lifelong	12h ♀: = 12h ♂: ↓ to 18 months, then = 8 h ♂/♀: ↓	All TRF groups: ↓ fat, ↓ BW, ↓ frailty indices ^a , ↑ feeding rhythm amplitude ^a , ↑ health-span indices ^a 8/12 h ♀: ↑ wheel-running rhythm amplitude ^a 8 h ♂ only: delayed onset of health reports; ↑ wheel-running activity and rhythm amplitude, ↑ lifespan	66

For studies testing multiple diet types, TRF onsets, and TRF durations, each regimen is separated by a slash (/).

^aEnhanced with 8 h TRF.

^bEnhanced with early TRF.

^cEnhanced under early TRF versus late.

^dEnhanced with maintained 6 weeks of constant TRF.

^eEnhanced under night TRF + wheel versus day.

Abbreviations: AL, ad libitum; ALT, alanine transaminase; AMPK, AMP-activated protein kinase; BDNF, brain-derived neurotrophic factor; BP, blood pressure; BW, body weight; CAF, cafeteria diet; CREB, cAMP response element-binding protein; DEG, differentially expressed genes; EF, energy expenditure; FAO, fatty acid oxidation; FGF21, fibroblast growth factor 21; GLP-1, glucagon-like peptide-1; HFD, high-fat diet; HR, heart rate; HSD, high-sugar diet; IGF-1, insulin-like growth factor 1; IL, interleukin; IR, insulin resistance; KO, knockout; LD, light/dark cycle; LDL/HDL-C, low/high-density lipoprotein cholesterol; LL, constant light; MCP-1, monocyte chemoattractant protein-1; mTOR, mechanistic target of rapamycin; NAD, nicotinamide adenine dinucleotide; PGC1 α , peroxisome proliferator-activated receptor- γ coactivator 1 α ; RER, respiratory exchange ratio; ROS, reactive oxygen species; SA- β -Gal, senescence-associated β -galactosidase; SD, standard diet; TC, total cholesterol; TCPI, T-complex protein 1; TG, triglyceride; TIM, timeless; TIMP-1, tissue inhibitor of metalloproteinases 1; TNF α , tumor necrosis factor α ; TRF, time-restricted feeding; UCP1, uncoupling protein 1; VO₂, oxygen consumption; WD, Western diet; WT, wild type.



attenuation of pathology-related and neuroinflammatory gene expression (136). Complementary findings from aging and obesity paradigms show preserved motor coordination, mitochondrial function, and neuronal redox balance, reflecting enhanced resilience of neural circuits to metabolic and circadian stress under TRF (16, 21, 127). These effects align with broader evidence linking circadian alignment to neuroprotection and the stability of the gut–brain axis (21), suggesting that TRF’s benefits for cognition may also arise in part through microbiome-mediated neuroimmune signaling and rhythmic regulation of metabolites such as short-chain fatty acids, tryptophan derivatives, and bile acids.

Although still limited, emerging evidence suggests that TRF may exert protective effects against cancer development and progression (**Figure 2; Table 1**). In murine models of lung adenocarcinoma, TRF delayed tumor progression, reprogrammed circadian metabolism, and restored rhythmicity in hepatic and intestinal gene expression (39, 115). Similarly, TRF slowed the emergence of neoplastic-prone tissue states during aging (114) and attenuated metabolic dysfunction associated with steatohepatitis and hepatocellular carcinoma in obese mice (27). Collectively, these results align with studies demonstrating that disrupted feeding–fasting cycles accelerate tumorigenesis and metabolic reprogramming (131), reinforcing the concept that temporal alignment of nutrient intake can modulate cancer susceptibility.

3.2.3. Female fertility: encouraging but controversial. More recently, in females, TRF has been found to enhance reproductive function through coordination of endocrine and metabolic pathways (**Figure 2; Table 1**). In mice, it improves ovarian clocks and estrous cyclicity, preserves ovarian reserve, and increases fertility markers via hepatic fibroblast growth factor 21 (FGF21) signaling, although more so under HFD feeding conditions (62, 73). In diurnal chickens and flies, aligning feeding with the light phase also improves egg quality and reproductive longevity (57, 79, 110). However, contrasting work in finches suggests that TRF is instead detrimental to reproductive fitness in both males and females (101, 102). Additional studies are needed to disentangle the relative contributions of feeding phase, caloric intake, and species-specific metabolic demands and to determine whether the reproductive benefits of TRF extend across sexes.

3.2.4. Key takeaways and knowledge gaps for future researchers using model organisms.

A defining feature of TRF is the alignment of feeding windows with the organism’s endogenous circadian activity phase, thereby reinforcing circadian oscillations and promoting systemic health. Across models, the most consistent and robust benefits occur when food intake coincides with the active phase, nighttime in nocturnal rodents and daytime in diurnal species, whereas misaligned feeding disrupts circadian clocks and blunts or abolishes these effects (1, 7, 9, 31, 55, 116, 142, 143) (**Table 1**). Within aligned feeding schedules, increasing attention has been given to whether earlier or later feeding onset within the active phase confers greater benefits. Current evidence suggests that earlier feeding windows enhance fat and body weight loss, insulin sensitivity, lipid metabolism, and BP regulation, while delayed feeding shows damped or no effect (60, 104, 125). These findings highlight the importance of considering both duration and phase of feeding when designing TRF protocols. The distinction between early and late TRF remains underexplored in model organisms, particularly beyond cardiometabolic health. Expanding this work will be key to developing phase-appropriate, translational TRF strategies for humans with diverse chronotypes and activity patterns.

Most of the current metabolic, cardiovascular, neurological, gut, and cancer data derive from nocturnal rodents under nutritional challenges such as HFDs, raising some uncertainty about efficacy in diurnal, metabolically normal species (**Table 1**). Studies in diurnal flies strongly support the idea that aligning feeding with the active phase preserves metabolic health, cardiac performance, gut integrity, and fecundity (43, 57, 127); work in chickens also indicates benefits for

fertility and egg quality (79, 110). Yet some mechanisms may not fully translate from invertebrates and birds to mammals. Encouragingly, the studies in pigs, a diurnal model physiologically similar to humans, show that TRF reprograms brain and gut gene expression, enhances microbial and digestive function, and even reduces body weight without a reduction in calories (132, 133). Continued investigations in diurnal mammalian models under normal dietary conditions are critical to establish whether TRF's health benefits extend beyond nocturnal physiology and to elucidate the mechanistic links between feeding time, circadian alignment/enhancement, and improved health.

Female animals remain markedly underrepresented in TRF research, despite emerging evidence for sex-specific differences in circadian regulation (8, 74, 123). When included, females exhibit not only improved reproductive outcomes (60, 62, 73, 79, 110) but also notable gains in cardiometabolic health (16, 43, 57, 62, 73, 127, 136) (**Table 1**). However, direct male-to-female comparisons reveal that these benefits are often less pronounced in females or show distinct responses, such as reduced food intake or improved sleep (16, 127, 136). Moreover, female rodents are known to exhibit greater resistance to HFD-induced weight gain and can maintain feeding rhythms under dietary challenge (94, 96, 100), suggesting that TRF effects and mechanisms likely differ fundamentally across sexes. Future studies should therefore incorporate balanced sex comparisons and evaluate TRF outcomes side by side to better delineate sex-specific mechanisms and responses.

Another limitation of the current TRF literature is analyses for age-specific and long-term effects. Many studies initiated TRF in young adulthood and continued for 12 weeks or less (**Table 1**). Nevertheless, several investigations have begun to address this gap. In mice, TRF maintained metabolic and inflammatory benefits into midlife, though the magnitude of improvement diminished with age (16, 19, 141). Similarly, in aged rats, TRF reduced hepatic steatosis, neoplastic lesions, and oxidative stress while improving lipid metabolism and neurotrophic signaling (114). Aging flies and hens have also exhibited prolonged fecundity and enhanced intestinal integrity under daytime TRF regimens (57, 79), suggesting that benefits do extend across the lifespan. Very recently, a lifelong TRF study in male and female mice further showed that TRF attenuated age-related increases in body weight and adiposity, improved behavioral rhythms, reduced frailty, and extended overall health span (66). Importantly, post-TRF studies indicate that some of these benefits can persist even after a return to ad libitum feeding, suggesting a degree of metabolic "memory" or reprogramming (19, 147). However, these studies are still sparse. Extending TRF paradigms to include more longitudinal, late-onset, and postintervention designs will be essential to determine whether TRF acts primarily as an acute circadian-metabolic reset or as a durable chrononutritional strategy for healthy aging.

3.3. Time-Restricted Feeding as a Circadian Enhancing Intervention to Improve Lifespan in Model Organisms

One of the most pressing questions is whether TRF can extend lifespan, as caloric restriction (CR) robustly does across multiple species (2, 46). Evidence has remained limited largely due to the substantial time and resources required for lifespan studies. In female *Drosophila*, restricting feeding to an 8-h daytime window increased median lifespan by 26%, although this regimen also reduced caloric intake (57) (**Table 1**). In mice, combining 30% CR with 12-h TRF during the active phase enhanced median lifespan extension to 35%, compared with 10% under CR alone (1) (**Table 1**). Recently, direct tests of TRF alone in mice found that a 12-h TRF regimen with largely isocaloric feeding was not sufficient to extend lifespan in either male or female mice (66). In contrast, restricting feeding to an 8-h window in the middle of the active phase extended lifespan



in male mice by 12%, although this intervention also reduced food intake by ~20% relative to ad libitum controls. Collectively, these findings suggest that meal timing can influence longevity outcomes, potentially in a sex-dependent manner, but additional work is needed to disentangle the independent contributions of feeding window duration, feeding phase, and caloric intake.

4. CLINICAL APPLICATION AND HEALTH OUTCOMES OF TIME-RESTRICTED EATING

Fasting is an ancient tradition that is ingrained in human history in spiritual, cultural, and medicinal contexts. Aside from personal experiments conducted on research subjects in the 19th and early 20th centuries (70), formal studies of fasting as an obesity treatment began in 1915. This initial research involved two obese individuals who underwent fasts lasting several days, with the production of acetoacetic acid used to determine the fasting duration (41). However, prolonged periods of food deprivation often proved difficult to sustain and presented safety issues, leading researchers to explore paradigms of shorter and more manageable periods of CR. This exploration gave rise to the modern framework of IF, which focuses on regular, planned periods of eating and noneating rather than continuous energy deprivation (30). TRE is a specific and highly studied form of IF that is defined by restricting the entire daily energy intake to a consistent, narrow window, typically 4 to 12 h, without necessarily restricting what is eaten (30, 108). This protocol has emerged as a viable solution for humans wishing to undergo dietary interventions without having to necessarily conform to a strict deprivation of food. Seminal work by Gill & Panda (44) explored the specific timing of caloric intake in humans and demonstrated that humans under ad libitum conditions tend to consume food in an erratic manner, spanning 15 h or longer, as well as a bias to eating later in the day. Modulating this erratic pattern by implementing a restrictive daily 10-h window of food intake for 16 weeks resulted in weight loss, increased perceived energy levels, and improvements in sleep in overweight individuals. Prior and subsequent studies in humans have confirmed these results, showing that TRE has a wide range of benefits including weight loss, body composition, and cardiometabolic markers. In the following sections, we attempt to identify the benefits of TRE and its ability to align circadian rhythms and human physiology.

4.1. Human Health Benefits of Time-Restricted Eating

One of the most consistent findings across the literature is the efficacy of TRE in promoting weight loss and improving body composition (**Table 2**). This outcome is largely achieved by the spontaneous reduction in daily caloric intake that occurs when the feeding window is shortened. Studies have reported a reduction of 150–600 kcal/day in energy intake under TRE, the magnitude of which is affected by the timing of the feeding window itself. In some studies, a direct comparison of early (e) versus late (l) TRE has been made, showing that eTRE often leads to a greater spontaneous reduction in energy intake over lTRE times (98, 140, 148). In studies where TRE led to a reduction of daily intake, weight loss of ~3–6% occurred. Conversely, other studies have utilized isocaloric diets to ensure that body weight remains unchanged during TRE, to delineate whether the benefits of TRE are indirectly attributed to a loss in weight or through direct action of TRE alone (29, 89, 121).

Body composition has also been used to determine the exact areas where body weight loss is occurring. TRE has been shown to lead to reductions in visceral fat (67, 121), ectopic fat, and intrahepatic fat depots. Additionally, TRE with resistance training (124) or applied to older populations (89) preserves muscular strength and lean mass, demonstrating TRE to be a viable and safe option for causing weight loss in desirable areas.



Table 2 Human clinical trials of TRE

Reference	Subjects	Trial	Intervention	Change in intake	Weight (% change)	Change in body composition	Change in glucoregulatory factors	Other changes
Gill & Panda 2015 (44)	n = 156, 21–55 years, M & F, non-shift workers	16 weeks	10–12 h TRE	-20.26%	-3.45%	BMI -1.15 kg/m ²	NA	↑ Sleep satisfaction, ↑ energy level, ↓ hunger at bedtime
Tinsley et al. 2017 (124)	n = 18, 20–24 years, M	8 weeks	4 h TRE + HIIT	-650 kcal/day	=	=	NA	NA
Gabel et al. 2018 (42)	n = 23, 25–65 years, M & F, with obesity	12 weeks	8 h TRE (10:00–18:00)	-341 kcal/day	≈ -3%	NA	NA	↓ BP
Sutton et al. 2018 (121)	n = 8, 56 ± 9 years, M, with prediabetes	5 weeks	6 h eTRE (8:00–14:00) versus isocaloric TRE by 3 h	=	=	NA	↓ IR	↓ BP, ↓ oxidative stress
Antoni et al. 2018 (5)	n = 13, 29–57 years, M & F	10 weeks	TRE by 3 h	Undefined reduction	=	-1.9% body fat	NA	Feasibility, social eating/drinking negatively impacted
Hutchison et al. 2019 (65)	n = 15, 55 ± 3 years, M, with T2DM	4 weeks	9 h eTRE (8:00–17:00) versus 9 h ITRE (12:00–21:00)	NA	eTRE: -1.23% ITRE: -0.76%	NA	Both: ↑ glucose tolerance eTRE: ↓ FG	↓ Fasting TG
Lee et al. 2020 (76)	n = 9, 65+ years, M & F, overweight	4 weeks	Self-selected 8 h TRE	NA	NA	NA	NA	Feasibility study in older adults
Wilkinson et al. 2020 (137)	n = 19, 59 ± 11 years, M & F, with metabolic syndrome	12 weeks	Self-selected 10 h TRE	-8.62% versus baseline	-3.37%	-1.01% body fat, -4% waist circumference, -3% BMI	NA	NA
Cienfuegos et al. 2020 (22)	n = 58, 45–47 years, M & F, with obesity	10 weeks	4 h TRE (15:00–19:00) versus 6 h TRE (13:00–19:00)	-550 kcal/day	-3.2% for both TRE	Both: ↓ fat mass 6 h TRE: ↓ lean mass	↓ FI, ↓ HOMA-IR	↓ Oxidative stress, ↓ BP
Martens et al. 2020 (89)	n = 22, 55–79 years, M & F, healthy	12 weeks	8 h TRE	=	NA	2.5% ↑ leg fat mass	↑ Glucose tolerance	↓ Hunger, safe and well tolerated
Lowe et al. 2020 (82)	n = 116, 18–64 years, M & F, with obesity	12 weeks	8 h TRE (12:00–20:00)	=	=	↓ Appendicular lean mass	No change in FG, FI, HOMA-IR or HbA1c levels	↓ Step count, ↓ BP
Jones et al. 2020 (69)	n = 16, 23 ± 1 year, M	4 weeks	8 h eTRE (8:00–16:00) versus CR	-400 kcal/day versus baseline	eTRE: -1.42% CR: -1.60% versus baseline	eTRE: -4.84% fat mass CR: -4.31% fat mass	eTRE: ↓ IR, ↑ skeletal muscle uptake of glucose	eTRE: ↑ postprandial skeletal muscle BCAA uptake

(Continued)



Table 2 (Continued)

Reference	Subjects	Trial	Intervention	Change in intake	Weight (% change)	Change in body composition	Change in glucoregulatory factors	Other changes
Che et al. 2021 (20)	n = 120, 18–70 year, M & F, with T2DM and overweight	12 weeks	10 h TRE (8:00–18:00)	-531 ± 102 kcal/day versus baseline	-4% from baseline	-6% BMI	↓ HbA1c, ↓ FG, ↓ HOMA-IR	↓ TG, ↓ TC, ↓ LDL-C; ↑ medication effect score
Zhao et al. 2023 (150)	n = 16, 40–70 years, M	8 weeks	10 h TRE	NA	NA	NA	Altered insulin 24 h profile and TG	↓ Morning cortisol, ↑ rhythmicity of adipose transcriptome
Zhang et al. 2022 (148)	n = 60, 22.1–23.8 years, M & F, with obesity	8 weeks	6 h eTRE (7:00–13:00) versus 6 h iTRE (12:00–18:00)	eTRE: -554.1 kcal/day, iTRE: -407.0 kcal/day	eTRE: -4.6%, iTRE: -3.7%	Both: ↓ fat mass eTRE: ↓ lean mass	eTRE: ↓ blood glucose, ↓ F1, ↓ HOMA-IR	Both: ↓ leptin eTRE: ↓ BP
Manoogian et al. 2022 (88)	n = 137, 23–59 years, M & F, firefighters	12 weeks	10 h TRE (9:00–19:00) versus SOC	TRE: -415 kcal/day, SOC: -318 kcal/day	TRE: -1.1%	=	↓ HbA1c in at-risk participants	TRE: ↑ feasibility, ↑ SF-36 score (quality of life)
Jamshed et al. 2022 (68)	n = 90, 25–75 year, M & F, with obesity	14 weeks	8 h eTRF+ER versus control+ER	NA	eTRE: -5.7%, control: -4.2%	=	No change in FG, insulin, HOMA-IR, or HbA1c levels	eTRF+ER: ↓ BP, ↑ mood
Xie et al. 2022 (140)	n = 90, 18–64 years, M & F	5 weeks	8 h eTRE (6:00–15:00) versus 8 h mTRE (11:00–20:00); self-selected 8-h window within each of the above times	eTRE: -240 kcal/day, mTRE: -159 kcal/day	eTRE: -2.5%, mTRE: =	eTRE: -0.60% body fat	eTRE: ↑ HOMA-IR, ↓ FG	eTRE: ↑ gut microbiota diversity, ↓ inflammation
Haganes et al. 2022 (50)	n = 131, 36.2 ± 6.2 years, F, with obesity	7 weeks	10 h TRE, HIIT, TRE+HIIT	NA	TRE+HIIT: -3.6kg	TRE+HIIT: ↓ fat mass, ↓ visceral fat	=	HIIT and TRE+HIIT: ↑ VO ₂ peak
Wei et al. 2023 (134)	n = 88, 18–75 years, M & F, with obesity and NAFLD	12 months	8 h TRE (8:00–16:00) versus ER	NA	TRE: -9.45% ER: -8.52%	Both: ↓ body fat, ↓ lean mass, ↓ visceral fat	TRE: ↑ HOMA-IR above ER	Both: ↑ liver health, ↓ intrahepatic TG

(Continued)



Table 2 (Continued)

Reference	Subjects	Trial	Intervention	Change in intake	Weight (% change)	Change in body composition	Change in glucoregulatory factors	Other changes
Pavlou et al. 2023 (98)	n = 75, 18–80 years, M & F, with T2DM and obesity	6 months	8 h TRE (12:00–20:00) versus 25% ER	TRE: –313 kcal/day ER: –197 kcal/day	TRE: –3.56% ER: –1.78%	TRE: ↓ fat mass, ↓ BMI	Both: ↓ HbA1c levels, ↓ MG	All groups: ↓ BW, ↑ cardiovascular and liver health markers TRE: ↑ adherence eTRE+ER: greater ↓ fat mass, ↓ BMI, ↓ leptin, ↓ FG, ↓ diastolic BP
Lin et al. 2023 (80)	n = 77, 18–65 years, M & F, with obesity	12 months	8 h TRE (12:00–20:00) versus 25% ER	TRE: –425 kcal/day, ER: –405 kcal/day	TRE: –4.87%, ER: –5.30%	NA	NA	NA
Dawson et al. 2024 (29)	n = 16, 31.1 ± 5.2 years, M & F	9 days	6 h eTRE (8:00–14:00)	=	=	NA	↓ MG, ↓ glycemic variability, ↓ FG, ↓ HOMA-IR	eTRE: ↓ hunger, no change in intestinal function
Quist et al. 2024 (103)	n = 92, 52–65 years, M & F, with obesity or prediabetes	12 weeks	10 h TRE (self-selected time)	NA	=	=	=	Selected lipid changes, high adherence
Zhou et al. 2024 (151)	n = 74, 18–70 years, M & F, with stage-1 hypertension	6 weeks	8 h TRE (9:00–17:00) + DASH diet versus diet alone	NA	TRE+DASH: –6.75%, DASH: –1.64%	TRE+DASH: ↓ body fat mass, ↓ extracellular water	=	TRE+DASH: greater ↓ BP, ↑ diurnal BP rhythm
Akashch et al. 2024 (4)	n = 50, M & F, 47.2 ± 1.8 years, with obesity	8 weeks	4 h TRE (15:00–19:00) versus 6 h TRE (13:00–19:00)	NA	–3.6%	↓ Fat mass, ↓ BMI, ↓ waist circumference	↓ HOMA-IR	↑ IGF1P2 and ↓ leptin when weight loss > 3.5% of baseline
Manoogian et al. 2024 (87)	n = 108, 18–75 years, M & F, with metabolic syndrome	12 weeks	8–10 h TRE (reduction of ≥ 4 h from baseline)	–350 kcal/day	–3%	↓ BMI, ↓ trunk fat	Improved HbA1c, improved glycemic variability	Improvements in TC and TG levels

(Continued)



Table 2 (Continued)

Reference	Subjects	Trial	Intervention	Change in intake	Weight (% change)	Change in body composition	Change in glucoregulatory factors	Other changes
Deng et al. 2024 (32)	n = 40, 25–65 years, M & F, with NAFLD	8 weeks	8 h early TRE versus late TRE	eTRE: -297.98 kcal/day, ITRE: -223.30 kcal/day	↓ BW	↓ Intrahepatic fat eTRE: -3.24% and ITRE: -3.51% Both: ↓ visceral/subcutaneous fat	Both: ↓ FG, ↓ FI, ↓ IR eTRE: ↓ HbA1c	Both: ↑ liver function eTRE: ↓ blood lipids ITRE: ↓ hs-CRP
Dote-Montero et al. 2025 (34)	n = 197, 30–60 years, M & F, with obesity	12 weeks	8 h eTRE (8:00–16:00) or 8 h ITRE (12:00–20:00), versus 8 h TRE (self-selected)	-164 to -307 kcal/day, depending on timing of TRE	eTRE: -2.9kg, ITRE: -2.4kg, sTRE: -3.1kg	eTRE: ↓ subcutaneous adipose tissue	eTRE: ↓ FG	Feasibility and safety was high
Guner & Aktac 2025 (48)	n = 30, 25–41 years, M & F	4 weeks	8 h TRE	=	↓ BW	↓ BMI, ↓ body fat	NA	↑ Impulsivity to food
Yu & Ueda 2025 (146)	n = 20, 18–26 years, F	8 weeks	8 h eTRE (8:00–16:00) versus 8 h ITRE (12:00–20:00)	NA	eTRE: -4.21%, ITRE: -2.32%	↓ Fat mass, maintained lean mass	NA	NA
Črešnovar et al. 2025 (23)	n = 93, 18–60 years, M & F, with metabolic syndrome	12 weeks	8 h eTRE+ER (8:00–16:00) versus 8 h ITRE+ER (12:00–20:00)	ER: -27%, TRE: =	-6%	eTRE: greater ↓ fat mass	eTRE: ↓ FG	eTRE: ↓ BP

Eating windows reported as local clock time.

Abbreviations: BCAAA, branched-chain amino acid; BMI, body mass index; BP, blood pressure; BW, body weight; DASH, Dietary Approaches To Stop Hypertension; ER, energy restriction; eTRE, early time-restricted eating; F, female; FG, fasting glucose; FI, fasting insulin; HbA1c, hemoglobin A1c; HIIT, high-intensity interval training; HOMA-IR, homeostatic model assessment of insulin resistance; hs-CRP, high-sensitivity C-reactive protein; IGFBP2, insulin-like growth factor-binding protein 2; IR, insulin resistance; LDL/HDL-C, low/high-density lipoprotein cholesterol; ITRE, late time-restricted eating; M, male; MG, mean glucose; mTRE, midday time-restricted eating; NA, not available; NAFLD, nonalcoholic fatty liver disease; RCT, randomized control trial; SOC, standard of care; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; TRE, time-restricted eating.



Evidence for the direct metabolic benefits of TRE is most clearly demonstrated by its impact on glycemic control, a change frequently observed independent of, or as an effect additive to, weight loss. A 2018 controlled feeding, randomized crossover trial (RCT) in men with prediabetes showed that TRE improved insulin sensitivity and reduced oxidative stress, even when calories were matched to maintain body weight (121). In clinical populations, this translates to tangible disease management; studies in adults with T2DM consistently report reduced hemoglobin A1c levels (HbA1c) and enhanced effectiveness of insulin treatment (87, 88, 98). TRE has also led to improvements in the efficacy of medications taken for individuals with T2DM (20).

Beyond core metabolic markers, TRE consistently shows positive impacts on cardiovascular risk factors, most notably BP. Reductions in both systolic and diastolic BP are a widespread finding across diverse cohorts, including those with obesity, metabolic syndrome, and hypertension (22, 42, 82, 121). The intervention's power is demonstrated by its synergistic effects: a 2024 RCT found that combining TRE with the Dietary Approaches to Stop Hypertension (DASH) diet yielded a greater reduction in BP than the DASH diet alone (151). Importantly, this study showed that TRE led to an increase in the diurnal rhythm of BP, which is a significant clinical finding, as an abnormal BP diurnal rhythm (nondipping) is associated with an increased risk of cardiovascular morbidity and mortality (56).

Beyond core outcomes, the benefits of TRE extend to improving cardiovascular health and mitigating cellular stress. Regarding lipid profile, while results can vary, several studies report significant improvements. For individuals with T2DM and overweight, a 10-h TRE protocol was found to significantly lower triglycerides (TGs), total cholesterol (TC), and low-density lipoprotein cholesterol levels (20). Furthermore, a study of TRE in subjects with metabolic syndrome showed overall improvements in TC and TG levels (87). This finding aligns with smaller trials showing a reduction in fasting TGs in men with T2DM following eTRE. A second key benefit is the reduction of oxidative stress, a direct indicator of cellular damage caused by metabolic imbalance. In a controlled, isocaloric study on men with prediabetes, a 6-h eTRE protocol significantly reduced oxidative stress markers, demonstrating an effect independent of weight loss (121). This direct benefit was also reported in subjects with obesity following both 4-h and 6-h TRE regimens (22). These findings collectively suggest that TRE modulates metabolic function and cellular health through a direct chronobiological pathway, delivering benefits that extend beyond simply reducing caloric intake.

4.2. Timing of Time-Restricted Eating

Research has investigated the relative contribution of the eating window's timing and duration in TRE (Table 2). Research shows that TRE can directly improve the rhythmicity of adipose transcriptome after an 8-week intervention (150). The accumulated data also strongly support the superiority of eTRE, where the eating window is deliberately shifted to the first half of the day (Figure 3). Some studies have shown that weight loss is increased by eTRE (34, 65, 140, 146, 148). This is often accompanied by a greater reduction in caloric intake. Additionally, glucoregulatory benefits are seen in eTRE versus lTRE, with improvements in glucose tolerance and insulin sensitivity along with reductions in fasting glucose and insulin resistance (23, 65, 121, 140, 148). Peak insulin sensitivity occurs early in the day (109), and the efficiency at which food is processed declines into the evening, suggesting that the benefits of eTRE are likely due to aligning caloric intake with the early-day period of optimal metabolic efficiency. It is important to note that many of the glucoregulatory measures themselves are subject to internal circadian regulation. Studies have attempted to correct this by measurements at specific times either following a fast or prior to the dictated meal timing. Long-term adaptation to a specific TRE protocol may also



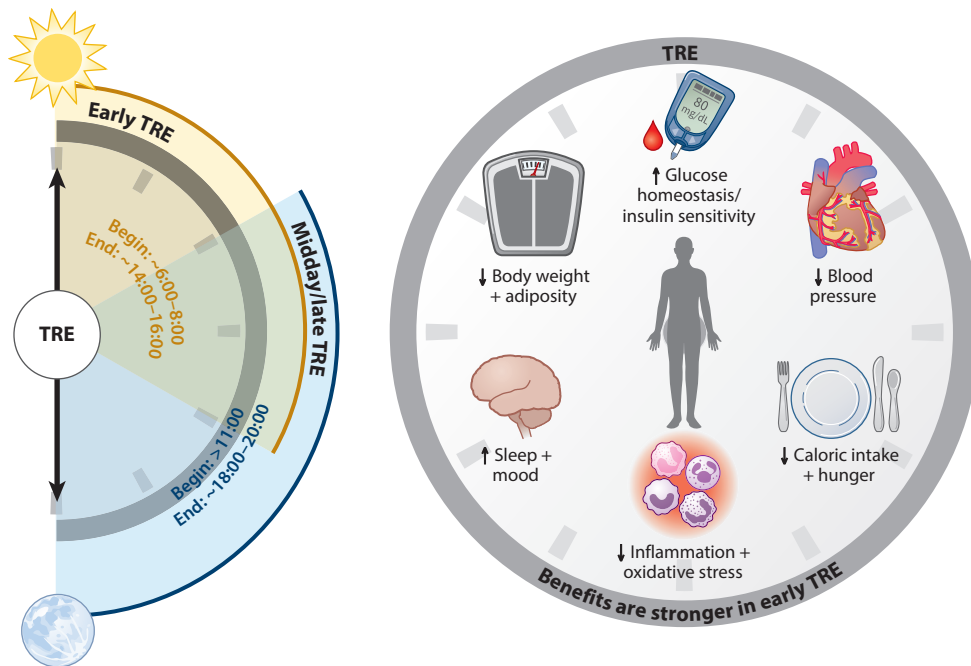


Figure 3

Time-restricted eating (TRE) improves health in humans, with notable benefits under early TRE. Schematic of the timings of early, midday, and late TRE paradigms tested in clinical trials and the various health benefits found in humans. While early or late TRE shows improvements, benefits are strongest and most consistent with early TRE.

influence these metabolic measures. The observation that human hunger peaks in the evening while metabolic efficiency peaks in the morning presents a remaining evolutionary or behavioral paradox for long-term adherence to eTRE.

4.3. Practicality of Time-Restricted Eating and Its Effect on Behavior

TRE has merit as an easy-to-implement lifestyle change that can be sustained long-term and widely adopted across diverse populations. Unlike other fasting regimes, such as energy restriction or IF, which require calorie deprivation and complex calorie counting, TRE simplifies the dietary framework by relying on the single, unambiguous rule of when to eat. This attribute is central to its feasibility as a public health intervention. Early studies investigated the practicality and behavioral impacts that TRE has. Early observational studies (44) successfully demonstrated the feasibility of self-selected 10–12-h daytime windows for free-living adults. Subsequent, more rigorous trials confirmed high adherence rates even for more restricted windows, such as the 4/6-h TRE protocol (22) and an 8-h window in high-risk groups (34), or even in groups undertaking shift work (88). The success in compliance is directly linked to the fact that participants spontaneously reduce their energy intake, with deficits documented up to 650 kcal/day, making the lifestyle adaptation straightforward and intuitive (124). While adherence is generally high, TRE is not devoid of behavioral impacts; a study showed that eTRE was having a negative impact on the subject's ability to socialize in the evenings (5), and another noted increased impulsivity to food (48), suggesting a temporary psychological and behavioral adjustment period during the

transition to a regimented eating schedule. However, these minor effects are often balanced by findings that TRE does not negatively alter general behavioral attitudes toward food or body image. Overall, the consensus remains that the sheer simplicity and accessibility of TRE provides a significant advantage in promoting sustainable, long-term metabolic health.

5. CONCLUSIONS

TRF and TRE have emerged as powerful interventions that align daily food intake with circadian rhythms, improving metabolic, cardiovascular, and cognitive health across diverse species, even without reducing calories. Across models ranging from flies to mammals, TRF restores rhythmic gene expression, enhances metabolic flexibility, protects against diet-induced disease, and, in some cases, promotes reproductive and neuroprotective benefits. In humans, TRE consistently improves body composition, glycemic control, and cardiovascular function, with the strongest benefits observed when eating is confined to the early part of the day. Yet, major gaps remain, as most mechanistic data derive from nocturnal males under dietary challenge, leaving the effects in diurnal, metabolically normal, and female models underexplored. Future work must therefore test phase-specific, longitudinal, and translational paradigms that reflect human diversity in chronotype and lifestyle. Altogether, the convergence of circadian biology and nutritional science positions TRF/TRE as one of the most promising, low-cost, and physiologically grounded strategies to improve health and aging.

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LITERATURE CITED

1. Acosta-Rodriguez V, Rijo-Ferreira F, Izumo M, Xu P, Wight-Carter M, et al. 2022. Circadian alignment of early onset caloric restriction promotes longevity in male C57BL/6J mice. *Science* 376:1192–202
2. Acosta-Rodriguez VA, Rijo-Ferreira F, Green CB, Takahashi JS. 2021. Importance of circadian timing for aging and longevity. *Nat. Commun.* 12:2862
3. Acosta-Rodriguez VA, Rijo-Ferreira F, van Rosmalen L, Izumo M, Park N, et al. 2024. Misaligned feeding uncouples daily rhythms within brown adipose tissue and between peripheral clocks. *Cell Rep.* 43:114523
4. Akasheh RT, Ankireddy A, Gabel K, Ezpeleta M, Lin S, et al. 2024. Effect of time-restricted eating on circulating levels of IGF1 and its binding proteins in obesity: an exploratory analysis of a randomized controlled trial. *Nutrients* 16:3476
5. Antoni R, Robertson TM, Robertson MD, Johnston JD. 2018. A pilot feasibility study exploring the effects of a moderate time-restricted feeding intervention on energy intake, adiposity and metabolic physiology in free-living human subjects. *J. Nutr. Sci.* 7:e22
6. Aouichat S, Chayah M, Bouguerra-Aouichat S, Agil A. 2020. Time-restricted feeding improves body weight gain, lipid profiles, and atherogenic indices in cafeteria-diet-fed rats: role of browning of inguinal white adipose tissue. *Nutrients* 12:2185
7. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. 2009. Circadian timing of food intake contributes to weight gain. *Obesity* 17:2100–2
8. Astafev AA, Mezhnina V, Poe A, Jiang P, Kondratov RV. 2024. Sexual dimorphism of circadian liver transcriptome. *iScience* 27:109483
9. Azemi AK, Siti-Sarah AR, Mokhtar SS, Rasool AHG. 2022. Time-restricted feeding improved vascular endothelial function in a high-fat diet-induced obesity rat model. *Vet. Sci.* 9:217
10. Bass J, Lazar MA. 2016. Circadian time signatures of fitness and disease. *Science* 354:994–99



11. Bass J, Takahashi JS. 2010. Circadian integration of metabolism and energetics. *Science* 330:1349–54
12. Berson DM, Dunn FA, Takao M. 2002. Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295:1070–73
13. Brown MR, Sen SK, Mazzone A, Her TK, Xiong Y, et al. 2021. Time-restricted feeding prevents deleterious metabolic effects of circadian disruption through epigenetic control of beta cell function. *Sci. Adv.* 7:eabg6856
14. Caliendo R, Streng AA, van Kerkhof LWM, van der Horst GTJ, Chaves I. 2021. Social jetlag and related risks for human health: a timely review. *Nutrients* 13:4543
15. Cassone VM. 2014. Avian circadian organization: a chorus of clocks. *Front. Neuroendocrinol.* 35:76–88
16. Chaix A, Deota S, Bhardwaj R, Lin T, Panda S. 2021. Sex- and age-dependent outcomes of 9-hour time-restricted feeding of a Western high-fat high-sucrose diet in C57BL/6J mice. *Cell Rep.* 36:109543
17. Chaix A, Lin T, Le HD, Chang MW, Panda S. 2019. Time-restricted feeding prevents obesity and metabolic syndrome in mice lacking a circadian clock. *Cell Metab.* 29:303–19.e4
18. Chaix A, Manoogian ENC, Melkani GC, Panda S. 2019. Time-restricted eating to prevent and manage chronic metabolic diseases. *Annu. Rev. Nutr.* 39:291–315
19. Chaix A, Zarrinpar A, Miu P, Panda S. 2014. Time-restricted feeding is a preventative and therapeutic intervention against diverse nutritional challenges. *Cell Metab.* 20:991–1005
20. Che T, Yan C, Tian D, Zhang X, Liu X, Wu Z. 2021. Time-restricted feeding improves blood glucose and insulin sensitivity in overweight patients with type 2 diabetes: a randomised controlled trial. *Nutr. Metab.* 18:88
21. Cheng WY, Ho YS, Chang RC. 2022. Linking circadian rhythms to microbiome-gut-brain axis in aging-associated neurodegenerative diseases. *Ageing Res. Rev.* 78:101620
22. Cienfuegos S, Gabel K, Kalam F, Ezpeleta M, Wiseman E, et al. 2020. Effects of 4- and 6-h time-restricted feeding on weight and cardiometabolic health: a randomized controlled trial in adults with obesity. *Cell Metab.* 32:366–78.e3
23. Črešnovar T, Habe B, Mohorko N, Kenig S, Jenko Praznikar Z, Petelin A. 2025. Early time-restricted eating with energy restriction has a better effect on body fat mass, diastolic blood pressure, metabolic age and fasting glucose compared to late time-restricted eating with energy restriction and/or energy restriction alone: a 3-month randomized clinical trial. *Clin. Nutr.* 49:57–68
24. Damasceno de Lima R, Fudoli Lins Vieira R, Rosetto Munoz V, Chaix A, Azevedo Macedo AP, et al. 2023. Time-restricted feeding combined with resistance exercise prevents obesity and improves lipid metabolism in the liver of mice fed a high-fat diet. *Am. J. Physiol. Endocrinol. Metab.* 325:E513–28
25. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U. 2000. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev.* 14:2950–61
26. Dantas Machado AC, Brown SD, Lingaraju A, Sivaganesh V, Martino C, et al. 2022. Diet and feeding pattern modulate diurnal dynamics of the ileal microbiome and transcriptome. *Cell Rep.* 40:111008
27. Das M, Kumar D, Saucedo C, Oberg A, Ellies LG, et al. 2024. Time-restricted feeding attenuates metabolic dysfunction-associated steatohepatitis and hepatocellular carcinoma in obese male mice. *Cancers* 16:1513
28. Davidson AJ, Sellix MT, Daniel J, Yamazaki S, Menaker M, Block GD. 2006. Chronic jet-lag increases mortality in aged mice. *Curr. Biol.* 16:R914–16
29. Dawson MA, Cheung SN, La Frano MR, Nagpal R, Berryman CE. 2024. Early time-restricted eating improves markers of cardiometabolic health but has no impact on intestinal nutrient absorption in healthy adults. *Cell Rep. Med.* 5:101363
30. de Cabo R, Mattson MP. 2019. Effects of intermittent fasting on health, aging, and disease. *N. Engl. J. Med.* 381:2541–51
31. de Goede P, Foppen E, Ritsema W, Korpel NL, Yi CX, Kalsbeek A. 2019. Time-restricted feeding improves glucose tolerance in rats, but only when in line with the circadian timing system. *Front. Endocrinol.* 10:554
32. Deng Y, Liu X, Sun Y, Zhou L, Li Q, et al. 2024. Effects of time-restricted eating on intrahepatic fat and metabolic health among patients with nonalcoholic fatty liver disease. *Obesity* 32:494–505



33. Deota S, Lin T, Chaix A, Williams A, Le H, et al. 2023. Diurnal transcriptome landscape of a multi-tissue response to time-restricted feeding in mammals. *Cell Metab.* 35:150–65.e4
34. Dote-Montero M, Clavero-Jimeno A, Merchan-Ramirez E, Osés M, Echarte J, et al. 2025. Effects of early, late and self-selected time-restricted eating on visceral adipose tissue and cardiometabolic health in participants with overweight or obesity: a randomized controlled trial. *Nat. Med.* 31:524–33
35. Dubrovsky YV, Samsa WE, Kondratov RV. 2010. Deficiency of circadian protein CLOCK reduces lifespan and increases age-related cataract development in mice. *Aging* 2:936–44
36. Dunlap JC. 1999. Molecular bases for circadian clocks. *Cell* 96:271–90
37. Eckel-Mahan KL, Patel VR, de Mateo S, Orozco-Solis R, Ceglia NJ, et al. 2013. Reprogramming of the circadian clock by nutritional challenge. *Cell* 155:1464–78
38. Erickson ML, Blackwell TL, Mau T, Cawthon PM, Glynn NW, et al. 2024. Age is associated with dampened circadian patterns of rest and activity: the Study of Muscle, Mobility, and Aging (SOMMA). *J. Gerontol. A Biol. Sci. Med. Sci.* 79:glae049
39. Fang G, Wang S, Chen Q, Luo H, Lian X, Shi D. 2023. Time-restricted feeding affects the fecal microbiome metabolome and its diurnal oscillations in lung cancer mice. *Neoplasia* 45:100943
40. Fishbein AB, Knutson KL, Zee PC. 2021. Circadian disruption and human health. *J. Clin. Investig.* 131:e148286
41. Folin O. 1915. On starvation and obesity, with special reference to acidosis. *J. Biol. Chem.* 21:183–92
42. Gabel K, Hoddy KK, Haggerty N, Song J, Kroeger CM, et al. 2018. Effects of 8-hour time restricted feeding on body weight and metabolic disease risk factors in obese adults: a pilot study. *Nutr. Healthy Aging* 4:345–53
43. Gill S, Le HD, Melkani GC, Panda S. 2015. Time-restricted feeding attenuates age-related cardiac decline in *Drosophila*. *Science* 347:1265–69
44. Gill S, Panda S. 2015. A smartphone app reveals erratic diurnal eating patterns in humans that can be modulated for health benefits. *Cell Metab.* 22:789–98
45. Green CB, Takahashi JS, Bass J. 2008. The meter of metabolism. *Cell* 134:728–42
46. Green CL, Lamming DW, Fontana L. 2022. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat. Rev. Mol. Cell Biol.* 23:56–73
47. Greenwell BJ, Trott AJ, Beytebiere JR, Pao S, Bosley A, et al. 2019. Rhythmic food intake drives rhythmic gene expression more potently than the hepatic circadian clock in mice. *Cell Rep.* 27:649–57.e5
48. Guner E, Aktac S. 2025. Time-restricted feeding can increase food-related impulsivity: a randomized controlled trial. *Nutr. Neurosci.* 28:28–36
49. Gutierrez-Monreal MA, Harmsen JF, Schrauwen P, Esser KA. 2020. Ticking for metabolic health: the skeletal-muscle clocks. *Obesity* 28(Suppl. 1):S46–54
50. Haganes KL, Silva CP, Eyjolfsson SK, Steen S, Grindberg M, et al. 2022. Time-restricted eating and exercise training improve HbA1c and body composition in women with overweight/obesity: a randomized controlled trial. *Cell Metab.* 34:1457–71.e4
51. Hara R, Wan K, Wakamatsu H, Aida R, Moriya T, et al. 2001. Restricted feeding entrains liver clock without participation of the suprachiasmatic nucleus. *Genes Cells* 6:269–78
52. Hardin PE. 2011. Molecular genetic analysis of circadian timekeeping in *Drosophila*. *Adv. Genet.* 74:141–73
53. Hastings MH, Maywood ES, Brancaccio M. 2018. Generation of circadian rhythms in the suprachiasmatic nucleus. *Nat. Rev. Neurosci.* 19:453–69
54. Hatori M, Vollmers C, Zarrinpar A, DiTacchio L, Bushong EA, et al. 2012. Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab.* 15:848–60
55. Hepler C, Weidemann BJ, Waldeck NJ, Marcheva B, Cedernaes J, et al. 2022. Time-restricted feeding mitigates obesity through adipocyte thermogenesis. *Science* 378:276–84
56. Hermida RC, Ayala DE, Mojón A, Fernández JR. 2013. Blunted sleep-time relative blood pressure decline increases cardiovascular risk independent of blood pressure level—the “normotensive non-dipper” paradox. *Chronobiol. Int.* 30:87–98
57. Hofacker AC, Knop M, Krauss-Etschmann S, Roeder T. 2025. Time-restricted feeding promotes longevity and gut health without fitness trade-offs. *FASEB J.* 39:e70627



58. Hojo H, Enya S, Arai M, Suzuki Y, Nojiri T, et al. 2017. Remote reprogramming of hepatic circadian transcriptome by breast cancer. *Oncotarget* 8:34128–40
59. Hood S, Amir S. 2017. The aging clock: circadian rhythms and later life. *J. Clin. Investig.* 127:437–46
60. Hosono T, Ono M, Daikoku T, Mieda M, Nomura S, et al. 2021. Time-restricted feeding regulates circadian rhythm of murine uterine clock. *Curr. Dev. Nutr.* 5:nzab064
61. Hou T, Su W, Duncan MJ, Olga VA, Guo Z, Gong MC. 2021. Time-restricted feeding protects the blood pressure circadian rhythm in diabetic mice. *PNAS* 118:e2015873118
62. Hua L, Feng B, Huang L, Li J, Luo T, et al. 2020. Time-restricted feeding improves the reproductive function of female mice via liver fibroblast growth factor 21. *Clin. Transl. Med.* 10:e195
63. Hua L, Li J, Yang Y, Jiang D, Jiang X, et al. 2023. Liver-derived FGF21 is required for the effect of time-restricted feeding on high-fat diet-induced fatty liver in mice. *FASEB J.* 37:e22898
64. Huang RC. 2018. The discoveries of molecular mechanisms for the circadian rhythm: the 2017 Nobel Prize in Physiology or Medicine. *Biomed. J.* 41:5–8
65. Hutchison AT, Regmi P, Manoogian EN, Fleischer JG, Wittert GA, et al. 2019. Time-restricted feeding improves glucose tolerance in men at risk for type 2 diabetes: a randomized crossover trial. *Obesity* 27:724–32
66. Iiams SE, Skinner NJ, Wight-Carter M, Acosta-Rodríguez VA, Green CB, Takahashi JS. 2026. Time-restricted feeding extends healthspan in both sexes and lifespan in male C57BL/6J mice. Preprint, bioRxiv. <https://www.biorxiv.org/content/10.1101/2025.10.22.683527v2>
67. Jamshed H, Beyl RA, Della Manna DL, Yang ES, Ravussin E, Peterson CM. 2019. Early time-restricted feeding improves 24-hour glucose levels and affects markers of the circadian clock, aging, and autophagy in humans. *Nutrients* 11:1234
68. Jamshed H, Steger FL, Bryan DR, Richman JS, Warriner AH, et al. 2022. Effectiveness of early time-restricted eating for weight loss, fat loss, and cardiometabolic health in adults with obesity: a randomized clinical trial. *JAMA Intern. Med.* 182:953–62
69. Jones R, Pabla P, Mallinson J, Nixon A, Taylor T, et al. 2020. Two weeks of early time-restricted feeding (eTRF) improves skeletal muscle insulin and anabolic sensitivity in healthy men. *Am. J. Clin. Nutr.* 112:1015–28
70. Kerndt PR, Naughton JL, Driscoll CE, Loxterkamp DA. 1982. Fasting: the history, pathophysiology and complications. *West. J. Med.* 137:379–99
71. Kohsaka A, Laposky AD, Ramsey KM, Estrada C, Joshu C, et al. 2007. High-fat diet disrupts behavioral and molecular circadian rhythms in mice. *Cell Metab.* 6:414–21
72. Kondratov RV, Kondratova AA, Gorbacheva VY, Vykhovanets OV, Antoch MP. 2006. Early aging and age-related pathologies in mice deficient in BMAL1, the core component of the circadian clock. *Genes Dev.* 20:1868–73
73. Konishi N, Matsumoto H, Hashimoto S, Gamage USK, Tachibana D, et al. 2022. Effects of time-restricted feeding and type of food on fertility competence in female mice. *Sci. Rep.* 12:7064
74. Krizo JA, Mintz EM. 2014. Sex differences in behavioral circadian rhythms in laboratory rodents. *Front. Endocrinol.* 5:234
75. Laothamatas I, Rasmussen ES, Green CB, Takahashi JS. 2023. Metabolic and chemical architecture of the mammalian circadian clock. *Cell Chem. Biol.* 30:1033–52
76. Lee SA, Sypniewski C, Bensadon BA, McLaren C, Donahoo WT, et al. 2020. Determinants of adherence in time-restricted feeding in older adults: lessons from a pilot study. *Nutrients* 12:874
77. LeGates TA, Fernandez DC, Hattar S. 2014. Light as a central modulator of circadian rhythms, sleep and affect. *Nat. Rev. Neurosci.* 15:443–54
78. Leng H, Thijs T, Desmet L, Vanotti G, Farhadipour M, Depoortere I. 2025. Time-restricted feeding reinforces gut rhythmicity by restoring rhythms in intestinal metabolism in a jetlag mouse model. *Cell. Mol. Gastroenterol. Hepatol.* 19:101440
79. Levkovich G, Shmulevitch R, Almagor D, Reshef L, Shiklov G, et al. 2024. Synchronizing food availability with the natural rhythm substantially improves reproduction and extends healthspan in laying hens. *Sci. Rep.* 14:18780

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80. Lin S, Cienfuegos S, Ezpeleta M, Gabel K, Pavlou V, et al. 2023. Time-restricted eating without calorie counting for weight loss in a racially diverse population: a randomized controlled trial. *Ann. Intern. Med.* 176:885–95
81. Longo VD, Panda S. 2016. Fasting, circadian rhythms, and time-restricted feeding in healthy lifespan. *Cell Metab.* 23:1048–59
82. Lowe DA, Wu N, Rohdin-Bibby L, Moore AH, Kelly N, et al. 2020. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: the TREAT randomized clinical trial. *JAMA Intern. Med.* 180:1491–99
83. Lowrey PL, Takahashi JS. 2011. Genetics of circadian rhythms in mammalian model organisms. In *Advances in Genetics*, Vol. 74: *The Genetics of Circadian Rhythms*, ed. S Brody. Academic Press
84. Manella G, Sabath E, Aviram R, Dandavate V, Ezagouri S, et al. 2021. The liver-clock coordinates rhythmicity of peripheral tissues in response to feeding. *Nat. Metab.* 3:829–42
85. Manoogian ENC, Chow LS, Taub PR, Laferrere B, Panda S. 2022. Time-restricted eating for the prevention and management of metabolic diseases. *Endocr. Rev.* 43:405–36
86. Manoogian ENC, Laferrere B. 2023. Time-restricted eating: what we know and where the field is going. *Obesity* 31(Suppl. 1):7–8
87. Manoogian ENC, Wilkinson MJ, O’Neal M, Laing K, Nguyen J, et al. 2024. Time-restricted eating in adults with metabolic syndrome: a randomized controlled trial. *Ann. Intern. Med.* 177:1462–70
88. Manoogian ENC, Zadourian A, Lo HC, Gutierrez NR, Shoghi A, et al. 2022. Feasibility of time-restricted eating and impacts on cardiometabolic health in 24-h shift workers: the Healthy Heroes randomized control trial. *Cell Metab.* 34:1442–56.e7
89. Martens CR, Rossman MJ, Mazzo MR, Jankowski LR, Nagy EE, et al. 2020. Short-term time-restricted feeding is safe and feasible in non-obese healthy midlife and older adults. *Geroscience* 42:667–86
90. Masri S, Papagiannakopoulos T, Kinouchi K, Liu Y, Cervantes M, et al. 2016. Lung adenocarcinoma distally rewires hepatic circadian homeostasis. *Cell* 165:896–909
91. Mieda M. 2020. The central circadian clock of the suprachiasmatic nucleus as an ensemble of multiple oscillatory neurons. *Neurosci. Res.* 156:24–31
92. Mohawk JA, Green CB, Takahashi JS. 2012. Central and peripheral circadian clocks in mammals. *Annu. Rev. Neurosci.* 35:445–62
93. Musiek ES, Holtzman DM. 2016. Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science* 354:1004–8
94. Omotola O, Legan S, Slade E, Adekunle A, Pendergast JS. 2019. Estradiol regulates daily rhythms underlying diet-induced obesity in female mice. *Am. J. Physiol. Endocrinol. Metab.* 317:E1172–81
95. Palluth L, Takahashi JS, Green CB. 2025. Keeping up with the nicotinamides: NADP(H), the forgotten circadian cofactor that keeps metabolic time. *Life Metab.* 4:loaf034
96. Palmisano BT, Stafford JM, Pendergast JS. 2017. High-fat feeding does not disrupt daily rhythms in female mice because of protection by ovarian hormones. *Front. Endocrinol.* 8:44
97. Palomba A, Tanca A, Abbondio M, Sau R, Serra M, et al. 2021. Time-restricted feeding induces *Lactobacillus*- and *Akkermansia*-specific functional changes in the rat fecal microbiota. *NPJ Biofilms Microbiomes* 7:85
98. Pavlou V, Cienfuegos S, Lin S, Ezpeleta M, Ready K, et al. 2023. Effect of time-restricted eating on weight loss in adults with type 2 diabetes: a randomized clinical trial. *JAMA Netw. Open* 6:e2339337
99. Peek CB, Affinati AH, Ramsey KM, Kuo HY, Yu W, et al. 2013. Circadian clock NAD⁺ cycle drives mitochondrial oxidative metabolism in mice. *Science* 342:1243417
100. Pettersson US, Walden TB, Carlsson PO, Jansson L, Phillipson M. 2012. Female mice are protected against high-fat diet induced metabolic syndrome and increase the regulatory T cell population in adipose tissue. *PLOS ONE* 7:e46057
101. Prabhat A, Batra T, Kumar V. 2020. Effects of timed food availability on reproduction and metabolism in zebra finches: molecular insights into homeostatic adaptation to food-restriction in diurnal vertebrates. *Horm. Behav.* 125:104820
102. Prabhat A, Buniyaadi A, Bhardwaj SK, Kumar V. 2023. Differential effects of continuous and intermittent daytime food deprivation periods on metabolism and reproductive performance in diurnal zebra finches. *Horm. Behav.* 152:105353



103. Quist JS, Pedersen HE, Jensen MM, Clemmensen KKB, Bjerre N, et al. 2024. Effects of 3 months of 10-h per-day time-restricted eating and 3 months of follow-up on bodyweight and cardiometabolic health in Danish individuals at high risk of type 2 diabetes: the RESET single-centre, parallel, superiority, open-label, randomised controlled trial. *Lancet Healthy Longev* 5:e314–25
104. Regmi P, Chaudhary R, Page AJ, Hutchison AT, Vincent AD, et al. 2021. Early or delayed time-restricted feeding prevents metabolic impact of obesity in mice. *J. Endocrinol.* 248:75–86
105. Reinke H, Asher G. 2016. Circadian clock control of liver metabolic functions. *Gastroenterology* 150:574–80
106. Reinke H, Asher G. 2019. Crosstalk between metabolism and circadian clocks. *Nat. Rev. Mol. Cell Biol.* 20:227–41
107. Reppert SM, Weaver DR. 2002. Coordination of circadian timing in mammals. *Nature* 418:935–41
108. Rothschild J, Hoddy KK, Jambazian P, Varady KA. 2014. Time-restricted feeding and risk of metabolic disease: a review of human and animal studies. *Nutr. Rev.* 72:308–18
109. Saad A, Dalla Man C, Nandy DK, Levine JA, Bharucha AE, et al. 2012. Diurnal pattern to insulin secretion and insulin action in healthy individuals. *Diabetes* 61:2691–700
110. Saibaba G, Ruzal M, Shinder D, Yosefi S, Druyan S, et al. 2021. Time-restricted feeding in commercial layer chickens improves egg quality in old age and points to lack of adipostat activity in chickens. *Front. Physiol.* 12:651738
111. Sato S, Solanas G, Peixoto FO, Bee L, Symeonidi A, et al. 2017. Circadian reprogramming in the liver identifies metabolic pathways of aging. *Cell* 170:664–77.e11
112. Sato S, Solanas G, Sassone-Corsi P, Benitah SA. 2022. Tuning up an aged clock: circadian clock regulation in metabolism and aging. *Transl. Med. Aging* 6:1–13
113. Scheer FA, Hilton MF, Mantzoros CS, Shea SA. 2009. Adverse metabolic and cardiovascular consequences of circadian misalignment. *PNAS* 106:4453–58
114. Serra M, Marongiu F, Pisu MG, Serra M, Laconi E. 2019. Time-restricted feeding delays the emergence of the age-associated, neoplastic-prone tissue landscape. *Aging* 11:3851–63
115. Shi D, Fang G, Chen Q, Li J, Ruan X, Lian X. 2023. Six-hour time-restricted feeding inhibits lung cancer progression and reshapes circadian metabolism. *BMC Med.* 21:417
116. Shiba A, de Goede P, Tandari R, Foppen E, Korpel NL, et al. 2024. Synergy between time-restricted feeding and time-restricted running is necessary to shift the muscle clock in male wistar rats. *Neurobiol. Sleep Circadian Rhythms* 17:100106
117. Sims BM, Goodlett BL, Allbee ML, Pickup EJ, Chiasson VL, et al. 2022. Time restricted feeding decreases renal innate immune cells and blood pressure in hypertensive mice. *J. Hypertens* 40:1960–68
118. Smith JAB, Murach KA, Dyar KA, Zierath JR. 2023. Exercise metabolism and adaptation in skeletal muscle. *Nat. Rev. Mol. Cell Biol.* 24:607–32
119. Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M. 2001. Entrainment of the circadian clock in the liver by feeding. *Science* 291:490–93
120. Sundaram S, Yan L. 2016. Time-restricted feeding reduces adiposity in mice fed a high-fat diet. *Nutr. Res.* 36:603–11
121. Sutton EF, Beyl R, Early KS, Cefalu WT, Ravussin E, Peterson CM. 2018. Early time-restricted feeding improves insulin sensitivity, blood pressure, and oxidative stress even without weight loss in men with prediabetes. *Cell Metab.* 27:1212–21.e3
122. Takahashi JS. 2017. Transcriptional architecture of the mammalian circadian clock. *Nat. Rev. Genet.* 18:164–79
123. Talamanca L, Gobet C, Naef F. 2023. Sex-dimorphic and age-dependent organization of 24-hour gene expression rhythms in humans. *Science* 379:478–83
124. Tinsley GM, Forsse JS, Butler NK, Paoli A, Bane AA, et al. 2017. Time-restricted feeding in young men performing resistance training: a randomized controlled trial. *Eur. J. Sport. Sci.* 17:200–7
125. Tsameret S, Chapnik N, Froy O. 2023. Effect of early versus late time-restricted high-fat feeding on circadian metabolism and weight loss in obese mice. *Cell. Mol. Life Sci.* 80:180
126. Verma AK, Singh S, Rizvi SI. 2023. Aging, circadian disruption and neurodegeneration: interesting interplay. *Exp. Gerontol.* 172:112076



127. Villanueva JE, Lavello C, Trujillo AS, Chandran S, Woodworth B, et al. 2019. Time-restricted feeding restores muscle function in *Drosophila* models of obesity and circadian-rhythm disruption. *Nat. Commun.* 10:2700
128. Vitaterna MH, Takahashi JS, Turek FW. 2001. Overview of circadian rhythms. *Alcohol Res. Health* 25:85–93
129. Vollmers C, Gill S, DiTacchio L, Pulivarthy SR, Le HD, Panda S. 2009. Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. *PNAS* 106:21453–58
130. Vosko AM, Colwell CS, Avidan AY. 2010. Jet lag syndrome: circadian organization, pathophysiology, and management strategies. *Nat. Sci. Sleep* 2:187–98
131. Walker WH 2nd, Kaper AL, Melendez-Fernandez OH, Bumgarner JR, Liu JA, et al. 2022. Time-restricted feeding alters the efficiency of mammary tumor growth. *Chronobiol. Int.* 39:535–46
132. Wang H, Li Q, Xu R, Su Y, Zhu W. 2023. Time-restricted feeding affects colonic nutrient substrates and modulates the diurnal fluctuation of microbiota in pigs. *Front. Microbiol.* 14:1162482
133. Wang H, Xia P, Lu Z, Su Y, Zhu W. 2023. Time-restricted feeding affects transcriptomic profiling of hypothalamus in pigs through regulating aromatic amino acids metabolism. *J. Sci. Food Agric.* 103:1578–87
134. Wei X, Lin B, Huang Y, Yang S, Huang C, et al. 2023. Effects of time-restricted eating on nonalcoholic fatty liver disease: the TREATY-FLD randomized clinical trial. *JAMA Netw. Open* 6:e233513
135. Welsh DK, Takahashi JS, Kay SA. 2010. Suprachiasmatic nucleus: cell autonomy and network properties. *Annu. Rev. Physiol.* 72:551–77
136. Whittaker DS, Akhmetova L, Carlin D, Romero H, Welsh DK, et al. 2023. Circadian modulation by time-restricted feeding rescues brain pathology and improves memory in mouse models of Alzheimer's disease. *Cell Metab.* 35:1704–21.e6
137. Wilkinson MJ, Manoogian ENC, Zadourian A, Lo H, Fakhouri S, et al. 2020. Ten-hour time-restricted eating reduces weight, blood pressure, and atherogenic lipids in patients with metabolic syndrome. *Cell Metab.* 31:92–104.e5
138. Wolff CA, Gutierrez-Monreal MA, Meng L, Zhang X, Douma LG, et al. 2023. Defining the age-dependent and tissue-specific circadian transcriptome in male mice. *Cell Rep.* 42:111982
139. Wu QJ, Sun H, Wen ZY, Zhang M, Wang HY, et al. 2022. Shift work and health outcomes: an umbrella review of systematic reviews and meta-analyses of epidemiological studies. *J. Clin. Sleep Med.* 18:653–62
140. Xie Z, Sun Y, Ye Y, Hu D, Zhang H, et al. 2022. Randomized controlled trial for time-restricted eating in healthy volunteers without obesity. *Nat. Commun.* 13:1003
141. Yang Y, Liu D. 2024. Impacts of time-restricted feeding on middle-aged and old mice with obesity. *J. Physiol.* 602:6109–23
142. Ye Z, Huang K, Dai X, Gao D, Gu Y, et al. 2024. Light-phase time-restricted feeding disrupts the muscle clock and insulin sensitivity yet potentially induces muscle fiber remodeling in mice. *Heliyon* 10:e37475
143. Yi X, Abas R, Raja Muhammad Rooshdi RAW, Yan J, Liu C, et al. 2025. Time-restricted feeding reduced blood pressure and improved cardiac structure and function by regulating both circulating and local renin-angiotensin systems in spontaneously hypertensive rat model. *PLOS ONE* 20:e0321078
144. Yoo SH, Yamazaki S, Lowrey PL, Shimomura K, Ko CH, et al. 2004. PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *PNAS* 101:5339–46
145. Yu EA, Weaver DR. 2011. Disrupting the circadian clock: gene-specific effects on aging, cancer, and other phenotypes. *Aging* 3:479–93
146. Yu Z, Ueda T. 2025. Early time-restricted eating improves weight loss while preserving muscle: an 8-week trial in young women. *Nutrients* 17:1022
147. Yun N, Nah J, Lee MN, Wu D, Pae M. 2023. Post-effects of time-restricted feeding against adipose tissue inflammation and insulin resistance in obese mice. *Nutrients* 15:2617
148. Zhang LM, Liu Z, Wang JQ, Li RQ, Ren JY, et al. 2022. Randomized controlled trial for time-restricted eating in overweight and obese young adults. *iScience* 25:104870
149. Zhang R, Lahens NF, Ballance HI, Hughes ME, Hogenesch JB. 2014. A circadian gene expression atlas in mammals: implications for biology and medicine. *PNAS* 111:16219–24



150. Zhao L, Hutchison AT, Liu B, Wittert GA, Thompson CH, et al. 2023. Time-restricted eating alters the 24-hour profile of adipose tissue transcriptome in men with obesity. *Obesity* 31:63–74
151. Zhou X, Lin X, Yu J, Yang Y, Muzammel H, et al. 2024. Effects of DASH diet with or without time-restricted eating in the management of stage 1 primary hypertension: a randomized controlled trial. *Nutr. J.* 23:65

