Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Time restricted eating

Evidence Summary

Restricting eating to the active phase of the day with a fasting window of at least 12 hours may help mitigate age-related disturbances in metabolic function and the risk for chronic disease.

Neuroprotective Benefit: Time-restricted eating may help restore natural rhythms to pathways involved in learning and memory, and mitigate metabolic risk factors associated with accelerated decline.

Aging and related health concerns: Circadian-aligned time-restricted eating may improve metabolic health and reduce the risk for chronic diseases during aging if combined with a high-quality diet.

Safety: Time-restricted eating is generally well-tolerated by healthy adults, but may not be appropriate for children or those at risk for malnutrition. Ease of compliance and potential benefits are influenced by timing of the eating window.

Availability: Lifestyle intervention	**Dose**: 16: 8 ratio of fasting to feeding with eating phase during the early-middle part of active phase (day) shows the most benefit in studies	**Chemical formula:** N/A **MW**: N/A
Half life: N/A	**BBB**: N/A	
Clinical trials: The results of clinical trials, primarily for metabolic conditions, have been mixed stemming from the large heterogeneity in trial design across studies.	**Observational studies**: Late night eating is associated with increased risks for mortality from a variety of age-related conditions, including cardiovascular disease and cancer.	

What is it?

Time restricted eating, also called time restricted feeding, refers to restricting food consumption to a defined daily window of time [1]. It is considered a form of intermittent fasting, as there are defined windows of feeding and fasting. The median daily eating window is about 14 hours. Time-restricted eating paradigms range in length, but generally involve feeding periods of 12 hours or less. The duration of the feeding window and the timing of the eating window relative to the natural sleep-wake (light: dark) cycle are important determinants of the overall effects. Optimal time-restricted eating windows are those that best align the endogenous circadian clock, the genetic machinery which runs the body's 24-hour rhythms in alignment with the Earth's light: dark cycle. Clinical studies of time-restricted eating have primarily been conducted in the context of metabolic disorders, such as obesity. While metabolic benefits are routinely seen in preclinical studies, the results from human clinical studies have been mixed. This is largely a reflection of the heterogeneity of design in these studies, and supports the notion that not all time-restricted eating paradigms are equally beneficial or effective.

Neuroprotective Benefit: Time-restricted eating may help restore natural rhythms to pathways involved in learning and memory, and mitigate metabolic risk factors associated with accelerated decline.

Types of evidence:

- 2 observational studies on eating patterns and cognition
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

There is very limited epidemiological data assessing whether adherence to a time-restricted feeding regimen is associated with a reduction in dementia risk. This information is difficult to obtain because it relies on people's self-reported eating habits, which often change over time, and the results can be confounded by differences in diet composition. An observational study including 3,342 individuals over age 55 in China assessed the association between food intake patterns and cognitive function [2]. Skipping breakfast, which is often a correlate for increased eating in the evening, was associated with a faster rate of cognitive decline (-0.14 points/year; 95% Confidence Interval [CI] -0.24 to -0.04), relative to those with a more evenly distributed daily food intake pattern. An observational study including 883 older adults in Southern Italy assessing demographic and dietary characteristics, found that individuals who practiced time restricted eating, as defined by eating within a daily window of 10 hours or less, were less likely to have cognitive impairment relative to those with no eating time restrictions (Odds ratio [OR] 0.28; 95% CI 0.07 to 0.90) [3]. Breakfast eaters also had lower odds of cognitive impairment in this study (OR: 0.37, 95% CI 0.16 to 0.89), though eating dinner showed no association. Together, this suggests that biasing eating toward the beginning of the day may help reduce the risk of age-related cognitive impairment. This pattern is consistent with the practice of chrononutrition, which is eating in alignment with the natural rhythms of the body [4]. Differences in diet quality and nutrient intake were also seen across groups, suggesting that both the timing and content of meals are important for optimizing brain health [3].

Human research to suggest benefits to patients with dementia:

Time-restricted eating has not been rigorously tested in dementia patients. Circadian dysfunction is a common feature of neurodegenerative diseases, including Alzheimer's disease [5]. Depending on the stage of disease, many patients experience disordered feeding, as they overeat if they can't remember having already eaten, or undereat due to a loss of appetite, the recognition of food, or self-feeding capacity [6]. Adherence to a regular routine where meals are consumed primarily during the daytime hours in a manner which allows for proper nutrition could potentially help restore circadian rhythmicity. Since time restriction of food intake leading to inadequate nutrient intake could do more harm than good, the optimal eating pattern for dementia patients may differ from healthy adults, and may need to be tailored to the individual based on the stage of disease.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Circadian rhythms: The primary benefit of time-restricted eating in preclinical models is the strengthening or restoration of circadian rhythms [7]. Every cell in the body has a 24-hour biological rhythm which leads to systematic functional changes over the course of the day [8]. The rhythm stems from a transcriptional feedback loop that serves as a molecular clock, such that the time-restricted availability of transcription factors influences the pattern in which genes are turned on and off over the course of the day. The rhythm of gene expression in a given tissue varies based on the function of the tissue, as genes are differentially expressed across tissue/cell types. A master clock, located in in the hypothalamus of the brain in a region called the suprachiasmatic nucleus (SCN), serves to synchronize all of the clocks across the body. While the master clock drives an endogenous rhythm, it can be reset by external inputs, namely the light-dark cycle. Circadian rhythms are evolutionarily ancient, and serve to align cellular functions with daily activity patterns.

Modern society has shifted daily activity patterns, such that they can become misaligned with the cellular rhythms [9]. This can result in the desynchronization of clocks across tissues, and a reduction in the quality of tissue function over time. Loss of rhythmicity within specific tissues or across the body is a common feature of aging and age-related diseases, especially neurodegenerative diseases. The restoration of circadian rhythms may be beneficial by helping return the body to a physiological state that is better aligned with evolution, resulting in an improved functional state.

Not all time-restricted eating paradigms will align with or improve circadian rhythms. This only occurs when feeding patterns are aligned with evolutionarily defined activity patterns, which for humans means during daytime hours. Indeed, when feeding is restricted to periods that are out of sync with the evolutionary activity pattern, circadian rhythms can become further disrupted, leading to an exacerbation of pathophysiology [7]. Time-restricted eating helps with the alignment of peripheral clocks primarily in metabolic tissues, like the liver, but can also impact cognitive function because the brain is the most metabolically active organ in the body, thus alterations to body metabolism can have an outsized effect on the brain. Calcium signaling is very important for neuronal function and activity. Due to rhythmic expression of calcium channels, there is a daily rhythm of calcium expression, which in turn influences the activity of calcium-dependent proteins involved in synaptic plasticity [10]. Dysregulation of calcium is a common feature of neurodegenerative diseases. Disruption to the circadian system may underlie some of the alterations to calcium, thus restoration of rhythms may help fix them.

Although the impact of time-restricted eating on cognition has been understudied relative to its impact on metabolic function, there is some evidence from preclinical studies that eating schedules can impact cognitive trajectories by mitigating or exacerbating the impact of factors that can impair brain function. Male diabetic mice (db/db model) were found to be more vulnerable to circadian dysregulation when placed in a non-natural light-dark cycle, relative to their wildtype counterparts [11]. Rhythmic gene expression was altered in the hippocampus, which was accompanied by impaired performance on cognitive tests and elevated tau hyperphosphorylation. Placing the mice on a time-restricted feeding schedule for eight hours during their active phase (night) largely prevented these effects in the brain. This schedule also mitigated weight gain and lipid elevations in response to the altered light-dark cycle. Similarly, active-phase time-restricted eating has been shown to prevent many of the negative effects of a high-fat diet in rodents [12]. Due to rhythms in the hippocampus, performance on learning and memory tasks tends to be significantly better during the active phase, relative to the inactive phase, but this difference is blunted in the context of a high-fat diet [13]. In addition to reducing liver damage and glucose dysregulation, active phase time-restricted feeding of a high-fat diet restored active-phase spatial memory performance and hippocampal synaptic plasticity. Active phase time-restricted feeding also improved hippocampal synaptic plasticity in a mouse model of accelerated aging (SAMP8) [14]. Additionally, night restricted eating mitigated aging-related hearing loss, memory loss, and grip strength loss in the SAMP8 mice [15]. Active-phase time restricted eating mitigated post-anesthesia disruptions to physiological rhythms as well as learning and memory impairments in male mice [16].

Metabolism/Microbiome: The body is primed to utilize fuel most efficiently at certain times of day, based on evolutionary activity patterns [1]. The rhythms in metabolic tissues are tuned to maximize the uptake and processing of nutrients during the active phase, which for humans is during the daylight hours. The post-prandial response depends on the time of day. Glucose tolerance and insulin sensitivity is higher in the morning, thus carbohydrates are more effectively metabolized early in the active phase [17]. Lipids and proteins are best utilized later in the active phase. The post-prandial rise in triglycerides is lowest during lunch (a mid-day meal), and greatest during the evening [18]. The metabolic tissues' clocks are also influenced by the rhythms of central and peripheral hormones [19]. The levels of these hormones can be impacted by the feeding schedule. For example, GLP-1 is a peripheral hormone important for glucose homeostasis and acts to entrain peripheral metabolic clocks in the pancreas, liver, and gut to nutrient intake patterns. Cortisol, a central hormone, also influences glucose homeostasis. The peripheral clocks in metabolic tissue are subject to entrainment by eating patterns through these hormones, as well as from the light-dark cycle via the master clock. When eating patterns are not aligned with the environmental light-dark cycle, the rhythms in peripheral metabolic tissues can become

dysregulated, and drive metabolic dysfunction. Since metabolic diseases are major risk factors for cognitive impairment, mechanisms that exacerbate these metabolic conditions, such as disrupted circadian rhythms, can accelerate cognitive decline.

The metabolism of food is impacted not only by the cells of our bodies, but also by the trillions of microbial cells that make up the gut microbiome [20; 21]. Like nearly every organism on Earth, the activity cycle of these microbes is driven by a circadian clock. This means that different species of bacteria are more active at different times of the day, and thus more likely to take up nutrients and produce certain kinds of metabolites at particular times of day [20]. Therefore, the combination of meal composition and meal timing can dictate the post-prandial milieu of microbiome-derived metabolites, such as short-chain fatty acids. The short-chain fatty acid, butyrate, has been shown to be neuroprotective, and levels of butyrate-producing microbes tends to increase in the context of time-restricted feeding [22].

Autophagy: Autophagy helps clear out damaged parts of the cell, and thus is a critical component of cellular homeostasis. Because they are non-dividing cells, autophagy is especially important for neurons. Insufficient induction of autophagy can lead to the accumulation of damaged proteins and organelles within the cell, which ultimately impairs cell function. Thus, mechanisms which enhance autophagy are expected to be neuroprotective.
Nutrient sensing pathways, including autophagy, show reciprocal crosstalk with the circadian clock [23]. Autophagy flux is rhythmic in metabolic tissues, such as the liver. Hepatic autophagy flux peaks during the afternoon and then decreases during the evening. However, this autophagy rhythm is influenced by both clock and nutrient signals, such that meal timing can reset the phase of rhythm. This process involves interplay between NAD+, sirtuins, and clock genes [24]. Sirtuins are important regulators of autophagy, such that SIRT1 promotes the induction of autophagy in response to a nutrient-depleted state, such as during a fasting period [25]. Fluctuations in levels of NAD+ influences the activity level of sirtuins, since NAD+ is a co-substrate of SIRT1 and NADH inhibits SIRT1. Core clock genes (Clock:Bmal) regulate the availability of the rate limiting enzyme in NAD+ synthesis, NAMPT [24].
mTOR is also an important regulator of nutrient sensing pathways and autophagy. There is a negative feedback loop between mTORC1 and the circadian clock [26]. Fasting periods promote the induction of autophagy, and when the fasting periods are aligned with the rhythm of these critical autophagy regulators driven by the endogenous circadian clock, the amplitude of the rhythms is increased, leading to a more robust induction of these protective mechanisms [1]. Adoption of an early time-restricted

eating paradigm (8AM to 2PM) for four days was shown to increase morning expression of SIRT1, and evening expression of mTOR and BDNF, suggesting that it amplifies autophagic rhythms [27].

Sleep: The effects of time-restricted eating are heavily intertwined with sleep. Just as the potential benefits of time-restricted eating can be dampened by a poor diet, they can also be mitigated by poor sleep, because sleep and time-restricted eating impact the same cardiometabolic parameters [28]. Inadequate sleep tends to lead to overeating, and if that occurs during the inactive phase, the negative metabolic impacts of this overconsumption are magnified. For shift workers, there is some evidence to suggest that restricting food intake to the daytime may mitigate some of the negative impacts of an altered sleep-wake cycle [29]. Under these conditions, time-restricted eating becomes a mechanism for minimizing metabolic harm, rather than a way to optimize metabolic health.

Food intake patterns can also influence sleep quality [30]. The cortisol and melatonin rhythms are important for the regulation of the sleep-wake cycle [31]. Cortisol promotes wakefulness. It increases during the early morning, peaking at wake-onset. Melatonin has an opposite rhythm, as it promotes sleep. Cortisol increases in response to food intake, especially foods high in simple sugars. Therefore, the daily cortisol profile is modified by the food intake pattern, such that the consumption of sugary foods during the evening can lead to an increase in cortisol at the wrong time and delay the onset of sleep. A systematic review of 14 studies assessing the impact of different time-restricted eating paradigms to melatonin and cortisol rhythms found that a Ramadan-style paradigm in which fasting occurs during the day and meal consumption occurs at sunset and sunrise, melatonin levels were reduced, and the cortisol rhythm was blunted [31]. Similarly, early (dinner skipping) time-restricted eating was associated with lower evening cortisol and slightly higher morning cortisol, while late eating (breakfast skipping) was associated with slightly lower morning cortisol. In a randomized cross-over trial including 20 healthy volunteers, consumption of a late dinner (10 PM), shifted the post-prandial phase into the sleeping phase, and increased evening plasma cortisol levels [32]. It also altered the overnight metabolic profile, such that glucose levels were elevated and the degree of oxidation of fatty acids was reduced. Having elevated evening blood glucose levels can suppress slow wave sleep, and result in more sleep fragmentation [30]. In contrast, consumption of a protein-rich meal in the early evening may facilitate sleep. Together, these studies suggest that limiting the intake of food, especially sugary foods, during the evening hours may enhance sleep quality.

Huntington's disease: POTENTIAL BENEFIT (Preclinical)
Sleep-wake cycle disturbances, such as delayed sleep onset related to a phase shift in melatonin rhythms, are one of the earliest symptoms of disease in Huntington's patients [33]. Circadian dysregulation interacts with Huntington's disease pathology, such that they exacerbate each other, capped off by the degeneration of the master clock center of the brain, the suprachiasmatic nucleus (SCN) in late-stage disease. Time-restricted feeding was able to improve locomotor activity, behavioral rhythms, as well as autonomic nervous system function, as evidenced by an increase in heart rate variability [33; 34]. These benefits were seen in both the Q175 and BACHD mouse models during an early disease stage (three months of age) with a feeding paradigm of six hour feeding in the middle of the active phase and an 18 hour fast. The expression profile of disease-associated genes was altered in response to this feeding regimen, and the improvement in motor performance was correlated with improved circadian rhythmicity.

Vascular dementia: POTENTIAL BENEFIT (Preclinical)
Intermittent fasting has been shown to improve endothelial function, suggesting that it may be vasoprotective [35]. Time-restricted eating protocols have been found to protect against cognitive impairment in rodent models of vascular dementia. In the bilateral common carotid artery stenosis model, male mice on a 16:8 fasting to feeding schedule had reduced neuronal loss and better learning and memory performance, relative to mice on ad libitum feeding schedule [36]. Similarly, time-restricted eating for six hours during the active period starting eight weeks after the induction of vascular damage resulted in higher hippocampal neuronal density and better cognitive performance [37]. Notably, astrocyte activation was not reduced, but since polarization was not analyzed, this could reflect the maintenance of a neuroprotective glial state [37].

APOE4 interactions: The specific effect of time-restricted eating on ApoE4 carriers has not been established. But, because metabolic dysfunction appears to be a common component of ApoE4-mediated risk, mechanisms that improve metabolic function, such as time-restricted eating may be expected to preferentially benefit this population.

Aging and related health concerns: Circadian-aligned time-restricted eating may improve metabolic health and reduce the risk for chronic diseases during aging if combined with a high-quality diet.

Types of evidence:

- 15 meta-analyses or systematic reviews on human observational or clinical trials of time-restricted eating on cardiometabolic factors
- 1 systematic review of human observational or clinical trials of time-restricted eating on pain
- 1 meta-analysis of epidemiological studies of eating patterns and mortality
- 1 meta-analysis of epidemiological studies of eating patterns and cardiovascular disease
- 3 epidemiological studies of eating patterns on mortality and/or cancer
- 2 prospective cohort studies on eating patterns and breast cancer risk
- 2 clinical trials on time-restricted eating for obesity with biomarker outcomes
- Numerous laboratory studies

Lifespan: COMPONENT OF CR-MEDIATED LIFESPAN EXTENSION IN MODEL ORGANISMS
Circadian dysregulation is a common feature of aging-related diseases, suggesting that the preservation of circadian rhythms may contribute to healthspan [38]. Many epidemiological studies have found associations between breakfast skipping and increased mortality risk [39; 40; 41], suggesting that eating in alignment with circadian rhythms may be beneficial for longevity. Epidemiological studies regarding the impact of time-restricted eating on human longevity are lacking, but there is supportive evidence from preclinical studies [35].
Caloric restriction is well established as a mechanism to promote lifespan extension in animal models, though it is generally not considered a practical strategy in humans due to the negative impacts on reproductive fitness. There has been increasing evidence indicating that part of the longevity-boosting effects of caloric restriction in these studies was related to the time-restricted eating of these animals. When placed on a calorie restricted diet, animals will tend to consume all of their food in a short window of time. For rodents, it is common that they will eat everything within a two-hour window, such that they are also undergoing a form of intermittent fasting. In male mice fed ad libitum, or once per day, mice that were fed a maintenance level of calories and those with 30% calorie restriction showed lifespan extension, 11% and 28%, respectively [42]. The effect on lifespan was independent of diet composition, suggesting that the effect was largely driven by the intermittent fasting component. Notably, the mice were fed at 3PM, which is out of alignment with their natural active phase and would be considered suboptimal for the facilitation of circadian driven metabolic health. Thus, additional

benefits may have been seen in these animals if they were fed in the middle of the night. In support of this, male C57Bl/6J mice subject to 30% calorie restriction showed different degrees of lifespan extension depending on the timing of food intake [43]. Caloric restriction with ad libitum food access (no fasting period) resulted in a maximum lifespan extension around 10%, while calorie restriction in addition to a fasting period of either 12 or 22 hours led to lifespan extension from 20 to 35%, depending on the timing of the fasting period. When the fasting period was aligned with the endogenous circadian clock, there were extensions to both median and maximum lifespan, suggestive of an improvement to healthspan as well. Indeed, circadian aligned feeding reduced the induction of age-related inflammation-associated gene expression. A similar effect was seen in Drosophila using an intermittent (20 hour) fasting regimen that did not reduce overall caloric intake [44]. Lifespan extension using this paradigm was dependent on the presence of an intact circadian clock, which may explain why it was largely ineffective when started in aged flies. Benefits were due to the night-specific induction of autophagy. Sirtuins, which interact with the circadian clock to regulate autophagy, are implicated in longevity, and may be one of the mechanisms involved [24].
Overall, time-restricted eating in a circadian aligned manner appears to work synergistically with caloric restriction to promote longevity. The benefits seen in preclinical rodent studies tend to be more dramatic than what is seen in clinical studies, likely because compliance is guaranteed in the rodents. Additionally, the rodent diets are standardized, whereas they can be highly variable in people. Epidemiological studies suggest that this pattern of eating is associated with reduced risk for a variety of chronic conditions that negatively impact lifespan, however, a time-restricted eating paradigm that optimizes lifespan in humans has not yet been determined. It is unclear whether there is an age-specific component, such that the practice needs to be undertaken at a specific stage of life for a minimum length of time to confer benefit.

Metabolic syndrome/obesity: MODEST BENEFIT DEPENDING ON PARADIGM
Time-restricted eating has been most extensively studied in the context of obesity, as a tool for promoting weight loss and improving metabolic health [7]. The metabolic effects have been inconsistent across studies, which is not surprising considering the differences in eating windows, fasting periods, diet quality, and populations [45]. A small amount of weight loss is commonly seen in these studies, irrespective of experimental paradigm, but this appears to stem primarily from inadvertent reduced caloric intake and mild dehydration. When caloric intake was unaffected, weight loss was generally not observed, but fat loss was sometimes observed, which may be related to improved metabolic flexibility [46]. The impact to specific metabolic parameters, such as glucose homeostasis or lipid levels, may be more greatly impacted by differences in the experimental paradigm.

The metabolic benefits of time-restricted eating primarily stem from the strengthening and alignment of eating with circadian rhythms and from the metabolic adaptations of fasting. The specific parameters of the time-restricted eating schedule determine the degree to which each of these mechanisms is activated. The benefits of fasting will be minimized in paradigms with a shorter fasting window, such as a 12:12 paradigm, while the circadian-related benefits will be diminished when the eating window occurs out of alignment with the natural light-dark cycle. As a result, benefits are most apparent in studies with a longer duration fast (~16 hours) in which the eating window occurs in the early to middle part of the active phase [17].

A systematic review examined metabolic health parameters in four studies using an early time-restricted feeding paradigm and 16 studies using a delayed time-restricted feeing paradigm [47]. The early paradigms were more likely to be associated with reduced energy intake and weight loss. Improved insulin sensitivity and fasting insulin levels were seen in an early eating study, but not in the late eating studies. Blood pressure was also significantly reduced in this early eating study, whereas decreases to blood pressure were only seen in conjunction with weight loss in the late eating studies. A decrease in oxidative stress markers was seen in the early paradigm, as well. Similarly, a systematic review of five studies (n=67 participants) found benefits to glucose and/or insulin markers in response to early time-restricted eating paradigms [48]. These findings are consistent with the circadian rhythm in insulin sensitivity [19]. Since the body is in a more insulin-resistant state during the evening/inactive phase, greater food consumption during evening hours is likely to exacerbate glucose dysregulation, while greater food consumption during the middle of the active phase is likely to improve glucose utilization. A loss or blunting of gene rhythmicity is seen in the context of obesity, particularly in adipose tissue, such that only about 2% of adipose genes are rhythmic in the obese, compared to about 8% in lean individuals [49]. A single-arm clinical trial in which 15 obese men practiced time-restricted eating with a 10-hour eating window (9:30 AM to 7:30 PM) for eight weeks resulted in significant reductions in body weight, fat mass, fasting plasma glucose, and HbA1c levels [50]. The expression profile of the subcutaneous adipose tissue was altered in response to this time-restricted eating paradigm. There was an upregulation of 117 genes, a down-regulation of 202 genes, and restoration in rhythmicity for 450 genes [49; 50]. Based on pathway analysis, many of the affected genes were involved in oxidative phosphorylation and mitochondrial function, similar to what has been seen in the context of caloric restriction protocols [50]. One of the affected genes was SREBF1, which is a key regulator of cholesterol metabolism [49]. Changes to particular expression networks were found to correlate with the changes to body mass, plasma insulin profiles, and plasma fatty acid profiles [49]. A separate clinical study including 11 overweight adults compared an early time-restricted eating schedule (8AM to 2PM) with a

control 12:12 eating schedule (8AM to 8PM) [27]. The early time-restricted eating paradigm led to an increase in early morning ketone levels and a reduction in 24-hour glucose levels, suggestive of an increase in fat utilization and metabolic flexibility. Additionally, there was an increase in autophagy-related markers (LC3 and SIRT1) in the morning, and a reduction in cortisol in the evening. Together, these suggest that the early eating paradigm, which is in better alignment with circadian rhythms, may be more likely to improve metabolic parameters. The majority of studies have utilized a delayed eating paradigm in order to better align with modern social eating norms, however the metabolic benefits may be less apparent in these studies.

Numerous studies have looked at the impacts of time-restricted eating in the context of the religious practice of Ramadan, in which individuals fast from both food and drink from sunrise to sunset and take meals at these day to night transitions [45]. Depending on the time of the year that this month-long practice takes place in different parts of the world, the length of the fast can vary from about eight to 15 hours. Since this feeding schedule is out of optimal circadian alignment, benefits are likely related to the fasting period. While a longer fast would be expected to offer more benefit, this could be offset by a shorter sleep period and the misalignment of feeding times. A meta-analysis of 72 studies (n=3,134 participants) found minimal impact on glucometabolic markers [51], while a meta-analysis of 91 studies (n=4,431participants) found reductions in levels of circulating lipids, such as triglycerides and cholesterol [52]. These findings are consistent with improvements in glucose homeostasis stemming largely from circadian alignment and enhancements to lipid metabolism with fasting. Consistent with this, the impacts on blood lipids were influenced by the length of the fast and the age of the person [52]. Sex also appears to be a mediating factor for cardiometabolic parameters in response to this type of fast [52; 53].

Metabolic flexibility refers to the ability of the body to adapt to changes in nutrient availability and to efficiently utilize them for energy [17]. The human body is designed to use carbohydrates most readily at the beginning of the day and to use lipids/fats and proteins more readily later in the day, however, when present, the body will preferentially use glucose (carbohydrates). During a long fasting period, the body burns through all of the easily accessible carbohydrates, and then transitions into a state of ketosis, in which the machinery to metabolize lipids is upregulated, and lipids are primarily used for fuel [1]. By alternating through periods of feeding and fasting, the body becomes better able to adapt to whatever type of nutrient is available and operates more efficiently. If the daily window of food consumption is too long and/or the degree of energy consumption is too high, the body will not burn through all of the sugars before the end of the fast and will end up storing fat rather than burning it. Studies suggest that

fasts more than 12 hours, typically around 15-16 hours, are most effective for preventing weight/fat gain [17].

The microbiome plays a role in mediating the metabolic effects of time-restricted eating [20]. A systematic review of 17 studies using intermittent fasting protocols found that both alternate day fasting and time-restricted feeding were able to remodel the intestinal microbiome [21]. A prominent feature was the change in the relative abundance of *Firmicutes* to *Bacteroidetes*, the two dominant phylum of bacteria in the human gut. *Bacteroidetes* rise during fasting periods, while *Firmicutes* increase after feeding. In the context of obesity, the number and diversity of *Bacteroidetes* are reduced relative to *Firmicutes*, and fasting protocols can help restore the balance. Metabolic markers are influenced by the composition of the microbiome. For example, increases in *Lactobacillus* and *Odoribacter* along with reductions *in Enterococcus* and *Streptococcus* are associated with improved insulin sensitivity [22]. Since the composition of the microbiome is also influenced by the composition of the diet, the impact of the timing of food consumption on the microbiome will ultimately be highly dependent on the types of foods being consumed.

In order to have long-lasting effects, the time-restricted eating paradigm needs to be maintained. The impacts to circadian rhythmicity, microbiome composition, and metabolic markers will revert shortly after cessation of the time-restricted eating paradigm, and will adapt to the new eating pattern [17]. The maintenance of an early time-restricted eating paradigm may be beneficial for reducing the risk of metabolic dysfunction with aging, however, the efficacy is likely to be highly influenced by diet quality.

Cardiovascular disease: POTENTIAL BENEFIT
Numerous studies have found an association between skipping breakfast and increased risk for cardiovascular disease or cardiovascular mortality [39; 54]. While these epidemiological studies do not directly assess time-restricted eating per se, they suggest that eating earlier in the day benefit cardiovascular health, while shifting food consumption more toward the late day or evening hours is harmful. This is likely related to the exacerbation of cardiometabolic risk factors with the disruption of circadian clocks in peripheral metabolic tissues due to misaligned eating patterns.
No time-restricted eating trials have looked specifically at cardiovascular parameters, such as cardiovascular mortality, stroke, myocardial infarction, heart failure, or blood pressure as primary outcomes [55]. A meta-analysis of 18 RCTs using intermittent fasting protocols, three of which used time-restricted eating, found that short-term changes in body weight and glucose were unlikely to be clinically significant, however, the quality of evidence was too low to make any definitive conclusions

about the benefit of fasting for cardiovascular parameters [55]. Similarly, the mixed results regarding blood pressure reflect the heterogeneity of experimental design across studies [56]. A complicating factor for the assessment of blood pressure is that it weakly follows a circadian rhythm, and food timing can contribute to the entrainment of this rhythm, such that the time of day and time in relation to food consumption can impact blood pressure readings. Blood pressure is highly sensitive to changes in sympathetic tone, which may be the major mechanism by which time-restricted eating can influence blood pressure. Fasting during the inactive phase can suppress sympathetic activity during this period, resulting in reduced blood pressure and the facilitation of sleep.
A meta-analysis of 28 studies examining the impact of time-restricted eating or Ramadan fasting with exercise performance found that changes to aerobic capacity were dependent on the fasting protocol [57]. While the results were mixed overall, there were general trends toward reduced aerobic capacity, based on VO_2 max, in the context of Ramadan fasting (Standardized Mean Difference [SMD] −2.204, 95% CI −2.745 to −1.663; $p < 0.001$), but improvements with traditional time-restricted eating (SMD 1.315, 95% CI 0.543 to 2.087; $p = 0.001$). There were no significant effects on muscle strength or anaerobic capacity for either paradigm, suggesting, that active phase time-restricted eating may help enhance cardiovascular conditioning.

Non-alcoholic fatty liver disease: POTENTIAL MINOR BENFIT
A meta-analysis of six studies found that fasting paradigms were associated with reductions in body weight and in liver enzymes, alanine aminotransferase (ALT), and aspartate transaminase (AST) [58]. However, there were no consistent effects on lipids, metabolic parameters, or liver fibrosis across studies, which is likely related to the heterogeneity of the fasting protocols examined.

Chronic pain: UNCLEAR BENEFIT
A systematic review including 11 RCTs and five observational studies examined the impact of dietary interventions on the management of chronic pain [59]. While there is no general consensus on the effects of intermittent fasting with respect to chronic pain, decreases in pain have been reported on certain questionnaires (SF-36 and AIMS2-2F), and efficacy was related to adherence to the diet. Inflammatory markers increase in response to eating, and during the periods of fasting there is a relative shift toward more anti-inflammatory markers. The improvement in glucose parameters seen with time-restricted eating may be an additional mechanism by which this eating paradigm reduces inflammatory pain, as high glucose is a pro-inflammatory stimulus.

Cancer: MAY REDUCE METABOLIC-RELATED RISK

Obesity increases the risk for cancer, and many obesity-related risk factors can influence cancer progression and prognosis [60]. For example, elevated insulin and chronic tissue inflammation, which are common features of obesity, can influence cancer progression. Circadian disruption is also associated with the facilitation of tumor growth. Therefore, time-restricted eating may be beneficial for cancer prevention by mitigating risk related to metabolic stress. Time-restricted feeding has been shown to slow tumor growth and restore circadian rhythms in preclinical models [61], however, not all tumor types appear to be responsive [60]. Since time-restricted eating appears to primarily reduce cancer risk by impacting metabolic factors, it is likely to be most impactful in the context of cancers in which metabolic risk plays a large role.

Metabolic dysfunction is a prominent risk factor for breast cancer [62]. Late night eating, leading to a shorter overnight fasting period, was found to be associated with a higher risk for breast and prostate cancers [63]. The use of time-restricted eating for preventing the reoccurrence of breast cancer has been assessed in a prospective cohort study. In a study of 2,413 women with a history of breast cancer without diabetes, those who fasted for less than 13 hours per night showed an increased risk for breast cancer reoccurrence relative to those who fasted longer than 13 hours (Hazard Ratio [HR] 1.36; 95% CI 1.05 to 1.76) [64]. Longer fasting was associated with better glucose homeostasis, based on HbA1c, and longer sleep. A small single-arm clinical trial in 22 breast cancer survivors, found that an eight week 16:8 (fast: eat) time-restricted eating paradigm reduced median Framingham cardiovascular disease risk (-15% relative change), though this pilot study was primarily designed to assess feasibility [65]. It should be noted that this study used a delayed eating paradigm (12PM to 8PM), which based on other studies may not be the optimal window for maximum metabolic benefit. A clinical trial assessing the use of time-restricted eating (10AM to 6PM) in combination with chemotherapy for women with breast cancer is currently ongoing (NCT05259410).

Safety: Time-restricted eating is generally well-tolerated by healthy adults, but may not be appropriate for children or those at risk for malnutrition. Ease of compliance and potential benefits are influenced by timing of the eating window.

Types of evidence:

- 16 meta-analyses or systematic reviews on human observational or clinical trials of time-restricted eating on cardiometabolic factors or chronic disease
- 3 clinical trials for time-restricted eating for obesity
- Numerous laboratory studies

Time-restricted eating has been well-tolerated in clinical studies conducted thus far [55; 59]. Headaches, dizziness, or light-headedness can occur during fasting periods if individuals inadvertently become dehydrated due to inadequate fluid consumption [66]. Adherence rates tend to be relatively high, generally in the range of 80% [46]. However, the trials range from the order of weeks to months, and to get lasting benefits, the eating paradigm needs to be maintained. Many of the trials were designed for easy compliance by using a later eating window, even though it may be suboptimal in terms of benefit [47]. This suggests that there may be tradeoffs in the selection of the eating window to ensure both metabolic benefit and long-term compliance. Since the changes to metabolic parameters readily reverse with the cessation of time-restricted eating, it generally does not induce long-term effects.

The potential effects of time-restricted eating cannot be considered apart from diet composition and eating window. While preclinical studies suggest that circadian-aligned time-restricted eating may mitigate some of the negative impacts of a poor diet, a misaligned eating window may exacerbate them.

Time-restricted eating may not be appropriate for children and adolescents who are actively growing, or for individuals with feeding difficulties, as it may impede adequate nutrient intake [21].

Drug interactions: Some medications need to be taken in a fed or fasted state at certain times or day, or with certain intervals in between [1]. For example, insulin doses typically need to be taken 8 hours apart in diabetics, which would be incompatible with a feeding window shorter than 8 hours. For drugs with a rhythmically expressed target, such as statins, appropriate time-restricted eating may enhance drug efficacy.

Sources and dosing:

Based on the studies conducted thus far, primarily for metabolic health, a 16:8 fasting to eating ratio in which the eating is done toward the early/middle of the active phase (i.e. around 9AM to 5PM) appears to confer the benefits of circadian regulation and intermittent fasting.

Research underway:

According to Clinicaltrials.gov, there are currently 81 active clinical trials using time-restricted eating. The majority of the studies involve metabolic or cardiometabolic conditions, as well as different types of cancer, including breast cancer, endometrial cancer, and colorectal cancer.

Search terms:

Pubmed, Google: Time-restricted eating/feeding

- Alzheimer's disease, dementia, cognition, brain, aging, lifespan, cardiovascular, cancer, microbiome, clinical trials, meta-analysis, systematic review, safety

Websites visited for Time-restricted eating:

- Clinicaltrials.gov

References:

1. Petersen MC, Gallop MR, Ramos SF *et al.* (2022) Complex physiology and clinical implications of time-restricted eating. *Physiological Reviews* **102**, 1991-2034https://journals.physiology.org/doi/abs/10.1152/physrev.00006.2022.

2. Chen H, Tao Y, Li M-D *et al.* (2022) Temporal patterns of energy intake and cognitive function and its decline: a community-based cohort study in China. *Life Metabolism*https://doi.org/10.1093/lifemeta/loac011.

3. Currenti W, Godos J, Castellano S *et al.* (2021) Association between Time Restricted Feeding and Cognitive Status in Older Italian Adults. *Nutrients* **13**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7827225/.

4. Flanagan A, Bechtold DA, Pot GK *et al.* (2021) Chrono-nutrition: From molecular and neuronal mechanisms to human epidemiology and timed feeding patterns. *Journal of neurochemistry* **157**, 53-72https://pubmed.ncbi.nlm.nih.gov/33222161/.

5. Musiek ES, Xiong DD, Holtzman DM (2015) Sleep, circadian rhythms, and the pathogenesis of Alzheimer Disease. *Experimental & Molecular Medicine* **47**, e148-e148https://doi.org/10.1038/emm.2014.121.

6. Fostinelli S, De Amicis R, Leone A *et al.* (2020) Eating Behavior in Aging and Dementia: The Need for a Comprehensive Assessment. *Frontiers in nutrition* **7**, 604488https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7772186/.

7. Schuppelius B, Peters B, Ottawa A *et al.* (2021) Time Restricted Eating: A Dietary Strategy to Prevent and Treat Metabolic Disturbances. *Frontiers in Endocrinology* **12**https://www.frontiersin.org/articles/10.3389/fendo.2021.683140.

8. Patke A, Young MW, Axelrod S (2020) Molecular mechanisms and physiological importance of circadian rhythms. *Nature Reviews Molecular Cell Biology* **21**, 67-84https://doi.org/10.1038/s41580-019-0179-2.

9. Farhud D, Aryan Z (2018) Circadian Rhythm, Lifestyle and Health: A Narrative Review. *Iranian journal of public health* **47**, 1068-1076https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6123576/.

10. Cavieres-Lepe J, Ewer J (2021) Reciprocal Relationship Between Calcium Signaling and Circadian Clocks: Implications for Calcium Homeostasis, Clock Function, and Therapeutics. *Frontiers in Molecular Neuroscience* **14**https://www.frontiersin.org/articles/10.3389/fnmol.2021.666673.

11. Peng X, Fan R, Xie L *et al.* (2022) Time-restricted feeding rescues circadian disruption-aggravated progression of Alzheimer's disease in diabetic mice. *The Journal of nutritional biochemistry* **110**, 109128https://pubmed.ncbi.nlm.nih.gov/35977665/.

12. Ye Y, Xu H, Xie Z *et al.* (2020) Time-Restricted Feeding Reduces the Detrimental Effects of a High-Fat Diet, Possibly by Modulating the Circadian Rhythm of Hepatic Lipid Metabolism and Gut Microbiota. *Frontiers in nutrition* **7**https://www.frontiersin.org/articles/10.3389/fnut.2020.596285.

13. Davis JA, Paul JR, Yates SD *et al.* (2021) Time-restricted feeding rescues high-fat-diet-induced hippocampal impairment. *iScience* **24**, 102532https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8188491/.

14. Davis JA, Paul JR, Mokashi MV *et al.* (2022) Circadian disruption of hippocampus in an early senescence male mouse model. *Pharmacology, biochemistry, and behavior* **217**, 173388https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9422145/.

15. Oike H, Ogawa Y, Azami K (2020) Long-Term Feeding of a High-Fat Diet Ameliorated Age-Related Phenotypes in SAMP8 Mice. *Nutrients* **12**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7285040/.

16. Song J, Chu S, Fang X *et al.* (2020) Time-restricted feeding alters isoflurane-induced memory deficits. *Translational neuroscience* **11**, 341-355https://pubmed.ncbi.nlm.nih.gov/33335774/.

17. Woodie LN, Oral KT, Krusen BM *et al.* (2022) The Circadian Regulation of Nutrient Metabolism in Diet-Induced Obesity and Metabolic Disease. *Nutrients* **14**, 3136https://europepmc.org/articles/PMC9370226.

18. Aoyama S, Shibata S (2020) Time-of-Day-Dependent Physiological Responses to Meal and Exercise. *Frontiers in nutrition* **7**, 18https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7059348/.

19. Chan K, Wong FS, Pearson JA (2022) Circadian rhythms and pancreas physiology: A review. *Front Endocrinol (Lausanne)* **13**, 920261https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7059348/.

20. Hernandez AR, Kemp KM, Burke SN *et al.* (2022) Influence of Aging, Macronutrient Composition and Time-Restricted Feeding on the Fischer344 x Brown Norway Rat Gut Microbiota. *Nutrients* **14**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9105022/.

21. Pinto FCS, Silva AAM, Souza SL (2022) Repercussions of intermittent fasting on the intestinal microbiota community and body composition: a systematic review. *Nutrition Reviews* **80**, 613-628https://doi.org/10.1093/nutrit/nuab108.

22. Lind S (2021) A Systematic Review of Time-Restricted Eating's Effect on Gut Microbiota and How It May Contribute to Cognitive Function. Independent thesis Basic level (degree of Bachelor) Student thesishttp://urn.kb.se/resolve?urn=urn:nbn:se:his:diva-21136.

23. Ma D, Li S, Molusky MM *et al.* (2012) Circadian autophagy rhythm: a link between clock and metabolism? *Trends in endocrinology and metabolism: TEM* **23**, 319-325https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3389582/.

24. Imai S-i, Guarente L (2016) It takes two to tango: NAD+ and sirtuins in aging/longevity control. *npj Aging and Mechanisms of Disease* **2**, 16017https://doi.org/10.1038/npjamd.2016.17.

25. Lee IH, Cao L, Mostoslavsky R *et al.* (2008) A role for the NAD-dependent deacetylase Sirt1 in the regulation of autophagy. *Proceedings of the National Academy of Sciences* **105**, 3374-3379https://www.pnas.org/doi/abs/10.1073/pnas.0712145105.

26. Greenhill C (2019) Circadian protein affects mTORC1 activity. *Nature Reviews Endocrinology* **15**, 65-65https://doi.org/10.1038/s41574-018-0144-8.

27. Jamshed H, Beyl RA, Della Manna DL *et al.* (2019) Early Time-Restricted Feeding Improves 24-Hour Glucose Levels and Affects Markers of the Circadian Clock, Aging, and Autophagy in Humans. *Nutrients* **11**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6627766/.

28. Gupta CC, Vincent GE, Coates AM *et al.* (2022) A Time to Rest, a Time to Dine: Sleep, Time-Restricted Eating, and Cardiometabolic Health. *Nutrients* **14**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8840563/.

29. Potter GDM, Wood TR (2020) The Future of Shift Work: Circadian Biology Meets Personalised Medicine and Behavioural Science. *Frontiers in nutrition* **7**, 116https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7426458/.

30. Mantantzis K, Campos V, Darimont C *et al.* (2022) Effects of Dietary Carbohydrate Profile on Nocturnal Metabolism, Sleep, and Wellbeing: A Review. *Frontiers in public health* **10**, 931781https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9326315/.

31. Chawla S, Beretoulis S, Deere A *et al.* (2021) The Window Matters: A Systematic Review of Time Restricted Eating Strategies in Relation to Cortisol and Melatonin Secretion. *Nutrients* **13**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8399962/.

32. Gu C, Brereton N, Schweitzer A *et al.* (2020) Metabolic Effects of Late Dinner in Healthy Volunteers-A Randomized Crossover Clinical Trial. *The Journal of clinical endocrinology and metabolism* **105**, 2789-2802https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7337187/.

33. Whittaker DS, Loh DH, Wang HB *et al.* (2018) Circadian-based Treatment Strategy Effective in the BACHD Mouse Model of Huntington's Disease. *Journal of biological rhythms* **33**, 535-554https://pubmed.ncbi.nlm.nih.gov/30084274/.

34. Wang HB, Loh DH, Whittaker DS *et al.* (2018) Time-Restricted Feeding Improves Circadian Dysfunction as well as Motor Symptoms in the Q175 Mouse Model of Huntington's Disease. *eNeuro* **5**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5752678/.

35. Balasubramanian P, DelFavero J, Ungvari A *et al.* (2020) Time-restricted feeding (TRF) for prevention of age-related vascular cognitive impairment and dementia. *Ageing research reviews* **64**, 101189https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7710623/.

36. Selvaraji S, Efthymios M, Foo RSY *et al.* (2022) Time-restricted feeding modulates the DNA methylation landscape, attenuates hallmark neuropathology and cognitive impairment in a mouse model of vascular dementia. *Theranostics* **12**, 3007-3023https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9065201/.

37. Andika FR, Yoon JH, Kim GS *et al.* (2021) Intermittent Fasting Alleviates Cognitive Impairments and Hippocampal Neuronal Loss but Enhances Astrocytosis in Mice with Subcortical Vascular Dementia. *The Journal of nutrition* **151**, 722-730https://pubmed.ncbi.nlm.nih.gov/33484139/.

38. Giebultowicz JM (2018) Circadian regulation of metabolism and healthspan in Drosophila. *Free radical biology & medicine* **119**, 62-68https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5910265/.

39. Chen H, Zhang B, Ge Y *et al.* (2020) Association between skipping breakfast and risk of cardiovascular disease and all cause mortality: A meta-analysis. *Clinical nutrition (Edinburgh, Scotland)* **39**, 2982-2988https://pubmed.ncbi.nlm.nih.gov/32085933/.

40. Yokoyama Y, Onishi K, Hosoda T *et al.* (2016) Skipping Breakfast and Risk of Mortality from Cancer, Circulatory Diseases and All Causes: Findings from the Japan Collaborative Cohort Study. *Yonago acta medica* **59**, 55-60https://pubmed.ncbi.nlm.nih.gov/27046951/.

41. Helo D, Appiah L, Bhende KM *et al.* (2021) The association of skipping breakfast with cancer-related and all-cause mortality in a national cohort of United States adults. *Cancer causes & control : CCC* **32**, 505-513https://pubmed.ncbi.nlm.nih.gov/33590466/.

42. Mitchell SJ, Bernier M, Mattison JA *et al.* (2019) Daily Fasting Improves Health and Survival in Male Mice Independent of Diet Composition and Calories. *Cell metabolism* **29**, 221-228.e223https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6326845/.

43. Acosta-Rodríguez V, Rijo-Ferreira F, Izumo M *et al.* (2022) Circadian alignment of early onset caloric restriction promotes longevity in male C57BL/6J mice. *Science (New York, NY)* **376**, 1192-1202https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9262309/.

44. Ulgherait M, Midoun AM, Park SJ *et al.* (2021) Circadian autophagy drives iTRF-mediated longevity. *Nature* **598**, 353-358https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9395244/.

45. Pellegrini M, Cioffi I, Evangelista A *et al.* (2020) Effects of time-restricted feeding on body weight and metabolism. A systematic review and meta-analysis. *Reviews in endocrine & metabolic disorders* **21**, 17-33https://pubmed.ncbi.nlm.nih.gov/31808043/.

46. Adafer R, Messaadi W, Meddahi M *et al.* (2020) Food Timing, Circadian Rhythm and Chrononutrition: A Systematic Review of Time-Restricted Eating's Effects on Human Health. *Nutrients* **12**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7763532/.

47. Xie Z, He Z, Ye Y *et al.* (2022) Effects of time-restricted feeding with different feeding windows on metabolic health: A systematic review of human studies. *Nutrition (Burbank, Los Angeles County, Calif)* **102**, 111764https://pubmed.ncbi.nlm.nih.gov/35820237/.

48. Bitsanis D, Giannakou K, Hadjimbei E *et al.* (2022) The Effect of Early Time-Restricted Feeding on Glycemic Profile in Adults: A Systematic Review of Interventional Studies. *The review of diabetic studies : RDS* **18**, 10-19https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9382685/.

49. Zhao L, Hutchison AT, Liu B *et al.* (2022) Time-restricted eating alters the 24-hour profile of adipose tissue transcriptome in men with obesity. *Obesity (Silver Spring, Md)*https://pubmed.ncbi.nlm.nih.gov/35912794/.

50. Zhao L, Hutchison AT, Liu B *et al.* (2022) Time-restricted eating improves glycemic control and dampens energy-consuming pathways in human adipose tissue. *Nutrition (Burbank, Los Angeles County, Calif)* **96**, 111583https://pubmed.ncbi.nlm.nih.gov/35150947/.

51. Faris MA, Jahrami H, BaHammam A *et al.* (2020) A systematic review, meta-analysis, and meta-regression of the impact of diurnal intermittent fasting during Ramadan on glucometabolic markers in healthy subjects. *Diabetes research and clinical practice* **165**, 108226https://pubmed.ncbi.nlm.nih.gov/32446800/.

52. Jahrami HA, Faris ME, A IJ *et al.* (2021) Does four-week consecutive, dawn-to-sunset intermittent fasting during Ramadan affect cardiometabolic risk factors in healthy adults? A systematic review, meta-analysis, and meta-regression. *Nutrition, metabolism, and cardiovascular diseases : NMCD* **31**, 2273-2301https://pubmed.ncbi.nlm.nih.gov/34167865/.

53. Faris AE, Jahrami HA, Alsibai J *et al.* (2020) Impact of Ramadan diurnal intermittent fasting on the metabolic syndrome components in healthy, non-athletic Muslim people aged over 15 years: a systematic review and meta-analysis. *The British journal of nutrition* **123**, 1-22https://pubmed.ncbi.nlm.nih.gov/31581955/.

54. Takagi H, Hari Y, Nakashima K *et al.* (2019) Meta-Analysis of Relation of Skipping Breakfast With Heart Disease. *The American journal of cardiology* **124**, 978-986https://pubmed.ncbi.nlm.nih.gov/31326073/.

55. Allaf M, Elghazaly H, Mohamed OG *et al.* (2021) Intermittent fasting for the prevention of cardiovascular disease. *The Cochrane database of systematic reviews* **1**, Cd013496https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8092432/.

56. Duan D, Bhat S, Jun JC *et al.* (2022) Time-Restricted Eating in Metabolic Syndrome-Focus on Blood Pressure Outcomes. *Current hypertension reports*, 1-13https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9446596/.

57. Correia JM, Santos I, Pezarat-Correia P *et al.* (2020) Effects of Intermittent Fasting on Specific Exercise Performance Outcomes: A Systematic Review Including Meta-Analysis. *Nutrients* **12**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7284994/.

58. Yin C, Li Z, Xiang Y *et al.* (2021) Effect of Intermittent Fasting on Non-Alcoholic Fatty Liver Disease: Systematic Review and Meta-Analysis. *Frontiers in nutrition* **8**, 709683https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8310935/.

59. Cuevas-Cervera M, Perez-Montilla JJ, Gonzalez-Muñoz A *et al.* (2022) The Effectiveness of Intermittent Fasting, Time Restricted Feeding, Caloric Restriction, a Ketogenic Diet and the Mediterranean Diet as Part of the Treatment Plan to Improve Health and Chronic Musculoskeletal Pain: A Systematic Review. *International journal of environmental research and public health* **19**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9180920/.

60. Das M, Webster NJG (2022) Obesity, cancer risk, and time-restricted eating. *Cancer and Metastasis Reviews* **41**, 697-717https://doi.org/10.1007/s10555-022-10061-3.

61. Serra M, Marongiu F, Pisu MG *et al.* (2019) Time-restricted feeding delays the emergence of the age-associated, neoplastic-prone tissue landscape. *Aging* **11**, 3851-3863https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6594823/.

62. Dong S, Wang Z, Shen K *et al.* (2021) Metabolic Syndrome and Breast Cancer: Prevalence, Treatment Response, and Prognosis. *Frontiers in oncology* **11**, 629666https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8027241/.

63. Kogevinas M, Espinosa A, Castelló A *et al.* (2018) Effect of mistimed eating patterns on breast and prostate cancer risk (MCC-Spain Study). *International journal of cancer* **143**, 2380-2389https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6220994/.

64. Marinac CR, Nelson SH, Breen CI *et al.* (2016) Prolonged Nightly Fasting and Breast Cancer Prognosis. *JAMA oncology* **2**, 1049-1055https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4982776/.

65. Kirkham AA, Ford KL, Topolnyski J *et al.* (2022) Time-Restricted Eating to Reduce Cardiovascular Risk Among Older Breast Cancer Survivors. *JACC: CardioOncology* **4**, 276-278https://www.jacc.org/doi/abs/10.1016/j.jaccao.2022.03.002.

66. Anton SD, Lee SA, Donahoo WT *et al.* (2019) The Effects of Time Restricted Feeding on Overweight, Older Adults: A Pilot Study. *Nutrients* **11**https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6682944/.

***Disclaimer**: Cognitive Vitality Reports® do not provide, and should not be used for, medical advice, diagnosis, or treatment. You should consult with your healthcare providers when making decisions regarding your health. Your use of these reports constitutes your agreement to the **Terms & Conditions**.*

If you have suggestions for drugs, drugs-in-development, supplements, nutraceuticals, or food/drink with neuroprotective properties that warrant in-depth reviews by ADDF's Aging and Alzheimer's Prevention Program, please contact INFO@alzdiscovery.org. To view our official ratings, visit Cognitive Vitality's Rating page.