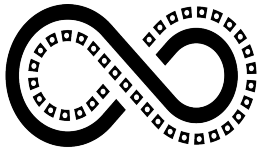


NORN GROUP

Longevity Interventions in Humans

Presented by Tara Mei on 05/22/2022

Discussion Summary

Paper(s): No single paper

1. Caloric Restriction
2. Metformin and other drugs
3. Parabiosis (?)

1. Caloric Restriction

CALERIE

Comprehensive **A**ssessment of **L**ong term **E**ffects of **R**educing **I**ntake of **E**nergy

What are the effects of **caloric restriction** on cardiovascular morbidity and mortality in humans?

Phase 1

Phase 2

25% CR below baseline over 2 years

SUBJECTS:

n=218

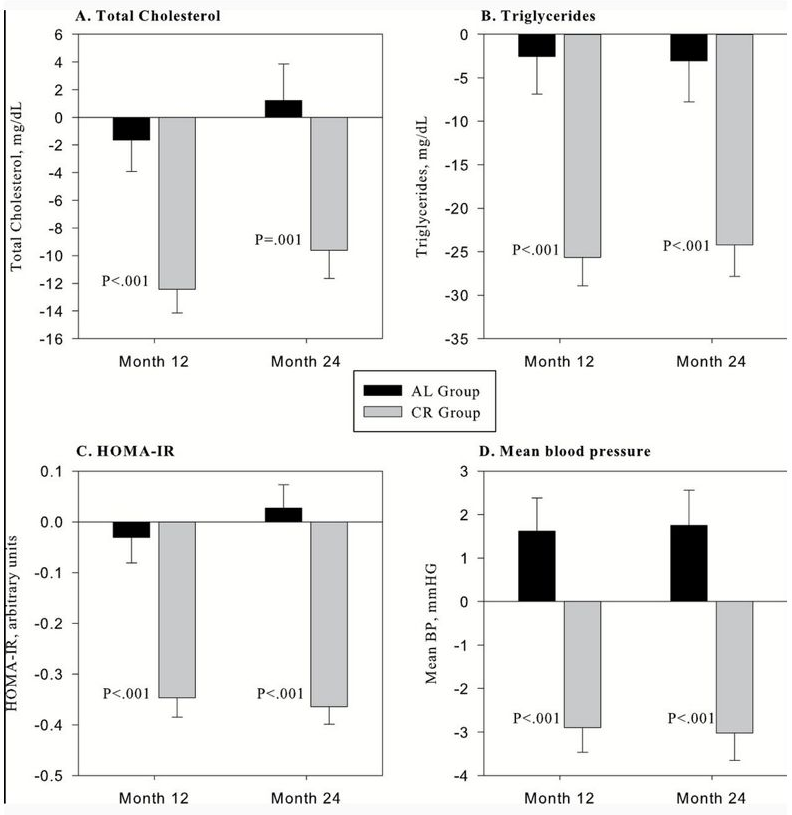
21-50 y.o. **men** (30%) + 21-47 y.o. **women** (70%)

BMI 22.0-28.0

No specific physical activity required

Everyone gets a multivitamin + mineral + calcium supplement

So what happened?



Decreased:

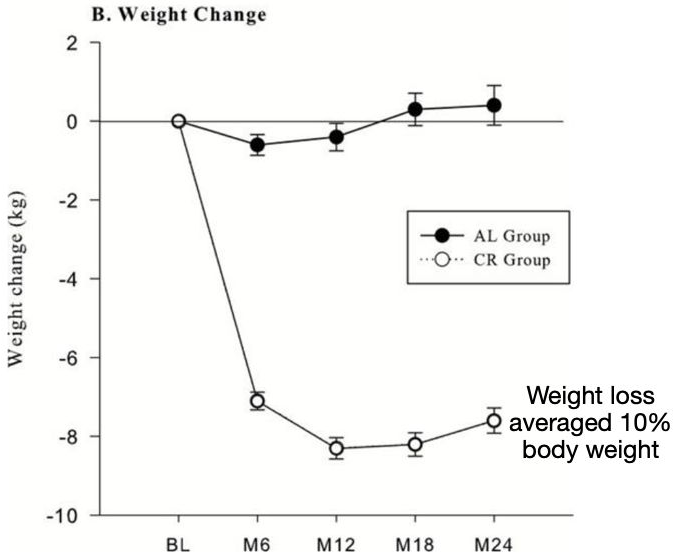
Total cholesterol

Triglycerides

Insulin resistance

Mean blood pressure

So what happened?



Weight loss, mostly due to body fat loss

Table 1.

Baseline study subject characteristics (Mean (SD)[*])

	Ad Libitum (n=75; 22M)	Calorie Restriction (n=143; 44M)
Race		
White	57 (76.0%)	111 (77.6%)
African American	11 (14.7%)	15 (10.5%)
Other	7 (9.3%)	17 (11.9%)
Age, y	37.9 (6.94)	38.0 (7.34)
Height, m	168.4 (8.31)	168.9 (8.60)
Baseline Weight, kg	71.5 (8.65)	72.0 (9.49)
Baseline BMI, kg/m^2	25.1 (1.64)	25.2 (1.78)
Body Fat, %	33.6 (6.57)	32.9 (6.07)
Fat free mass, kg	47.6 (8.61)	48.5 (9.21)
Energy and macronutrient intake		
Energy intake, kcal/d	2390 (384.8)	2467 (405.6)
Protein, g/kg/d	1.2 (0.04)	1.2 (0.02)
Protein, % of energy	17.2 (3.48)	16.6 (3.04)
Fat, % of energy	34.7 (5.12)	33.5 (4.93)
Carbohydrates, % of energy	45.1 (6.33)	46.8 (6.48)

Overweight (BMI): ≥ 25

Overweight (Body Fat Percentage):

≥ 32% (women)
≥ 26% (men)

Adverse effects?

No effect on depression, verbal memory, sexual function, perceived hunger, eating disorder pathology

BUT

Decrease in lumbar spine + femoral neck bone mineral density (data not shown) in CR

Increase in reproductive disorders + skin disorders in CR

study.

	Ad libitum		Caloric Restricted					
	Overall (*n*=75)		Overall (*n*=143)		NormalWeight[1] (*n*=68)		Overweight[1] (*n*=75)	
System Organ Class	Pct. Pts[2]	No. Events[3]	Pct. Pts[2]	No. Events[3]	Pct. Pts[2]	No. Events[3]	Pct. Pts[2]	No. Events[3]
Overall	96.0%	1,337	95.1%	1,995	97.1%	1164	93.3%	831
Gastrointestinal Disorders	56.0%	168	51.7%	289	60.3%	137	44.0%	152
General Disorders	53.3%	171	48.3%	188	52.9%	109	44.0%	79
Immune System Disorders	21.3%	36	16.1%	47	17.6%	26	14.7%	21
Infections & Infestations	70.7%	156	62.2%	239	67.6%	133	57.3%	106
Injury, Poisoning & Procedural Complications	44.0%	65	28.7%	67	30.9%	33	26.7%	34
Musculoskeletal & Connective Tissue Disorders	57.3%	206	52.4%	224	63.2%	137	42.7%	87
Nervous System Disorders	61.3%	298	58.7%	508	69.1%	347	49.3%	161
Psychiatric Disorders	20.0%	32	16.8%	49	17.6%	25	16.0%	24
Reproductive Disorders	14.7%	46	24.5%	133	36.8%	77	13.3%	56
Respiratory, Thoracic & Mediastinal Disorders	46.7%	108	41.3%	178	44.1%	97	38.7%	81
Skin & Subcutaneous Tissue Disorders	10.7%	16	15.4%	30	19.1%	18	12.0%	12

[1] Normal weight: 22.0 ≤ BMI < 25.0 kg/m²; Overweight: 25.0 ≤ BMI < 28.0 kg/m²
[2] Percent of participants who experienced at least one adverse event in that system organ class at least once
[3] Total number of AEs in that system organ class including multiple events from the same participant
AL = *Ad libitum* treatment group; BMI = body mass index; Pct = percent; Pts = participants

Open questions

Do the effects of CR come from lower calorie consumption, or the weight loss that accompanies lower calorie consumption?

Would the changes in cholesterol, BP, etc be “good” for already healthy individuals?

Study didn’t achieve CR target (11.7% vs 25%). What would happen if it did?

How do you choose which adverse effects to look for?

2. Metformin

Small molecule drug to treat Type 2 diabetes

Safe, orally-administered, cheap, widely available

Already used for other stuff

ELSEVIER

Ageing Research Reviews
Volume 40, November 2017, Pages 31-44

Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: A systematic review and meta-analysis

Jared M. Campbell [a, b], Susan M. Bellman [a], Matthew D. Stephenson [a], Karolina Lisy. [c]

Diabetics on **metformin**:

Lower mortality than non-diabetics + other diabetics

Lower colorectal, **breast**, **lung cancer** than other diabetics

Less cardiovascular disease than other diabetics

Metformin Use Associated with Reduced Risk of Dementia in Patients with Diabetes: A Systematic Review and Meta-Analysis

Jared M Campbell [1] [2], Matthew D Stephenson [1], Barbora de Courten [3], Ian Chapman [4], Susan M Bellman [1], Edoardo Aromataris [1]

Affiliations + expand

PMID: 30149446 PMCID: PMC6218120 DOI: 10.3233/JAD-180263

Free PMC article

Metformin-inclusive therapy reduces the risk of stroke in patients with diabetes: a 4-year follow-up study

Yuan-Yang Cheng [1], Hsin-Bang Leu [2], Tzeng-Ji Chen [3], Chen-Ling Chen [4], Chia-Hua Kuo [5], Shin-Da Lee [6], Chung-Lan Kao [7]

Affiliations + expand

PMID: 24119365 DOI: 10.1016/j.jstrokecerebrovasdis.2013.09.001

Assumptions

1. Mortality + disease changes in diabetics taking metformin can be **generalised** to the non-diabetic population taking metformin
2. Mortality + disease changes in diabetics taking metformin/other drugs are **independent** of those drugs' effect on the diabetes itself

Potential confounding factors

1. Patients taking metformin tend to be younger + have shorter disease durations
2. Follow-up periods often <5 years

NIH U.S. National Library of Medicine

ClinicalTrials.gov

Home > Search Results > Study Record Detail

Metformin in Longevity Study (MILES). (MILES)

14 ~70 y.o. subjects with impaired glucose tolerance

1700mg/day metformin for 6 weeks

Participants are their own controls (6 weeks metformin, 6 weeks placebo)

Does metformin cause physiological and transcriptomic changes in muscle and adipose tissue?

6-year clinical trials

3,000 individuals

Age range 65-79

Does metformin delay age-related diseases?

Other stuff

Which FDA-approved drugs might be repurposed as **gerotherapeutics**?

Points system

PRECLINICAL

- effects on aging hallmarks

-improved rodent life/ healthspan

- “a good study”

- non-ITP rodent lifespan studies

CLINICAL

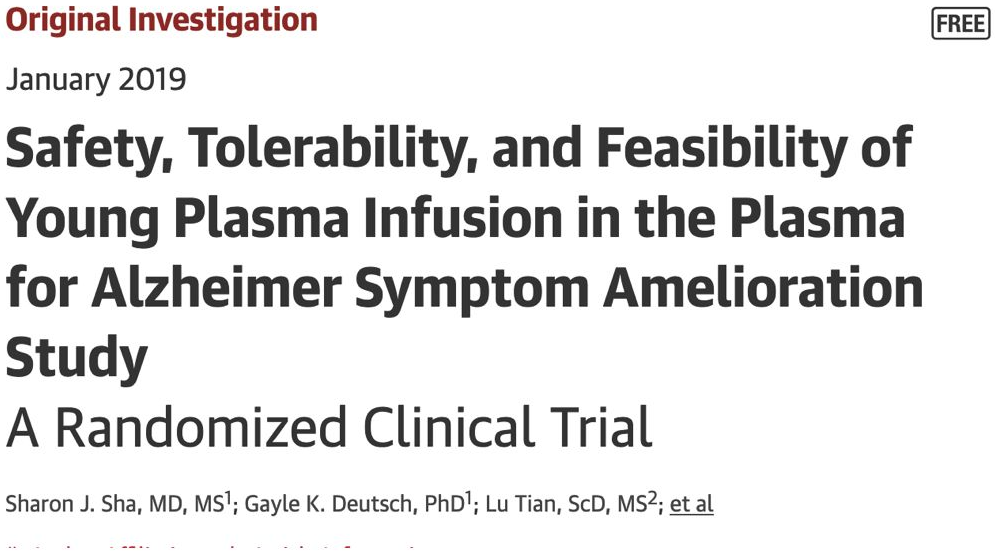
- effects on off-target diseases

- interventional studies > observational studies

Gerotherapeutics	Hallmarks of aging	Preclinical healthspan	Preclinical lifespan	Human healthspan	Human mortality	Score (out of 12)
SGLT-2 inhibitors	2	2	2	3	3	12
Metformin	2	2	1	3	3	11
Acarbose	2	2	2	3	0 (Not assessed)	9
Rapamycin/rapalogs	2	2	2	3*	0 (Not assessed)	9
Methylene blue	2	2	2	3*	0 (Not assessed)	9
ACEi/ARB	2	2	1	3	0	8
Dasatinib + (quercetin)	2	2	1	1	0 (Not assessed)	6
Aspirin	2	2	2	0 (Not assessed)	0 (Not assessed)	6
N-acetyl cysteine	1	2	2	0 (Not assessed)	0 (Not assessed)	5

Combinations of drugs?

3. Parabiosis (?)



Original Investigation

FREE

January 2019

Safety, Tolerability, and Feasibility of Young Plasma Infusion in the Plasma for Alzheimer Symptom Amelioration Study

A Randomized Clinical Trial

Sharon J. Sha, MD, MS[1]; Gayle K. Deutsch, PhD[1]; Lu Tian, ScD, MS[2]; et al

Is young plasma safe, feasible, and tolerable in patients with mild-moderate Alzheimer's disease dementia?

4 weekly infusions of 250ml male plasma (18-30 y.o.) or 250ml saline

SUBJECTS:

n=18

50-90 y.o. men and women

Study partner who knows patient well attends all visits with patients

So what happened?

Seems feasible!

- No serious adverse effects

- Mild/moderate effects: hypertension, dizziness, headache

…but can’t determine effect yet

- n too small, treatment duration too short

- No changes observed except in functional abilities