Vitamin C and infections.

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Dose-response analysis of the Karlowski (1975) trial

The main publication of Karlowski (1975) was in JAMA:
https://www.ncbi.nlm.nih.gov/pubmed/163386
The SE values for the four groups were published in a parallel publication (Table 1):
https://www.ncbi.nlm.nih.gov/pubmed/1106302
https://doi.org/10.1111/j.1749-6632.1975.tb29309.x

vitamin C g/day	Group	Karlowski (1975)	Effect in %	No of colds	SE	Var	Weight for linear regression Inverse Var
0	#0	7.14	0.00%	65	0.46	0.21	4.726
3	#1	6.46	-9.52%	56	0.39	0.15	6.575
3	#2	6.71	-6.02%	52	0.53	0.28	3.560
6	#3	5.92	-17.09%	76	0.40	0.16	6.250

Calculation of dose response using the inverse variance weight:
Change indicates the effect of vitamin C in percentages.

```
> Karlowski
    Change InvVar Dose vitC
1   0.000  4.726    0    0
2  -9.524  6.575    3    1
3  -6.022  3.560    3    1
4 -17.087  6.250    6    1

> Karlowski0  <- lm(Karlowski$Change ~ Karlowski$Dose, weights = Karlowski$InvVar)
> summary(Karlowski0)

Coefficients:
                 Estimate Std. Error t value Pr(>|t|)
(Intercept)      0.1379     1.4812   0.093   0.9343
Karlowski$Dose  -2.8534     0.3827  -7.456   0.0175 *

Residual standard error: 3.785 on 2 degrees of freedom
Multiple R-squared:  0.9653,    Adjusted R-squared:  0.9479
F-statistic: 55.59 on 1 and 2 DF,  p-value: 0.01752
```

Comparison of **uniform** vitamin C effect versus **uniform + linear** vitamin C effect:
Inclusion of the linear effect improves the statistical model by Chisq (1 df) = 9.78, p = 0.0017.

```
> Karlowski1  <- lm(Karlowski$Change ~ Karlowski$vitC, weights = Karlowski$InvVar)
> Karlowski2  <- lm(Karlowski$Change ~ Karlowski$vitC + Karlowski$Dose, weights = Karlowski$InvVar)

> lrtest(Karlowski1,Karlowski2)
Likelihood ratio test

Model 1: Karlowski$Change ~ Karlowski$vitC
Model 2: Karlowski$Change ~ Karlowski$vitC + Karlowski$Dose
  #Df   LogLik Df  Chisq Pr(>Chisq)
1   3 -11.2152
2   4  -6.3212  1 9.7879   0.001757
---
```

Dose-response analysis of the Anderson (1974) trial

The Anderson (1974) data were published (Table II)

Placebo group #4 is for reasons described on p. 40 (Table 16) of Hemilä (2006) [1].
Table II gives the mean duration of colds as follows:

vitamin C g/day	Group	Reported Total no. colds	Reported Total days in group	Calculated Days per episode	Imputed SD	SE	Var	Weight for linear regression Inverse Var	Effect in %
0	#4	437	1539	3.522	3.205	0.15	0.0235	42.549	0.00%
4	#7	417	1325	3.177	2.891	0.14	0.0200	49.876	-9.78%
8	#8	483	1380	2.857	2.600	0.12	0.0140	71.450	-18.87%

SD= 0.91*mean

Anderson (1974) did not publish the SD for the observations.
Above, SD is imputed with ratio SD = 0.91 * mean. See the last page of this document.
Furthermore, in Anderson (1972) the SD per mean ratio was 0.97 and 0.82 in the vitamin C and placebo groups, see the last page. Thus, the ratio 0.92 is also close to the ratios of Anderson's earlier study.

```
> A1974
  Change InvVar Dose vitC
1   0.00 42.549    0    0
2  -9.78 49.876    4    1
3 -18.87 71.450    8    1

> Anderson0  <- lm(A1974$Change ~  A1974$Dose, weights = A1974$InvVar)
> summary(Anderson0)

Coefficients:
             Estimate Std. Error t value Pr(>|t|)
(Intercept) -0.13778    0.27584   -0.50    0.705
A1974$Dose  -2.35178    0.04818  -48.81    0.013 *


Residual standard error: 2.011 on 1 degrees of freedom
Multiple R-squared:  0.9996,    Adjusted R-squared:  0.9992
F-statistic:  2382 on 1 and 1 DF,  p-value: 0.01304
```

Table 5. Subgroup comparison of the Anderson (1972) trial by contact with children.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1940935

The ratio between SD and mean was calculated from the overall results of the trial Anderson (1972) reported that (Table II):

Vitamin C group
Among 407 participants, for “days confined to house” SE = 0.101, corresponding to SD = 2.038.
The mean “days confined to house” was 1.30 so that the ratio = 1.567 (= 2.038/1.30)
Placebo group
Among 411 participants, for “days confined to house” SE = 0.138, corresponding to SD = 2.798.
The mean “days confined to house” was 1.87 so that the ratio = 1.496 (= 2.798/1.87)

The ratio of 1.57 was used for the imputation of the SD from the subgroup means.

Anderson (1972) reported that (Tables I and IV):

	Vitamin C	**Placebo**	**Effect of vitamin C**
Contact with young children			
Yes			
Days confined to house:	1.31	2.43	-46.1%
Imputed SD:	2.06	3.82	
No of participants:	140	148	
No			
Days confined to house:	1.30	1.56	-16.7%
Imputed SD:	2.04	2.45	
No of participants:	267	263	

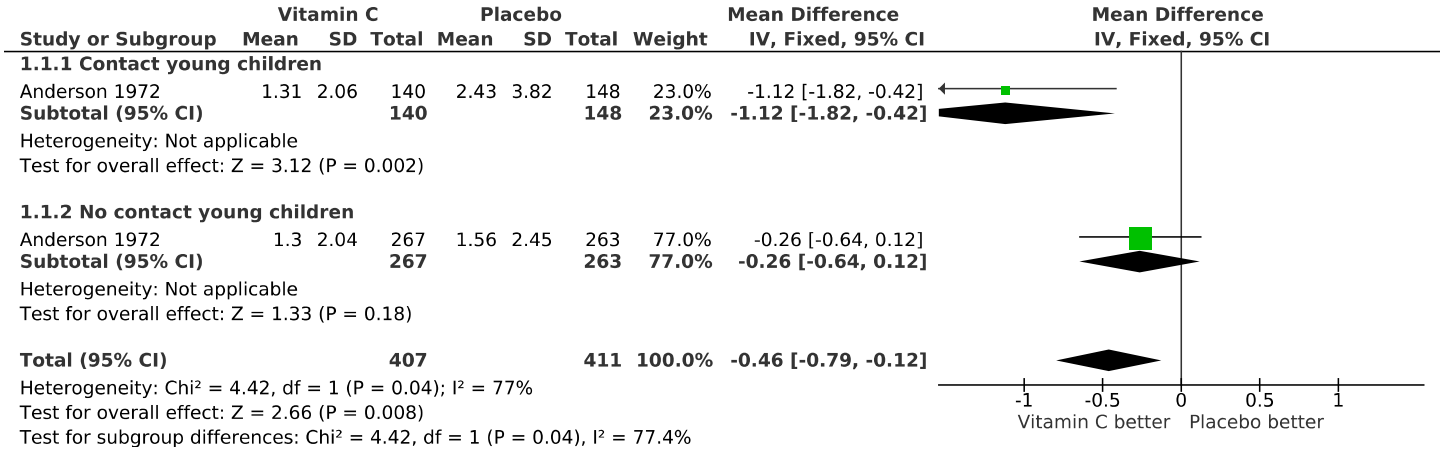


Table 5. Subgroup comparison of the Anderson (1972) trial by usual colds.

Anderson (1972) reported that (Tables I and IV):

The ratio 1.6 was used in the imputation of the SD for the means of the subgroups, see above.

Usual colds per winter	Vitamin C	Placebo	Effect of vitamin C
≥2 colds			
Days confined to house:	1.31	2.29	-42.8%
Imputed SD:	2.06	3.60	
No of participants:	211	192	
0-1 colds			
Days confined to house:	1.30	1.50	-13.3%
Imputed SD:	2.04	2.36	
No of participants:	196	219	

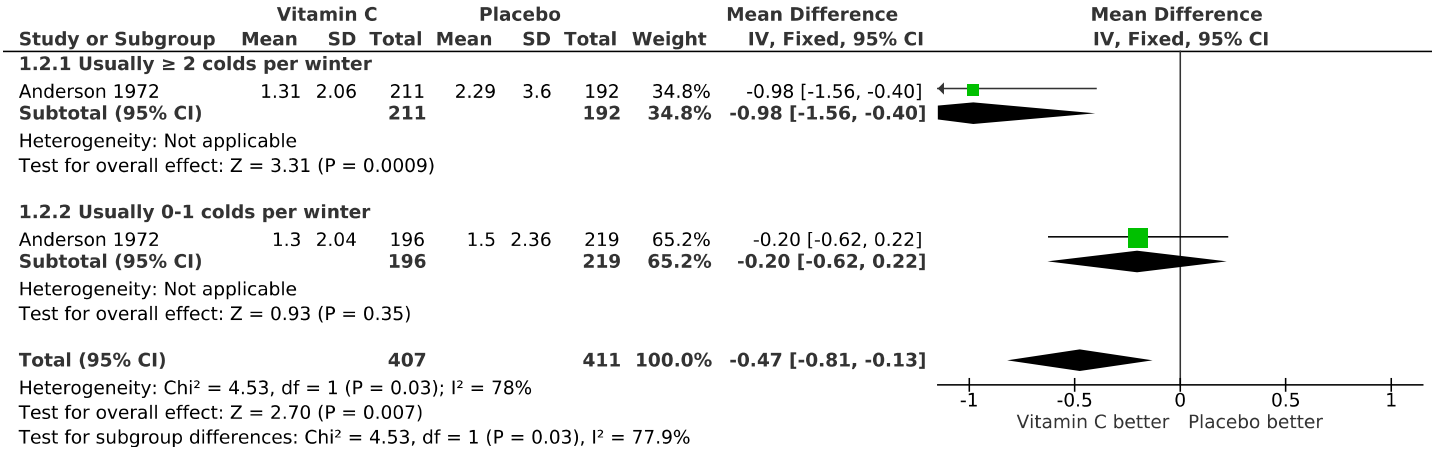


Table 5. Subgroup comparison of the Carr (1981) trial by living together or living apart.
https://www.ncbi.nlm.nih.gov/pubmed/7048833

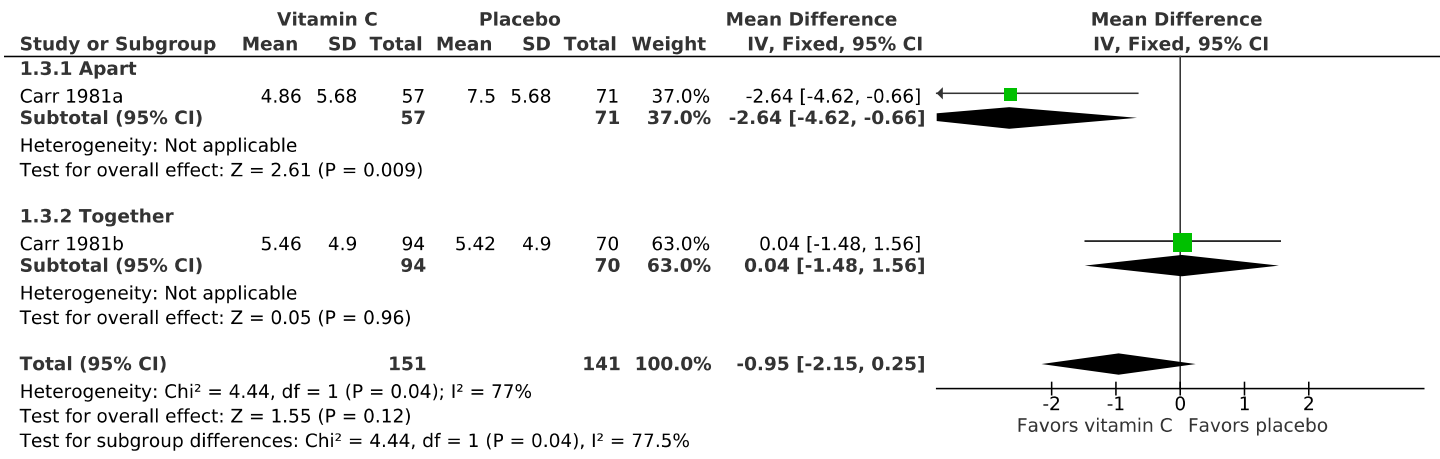
Carr (1981) reported that (Table 2):

	Vitamin C	Placebo	Effect of vitamin C
Living apart			
Mean duration of colds:	4.86	7.50	-35.2%
No of colds:	94	71	
Living together			
Mean duration of colds:	5.46	5.42	+0.7%
No of colds:	57	70	

SD for the duration of colds among twins living apart was calculated from the reported P < 0.01.
Assuming P =0.009 corresponds to t(127 df) = 2.62, which corresponds to SD 5.68 days.
That SD value was used for both the vitamin C and placebo groups of twins living apart.

SD for twins living together was estimated from the relation that the ratio of SD/mean = 0.91 covers 80% of the reported ratios so that this ratio is conservative, see the last page.
Thus SD = 4.9 days(=0.91*5.4 days) was used as the imputed SD for twins living together.

The test for subgroup differences Chi^2 (1 df)= 4.44 corresponds to P = 0.035.



Calculation of the ratio for common cold duration SD per mean for imputations

The imputation of SD was based on the analysis of 67 vitamin C and zinc lozenge study groups for which SD and mean were reported, see below.
The median for the ratio of SD/mean was 0.58 and the 80th percentile was 0.91.
The latter ratio **0.91** was used as the ratio to impute the SD value for the Carr (1981) trial.
The vitamin C trials are listed in Hemilä and Chalker (2013)
https://www.ncbi.nlm.nih.gov/pubmed/23440782
http://www.mv.helsinki.fi/home/hemila/CC
and the zinc lozenge trials are listed in Hemilä (2011)
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3136969

	Treatment groups			Placebo groups		
	Duration in days			Duration in days		
Vitamin C trials	**mean**	**SD**	**Ratio**	**mean**	**SD**	**Ratio**
Prevention trials						
Anderson-1972	3.96	3.84	**0.97**	4.18	3.43	**0.82**
Charleston-1972	3.55	1.93	**0.55**	4.21	0.82	**0.20**
Clegg-1975	7.2	3.1	**0.43**	7.6	3	**0.39**
Elwood-1976	5.97	5.73	**0.96**	6.38	6.33	**0.99**
Himmelstein 1998sed	2.5	1.1	**0.44**	4.2	3.5	**0.83**
Johnston 2014	2.2	1.4	**0.64**	5.4	4.5	**0.83**
Karlowski 1975a (#2)	6.71	3.82	**0.57**	7.14	3.71	**0.52**
Karlowski 1975d (#3 vs #1)	5.92	3.49	**0.59**	6.46	2.92	**0.45**
Van Straten-2002	1.8	2.98	**1.66**	3.1	4.65	**1.50**
Peters-1993 Runners	6	0.99	**0.17**	5.8	2.46	**0.42**
Peters 1993a Sedentary	4.2	2.14	**0.51**	5.6	3.18	**0.57**
Sabiston-1974	4.3	3	**0.70**	6	3	**0.50**
Bancalari 1984	3.4	2.77	**0.82**	4.5	2.92	**0.65**
Constantini 2011 Male	5.5	5	**0.91**	10.4	7.1	**0.68**
Constantini 2011a Female	8.6	5.5	**0.64**	7.4	8.2	**1.11**
Ludvigsson-1977 Pilot	8.9	5.96	**0.67**	14.53	9.75	**0.67**
Ludvigsson-1977a Large	9.54	8.65	**0.91**	10.14	11.6	**1.14**
Ritzel-1961	1.8	1.29	**0.71**	2.6	1.29	**0.49**
Wilson_1973 Girls	2.62	3.67	**1.40**	3.1	4.15	**1.34**
Wilson_1973a Boys	2.68	5.01	**1.87**	2.48	3.29	**1.33**
Treatment trials						
Audera 2001 (1 g/day)	10.1	7	**0.69**	8.5	6.67	**0.79**
Audera 2001a (3 g/day)	10.4	6.67	**0.64**			
Elwood 1977	5.89	2.77	**0.47**	6.29	2.78	**0.44**
Tyrrell 1977 (Males)	7.41	3.59	**0.48**	7.57	3.79	**0.50**
Tyrrell 1977a (Females)	8.96	5.3	**0.59**	8.24	4.78	**0.58**
Zinc lozenge trials						
Douglas 1987	12.10	9.80	**0.81**	7.70	9.80	**1.27**
Godfrey 1992	4.86	2.70	**0.56**	6.13	2.70	**0.44**
Macknin 1998	9.37	4.81	**0.51**	9.50	4.53	**0.48**
Mossad 1996	5.20	2.83	**0.54**	9.38	5.47	**0.58**
Petrus 1998	5.29	2.57	**0.49**	7.06	3.91	**0.55**
Prasad 2000	4.44	1.56	**0.35**	8.09	1.81	**0.22**
Prasad 2008	4.00	1.04	**0.26**	7.12	1.26	**0.18**
Turner 2000 A	7.41	3.88	**0.52**	7.55	3.96	**0.52**
Turner 2000 B	6.89	3.35	**0.49**			
Turner 2000 C	7.90	4.20	**0.53**			
		Median	**0.58**			
		Mean	**0.69**			
		Count	**67**			

		Ratio of SD/mea
		0.17
	SD/mean	0.18
	ratio	0.20
	ordered	0.22
	to find	0.26
	quartiles	0.35
		0.39
		0.42
		0.43
		0.44
		0.44
		0.44
		0.45
		0.47
		0.48
		0.48
	1nd quartile	0.49
		0.49
		0.50
		0.50
		0.50
		0.51
		0.51
		0.52
	Half of the ratios	0.52
	are between	0.52
	0.49 and 0.82	0.53
		0.54
		0.55
		0.55
		0.56
		0.57
	33	0.57
	Median	0,580
	33	0.58
		0.59
		0.59
		0.64
		0.64
		0.64
		0.65
		0.67
		0.67
		0.68
		0.69
		0.70
		0.72
		0.79
		0.81
	3rd quartile	**0.82**
		0.82
		0.83
		0.83
	80th percentile	**0.91**
		0.91
		0.96
		0.97
Elwood-1976		0.99
Constantini 2011a Female		1.11
Ludvigsson-1977a Large		1.14
Douglas		1.27
These might be classified as outliers	Wilson	1.33
	Wilson	1.34
	Wilson	1.40
	van Straten	1.50
	van Straten	1.66
	Wilson	1.87
	Total count	**67**