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Interventions Tend To Combine Synergistically To Extend Life Span A Little, But The Typical Improvement Is Statistically Insignificant

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1 Abstract

I used the results of previous life span experiments to test the statistical hypothesis that interventions tend to work as well individually as in combination. I included previous experimental results reporting the risk of people dying from any cause, and changes to the mean and maximum life spans of lab animals, Combinations trended toward extending life spans more in all three, but the improvements were statistically insignificant.

2 Introduction

Aging isn't for sissies.

Getting old means wrinkles, heart disease, cancer, and ultimately saying good bye to loved ones at the cemetery[1].

Scientists have diligently tried to fight aging thousands of ways, including apple[1], going to church[2], exercise[3], and even candy[4][2]

They've uncovered chemical pathways associated with aging. These include calories eaten[5], antioxidants[6], insulin[7] and mTOR[8][3].

It's possible these chemical pathways might work together synergistically[9].

On the other hand, it's also possible they might inhibit each other, or even be toxic[10].

I combed through the published results of thousands of life span experiments, and statistically tested whether there tends to be a difference between how much single and combined interventions affect life span.

[1] Other than that, Mrs. Lincoln, how did you like the play?

[2] My big spread sheet of life span experiments currently summarizes 12,102 experiments that tested the effects of 3,578 interventions.

[3] "mTOR" is an acronym for "mammalian Target Of Rapamycin".

3 Materials and Methods

The data came from my big spread sheet of life span experiments[4]

I distinguished between single interventions and their combinations by searching its "intervention" and "dose" columns for words like "and", "mix", "complex", "(M)editer(anean diet)", "respectively", etc... The remaining experiments were assumed to test single interventions. I further categorized the experiments by the type of life span they measured:

- mean life spans from animal experiments,
- maximum life spans from animal experiments, and
- the relative risk of dying from any cause in human experiments.

These three types of life spans are defined on page 11.

To determine which statistical method to use to compare the results of single and combined interventions, I checked whether the later were "normally distributed" with the Anderson-Darling test.

It said they're not[5].

Therefore, I used the Wilcoxon Mann-Whitney non-parametric method to test if there was a statistically significant difference between the effect of single and combined interventions on all three life spans reported[6].

[4] The spread sheet is described on page 9.
[5] Detailed results of the normality tests are on page 10
[6] Version 1.12.0-1 of the free and open source spread sheet program called "gnumeric" was used for all statistical calculations.

4 Results

At first glance, combinations of interventions seemed to be better at extending all three measures of life span. However, the advantages were all statistically insignificant[7] .

Change in the mean life span of animals

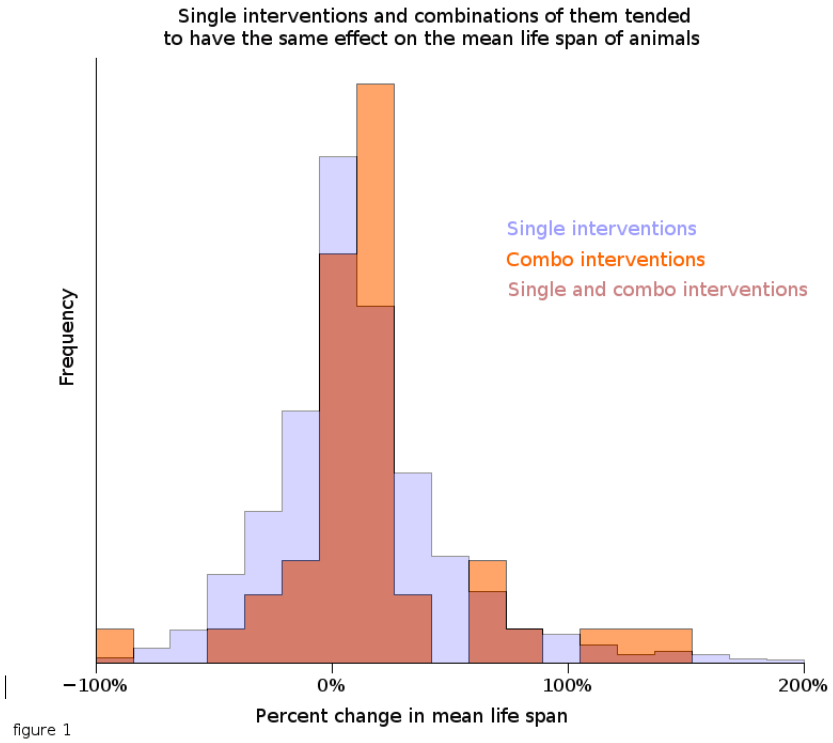

figure 1

	single intervention animal mean life spans	combo animal mean life spans	Total
Wilcoxon-Mann-Whitney Test			
N	8493	45	8538
U	169217.5	212967.5	382185
Ties	125446		
Statistic	214002.5		
U-Statistic	169217.5		
p-Value	0.185		
Descriptive Statistics			
Mean	16%	19%	
Standard Error	1%	6%	
Median	7%	13%	
Mode	0%	21%	
Standard Deviation	60%	40%	
Sample Variance	36%	16%	
Kurtosis	11661%	299%	
Skewness	750%	104%	
Range	1471%	225%	
Minimum	−100%	−87%	
Maximum	1371%	138%	
Sum	132615%	833%	
Count	8493	45	

figure 2

[7] As they say in Latin, "Proximo sed nolo fumigare." (Close, but no cigar.)

Change in the maximum life span of animals

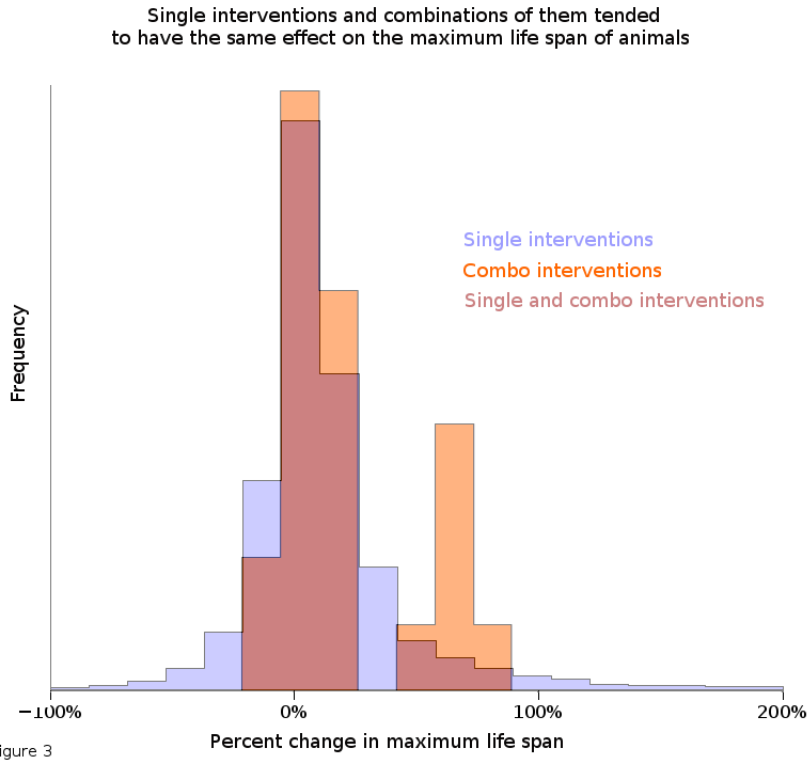

figure 3

	single intervention animal max life spans	*combo animal max life spans*	*Total*
Wilcoxon-Mann-Whitney Test			
Rank-Sum	4722762.5	43565.5	4766328
N	3064	23	3087
U	27182.5	43289.5	70472
Ties	76944		
Statistic	43565.5		
U-Statistic	27182.5		
p-Value	0.059		
Descriptive Statistics			
Mean	14%	21%	
Standard Error	1%	6%	
Median	6%	11%	
Mode	0%	0%	
Standard Deviation	48%	27%	
Sample Variance	23%	7%	
Kurtosis	36066%	−35%	
Skewness	1372%	96%	
Range	1600%	92%	
Minimum	−100%	−12%	
Maximum	1500%	80%	
Sum	41564%	492%	
Count	3064	23	

figure 4

Hazard ratio of people dying from any cause

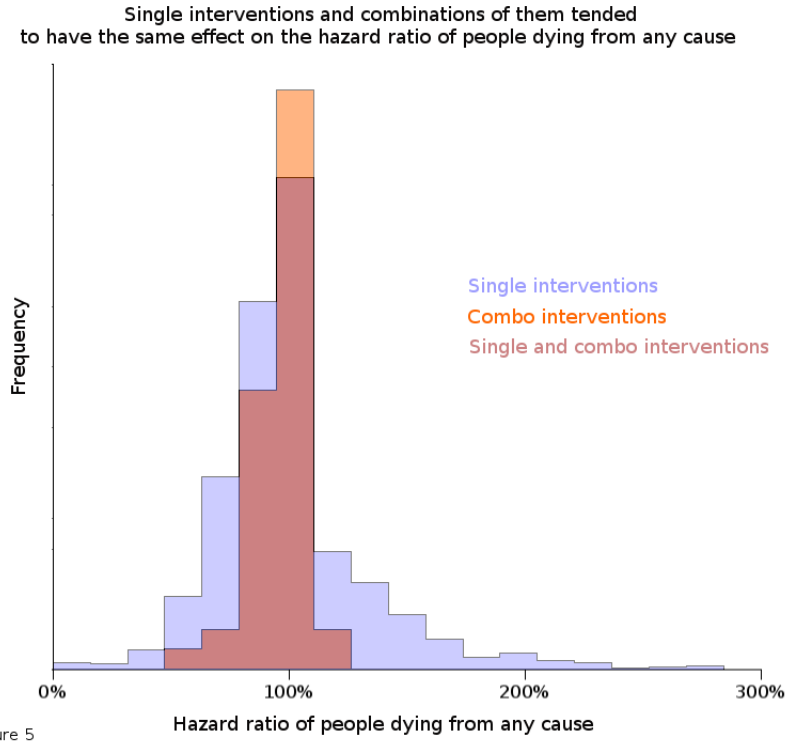

figure 5

	single intervention human hazard	*combo human hazard ratios*	*Total*
Wilcoxon-Mann-Whitney Test			
Rank-Sum	1366808.5	41872.5	1408681
N	1630	48	1678
U	37543.5	40696.5	78240
Ties	28998		
Statistic	41872.5		
U-Statistic	37543.5		
p-Value	0.634		
Descriptive Statistics			
Mean	106%	97%	
Standard E	1%	2%	
Median	97%	100%	
Mode	100%	102%	
Standard D	56%	11%	
Sample Va	32%	1%	
Kurtosis	5600%	149%	
Skewness	575%	−115%	
Range	972%	49%	
Minimum	0%	63%	
Maximum	972%	112%	
Sum	172397%	4633%	
Count	1630	48	

figure 6

5 Discussion

It's (a little) interesting that combined interventions trended toward working better for all three measures of life span.

Maybe this is evidence for the old adage to eat a balanced diet.

Certain interventions might be more synergistic than others.

It might be interesting to compare the effectiveness of individual interventions to combinations of the same interventions.

If a combination has actually been tested, those specific results should be more useful than the generalization in this paper.

Since the number of interventions doesn't appear to predict how much life is extended, maybe the best strategy is to consider interventions on a case by case basis.

My big spread sheet of life span experiments can be searched for interventions that performed well, and whose results have been duplicated.

6 Conclusion

Single and combined interventions tend to have similar effects on life span.

References

1. Whole apple extracts increase lifespan, healthspan and resistance to stress in Caenorhabditis elegans, Journal of Functional Foods, Available online 9 May 2013, Elena M. Vayndorf et al.

2. Journal of the American Board of Family Medicine, Religious Attendance: More Cost-Effective Than Lipitor? 03/07/2006, Daniel E. Hall, MD, Mdiv

3. sInt J Obes (Lond). 2005 Aug;29(8):894-902, The effects of physical activity and body mass index on cardiovascular, cancer and all-cause mortality among 47 212 middle-aged Finnish men and women, Hu G, Tuomilehto J, Silventoinen K, Barengo NC, Peltonen M, Jousilahti P.

4. Life is sweet: candy consumption and longevity, I-Min Lee, Ralph S Paffenbarger Jr, BMJ VOLUME 317 19-26 DECEMBER 1998

5. Revista Clinica Espan˜ola 15 Octobre 195 pp. 25-27.

6. N Engl J Med 1996 May 2;334(18):1156-62, Dietary antioxidant vitamins and death from coronary heart disease in postmenopausal women. Kushi LH, Folsom AR, Prineas RJ, Mink PJ, Wu Y, Bostick RM. Division of Epidemiology, University of Minnesota School of Public Health, Minneapolis 55454-1015, USA.

7. Evidence for lifespan extension and delayed age-related biomarkers in insulin receptor substrate 1 null mice. Selman C, Lingard S, Choudhury AI, Batterham RL, Claret M, Clements M, Ramadani F, Okkenhaug K, Schuster E, Blanc E, Piper MD, Al-Qassab H, Speakman JR, Carmignac D, Robinson IC, Thornton JM, Gems D, Partridge L, Withers DJ.

8. Cell Cycle. 2011 Dec 15;10(24), Rapamycin increases lifespan and inhibits spontaneous tumorigenesis in inbred female mice, Anisimov VN, Zabezhinski MA, Popovich IG, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Rosenfeld SV, Blagosklonny MV.

9. Stem Cell 100, http://www.stemcell100.com/

10. Stephen Spindler, Eurosymposium on Healthy Aging, Brussels on December 12th, 2012, Life Extension Mix.

7 Specifications of Kingsley's Big Spread Sheet of Life Span Experiments

Whenever scientists test an intervention to see if it effects life span, I try to summarize the results in a big computer spread sheet.

As of August 17th, 2013, a tiny part of it looked like...

A small part of Kingsley's big spread sheet of life span experiments

	A	B	C	D	E	F	G	H	I	J	K	L	M
1	Species	Sub species and conditions	Gender	Intervention	Dose	Age At Start Of Intervention or when tested	Change in Mean or Median Life Span	Change in Maximum Life Span	Unspecified "Change in Life Span"	Relative risk or hazard ratio of dying from any cause	Have copy of paper	year	citation
7075	mouse	swiss albino	male (m	levodopa	1 mg/g of ch	4-5 weeks of a	6%				y	1974	Proc Natl
7076	mouse	swiss albino	male (m	levodopa	40 mg/g of c	4-5 weeks of a	>13%				y	1974	Proc Natl
7077	mouse	swiss albino		levodopa	1 mg/g chow	4-5 weeks of a	7%	−14%			y	1977	Cotzias G
7078	mouse	swiss albino		levodopa	20 mg/g cho	4-5 weeks of a	10%	12%			y	1977	Cotzias G
7079	mouse	swiss albino		levodopa	40 mg/g cho	4-5 weeks of a	43%	12%			y	1977	Cotzias G
7080	mouse	swiss albino		levodopa	40 mg/g cho	4-5 weeks of a	51%				y	1977	Cotzias G
7081	mouse	swiss albino	male	levodopa	40 mg/g chow	started at 4 to	55%				y	1981	Papavasili
7082	nematod	Caenorhabditis elegar		L-glucose	0.02		19%	0%			y	2009	Cell Metal
7083	fruit fly			l-gulonolactone	800 mM starting at 1 day of		−40%	−37%			y	1991	Ascorbic
7084	fruit fly			l-gulonolactone	80 mM starting at 1 day of a		−9%	−9%			y	1991	Ascorbic
7085	fruit fly			l-gulonolactone	8 mM starting at 1 day of ag		−4%	−9%			y	1991	Ascorbic
7086	fruit fly	diet restricted		l-histidine	.21 g/l		0%					2009	Nature. 2
7087	human	Taiwanese	male	libido						81%		2007	Int J Epide
7088	fruit fly	Oregon-R		licorice extract	100 mg		40%	0%				2005	Doug Skr
7089	fruit fly	Oregon-R		licorice extract	200 mg		25%	0%				2005	Doug Skr
7090	mouse	C57BL/6 x C	male	Life Extension Mix	12.5g/kg diet		−9%	−12%				2012	Stephen
7091	human	Swedish	75-84 ye	lifestyle behaviors associ	lowest risk	75	+6.1 years					2012	D. Rizzuto

figure 7

life span experiments summarized	12,102*
species	61*
interventions tested	3,578*
percent changes in mean or median life span reported	8,738
percent changes in maximum life span reported	3,247
relative risks and hazard ratios of dying from any cause reported	1,760
reports summarized	2,254*

"*" = unique values

price $US 1,000,000

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8 Normality tests

Anderson-Darling Test	combo animal mean life spans	combo animal max life spans	combo human hazard ratios
Alpha	0.05	0.05	0.05
p-Value	2.20376344954231E−07	0.00049663436214	0.00846843062229
Statistic	2.93963212863608	1.56718149735629	1.06607977920636
N	45	23	48
Conclusion	Not normal	Not normal	Not normal

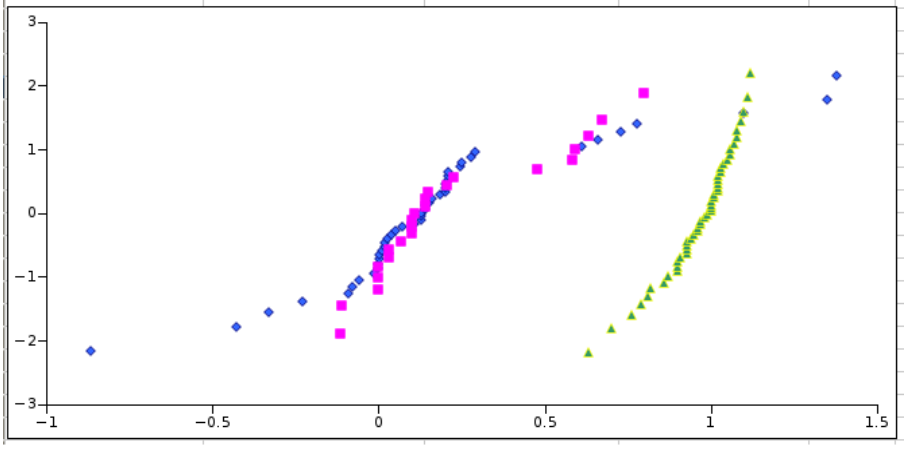

figure 8

9 Definitions

1. Percent change in the average, mean or median life span

   These are routinely reported for animal experiments. The average life span is how long the average animal lived. Mathematicians call it the "mean". A related measure is the "median" life span, which is how long half the animals lived. The percent change can be calculated by

   $$\frac{average\,life\,span\,of\,animals\,given\,an\,intervention}{average\,life\,span\,of\,animals\,not\,given\,the\,intervention} - 1$$

   Bigger increases in the average life span are better. A change of "0%" would mean the intervention had no effect. 100% would indicate the intervention doubled the average life span.

2. Percent change in maximum life span

   Maximum life span is also reported for animal experiments. It's how long the oldest of the old lived. It might be the oldest age reached by any lab animal, or the average age that the last few died at[8]. The percent change can be calculated by

   $$\frac{maximum\,life\,span\,of\,animals\,given\,an\,intervention}{maximum\,life\,span\,of\,animals\,not\,given\,the\,intervention} - 1$$

   Bigger increases in maximum life span are better. A change of "0%" means the intervention had no effect. 100% would indicate the intervention doubled the maximum life span.

3. Relative risk, odds ratio or hazard ratio of dying from any cause.

   These are used for human studies. They measure how likely it is that people died in a given time period, which is often a few years around age 60. 60 years is closer to the average human lifespan than the maximum, so it seems to me to be comparable to the mean animal life span experiments described above. Because these experiments are quicker than the mean and maximum life span experiments described above, they're more economical for long lived species like people. The relative risk of dying from any cause can be calculated by

   $$\frac{\frac{the\,number\,of\,people\,who\,were\,given\,the\,intervention\,and\,died}{the\,total\,number\,of\,people\,given\,the\,intervention}}{\frac{the\,number\,of\,people\,who\,were\,not\,given\,the\,intervention\,and\,died}{the\,total\,number\,of\,people\,given\,the\,intervention}}$$

   Lower relative risks are better. A relative risk of 1 means the intervention had no effect. 95% would mean people lived a little longer.

[8] For example, the maximum life span might be when the last 5% died.