

# 언제, 얼마나 먹을까?



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## When and how much to eat

Seong Gi An, MD

Seoul Central Convalescent Hospital

Three meals plus snacks daily  
has become the **norm** during the **past half-century**,  
such that a majority of American children are accustomed to this eating pattern.

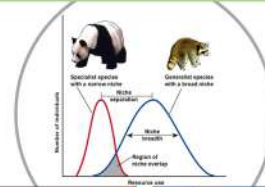
Proc Natl Acad Sci U S A. 2014 Nov 25;111(47):16647-53



*many myths and presumptions  
concerning diet and health, including that  
it is important to eat **three or more meals per day on a regular basis***

Proc Natl Acad Sci U S A. 2014 Nov 25;111(47):16647-53

Environmental heterogeneity generates diversifying selection, either in space or time. ...  
Thus ecological **specialists evolve** in environments that are relatively **homogeneous** in space and time whereas  
ecological **generalists evolve** in environments that are **heterogeneous** in either dimension.



### Specialist

Small/narrow niche  
Limited/unique diet requirements  
More likely to suffer from habitat loss and become endangered  
Does not tolerate environmental changes  
Commonly found in stable climax communities  
Examples: kouia, giant panda, walrus

### Generalist

Large/wide niche  
Wide range of diet – usually omnivores  
Tolerates a wide range of environmental variations  
Tolerates environmental changes  
Commonly invasive species  
Examples: cockroaches, rats, raccoon

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6. 언제 먹을까?
7. 언제부터 얼마나 먹을까?
8. 개인적인 경험 및 추천

## 왜 ‘먹는다는 것’인가

### Individual Nutrient Approach

Nutrients & bioactive components  
strong evidence for preventive effects of vitamin  
E, B vitamins, and n-3 fatty acids and  
deleterious effects of saturated fat on dementia

### Whole-diet Approach

Diet pattern study  
better adherence to a Mediterranean diet is  
associated with less cognitive decline, dementia,  
or Alzheimer disease

specific foods with evidence of neuroprotection are green leafy vegetables, other vegetables, berries, and seafood.

Table 1. Prospective studies relating the Mediterranean diet to cognitive change and incident dementia.

Author	N	Outcome	Result	Notes
NIH (Morris et al. <sup>11</sup> )	960	Alzheimer's disease/global cognition	↓	Good
Good (Chadwick et al. <sup>12</sup> )	491	MCI	↓	Good
Sweden (Kivimaki et al. <sup>13</sup> )	1189	Dementia	↓	Whole population
NIH (Cheng et al. <sup>14</sup> )	968	Global cognition	↓	Good
HealthABC (Morris et al. <sup>15</sup> )	2126	MCI	↓	Good
IRCADE (Fargnoli et al. <sup>16</sup> )	17,478	MCI	↓	Whole population
NIH (Morris et al. <sup>17</sup> )	4,174	Global cognition	↓	Whole population
Castle et al. (Hogarty et al. <sup>18</sup> )	884	MCI	↓	Whole population
NIH (Morris et al. <sup>19</sup> )	2284	Global cognition	↓	Whole population
NIH (Morris et al. <sup>20</sup> )	14,038	Global cognition	↓	Whole population
CHAD (Cheng et al. <sup>21</sup> )	2196	Global cognition	↓	Good
Spain (Baria-Rodriguez et al. <sup>22</sup> )	1111	MCI	↓	Whole population
US (Lee et al. <sup>23</sup> )	1480	MCI/AD	↓	Whole population
NIH (NIH Cognitive et al. <sup>24</sup> )	2884	Alzheimer's disease	↓	Whole population

Adv Nutr. 2015 Mar 13;6(2):154-68  
Ann N Y Acad Sci. 2016 Mar;1367(1):31-7



Developed by Martha Clark Morris, PhD, a Rush nutritional epidemiologist and her colleagues


Eat	Don't Eat
<ul style="list-style-type: none"> <li>Green leafy vegetables (like spinach and salad greens): at least six servings a week</li> <li>Other vegetables: at least one a day</li> <li>Nuts: five servings a week</li> <li>Berries: two or more servings a week</li> <li>Beans: at least three servings a week</li> <li>Whole grains: three or more servings a day</li> <li>Fish: once a week</li> <li>Poultry (like chicken or turkey): two times a week</li> <li>Olive oil: use it as your main cooking oil</li> <li>Wine: one glass a day</li> </ul>	<ul style="list-style-type: none"> <li>Red meat: more than four servings a week</li> <li>Butter and stick margarine: more than a tablespoon daily</li> <li>Cheese: more than one serving a week</li> <li>Pastries and sweets: more than five servings a week</li> <li>Fried or fast food: more than one serving a week</li> </ul>

### Mediterranean-DASH Intervention for Neurodegenerative Delay

## MIND

(Investigators at Rush University)

DASH (Dietary Approaches to Stop Hypertension)



MIND is a hybrid of the DASH and Mediterranean diets, but with modifications that reflect the most compelling scientific evidence on foods and nutrients that protect the brain. *Ann N Y Acad Sci.* 2016 Mar;1367(1):31-7.

## 왜 '먹는다는 것'인가


음식(영양소, 수퍼푸드)이나 다이어트(요법)가 아니라 일상으로서의 '먹는다'는 행위에 초점을 맞추면 좀 더 다양한 주제를 다룰 수 있다.



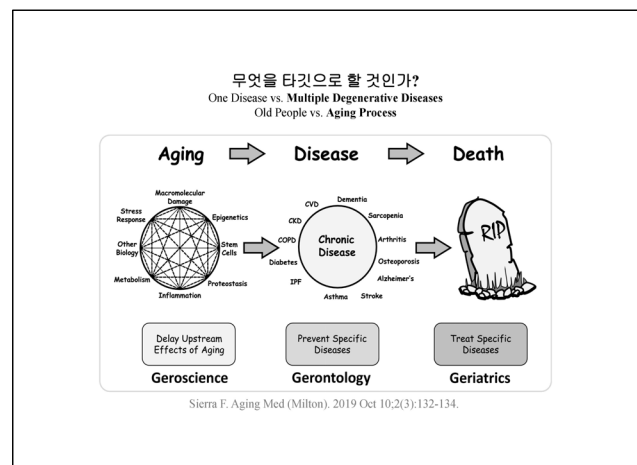
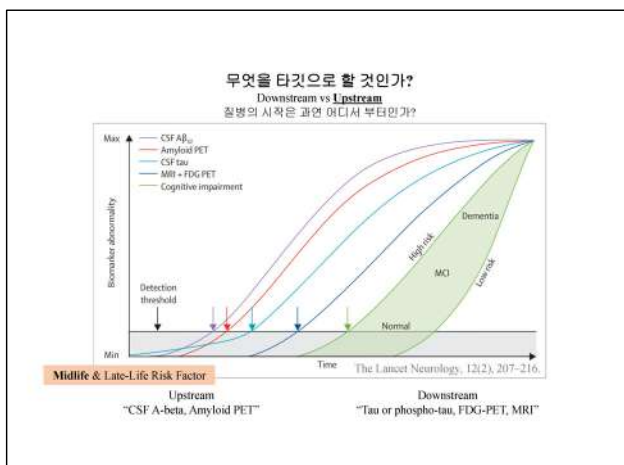
치매와 먹는다는 것  
없나, 언제 먹을 것인가?  
무엇을 먹을래?  
무엇을 먹지 말래?

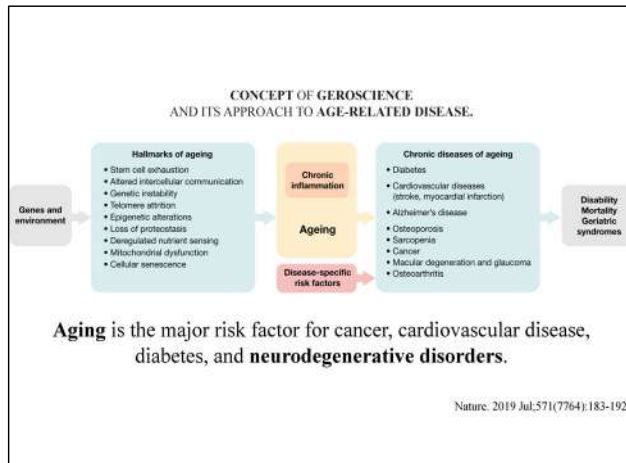
## 무엇을 타겟으로 할 것인가?

Brain vs. Whole Body  
뇌의 문제를 뇌로만 설명할 수 있는가?  
(심신이연론 & 뇌신이연론)



Psychosomatic medicine, Mind-body medicine, Body-oriented psychology, Gut-brain axis  
"Wholeness and Interconnectedness"

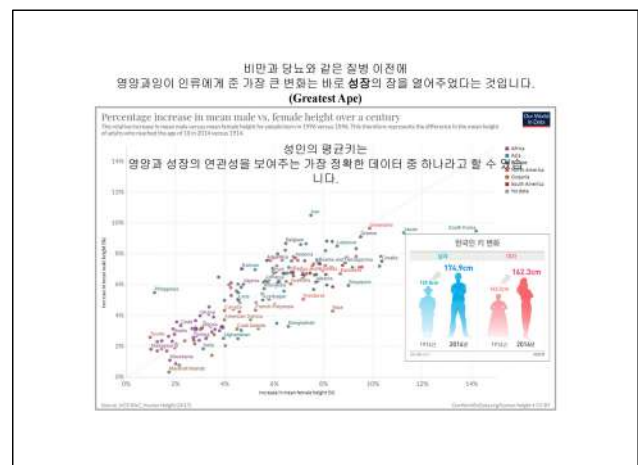
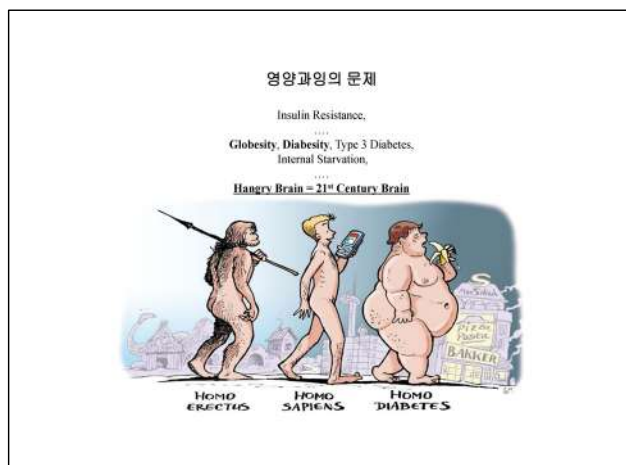




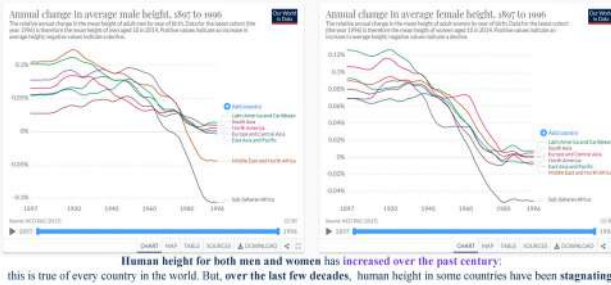
치매와 먹는다는 것  
얼마나, 언제 먹을 것인가?  
무엇을 먹을까?  
무엇을 먹지 말까?  
...

**오늘의 주제**

노화와 먹는다는 것  
얼마나, 언제 먹을 것인가?  
무엇을 먹을까?  
무엇을 먹지 말까?  
...



그러나 그 풍요로움의 혜택은 이제 끝을 맞이하는 듯하다.



그리고 다른 한편 호모 사피엔스라는 우리 종의 생활사까지도 변화시키고 있습니다.  
(Life history evolution)



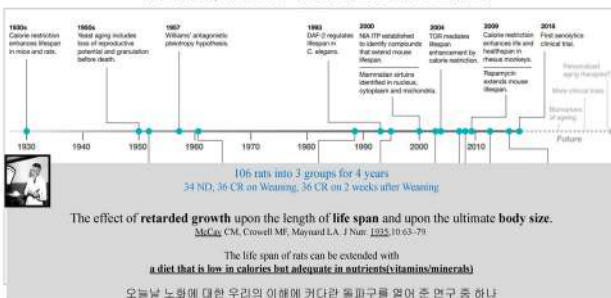
그리고 어쩌면 장수와 불멸을 향한 인류의 오래된 꿈에도 종말을 고하고 있을지도 모릅니다.

**A Potential Decline in Life Expectancy in the United States in the 21st Century**  
The trend in the life expectancy of humans during the past thousand years has been characterized by a slow, steady increase—a pattern frequently punctuated by a volatility in death rates caused by epidemics and pandemic infectious diseases, famines, and war.

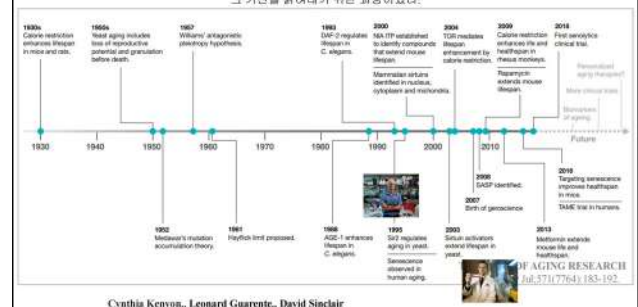
From our analysis of the effect of **obesity on longevity**, we conclude that the steady rise in life expectancy during the past two centuries may soon come to an end.

먹는다는 것의 문제는  
아주 짧은 시기동안 부족함에서 풍요로움으로 바뀌면서  
인류의 현재와 미래에 엄청난 변화를 주고 있다.

백년에 가까운 노화연구의 대부분은  
먹는다는 것, 즉 얼마나 먹을까에 초점을 맞추고 있다.

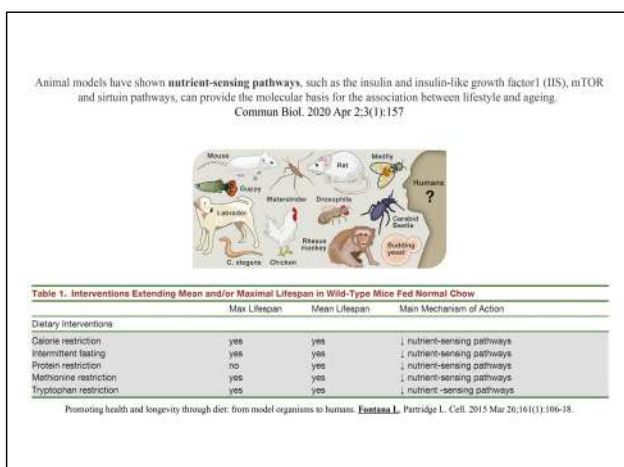
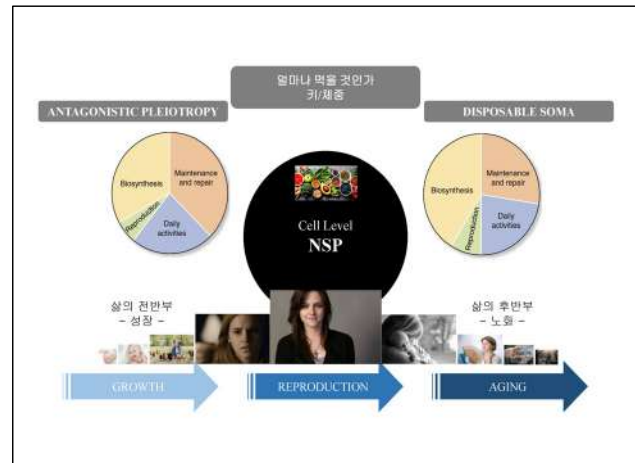
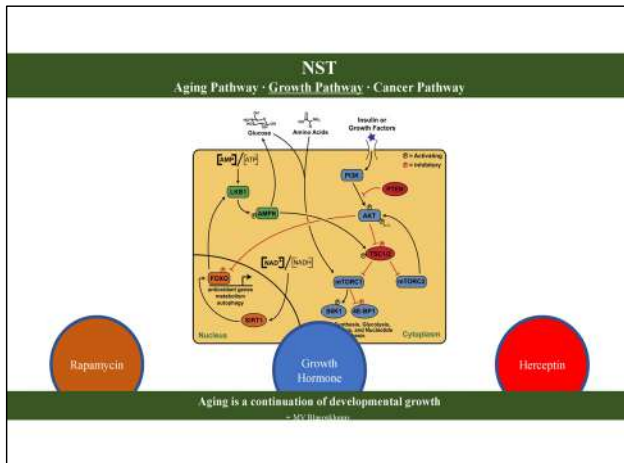


이후의 많은 연구들은  
백케어의 연구의 재현이거나 변형이었으며  
그 기전을 밝혀내기 위한 과정이었다.





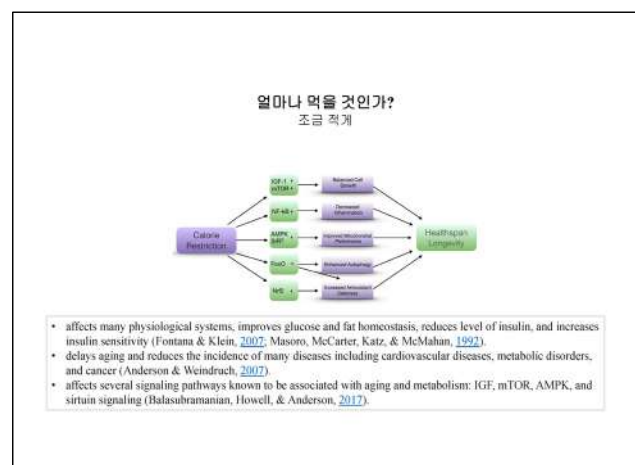




**Interventions to increase healthspan and/or lifespan**

Intervention	Target or process	Major effects
Rapamycin	mTOR	Geroprotective effects in mice and dogs. Human clinical trials with rapamycin and rapalogos are underway.
Senolytics	Cellular senescence	Protective against age-related disease in mice. Ongoing clinical trials in human diseases, including arthritis and eye degeneration.
NAD precursors	NAD metabolism	Geroprotective in animal models. Supplements available for human consumption, but no clinical trials have been reported yet.
Sirtuin-activating compounds	Sirtuins	Geroprotective in rodents and non-human primates but mixed results in humans. SIRT2104 may have effects beyond mitigating some age-associated conditions.
Metformin	Mitochondrial respiration	Associated with increased lifespan in human patients with diabetes and decrease of risk of cancer. TAME trial is planned to test effects in individuals without diabetes.
Exercise	Unknown	Associated with reduced risk of age-related disease, improved quality of life and increased lifespan in humans.
Calorie restriction	Several targets, including mTOR and sirtuins	Enhanced lifespan and protection from disease in worms, flies, mice, rats and non-human primates. Associated with decreased risk factors for disease in humans.

Nature. 2019 Jul;571(7764):183-192.



## 얼마나 적게 먹을 것인가? 15% ~ 60%

Caloric intake can be restricted in a **variety of ways**: percentage CR, macronutrient limitation, or exercise-induced restriction. Percentage of restriction of total calories spans from **mild (15% energy restriction)** to **severe (60% restriction)** (1-4) and can be supplemented with physical activity (1, 4, 5). Alternatives for CR include changes in the proportion of macronutrients, such as hyperprotein compared with hypoprotein diets (6), or ketogenic diets with a high lipid, low carbohydrate content (7-9).

In monkeys from the Wisconsin National Primate Research Center (WNPRC), **30% lifelong restriction** was sufficient to cause a 50% reduction in neoplastic events, gastrointestinal adenocarcinoma being the most common (25). Similarly, CR at a young age (30% restriction) reduced the incidence of cancer in monkeys from the National Institute of Aging (NIA), despite great genetic differences between them and the WNPRC monkeys. Overall, chronic CR has been demonstrated to be an effective dietary intervention for the treatment of many noncommunicable chronic diseases.

Adv Nutr. 2019 May 1;10(3):520-536.



## CRON-diet (Calorie Restriction with Optimal Nutrition)

In 1994, Brian M. Delaney, Lisa Walford, and Roy Walford, along with several others, founded CR Society International.

Biochem J  
(1991) 9, 261 - 1993 9, 261



<http://www.crsociety.org/>

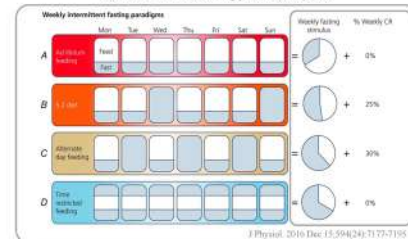
## Low-calorie diets

- 5:2 diet: an intermittent fasting diet popularized by Michael Mosley in 2012.
- Intermittent fasting: Cycling between non-fasting and fasting as a method of calorie restriction.
- Body for Life: A calorie-control diet, promoted as part of the 12-week *Body for Life* program.
- Cookie diet: A calorie control diet in which low-fat cookies are eaten to quell hunger, often in place of a meal.
- The Hacker's Diet: A calorie-control diet from *The Hacker's Diet* by John Walker. The book suggests that the key to reaching and maintaining the desired weight is understanding and carefully monitoring calories consumed and used.
- Nutrisystem diet: The dietary element of the weight-loss plan from Nutrisystem, Inc. Nutrisystem distributes low-calorie meals, with specific ratios of fats, proteins and carbohydrates.
- Weight Watchers diet: Foods are assigned point values; dieters can eat any food with a point value provided they stay within their daily point limit.

## PRACTICAL ALTERNATIVE TO CHRONIC CALORIC RESTRICTION

### Caloric Restriction - Intermittent Fasting

Intervals of intermeal fasting per circadian period



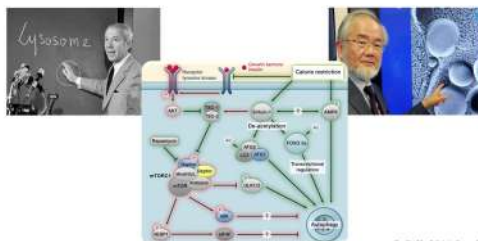
## Autophagy

(Cell "Cleaning System")

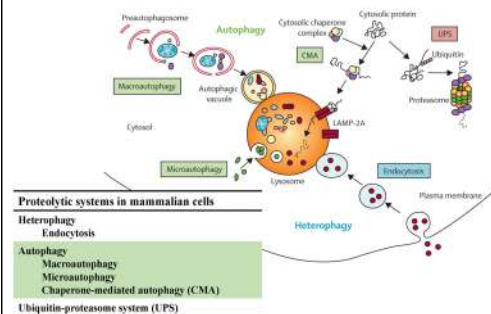
Intervals of intermeal fasting per circadian period and induce autophagy.

Belgian biologist **Christian de Duve**,  
Nobel Prize in Physiology or Medicine in 1974.

Japanese cell biologist **Yoshinori Ohsumi**,  
Nobel Prize in Physiology or Medicine in 2016.



G Cell. 2011 Sep 2;146(5):682-95



Autophagy and Neurodegeneration: When the **Cleaning Crew** goes on Strike.  
Martinez-Vicente M, Cuervo AM. Lancet Neurol. 2007 Apr;6(4):352-61.

**Autophagy** is the **major intracellular degradation system** by which **cytoplasmic materials** are delivered to and degraded in the **lysosome**.

The purpose of autophagy is not the simple elimination of materials, but instead, autophagy serves as a **dynamic recycling system** that produces **new building blocks** and **energy** for cellular renovation and homeostasis.

Autophagy's role in **metabolic adaptation**, **intracellular quality control**, and **renovation during development and differentiation**.

Cell. 2011 Nov 11;147(4):728-41

Approximately 1%–1.5% of cellular proteins are catabolized per hour by autophagy, even under nutrient-rich conditions in the liver.

Nevertheless, basal autophagy acts as the **quality-control machinery** for cytoplasmic components, and it is **crucial for homeostasis of various postmitotic cells**, such as neurons and hepatocytes.

Cell. 2011 Nov 11;147(4):728-41

While MA (macroautophagy) is the most immediate responder to starvation in many cells – with an activation peak at around 6 hours – CMA (chaperone-mediated autophagy) exhibits enhanced activity by 10 hr of starvation and reaches a plateau of maximal activation by 36 hr.

Am J Physiol. 1995 Nov;269(5 Pt 1):C1200-8, Eur J Biochem. 1995 Feb 1;227(3):792-800

Increasing evidence suggests that a **low-calorie diet** might be a **promising adjuvant therapeutic strategy** for slowing or preventing the pathogenesis and progression of AD through the **induction of autophagy**.



Yang Y, et al. Food Funct. 2020 Feb 26;11(2):1211-1224

**Table 1** Functional effects of diet in transgenic mouse models of AD

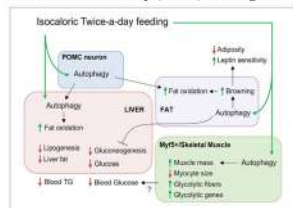
Intervention	Regimen	Initiation age (month)	Treatment duration	Mice	Changes behavior	In Validation assays	Changes pathological features	Ref
Low-caloric diet	30% CR	3	9-month	Tg2576	Not tested	-	Reduced amyloid load	12
Low-caloric diet	40% CR	3	17-month	3xTgAD	Improved cognitive performance	CF, MWM	Reduced amyloid load and pathogenesis	14
Low-caloric diet	30% CR	4	4-month	Forebrain-specific cDKO	Improved cognitive performance	NOR, CFC	Reduced pathogenesis	15
Low-caloric diet	Gradual reduction	4-5	3-month	Tg4510	Partially improved cognitive performance	CF, NOR, CFC	No changes in tau pathogenesis	16
Low-caloric diet	40% CR	3-4	6-week	J20	Not tested	-	Reduced amyloid load	14
Low-caloric diet	40% CR	2-3	15-week	APP/PS1	Not tested	-	Reduced amyloid load	14
High-fat diet	50% HF	3-4	5-6-month	Tg2576	Impaired cognitive performance	MWM	Promoted amyloid load	12

DKO, conditional double knockout of presenilin-1 and presenilin-2; CFC, contextual fear conditioning; CR, caloric restriction; HF, high fat; MWM, Morris water maze; NOR, novel object recognition; CF, open field.

Yang Y, et al. Food Funct. 2020 Feb 26;11(2):1211-1224

동일한 양을 먹어도 자가포식작용을 활성화 시키면 유사한 효과를 얻을 수 있다.

#### Isocaloric Twice-a-day (ITAD) Feeding Model

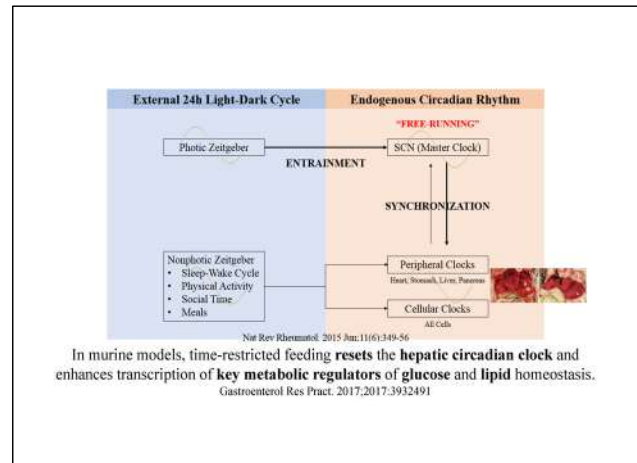
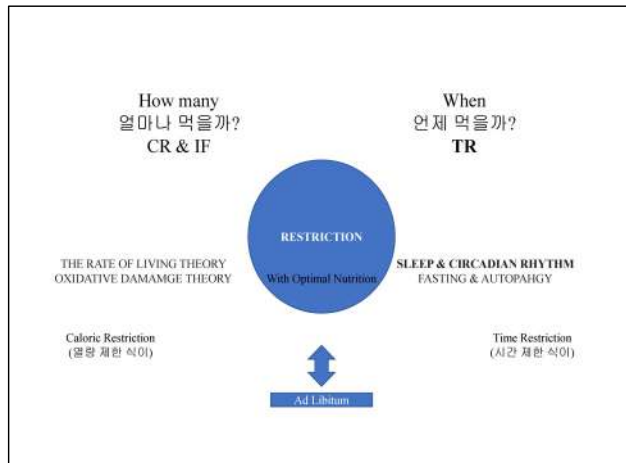


- Isocaloric twice-a-day (ITAD) feeding impacts autophagy in multiple tissues
- ITAD feeding promotes diverse metabolic benefits in multiple tissue systems
- ITAD feeding prevents age- and obesity-associated metabolic defects
- Tissue-specific autophagy contributes to distinct benefits of ITAD feeding

Cell Metab. 2017 Dec 5;26(6):856-871







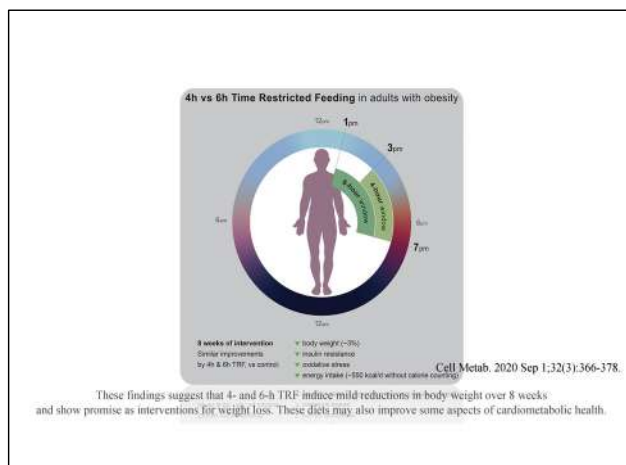
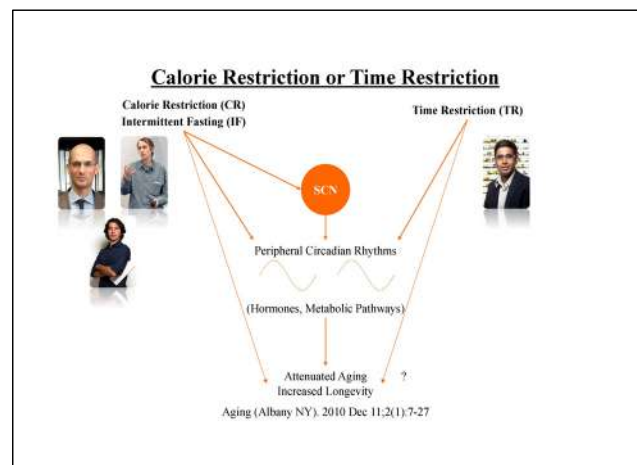
**Time-restricted feeding (TRF),**  
where **food access** is restricted to **8 hr during the active phase**,  
without changing the overall caloric intake or nutrient composition compared to ad libitum

**Circadian rhythms** have evolved and permit organisms to effectively respond to the predictable daily change in the light:dark cycle and the resultant rhythms in **food availability in nature**.

Whereas light is the dominant timing cue for the SCN oscillator, **time of food intake** affects the phase of the clocks in **peripheral tissues** (15), including liver, muscle, and adipose tissues.

**Three meals plus snacks daily** has become the **norm** during the past half-century, such that a majority of American children are accustomed to this eating pattern.

Proc Natl Acad Sci U S A. 2014 Nov 25;111(47):16647-53



먹는다는 것  
왕의 문제인지 양의 문제인지  
채식 - CR (1일 2식) - TR - TR+IF



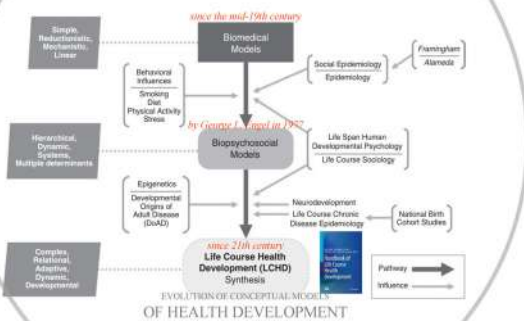
언제부터 적게 먹을 것인가?

Despite the well-known benefits of chronic CR, long-term energy restriction is not likely to be a feasible healthy lifestyle strategy in humans due to **poor sustained adherence**, and presents additional concerns if applied to **normal weight older adults**.  
J Physiol. 2016 Dec 15;594(24):7177-7195

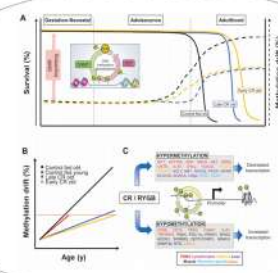


Notably, **early CR onset** may cause a **different and even an opposite effect** on physiological outcomes in animal models such as **body weight**. Furthermore, CR directly affects the DNA methylation/demethylation cycle, histone and protein modifiers like SIRT6, and miRNAs, to orchestrate the **adaptive and long-lasting response**, leading to increased lifespan and health span.  
Adv Nutr. 2019 May 1;10(3):520-536.

#### SENSITIVE PERIOD & DEVELOPMENTAL PLASTICITY



언제부터 적게 먹을 것인가?



Adv Nutr. 2019 May 1;10(3):520-536

The Effect of **Retarded Growth** upon the **Length of Life Span** and upon the **Ultimate Body Size**.  
McCay CM, Crowell MF, Maynard LA. J Nutr. 1935;10:63-79.



Switch in Use of CR  
from a focus on Development to Aging

Roy Lee Walford (1924-2004)

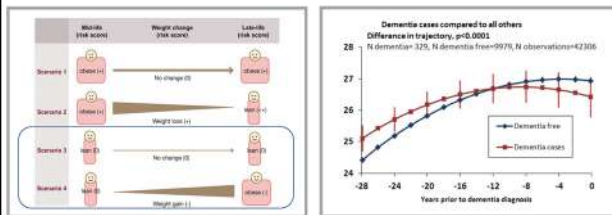
**Dietary Restriction in Mice Beginning at 1 Year of Age: Effect on Life-span and Spontaneous Cancer Incidence.**  
Weindruch R, Walford RL. Science. 1982 Mar 12;215(4538):1415-8.

Young, healthy individuals achieved 15% CR and 8 kg weight loss over 2 years  
Energy expenditure (24 hr and sleep) was reduced beyond weight loss.  
Oxidative stress was also reduced, supporting two long-standing theories of aging  
Cell Metab. 2018 Apr 3;27(4):805-815.e4.

	Ad Libitum Group (Control, n = 18)			Calorie Restriction Group (n = 34)		
	Baseline	ΔY1	ΔY2	Baseline	ΔY1	ΔY2
Age (years)	39.9 ± 5.4	—	—	40.2 ± 5.7	—	—
Weight (kg)	71.0 ± 8.3	0.8 ± 0.6	1.8 ± 0.6	71.9 ± 8.7	-5.4 ± 0.4*	-8.7 ± 0.4*
BMI (kg/m <sup>2</sup> )	25.5 ± 1.6	0.2 ± 0.2	0.5 ± 0.2	25.7 ± 1.5	-1.4 ± 0.2*	-3.2 ± 0.2*
Body fat (%)	30.9 ± 5.5	0.2 ± 0.4	1.4 ± 0.4*	34.2 ± 6.6	-5.8 ± 0.3*	-4.5 ± 0.3*
Fat mass (kg)	23.4 ± 4.0	0.4 ± 0.4	1.4 ± 0.4*	24.7 ± 5.0	-8.7 ± 0.3*	-8.9 ± 0.3*
Fat-free mass (kg)	48.5 ± 8.1	1.3 ± 0.3	-0.1 ± 0.3	47.8 ± 8.7	-2.9 ± 0.2*	-1.1 ± 0.2*
Energy requirement (kcal/day)	1782 ± 242	—	—	1747 ± 248	—	—
24hEE (kcal/day)	1893 ± 250	-90 ± 28*	-81 ± 28*	1834 ± 254	-209 ± 21*	-186 ± 21*
SleepEE (kcal/day)	1523 ± 219	13 ± 25	-6 ± 25	1500 ± 197	-170 ± 18*	-180 ± 18*
TEEE (kcal/day)	121.4 ± 26.7	-5.1 ± 3.9*	-13.3 ± 3.6*	115.9 ± 24.4	-23.5 ± 2.7*	-20.9 ± 2.7*
T4 (μg/dL)	7.6 ± 0.9	0.01 ± 0.02	0.14 ± 0.02*	7.1 ± 1.5	-0.29 ± 0.17*	-0.73 ± 0.17*
TSH (μU/mL)	1.63 ± 1.25	-0.04 ± 0.11	-0.26 ± 0.11*	1.31 ± 0.63	-0.15 ± 0.08*	-0.16 ± 0.08*
Lepelin (pg/mL)	183.6 ± 146.0	-0.52 ± 1.6	-0.63 ± 1.8	180.9 ± 171.5	-11.4 ± 1.2*	-9.2 ± 1.2*
Insulin (μU/mL)	6.5	0.7 ± 0.5	0.5 ± 0.5	5.1 ± 2.4	-1.5 ± 0.4*	0.2 ± 0.4
2,3-bisnor-PP2C-40 (pg/mg CR)	2.17 ± 1.03	-0.09 ± 0.17	-0.07 ± 0.17	2.16 ± 0.87	-0.42 ± 0.32*	-0.49 ± 0.32*

Baseline data are presented as means ± SD. Change from baseline data is the adjusted LS mean ± SE from the mixed linear models, which includes the baseline value as a covariate. BMI, body mass index; 24hEE, 24-hr energy expenditure; SleepEE, energy expenditure during sleep (02:00-05:00 h); T4, thyroxine; TSH, thyroid-stimulating hormone.  
\*Denotes significant within-group change from baseline (p < 0.05).

### 노년기 체중감소는 치매의 위험인자



이덕희 / Obesity Reviews 18, 129-139, 2017

### PERSPECTIVES ON HEALTHCARE REFORM

#### LIFESTYLE MEDICINE: TREATING THE CAUSES OF DISEASE

Mark A. Hyman, MD; Dean Ornish, MD; Michael Roizen, MD

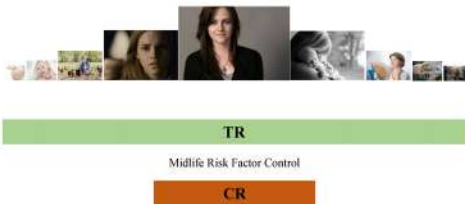
Mark A. Hyman, MD, is a contributing editor of *Alternative Therapies in Health and Medicine*. He recently launched the Functional Medicine Foundation, based in New York, New York, to promote awareness of, fund research on, and educate the public about functional medicine. Dean Ornish, MD, is clinical professor of medicine at the University of California, San Francisco. Michael Roizen, MD, is chief wellness officer and chair of the Wellness Institute at Cleveland Clinic, Ohio. (*Alternative Health Med.* 2009;15(6):12-14.)

education or practice. It should be the foundation of our health-care system.

For example, the recent "EPIC" study published in the *Archives of Internal Medicine* studied 23,000 people's adherence to 4 simple behaviors (not smoking, exercising 3.5 hours a week, eating a healthy diet [fruits, vegetables, beans, whole grains, nuts, seeds, and limited amounts of meat], and maintaining a healthy weight [BMI <30]). In those adhering to these behaviors, 93% of diabetes, 81% of heart attacks, 50% of strokes, and 36% of all cancers were prevented.

The European Prospective Investigation into Cancer and Nutrition (EPIC) study is one of the largest cohort studies in the world, with more than half a million (521,000) participants recruited across 10 European countries and followed for almost 15 years.

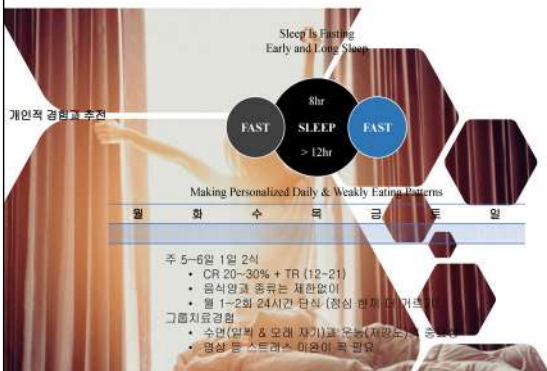
### 언제, 얼마나 먹을 것인가? Life Course Approach



### Scientific + Empirical Recommendation

#### Protected Environment

- CR with Optimal Nutrition (Macronutrient Restriction without Micronutrient Deficiency)
  - CR with Ideal BW
  - Slow and Cold Life
- TR
  - Food consumed for < 10h per day
  - Skipping breakfast or dinner
- No snacks esp. night snack
  - No healthy late-night snacks
- Sleep as most Effective & Efficient Fasting
  - Total Sleep Time + Fasting Time at Day = Total Fasting Time
- Mild to Moderate Exercise
- Stress Management and Relaxation
- Slow for Metabolic Adaptation



### 개인적 경험과 추천

가장 이상적인 제한 식이 방법을 적용할 수 있는 환자군  
(요양병원 입원 환자 중 경관유동식 환자)  
600 ~ 1200칼로리  
Without Malnutrition & Chronic Inflammation

