

International Journal of Agriculture Extension and Social Development

Volume 7; Issue 7; July 2024; Page No. 211-216

Received: 20-05-2024
Accepted: 24-06-2024

Indexed Journal
Peer Reviewed Journal

The impact of continuous calorie restriction and fasting on cognition in adults

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DOI: <https://doi.org/10.33545/26180723.2024.v7.i7c.793>

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Abstract

Ongoing investigation into the impacts of calorie restriction continues to captivate individuals who are curious about its potential to extend human lifespan and improve overall health. Research conducted on animals has shown significant benefits to health and lifespan through continuous calorie restriction (CCR) and fasting. Nevertheless, there are lingering worries over the effects of limiting calorie consumption on human health and cognition. Considering the rising evidence of cognitive deficits in eating disorders, conducting research that examines reduced calorie intake in healthy individuals in an ethical manner could provide insights into the understanding of restrictive eating disorders. This review synthesizes the current literature on the effects of CCR (caloric restriction) and fasting on cognitive performance in healthy adult subjects. Out of the 33 research examining the relationship between CCR (caloric restriction) and fasting in humans, 23 showed notable alterations in cognition. Although there are differences in cognitive domains, the findings indicate that CCR has positive effects on inhibition, processing speed, and working memory, but it may have negative effects on cognitive flexibility. Fasting studies indicate that fasting is linked to declines in cognitive flexibility and psychomotor ability. In summary, the findings of this research indicate that the extent of calorie restriction, namely its severity, is the primary factor that determines cognitive enhancements rather than impairments. For persons who are consistently limiting their activities, this can lead to severe and permanent repercussions. Nevertheless, there are conflicting results about the influence of CCR and fasting on this particular component of human functioning, indicating the need for additional research to comprehend the advantages and disadvantages of various forms of calorie restriction.

Keywords: Calorie restriction, cognitive function, fasting, intermittent fasting

Introduction

Calorie restriction is a method that has been extensively examined for its possible advantages in extending lifespan and has garnered significant attention from researchers throughout the years. Calorie restriction, or energy limitation, refers to the act of decreasing the daily calorie intake while ensuring sufficient nutrient consumption. This approach has undergone extensive examination in several animal models and has demonstrated the ability to enhance longevity and enhance overall health. While the precise mechanisms underlying the impact of calorie restriction on lifespan remain incompletely comprehended, numerous suggestions have been put forth. Scientists studying the effects of continuous calorie restriction (CCR) and fasting diets on health have discovered numerous possible physical health advantages in animals and, more recently, in humans. Therefore, there is an increasing endorsement for various dietary regimens, with proponents of Caloric Restriction (CCR) and fasting asserting that adhering to these regimens might result in health advantages such as extended lifespan and defence against dementia and Alzheimer's disease (Van *et al.*, 2016) [28].

We identified a total of three studies that directly investigated the effects of CCR (caloric restriction) and fasting on cognitive function in adult subjects (Teong *et al.*, 2021) [25]. While the results of these studies indicate that there are no notable distinctions in the effects of CCR and

fasting on cognition, further study is required to directly compare these two dietary approaches. In order to fill this vacuum in information, we analyse research that have evaluated cognitive abilities in individuals who followed CCR diets, as well as those who practiced fasting. We examine disparities in psychomotor speed, set-shifting aptitude, and cognitive adaptability as well as working and prospective memory capacity; and reflective impulsivity (McCay, 1935) [19].

The concept of continuous calorie restriction and its associated health advantages.

CCR stands for caloric restriction, which is the deliberate reduction in energy consumption, typically done to achieve weight loss. Individuals who adhere to a CCR (Calorie Restriction with Optimal Nutrition) regimen often decrease their daily energy consumption by approximately 15% to 30%. The study of Caloric Restriction (CCR) has gained increasing attention due to its ability to increase lifespan and enhance overall health in various creatures, by restricting food intake while ensuring optimal nutrition (Van, 2016) [28]. McCay *et al.* were the first to demonstrate that healthy mice, whose daily energy intake was lowered, had a longer lifespan compared to a control group that was fed freely. Multiple empirical research have substantiated this fact in insects (Harshman LG, *et al.*, 2001) [5]. While the precise mechanisms are still not completely understood, these

findings have attracted the interest of individuals studying similar impacts in human populations. The recent CALERIE study, which examined the long-term effects of reducing energy intake in people, found positive improvements in body composition, weight, cardiovascular health, and glucoregulatory function (Weindruch *et al.*, 1986)^[31].

The researchers at CALERIE conducted a study to examine the impact of Caloric Restriction without Malnutrition (CCR) on individuals with both overweight and healthy weight. The study lasted for a period of up to 24 months. The study demonstrated enhancements in physiological, psychological, and behavioral aspects (Redman *et al.*, 2007)^[20]. The interest in the advantages of CCR, specifically in terms of weight loss, is not limited to the scientific community, as public awareness of its benefits continues to increase significantly. Obesity is a widespread and serious problem affecting the global population, with approximately 13% of adults worldwide classified as obese (Dorling *et al.*, 2020)^[6].

The practice of fasting and its positive effects on health

Fasting is the intentional act of refraining from consuming food, beverages, or both, typically for the purpose of improving health, practicing religious beliefs, or for other personal motivations. Intermittent fasting (IF) is a prevalent fasting method characterized by alternating periods of regular eating and complete or limited food consumption. Intermittent fasting (IF) encompasses many fasting methods, such as alternate-day fasting (fasting every other day), time-restricted feeding (fasting within a specific daily time frame, like during Ramadan), or whole-day fasting (usually fasting completely for 1-2 days per week) (Tinsley, 2015)^[27].

Multiple research indicates that adhering to fasting regimens can yield advantages. Animals that practice alternate-day fasting have a decrease in body fat, heart rate, and blood pressure. These effects seem to be exclusive to intermittent fasting (IF) and not merely calorie restriction (CR). Undoubtedly, mice who were fed according to an intermittent fasting (IF) regimen with a 15%–30% decrease in food consumption experienced more significant improvements compared to those that were treated to a daily calorie-restricted diet with a 40% reduction (Mager *et al.*, 2006)^[15]. Additional research conducted on rodents indicates that fasting has the potential to decrease insulin resistance, lower the likelihood of developing cardiovascular disease, slow down the advancement of cancer, and protect against neurodegeneration in the brain (Mattson, 2017)^[17].

Preliminary findings in rodents indicate that intermittent fasting (IF) is at least equally successful as calorie restriction (CCR) diets in terms of promoting health advantages, such as weight loss and enhanced insulin sensitivity. Nevertheless, the available evidence substantiating the health advantages of fasting for humans is restricted to a small number of randomised controlled trials and observational studies, most of which have relatively small sample sizes and limited duration. Two recent evaluations of intermittent fasting (IF) and its advantages for humans discovered that the majority of studies focused on the reduction of body weight and health outcomes connected to obesity while paying little attention to secondary outcomes such as cognitive function (Horne,

2017)^[11].

The impact of continuous calorie restriction, fasting, and cognition

Considering the potential health advantages of calorie restriction in humans, there is a need to examine the effects of calorie restriction and fasting on the brain. One idea elucidated by Mattson examines the hypothesis that the human brain has developed to offer a competitive edge in times of food scarcity, by assuring optimal cognitive performance throughout the search for nutrition. This implies that fasting and caloric restriction (CCR) may have beneficial impacts on brain function. Nevertheless, considering the significant glucose needs of executive function, it is plausible that CCR could potentially have negative effects on certain aspects of cognitive performance. Cognitive function refers to a wide range of mental activities that help us acquire information and understanding. The human cognitive system enables the perception, reasoning, storage, and manipulation of information, as well as problem-solving depending on existing information.

Some studies indicate that CCR has a detrimental effect on attentional processes and cognitive flexibility. However, another study suggests that CCR may help mitigate age-related cognitive decline. Generally, reviews are scarce regarding the immediate effect of CCR on cognitive abilities in people. A recent review has substantiated the existing modest evidence, while another study has shown that short-term fasting is linked to cognitive impairments, specifically affecting higher-order processes such as attention and flexibility. It is important to highlight that these evaluations emphasize the necessity for additional long-term studies on fasting. Furthermore, due to inconsistencies and limitations in the methods used in current studies, the effect of fasting on cognition is still largely uncertain. In addition, other reviews analyse the effects of CCR, fasting, and cognition individually, or the authors restrict their search to studies that incorporate an additional variable, such as exercise, glucose metabolism, or age-related disease.

Methods

A search of the PsycINFO database was carried out in October 2018 and subsequently updated in January 2023. In the original evaluation, the process of searching the database included entries from the earliest available date up until October 2018. In the amended review, the search for relevant literature was conducted from October 2018 to January 2023, including both of these months. We exclusively incorporated empirical investigations that assessed cognitive function following the alteration of overall energy consumption in adult human volunteers (aged 18 years or older). We incorporated empirical investigations that explored CCR, fasting, or a combination of both. CCR is defined as a purposeful decrease in energy consumption to less than 100% (i.e., studies where food intake was reduced but some food was still permitted). We have seen studies with a range of CCR values between 17% and 80%. Fasting was defined as a period of complete elimination of energy intake, meaning that there was no consumption of foods or fluids containing calories, for a minimum duration of 4 hours.

Based on the research encompassed intermittent fasting (IF), alternate-day fasting, time-restricted feeding, and several other fasting strategies. The majority of the studies included in our analysis had unrestricted access to water, but we did not have a specific criterion for this in our search. The cognitive domains examined were attention, inhibition, set-shifting, processing speed, working memory (WM), and psychomotor speed. Attention is the cognitive process that enables us to actively analyse specific stimuli, while inhibition is a cognitive control mechanism that allows us to suppress irrelevant stimuli. Set shifting is a cognitive function that involves the capacity to redirect attention from one task to another. Processing speed pertains to the velocity at which an individual can perceive and process information. Working memory (WM) is a component of the memory system that briefly holds and processes

information. Psychomotor speed is the duration between cognitive processing and physical response. The exclusion criteria for our study were as follows: the inclusion of exercise as an intervention that differed between control and restriction groups, the comparison of specific dietary manipulations such as low-carbohydrate, high-fat diet or Mediterranean diet, unpublished work such as dissertation studies, participants diagnosed with an eating disorder, and the use of quasi-experimental methods such as observations or interventions.

After applying the inclusion and exclusion criteria, the initial search produced 936 items, which were then narrowed down to 25. After the search was updated, a total of 15 articles were found. However, after considering the inclusion and exclusion criteria, the number of articles was decreased to 8.

Table: The impact of ongoing calorie restriction on cognitive function and the influence of fasting on cognitive abilities (without any intake of food or calorie-containing fluids, limited to water only).

Population sample	Duration (d)	Energy reduction (%)	Working memory	Attention	Processing speed	Reference
42 adults with overweight	180	30	–	No change	No change	Cheatham <i>et al.</i> , 2009 [4]
106 adults with overweight	365	28	Increases	–	No change	Brinkworth <i>et al.</i> , 2009 [2]
93 adults with obesity	56	30	Increases	No change	Increases	Halyburton <i>et al.</i> , 2007 [9]
50 adults with obesity	116	24	No change	–	No change	Siervo <i>et al.</i> , 2012 [23]
44 adults with obesity	56	30	No change	No change	No change	Pearce <i>et al.</i> , 2012 [37]
60 healthy adults	16	100	–	–	–	Bolton <i>et al.</i> , 2014 [38]
60 healthy adults	18	100	No change	No change	No change	Pender <i>et al.</i> , 2014 [39]
80 female students	14	100	No change	–	No change	Benton and Parker, 1998 [1]
18 male athletes	18	100	–	increases	increases	Tian <i>et al.</i> , 2011 [26]
33 female students	20	100	–	–	–	Howard <i>et al.</i> , 2020 [13]

Table: An investigation of the impact of continuous calorie restriction and fasting on cognitive function.

Population sample	Duration (d)	Energy reduction (%)	Working memory	Attention	Processing speed	Reference
43 individuals, aged 35–75y, with central obesity	28	100% and 20% (500kcal deficit)	Decrease in the fasting group	–	–	Kim <i>et al.</i> , 2020 [14]
46 women with overweight or obesity	56	70%	–	Increases in both group	Increases in both group	Teong <i>et al.</i> , 2021 [25]
17 healthy or with overweight female participants	7.5	100% and 70%	No change	No change	No change	Zajac <i>et al.</i> , 2021 [36]

Findings

In this analysis, we examine research that evaluated the effects of fasting, caloric restriction (CCR), or a combination of both. Out of the research examined, 15 were CCR studies and 16 were fasting studies. Only three studies explicitly compared the cognitive effects of CCR and IF. Out of the 33 research in total, 11 employed between-participant designs whereas the remaining studies utilised within-participant designs. The impact of CCR and fasting on all cognitive domains mentioned is consolidated.

Attention

The majority of our everyday duties necessitate us to observe distinct stimuli and frequently include the requirement to maintain our focus or shift it as needed until a task is finished. Occupations that entail mechanical or medical operations carry risks due to decreased focus. Therefore, it is crucial to comprehend the effects of CCR and fasting on this specific field. Studies on the effects of continuous calorie restriction (Martin, 2013) [16].

Across 5 trials, researchers saw no alterations in attention following CCR. However, an enhancement in attention was documented in 3 studies, whereas a decline in attention was noted in 1 study. Overweight individuals who reduced their calorie intake by 25% over a period of 168 days did not experience any alterations in attention, as assessed by Conner's Continuous Performance Test II. This test evaluates attention, concentration, inattention, and impulsivity. Seven more investigations employing various attentional tasks failed to observe any significant disparities in attention between controlled calorie restriction (CCR) and unrestricted eating (Rosvold, 1953) [22].

Working memory

Multiple research employed a digit-span task. Digit span is frequently employed as an assessment of one's ability to retain and recall numbers in short-term memory. The task necessitates the participants to promptly recollect a sequence of numbers in the accurate sequence immediately following the presentation of the numbers. The digit-span backward task involves the participant's ability to recall a

series of numbers in the opposite order they were presented (Halyburton, 2007)^[9].

A study assessed the ability of participants to remember a sequence of numbers, known as digit span memory. The participants were divided into two groups: one group consumed low-fat foods, while the other group consumed low-carbohydrate foods. Both groups had their calorie intake reduced by 30%. The researchers discovered that the ability to remember and repeat a series of numbers in reverse order was considerably enhanced in both groups after 8 weeks of cognitive training. However, the absence of a control group raises the likelihood that the observed improvement may be attributed to practice effects rather than the intervention itself (Buffenstein, 2000)^[3].

Processing speed

The researchers found that reaction time was more impaired on fasting days for participants during medium-difficulty tasks than for lower or higher-rated tasks. The authors suggested their findings highlight the importance of considering the role played by task demands and their level of difficulty when comparing studies that attempt to measure a particular cognitive domain after calorie reduction.

Discussion

On the whole, research on calorie restriction (CCR) were more inclined to report benefits in cognitive function, whereas studies on fasting were more likely to report deficits. This suggests that the extent and duration of calorie restriction may have significant effects on the direction of any influence on cognition. A moderate reduction in calorie intake may be linked to enhancements in certain cognitive areas, whereas extreme restriction or prolonged total fasting is more likely to result in a decline in performance (Solianik, 2020)^[23].

The majority of deficits were noted in the areas of cognitive flexibility and motor response speed, in both fasting and continuous calorie restriction (CCR) investigations. Two separate investigations (studies 71 and 72) found that the capacity to shift between tasks reduced following a 20-hour fast and a 48-hour fast, respectively. Additionally, research from the literature on caloric restriction (CCR) indicated deficits in set-shifting ability after extreme caloric restriction (75%) over a period of 2 days. This is most similar to the 5:2 Intermittent Fasting (IF) diet, when calorie consumption is reduced by 75% for two days per week. The sole study that observed a notable distinction between fasting and continuous calorie restriction (CCR), specifically in relation to working memory (WM), also replicated the effects of a 5:2 diet. Two This implies that the level of cognitive reserve (CR) may have a significant impact on alterations in set-shifting and working memory (WM) capacity during the process of dieting.

All three fasting studies that assessed psychomotor speed found notable deficits. Significantly, these studies specifically selected physically fit university students, and their results were comparable to research conducted on young individuals diagnosed with AN.⁷⁹ Hence, conducting further research to examine the impact of fasting, a form of restrictive eating, on psychomotor speed would contribute to our comprehension of a potential cognitive profile for eating

disorders (EDs). The majority of enhancements were noted in the areas of inhibition, working memory (WM), and attention (in 9 studies). The majority of these studies focused on CCR, but interestingly, 2 fasting trials indicated a positive impact on attention.

Ultimately, the literature presented conflicting results about the effects of CCR and fasting on processing speed.

Conclusion

In general, it seems that the duration of fasting and the extent of calorie reduction, such as a 50% reduction through Caloric Restriction (CCR) compared to a complete reduction through fasting, are both significant factors that can impact cognitive performance. Further research could provide additional clarity by conducting experiments on participants who experience different levels of limitation. The animal research conducted by Vitousek *et al.* could offer a valuable perspective for interpreting the literature. According to their review, there is a point at which reducing food intake can improve cognition. However, beyond this point, it may have negative effects on cognitive functioning and physical health. This has significant consequences for eating disorders characterized by severe and prolonged caloric restriction, as well as regimens that involve intermittent fasting. In these cases, the objective of optimizing health must be carefully balanced with the delicate distinction between optimal and suboptimal caloric restriction (Vitousek, 2004)^[29, 30].

References

1. Benton BD, Parker PY. Breakfast, blood glucose, and cognition. *Am J Clin Nutr.* 1998 Oct;67(4):772S-778S. doi:10.1093/ajcn/67.4.772S
2. Brinkworth GD, Buckley JD, Noakes M, *et al.* Long-term effects of a very low-carbohydrate diet and a low-fat diet on mood and cognitive function. *Arch Intern Med.* 2009 Oct 12;169(18):1873-1880. doi:10.1001/archinternmed.2009.329
3. Buffenstein R, Karklin A, Driver HS. Beneficial physiological and performance responses to a month of restricted energy intake in healthy overweight women. *Physiol Behav.* 2000 Mar 1;68(3):439-444. doi:10.1016/s0031-9384(99)00222-x
4. Cheatham RA, Roberts SB, Das SK, *et al.* Long-term effects of provided low and high glycemic load low energy diets on mood and cognition. *Physiol Behav.* 2009 Dec 7;98(4):374-379. doi:10.1016/j.physbeh.2009.06.015
5. Clancy DJ, Gems D, Harshman LG, *et al.* Extension of life-span by loss of CHICO, a Drosophila insulin receptor substrate protein. *Science.* 2001 Apr 6;292(5514):104-106. doi:10.1126/science.1057991
6. Dorling JL, van Vliet S, Huffman KM, *et al.*; CALERIE Study Group. Effects of caloric restriction on human physiological, psychological, and behavioral outcomes: highlights from CALERIE phase 2. *Nutr Rev.* 2020 Feb 1;79(2):98-113. doi:10.1093/nutrit/nuaa085
7. Global Health Observatory. Obesity factsheet. 2016. Available from: <https://www.who.int/news-room/factsheets/detail/obesity-and-overweight>. Accessed February 6, 2023.

8. Gudden J, Arias Vasquez A, Bloemendaal M. The effects of intermittent fasting on brain and cognitive function. *Nutrients*. 2021 Oct 20;13(11):3166. doi:10.3390/nu13113166
9. Halyburton AK, Brinkworth GD, Wilson CJ, *et al.* Low- and high-carbohydrate weight-loss diets have similar effects on mood but not cognitive performance. *Am J Clin Nutr*. 2007 Sep;86(3):580-587. doi:10.1093/ajcn/86.3.580
10. Hanjani N, Vafa MR. Calorie restriction, longevity and cognitive function. *Nutr Food Sci Res*. 2016;3:1-4. doi:10.18869/acadpub.nfsr.3.1.1
11. Horne BD, Muhlestein JB, Anderson JL. Health effects of intermittent fasting: hormesis or harm? A systematic review. *Am J Clin Nutr*. 2015 Aug;102(2):464-470. doi:10.3945/ajcn.115.109553
12. Houthoofd K, Vanfleteren JR. Public and private mechanisms of life extension in *Caenorhabditis elegans*. *Mol Genet Genomics*. 2007 Dec;277(6):601-617. doi:10.1007/s00438-007-0225-1
13. Howard M, Roiser JP, Gilbert SJ, *et al.* Short-term fasting selectively influences impulsivity in healthy individuals. *Front Psychol*. 2020 Jul 28;11:1644. doi:10.3389/fpsyg.2020.01644
14. Kim C, Pinto AM, Bordoli C, *et al.* Energy restriction enhances adult hippocampal neurogenesis-associated memory after four weeks in an adult human population with central obesity; a randomized controlled trial. *Nutrients*. 2020 Mar;12(3):638. doi:10.3390/nu12030638
15. Mager DE, Wan R, Brown M, *et al.* Caloric restriction and intermittent fasting alter spectral measures of heart rate and blood pressure variability in rats. *FASEB J*. 2006 Mar;20(4):631-637. doi:10.1096/fj.05-5263com
16. Martin CK, Anton SD, Han H, *et al.* Examination of cognitive function during six months of calorie restriction: results of a randomized controlled trial. *Rejuvenation Res*. 2007 Jun;10(2):179-190. doi:10.1089/rej.2006.0502
17. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. *Ageing Res Rev*. 2017 Nov;39:46-58. doi:10.1016/j.arr.2016.10.005
18. Mattson MP. Lifelong brain health is a lifelong challenge: from evolutionary principles to empirical evidence. *Ageing Res Rev*. 2015 Nov;20:37-45. doi:10.1016/j.arr.2014.12.011
19. McCay CM, Crowell MF, Maynard LA. The effect of retarded growth upon the length of life span and upon the ultimate body size: one figure. *J Nutr*. 1935 Jan 1;10(1):63-79. doi:10.1093/jn/10.1.63
20. Redman LM, Heilbronn LK, Martin CK, *et al.*; Pennington CALERIE Team. Effect of calorie restriction with or without exercise on body composition and fat distribution. *J Clin Endocrinol Metab*. 2007 Mar;92(3):865-872. doi:10.1210/jc.2006-2184
21. Rochon J, Bales CW, Ravussin E, *et al.*; CALERIE Study Group. Design and conduct of the CALERIE study: comprehensive assessment of the long-term effects of reducing intake of energy. *J Gerontol A Biol Sci Med Sci*. 2011 Jan;66(1):97-108. doi:10.1093/gerona/glq168
22. Rosvold HE, Mirsky AF, Sarason I, *et al.* A continuous performance test of brain damage. *J Consult Psychol*. 1956 Dec;20(6):343-350. doi:10.1037/h0043220
23. Siervo M, Nasti G, Stephan BCM, *et al.* Effects of intentional weight loss on physical and cognitive function in middle-aged and older obese participants: a pilot study. *J Am Coll Nutr*. 2012 Feb;31(1):79-86. doi:10.1080/07315724.2012.10720012
24. Solianik R, Zlibinait_e L, Drozdova-Statkevicien_e M, *et al.* Forty-eight-hour fasting declines mental flexibility but improves balance in overweight and obese older women. *Physiol Behav*. 2020 Dec 1;223:112995. doi:10.1016/j.physbeh.2020.112995
25. Teong XT, Hutchison AT, Liu B, *et al.* Eight weeks of intermittent fasting versus calorie restriction does not alter eating behaviors, mood, sleep quality, quality of life and cognitive performance in women with overweight. *Nutr Res*. 2021 Aug;92:32-39. doi:10.1016/j.nutres.2021.06.006
26. Tian HH, Aziz AR, Png W, *et al.* Effects of fasting during Ramadan month on cognitive function in Muslim athletes. *Asian J Sports Med*. 2011 Sep;2(3):145-153. doi:10.5812/asjasm.34824
27. Tinsley GM, La Bounty PM. Effects of intermittent fasting on body composition and clinical health markers in humans. *Nutr Rev*. 2015 Nov;73(11):661-674. doi:10.1093/nutrit/nuv041
28. Van Cauwenberghe C, Vandendriessche C, Libert C, *et al.* Caloric restriction: beneficial effects on brain aging and Alzheimer's disease. *Mamm Genome*. 2016 Aug;27(7-8):300-319. doi:10.1007/s00335-016-9647-6
29. Vitousek KM, Gray JA, Grubbs KM. Caloric restriction for longevity: I. Paradigm, protocols and physiological findings in animal research. *Euro Eating Disorders Rev*. 2004 Sep;12(5):279-299. doi:10.1002/erv.594
30. Vitousek KM. The case for semi-starvation. *Euro Eating Disorders Rev*. 2004 Sep;12(5):275-278. doi:10.1002/erv.593
31. Weindruch R, Walford RL, Fligiel S, *et al.* The retardation of aging in mice by dietary restriction: longevity, cancer, immunity and lifetime energy intake. *J Nutr*. 1986 Apr;116(4):641-654. doi:10.1093/jn/116.4.64109
32. Weiss EP, Racette SB, Villareal DT, *et al.* Washington University School of Medicine CALERIE Group. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. *Am J Clin Nutr*. 2006 Nov;84(5):1033-1042. doi:10.1093/ajcn/84.5.1033
33. Yu Q, Zou L, Kong Z, *et al.* Cognitive impact of calorie restriction: a narrative review. *J Am Med Dir Assoc*. 2020 Nov;21(11):1394-1401. doi:10.1016/j.jamda.2020.05.047
34. Zajac I, Herreen D, Hunkin H, *et al.* Modified fasting compared to true fasting improves blood glucose levels and subjective experiences of hunger, food cravings and mental fatigue, but not cognitive function: results of an acute randomised cross-over trial. *Nutrients*. 2021 Jan;13(1):65. doi:10.3390/nu13010065
35. Pearce MS, Salotti JA, Little MP, McHugh K, Lee C,

- Kim KP, *et al.* Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *The Lancet*. 2012 Aug 4;380(9840):499-505.
38. Bolton P, Lee C, Haroz EE, Murray L, Dorsey S, Robinson C, *et al.* A transdiagnostic community-based mental health treatment for comorbid disorders: development and outcomes of a randomized controlled trial among Burmese refugees in Thailand. *PLoS medicine*. 2014 Nov 11;11(11):e1001757.
39. Pender DJ. Endolymphatic hydrops and Ménière's disease: A lesion meta-analysis. *The Journal of Laryngology & Otology*. 2014 Oct;128(10):859-865.