Design of dose-escalation trials

R. A. Bailey

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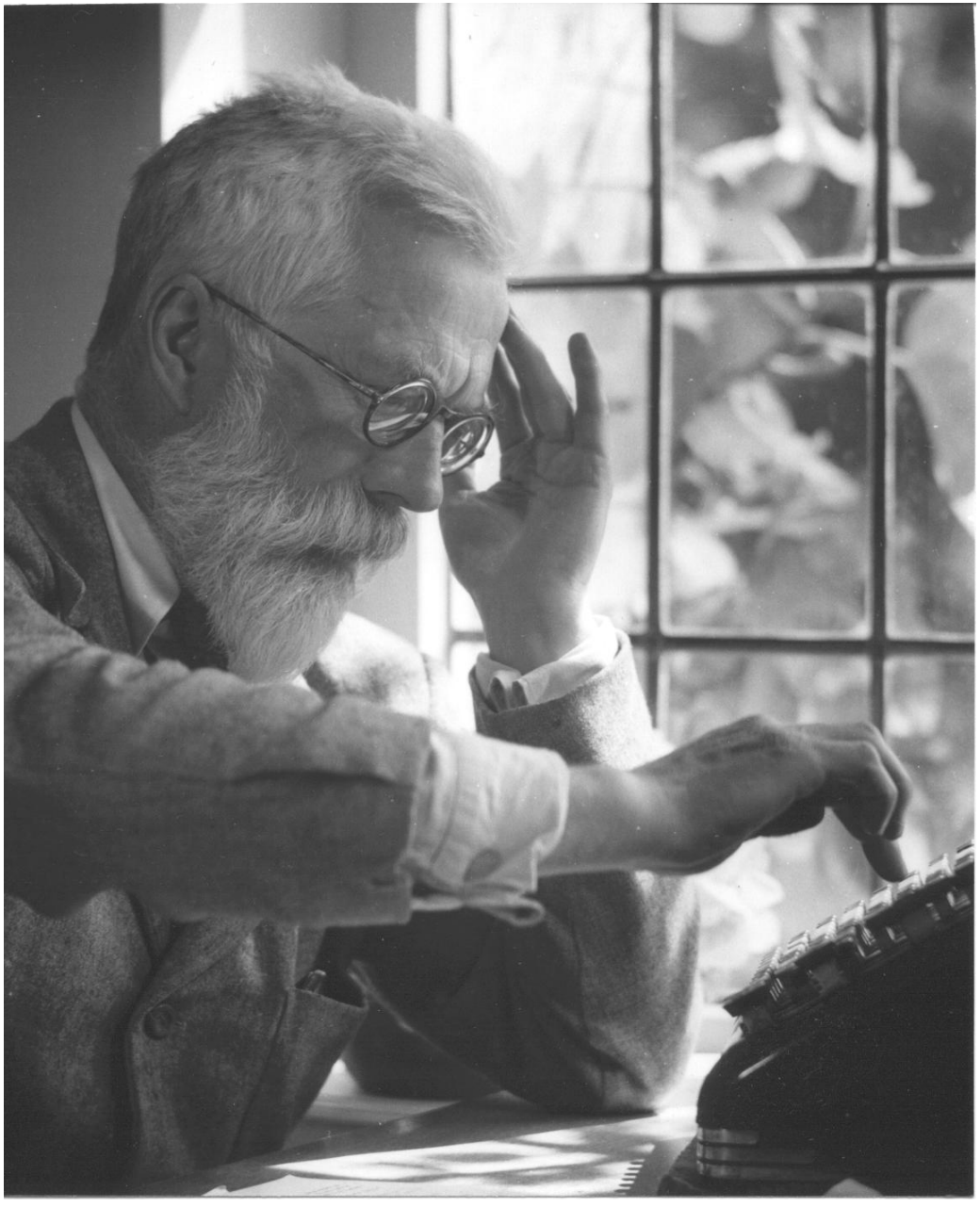
Fisher Memorial Lecture,
Dublin, July 2008

What does a statistician do? I



What can the data tell us? Is there a simple story?

"Fisher … pulled out—weeds."

1952 portrait by Barrington Brown, reproduced by permission of the Fisher Memorial Trust

What does a statistician do? II

"Nature … will best respond to a logical and carefully thought out questionnaire."

1924 portrait, courtesy of Joan Box

Design of the TeGenero trial

First-in-Man trial of a monoclonal antibody on healthy volunteers, March 2006: 4 cohorts of 8 volunteers each.

Cohort	TGN1412		Placebo
	Dose mg/kg body-weight	Number of Subjects	Number of Subjects
1	0.1	6	2
2	0.5	6	2
3	2.0	6	2
4	5.0	6	2

What happened to Cohort 1 on 13 March 2006

Healthy Volunteer	Randomised to	Time of intravenous administration	Time of transfer to critical care
A	TGN1412 8.4mg	0800	2400
B	Placebo	0810	
C	TGN1412 6.8mg	0820	2350
D	TGN1412 8.8mg	0830	0030
E	TGN1412 8.2mg	0840	2040
F	TGN1412 7.2mg	0850	0050
G	TGN1412 8.2mg	0900	0100
H	Placebo	0910	

The Royal Statistical Society's Working Party on Statistical Issues in First-in-Man Studies: Membership

Dipti Amin, Senior Vice-President, Quintiles
R. A. Bailey, Professor of Statistics, QMUL
Sheila Bird, Principal Scientist/Statistician, MRC Biostatistics Unit
Barbara Bogacka, Reader in Probability and Statistics, QMUL
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What does block mean?

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What does block mean? strata? randomize?

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Planned analysis of the TeGenero trial

Cohort	TGN1412		Placebo
	Dose	Number	Number
1	1	6	2
2	2	6	2
3	3	6	2
4	4	6	2

If all responses are uncorrelated with variance σ^2 then
Variance (dose $i-$ placebo) in cohort i is $\left(\frac{1}{6}+\frac{1}{2}\right)\sigma^2 = \frac{2}{3}\sigma^2$

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- Different types of people can volunteer at different times.

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There have been many trials, in many topics, where, with hindsight, cohort effects swamp treatment effects.
The Experimental Medicines Group of the Association of the British Pharmaceutical Industry (ABPI) says that trials should always be designed on the assumption that there will be cohort effects.

Analysis of the TeGenero trial with cohort effects

Cohort	TGN1412		Placebo
	Dose	Number	Number
1	1	6	2
2	2	6	2
3	3	6	2
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$$\text{Variance (dose } i - \text{ placebo) in cohort } i = \left(\frac{1}{6} + \frac{1}{2}\right)\sigma^2 = \frac{2}{3}\sigma^2.$$

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$$\text{So variance (dose } i - \text{ dose } j) = \left(\frac{2}{3} + \frac{2}{3}\right)\sigma^2 = \frac{4}{3}\sigma^2.$$

Senn's proposed design

Cohort	TGN1412		Placebo
	Dose	Number	Number
1	1	4	4
2	2	4	4
3	3	4	4
4	4	4	4

Senn's proposed design

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The TeGenero design is inadmissible because everything can be estimated, from the same resources, with smaller variance, by another design.

Dose-escalation trials: standard designs

There are n doses, with dose 1 $<$ dose 2 $< \cdots <$ dose n.

0 denotes the placebo.

There are n cohorts of m subjects each.

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Cohort 1 subjects may receive only dose 1 or placebo.

In Cohort i, some subjects receive dose i;
no subject receives dose j if $j > i$.

Put $s_{ki} =$ number of subjects who get dose i in cohort k. Then

$$s_{ki} > 0 \quad \text{if} \quad i = k$$
$$s_{ki} = 0 \quad \text{if} \quad i > k.$$

Scaled variance

Assume that the expectation of the response of a subject who gets dose i in cohort k is $\tau_i + \beta_k$, and that responses are uncorrelated with common variance σ^2.

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so define the scaled variance v_{ij} to be

$$\frac{\text{Variance (dose } i - \text{ dose } j) \times \text{number of observations}}{2(n+1)\sigma^2}.$$

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Aim:

- only doses 0 and k in cohort k
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Example: $n = 4$, $m = 10$

Dose	0	1	2	3	4
Cohort 1	2	8	0	0	0
Cohort 2	2	0	8	0	0
Cohort 3	2	0	0	8	0
Cohort 4	2	0	0	0	8

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$$v_{0i} = \frac{n+1}{2} \qquad v_{ij} = n+1$$

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Example: $n = 4, m = 8$

Dose	0	1	2	3	4
Cohort 1	4	4	0	0	0
Cohort 2	4	0	4	0	0
Cohort 3	4	0	0	4	0
Cohort 4	4	0	0	0	4

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$$v_{0i} = \frac{2n}{n+1} \qquad v_{ij} = \frac{4n}{n+1}$$

Lessons from experience with block designs: I

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Principle

In each cohort, no treatment should be allocated to more than half of the subjects.

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Principle

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Each cohort should have as many different treatments as possible.

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In Cohort 1: $\frac{m}{2}$ subjects get dose 1; $\frac{m}{2}$ subjects get placebo.

In Cohort k: $\frac{m}{2}$ subjects get dose k; remaining subjects are allocated to placebo and doses 1 to $k-1$ according to some rule.

Strict halving design

Remaining subjects are allocated as in Cohort $k-1$ with numbers halved.

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Example: $n = 4, m = 16$

Dose	0	1	2	3	4
Cohort 1	8	8	0	0	0
Cohort 2	4	4	8	0	0
Cohort 3	2	2	4	8	0
Cohort 4	1	1	2	4	8

Uniform halving design

Remaining subjects are allocated as equally as possible to treatments 0 to $k-1$, with larger values given to make the 'replication so far' as equal as possible.

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Example: $n = 4$, $m = 8$

Dose	0	1	2	3	4
Cohort 1	4	4	0	0	0
Cohort 2	2	2	4	0	0
Cohort 3	1	1	2	4	0
Cohort 4	1	1	1	1	4

Catch-up halving design

Remaining subjects are allocated to treatments 0 to $k-1$ to make the 'replication so far' as equal as possible, with lower doses favoured if there is a tie.

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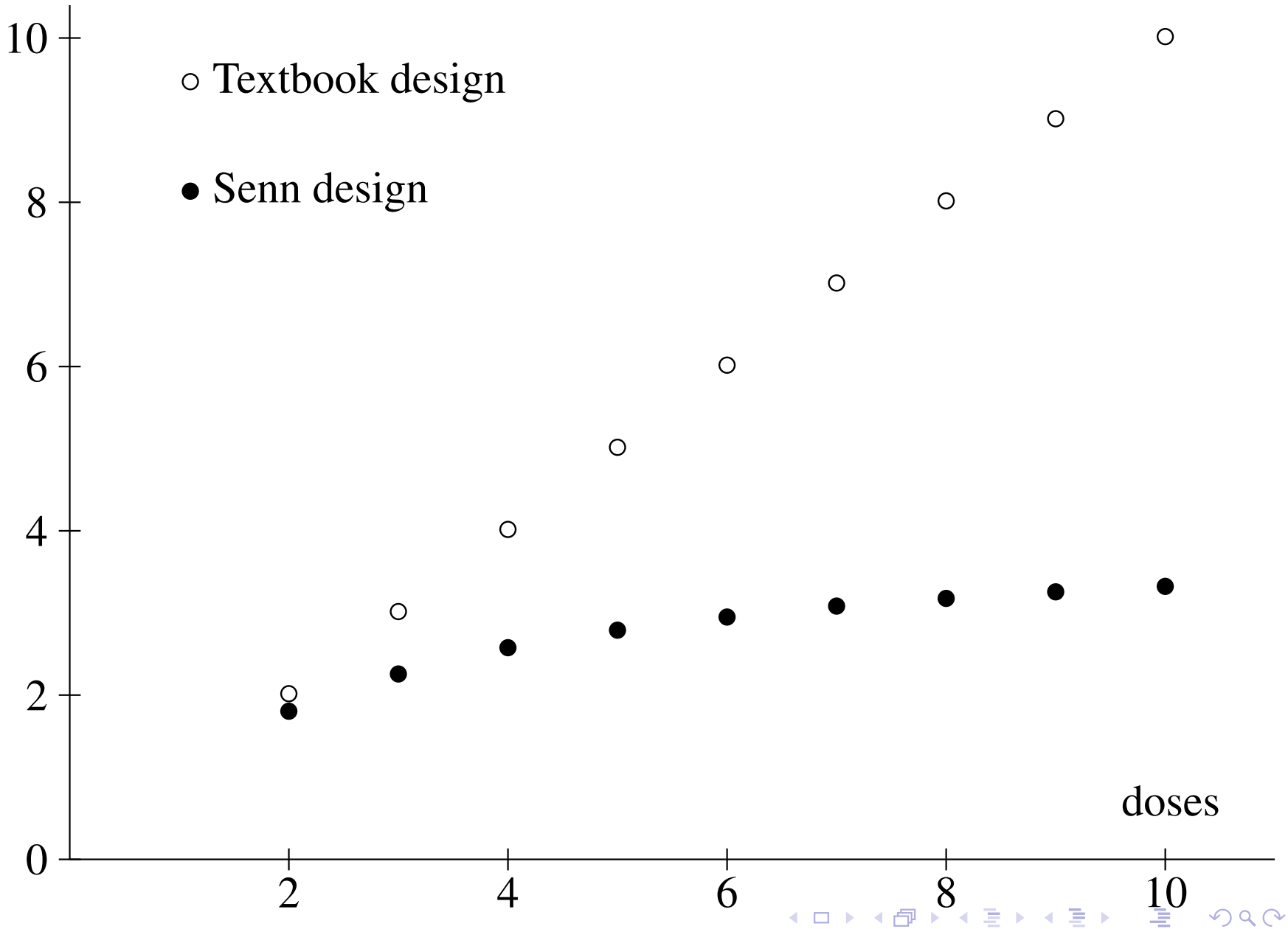
Example: $n = 4$, $m = 10$

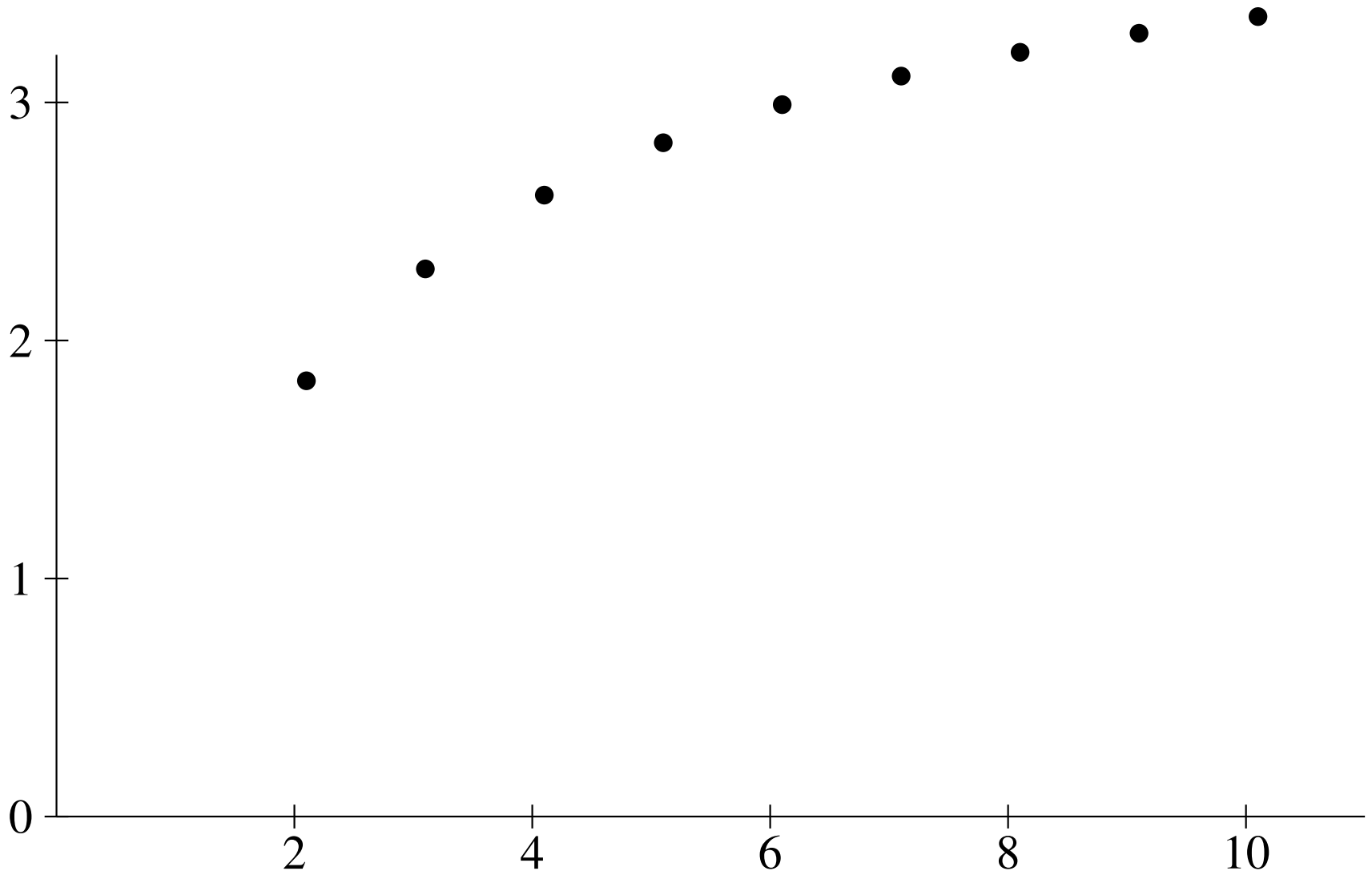
Dose	0	1	2	3	4
Cohort 1	5	5	0	0	0
Cohort 2	3	2	5	0	0
Cohort 3	1	1	3	5	0
Cohort 4	1	1	1	2	5

Average scaled pairwise variance

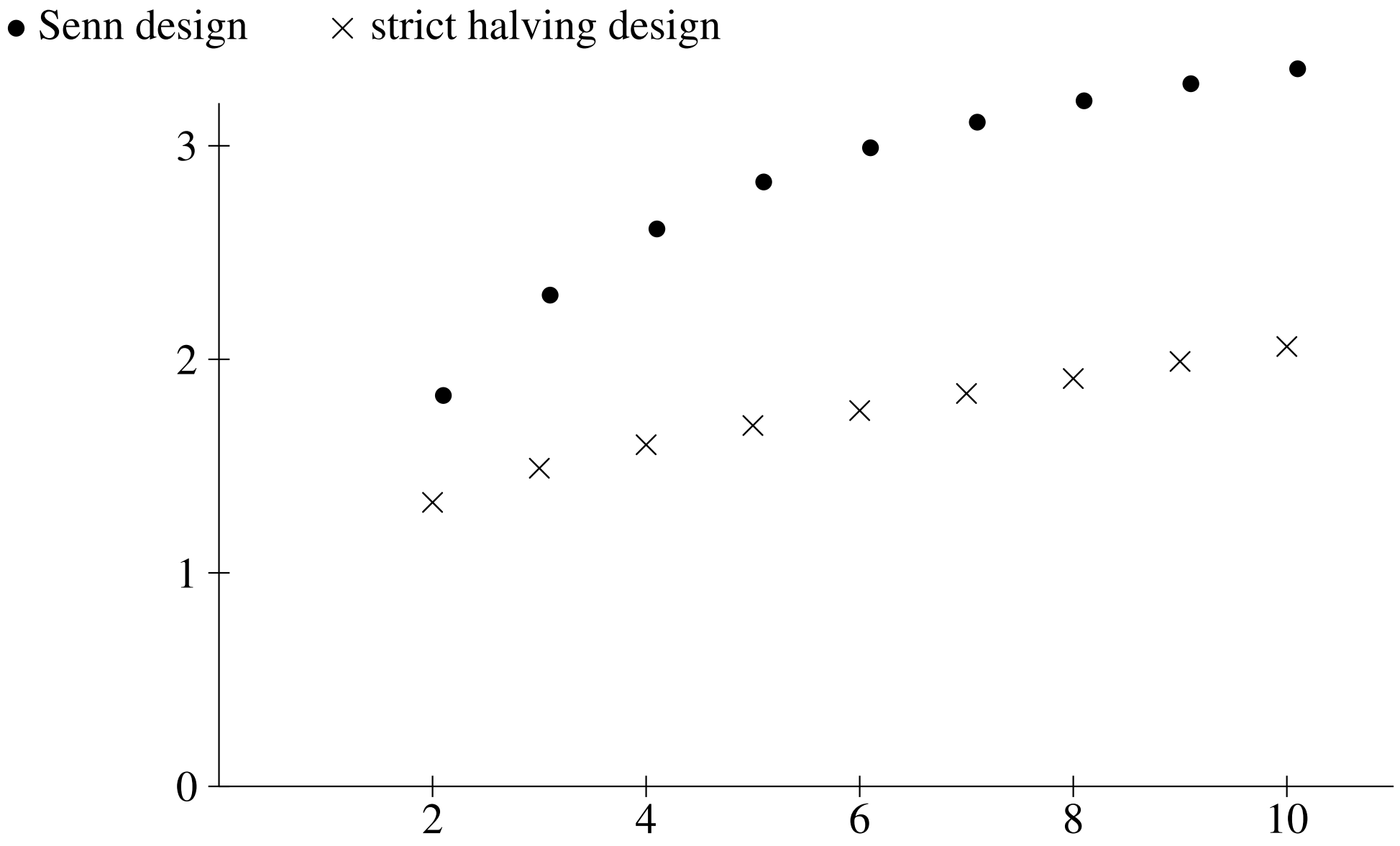


Average scaled pairwise variance: continued

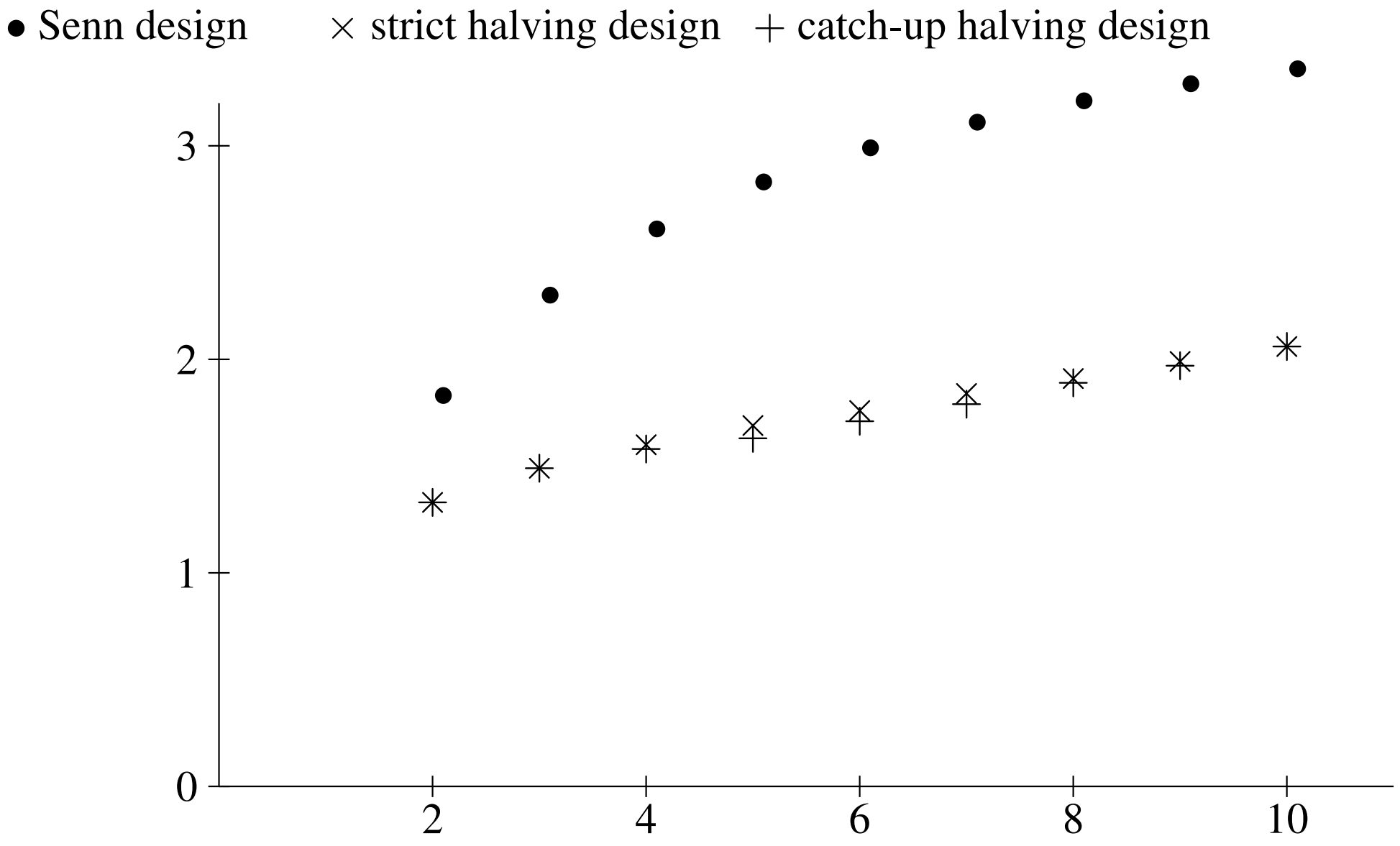
- Senn design



Average scaled pairwise variance: continued



Average scaled pairwise variance: continued



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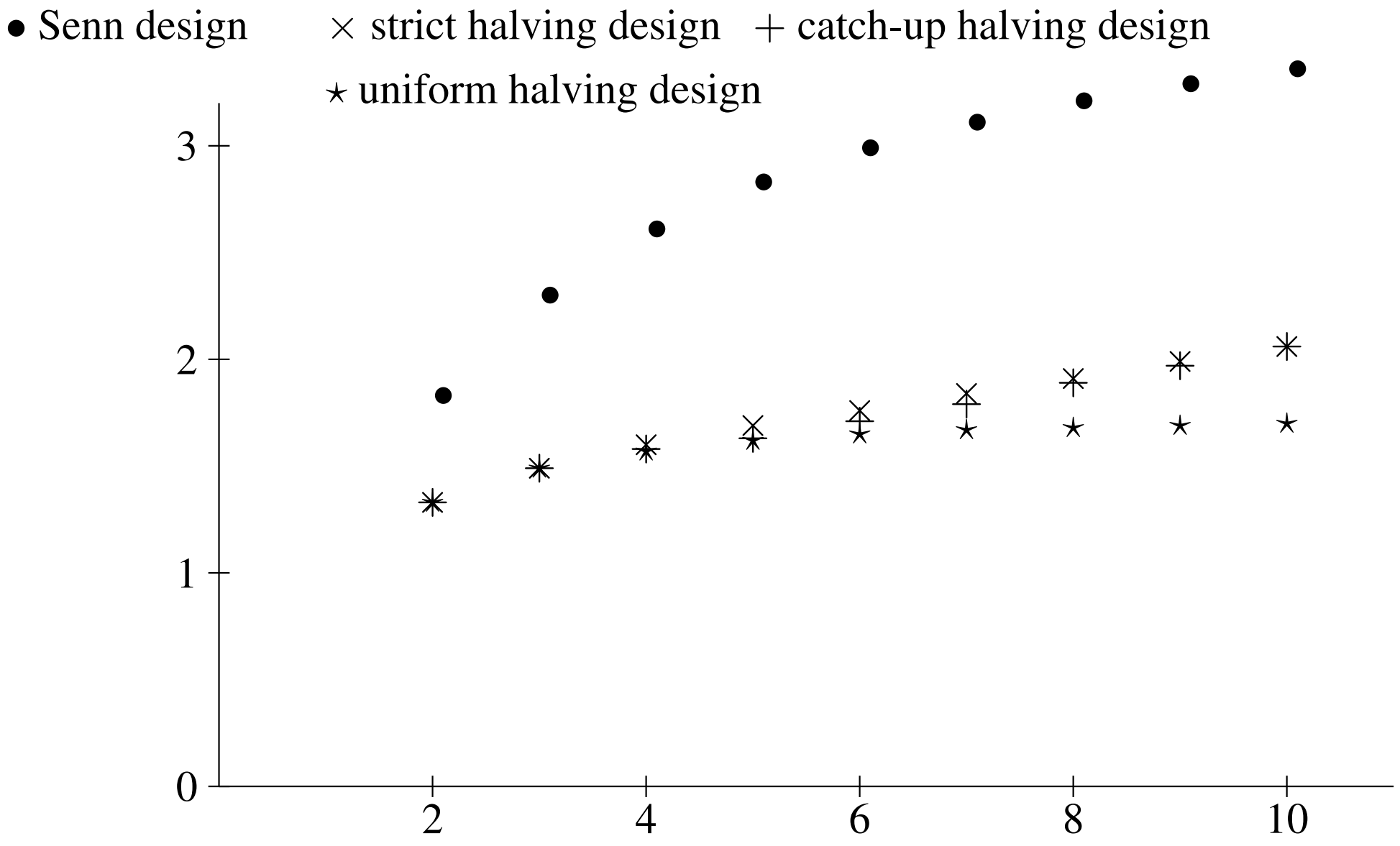

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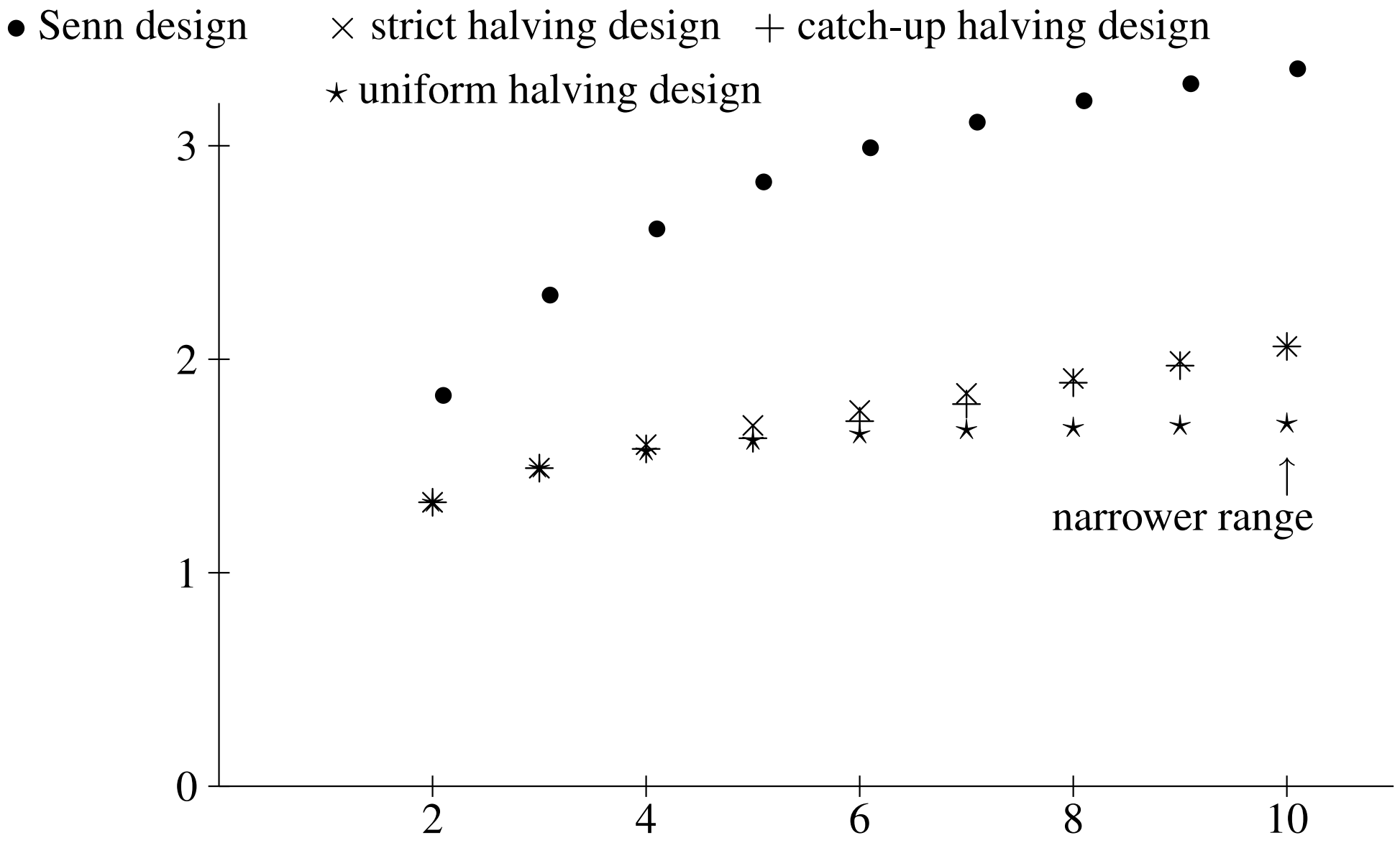

Lessons from experience with block designs: II

If we transpose the matrix,
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In the standard designs, the highest dose has all of its subjects in the final cohort, so no contrast between this cohort and other cohorts can be orthogonal to that dose.

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Principle

There should be one more cohort than there are doses.

Dose-escalation trials: extended designs

There are n doses, with dose 1 $<$ dose 2 $<\cdots<$ dose n.

0 denotes the placebo.

There are $n+1$ cohorts of m subjects each.

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There are n doses, with dose 1 $<$ dose 2 $< \cdots <$ dose n.

0 denotes the placebo.

There are $n+1$ cohorts of m subjects each.

Cohort 1 subjects may receive only dose 1 or placebo.

In Cohort i, for $2 \leq i \leq n$, some subjects receive dose i;
no subject receives dose j if $j > i$.

In Cohort $n+1$, any dose, or placebo, may be used.

Extended textbook design

Maintain overall equal replication in the final cohort.

$$s_{n+1,i} = \frac{m}{n+1} \qquad \text{for } i = 0, \ldots, n$$

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Example: $n = 4$, $m = 10$

Dose	0	1	2	3	4
Cohort 1	2	8	0	0	0
Cohort 2	2	0	8	0	0
Cohort 3	2	0	0	8	0
Cohort 4	2	0	0	0	8
Cohort 5	2	2	2	2	2

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$$v_{0i} = \frac{(n+1)(n+2)}{2(2n+1)} \qquad v_{ij} = \frac{(n+1)^2}{2n+1}$$

Extended Senn design

In the final cohort,
compensate for the previous over-replication of placebo.

$$s_{n+1,i} = \begin{cases} 0 & \text{if } i = 0 \\ \dfrac{m}{n} & \text{otherwise} \end{cases}$$

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Example: $n = 4, m = 8$

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Cohort 2	4	0	4	0	0
Cohort 3	4	0	0	4	0
Cohort 4	4	0	0	0	4
Cohort 5	0	2	2	2	2

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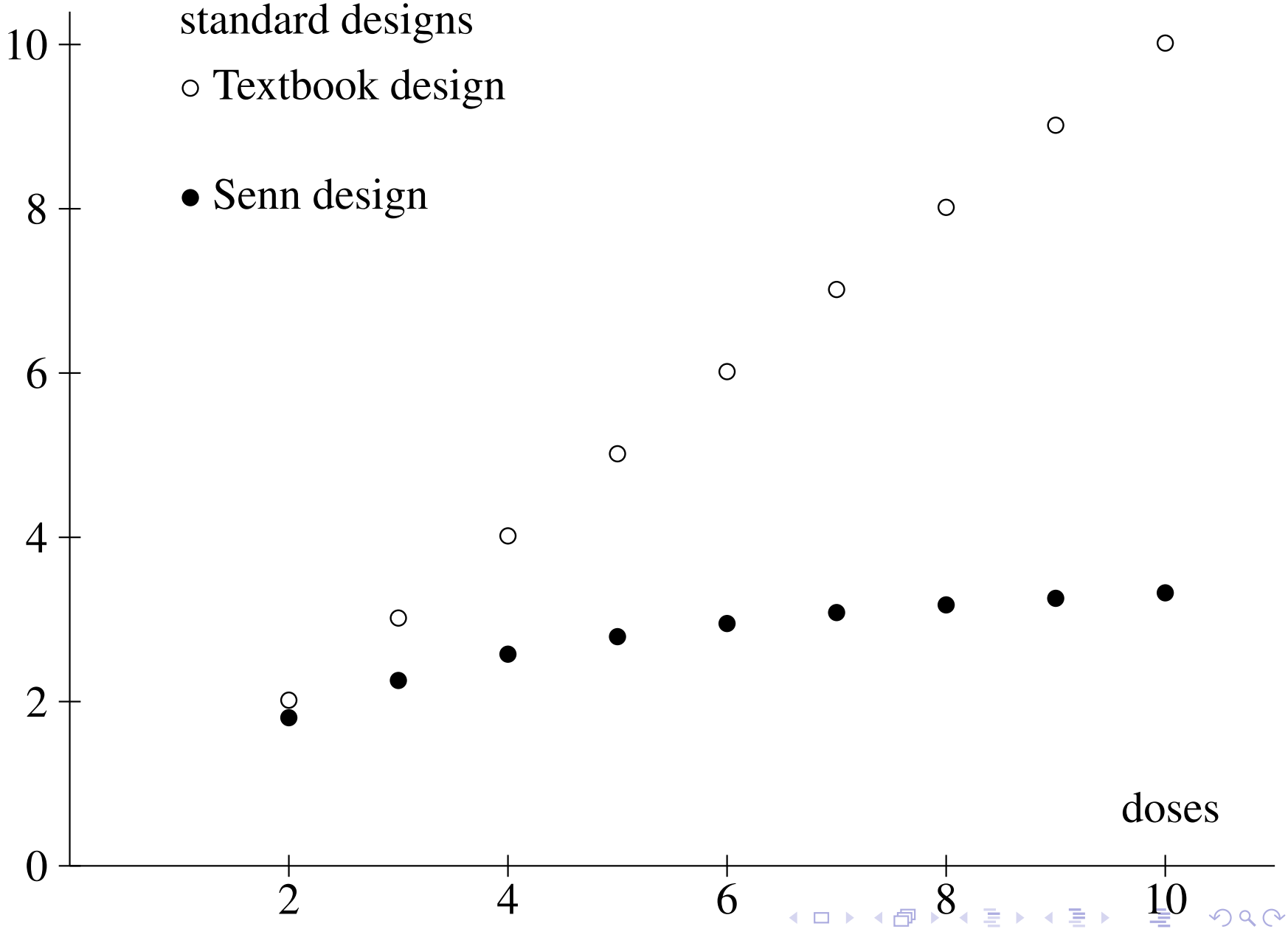
Cohort 4	4	0	0	0	4
Cohort 5	0	2	2	2	2

$$v_{0i} = \frac{2(n^2+4)}{n(n+4)} \qquad v_{ij} = \frac{4n}{n+4}$$

Average scaled pairwise variance (again)



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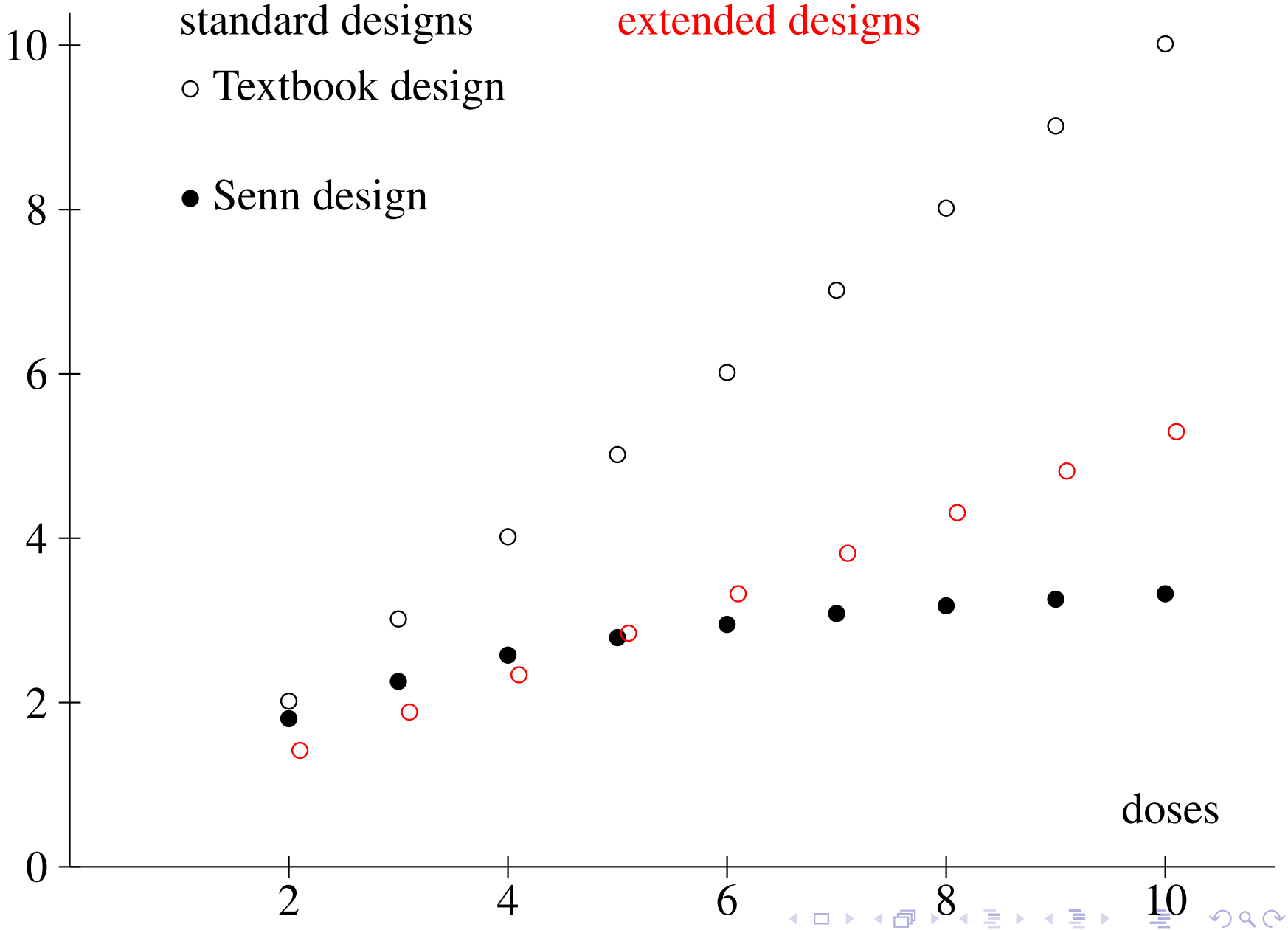

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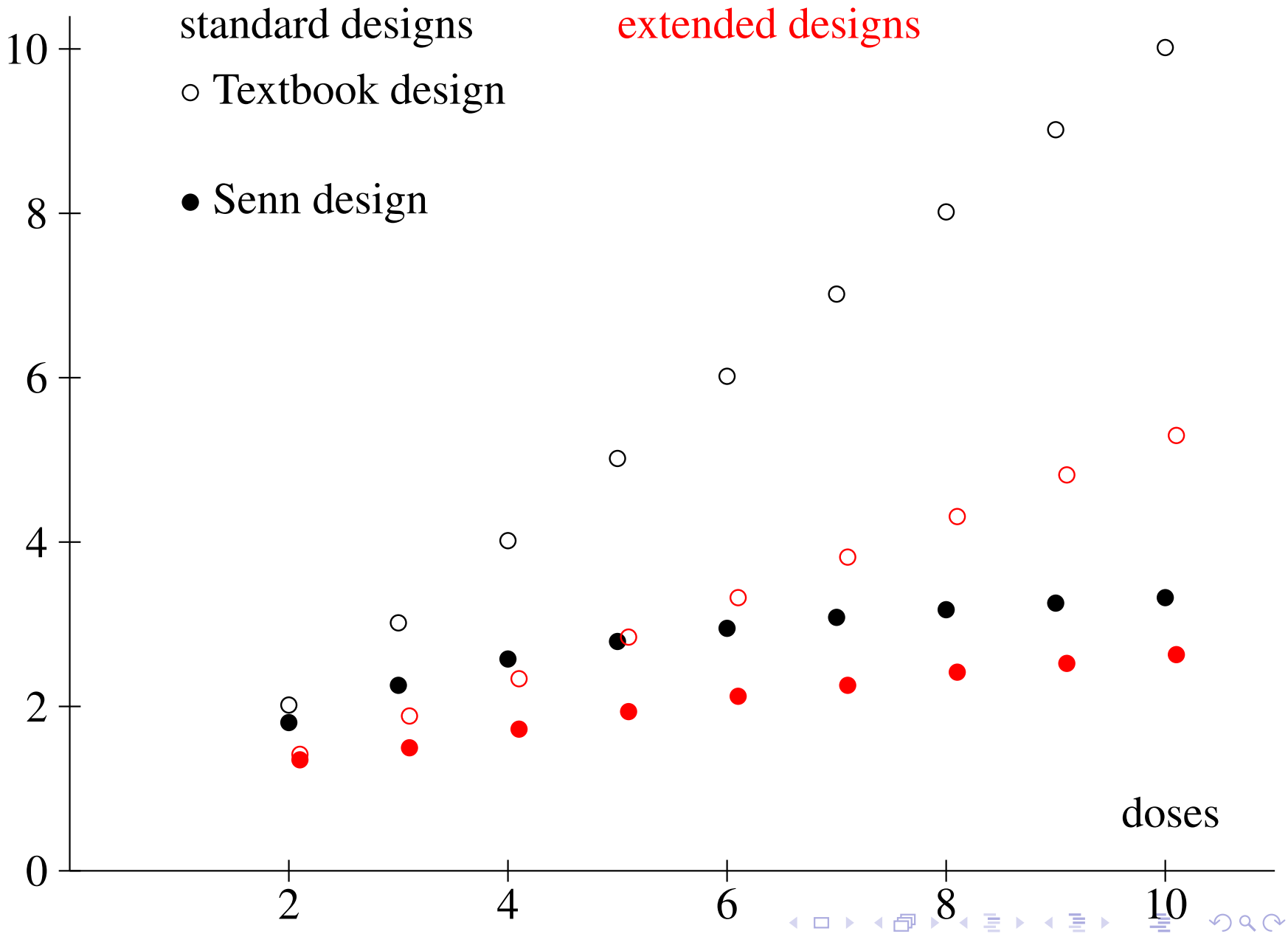

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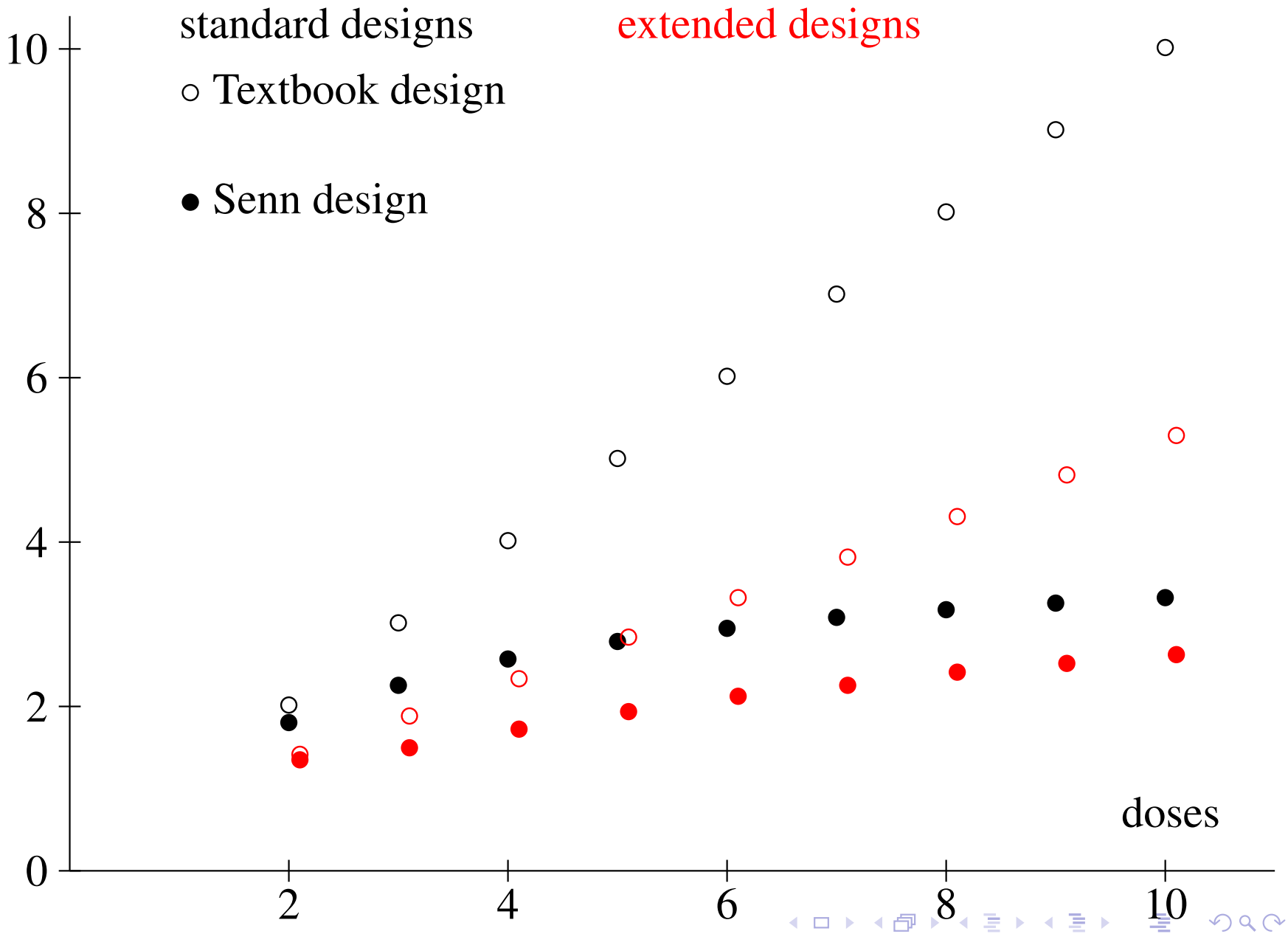

Extended halving designs

In all of the standard halving designs,
the largest pairwise variances are those involving the highest dose.
The extra cohort should try to redress this.

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The extra cohort should try to redress this.

Is it better to aim for equal replication in the final cohort,
or equal replication overall?

Uniform extension

The replications in the extra cohort as are equal as possible, with larger values given to those doses with lower replication so far.

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Example: $n = 4, m = 8$

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The replications in the extra cohort make the overall replications as equal as possible, with any inequalities favouring the higher doses.

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Compromise extension

About half the subjects in the final cohort are equally split between all treatments,
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	1	1	1	1	1

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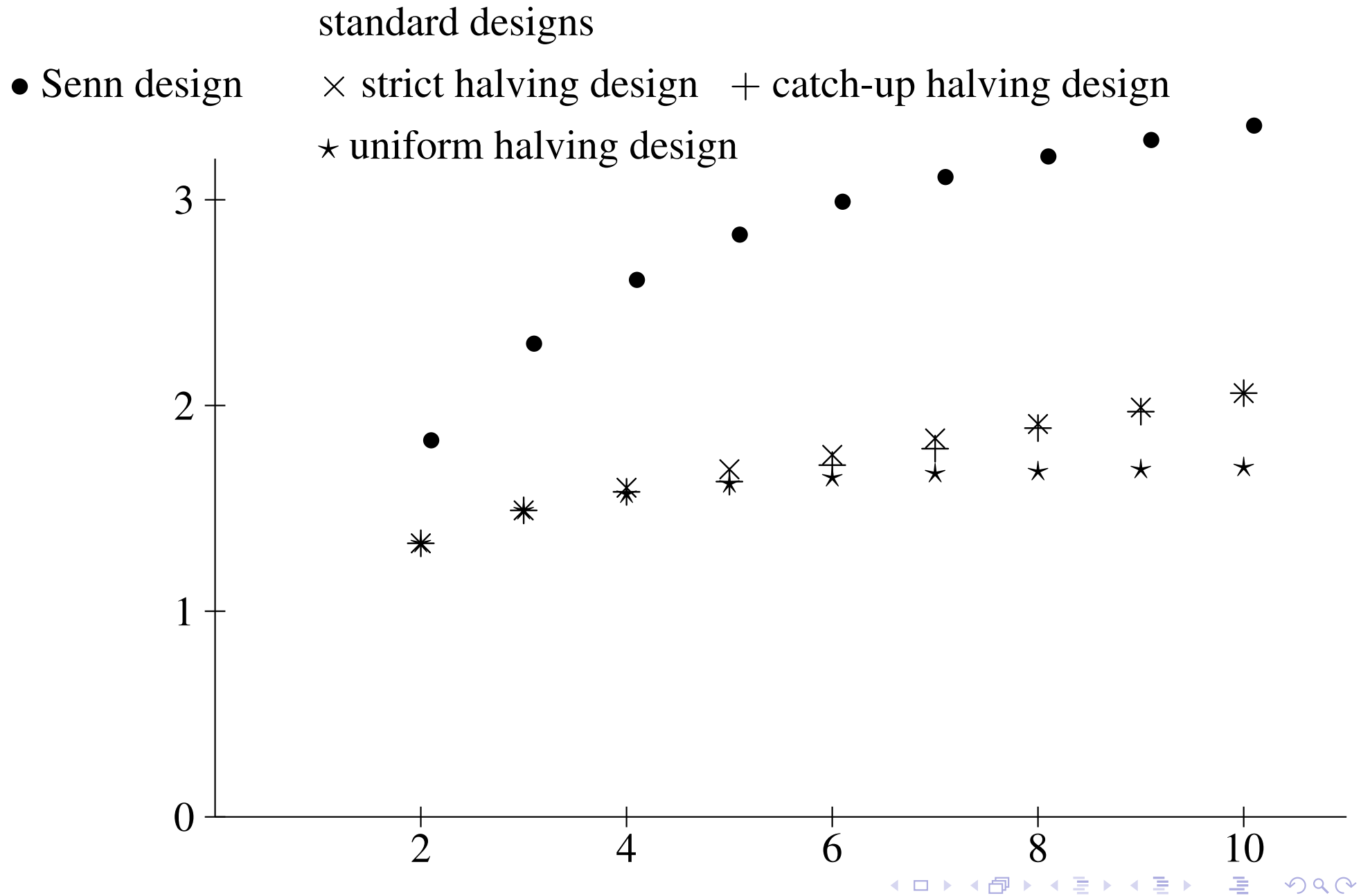
					1
				1	1
Cohort 5	1	1	1	2	3

Average scaled pairwise variance: continued (again)



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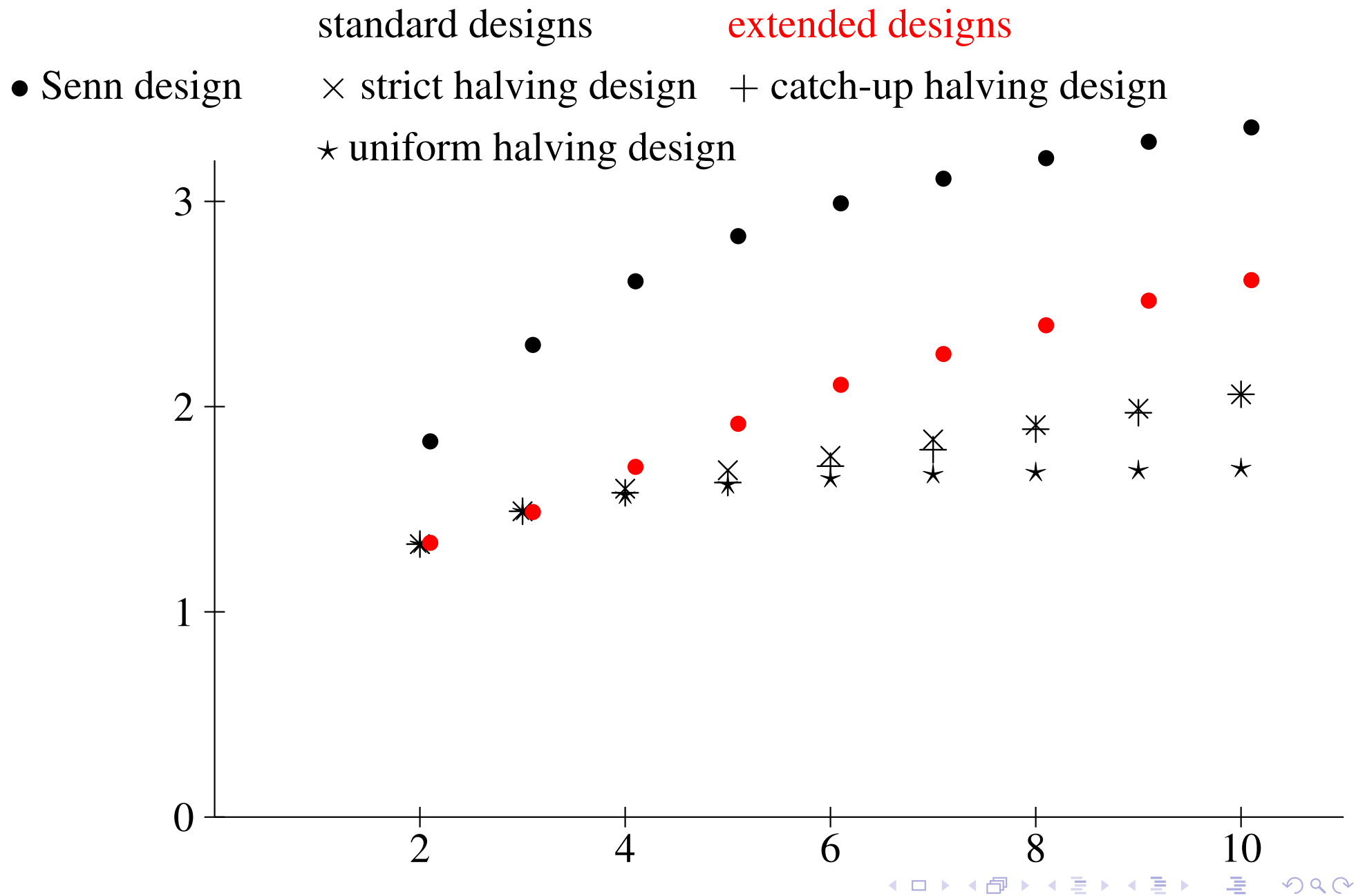

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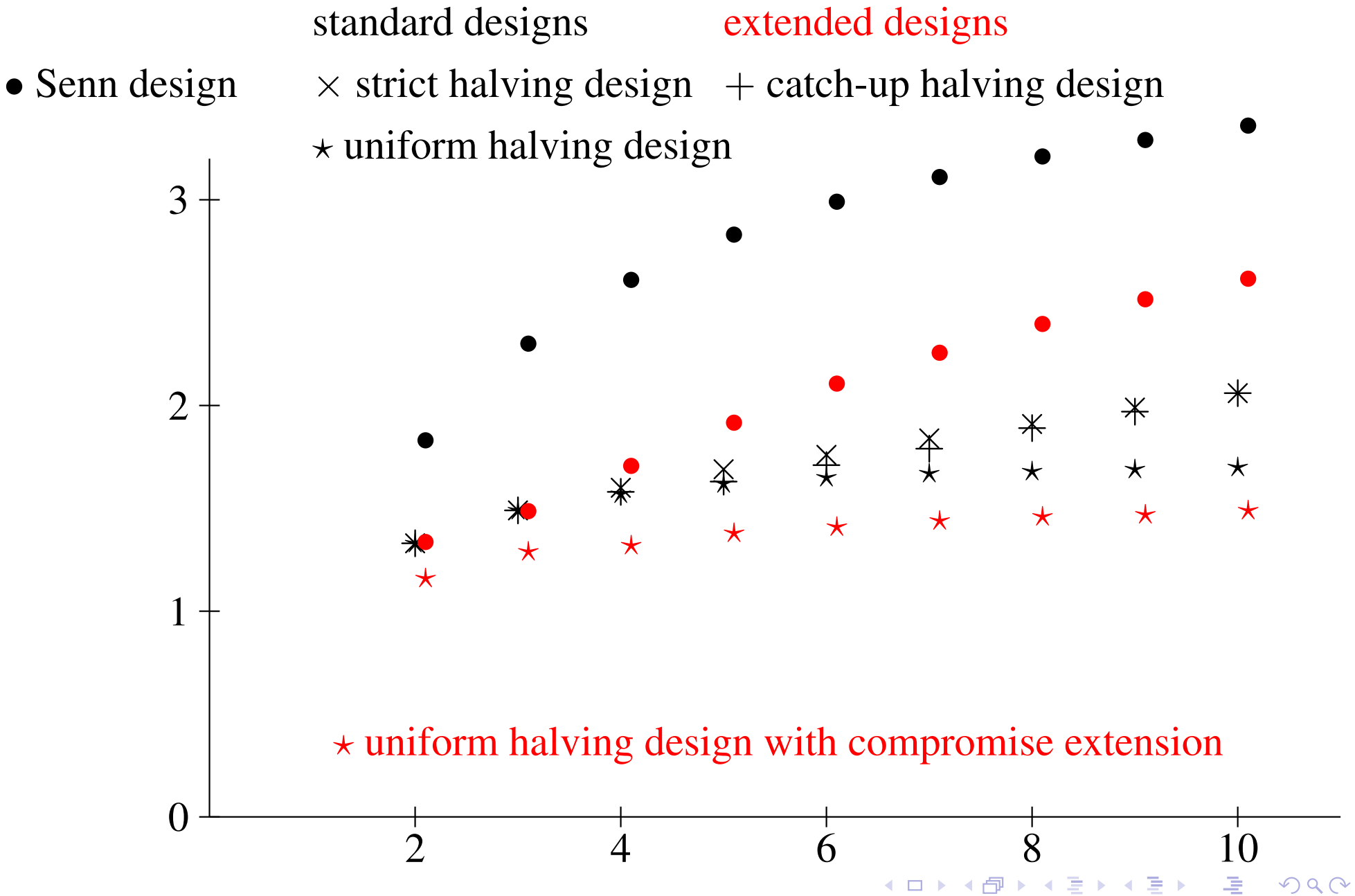

Two designs for 4 doses using 40 subjects

St T

Numbers of subjects

Dose	0	1	2	3	4
Cohort 1	2	8	0	0	0
Cohort 2	2	0	8	0	0
Cohort 3	2	0	0	8	0
Cohort 4	2	0	0	0	8

Actual pairwise variances/σ^2

	1	2	3	4
0	0.625	0.625	0.625	0.625
1		1.250	1.250	1.250
2			1.250	1.250
3				1.250

Ex UH Co

Dose	0	1	2	3	4
Cohort 1	4	4	0	0	0
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Cohort 3	1	1	2	4	0
Cohort 4	1	1	1	1	4
Cohort 5	1	1	1	2	3

	1	2	3	4
0	0.222	0.285	0.348	0.370
1		0.285	0.348	0.370
2			0.330	0.378
3				0.375

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Actual pairwise variances/σ^2

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0	0.625	0.625	0.625	0.625
1		1.250	1.250	1.250
2			1.250	1.250
3				1.250

average 1.00

Ex
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Dose	0	1	2	3	4
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1		0.285	0.348	0.370
2			0.330	0.378
3				0.375

average 0.33

Random cohort effects

Now assume that the expectation of the response of a subject who gets dose i in cohort k is τ_i, and that cohort effects are uncorrelated random variables with common variance σ_C^2.

$$\text{Put } \mathbf{C}_{\alpha\beta} = \begin{cases} 1 & \text{if subjects } \alpha \text{ and } \beta \text{ are in the same cohort} \\ 0 & \text{otherwise.} \end{cases}$$

Then the variance-covariance matrix of the responses is

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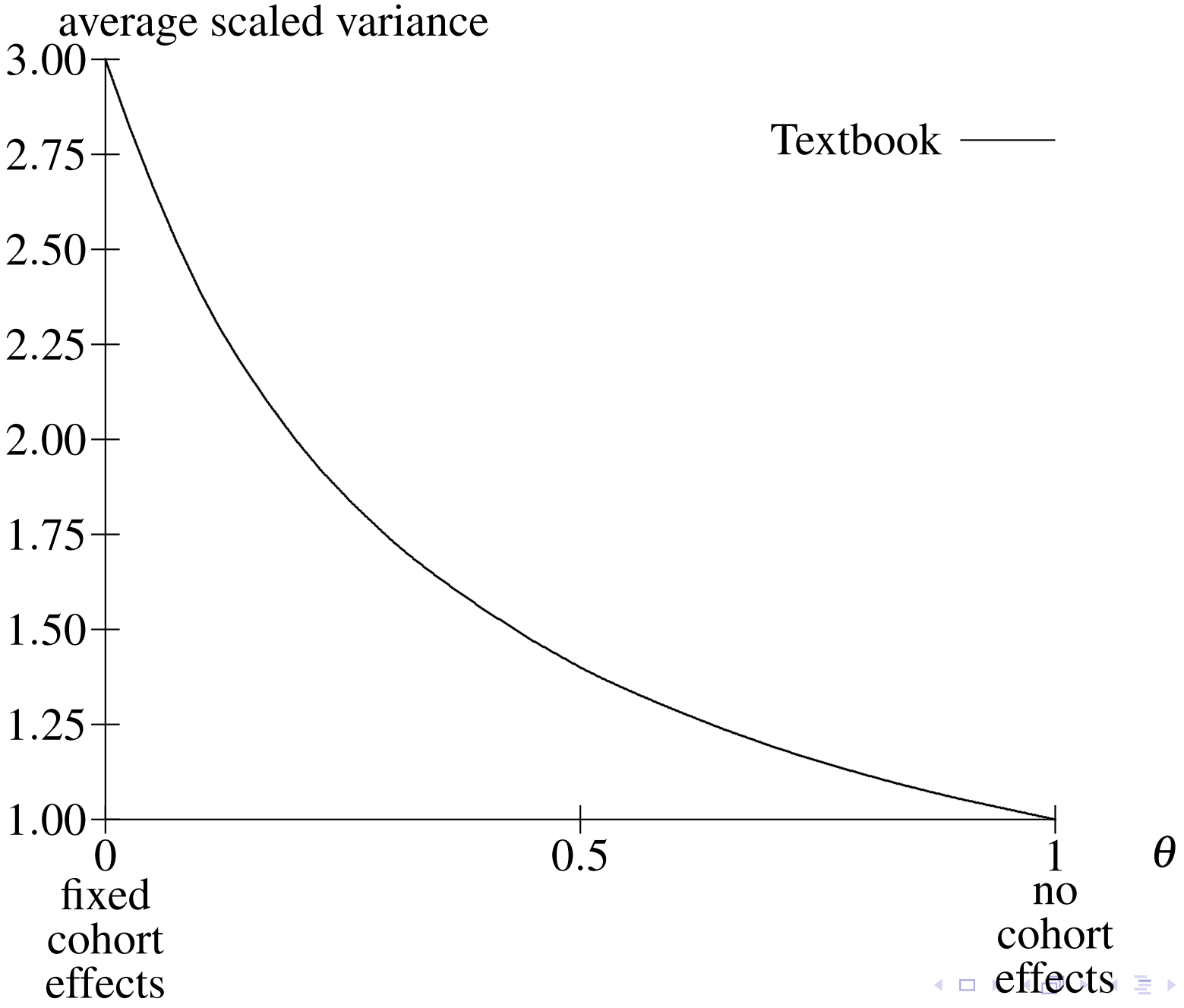
$$\sigma^2\mathbf{I} + \sigma_C^2\mathbf{C} \quad = \quad \sigma^2 \underbrace{\left(\mathbf{I} - \frac{1}{m}\mathbf{C}\right)}_{\text{within cohorts}} \quad + \quad \sigma^2\theta^{-1} \underbrace{\frac{1}{m}\mathbf{C}}_{\text{between cohorts}}$$

where $\sigma^2 + m\sigma_C^2 = \theta^{-1}\sigma^2$,
so $\theta \in [0,1]$ with $\theta = 0$ if cohort effects are fixed
$\theta = 1$ if cohort effects are zero.

Average scaled variance for 3 doses in 3 cohorts



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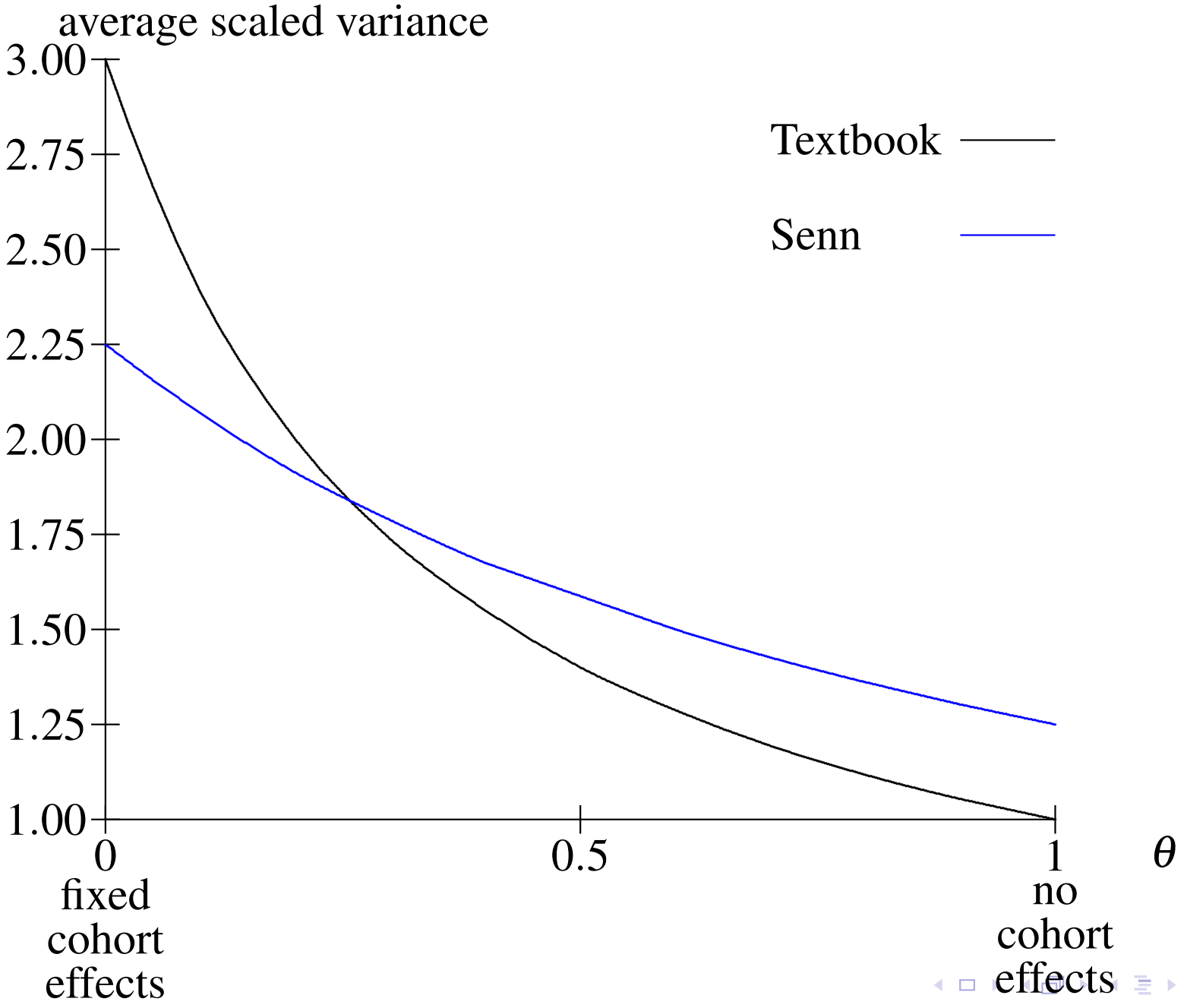

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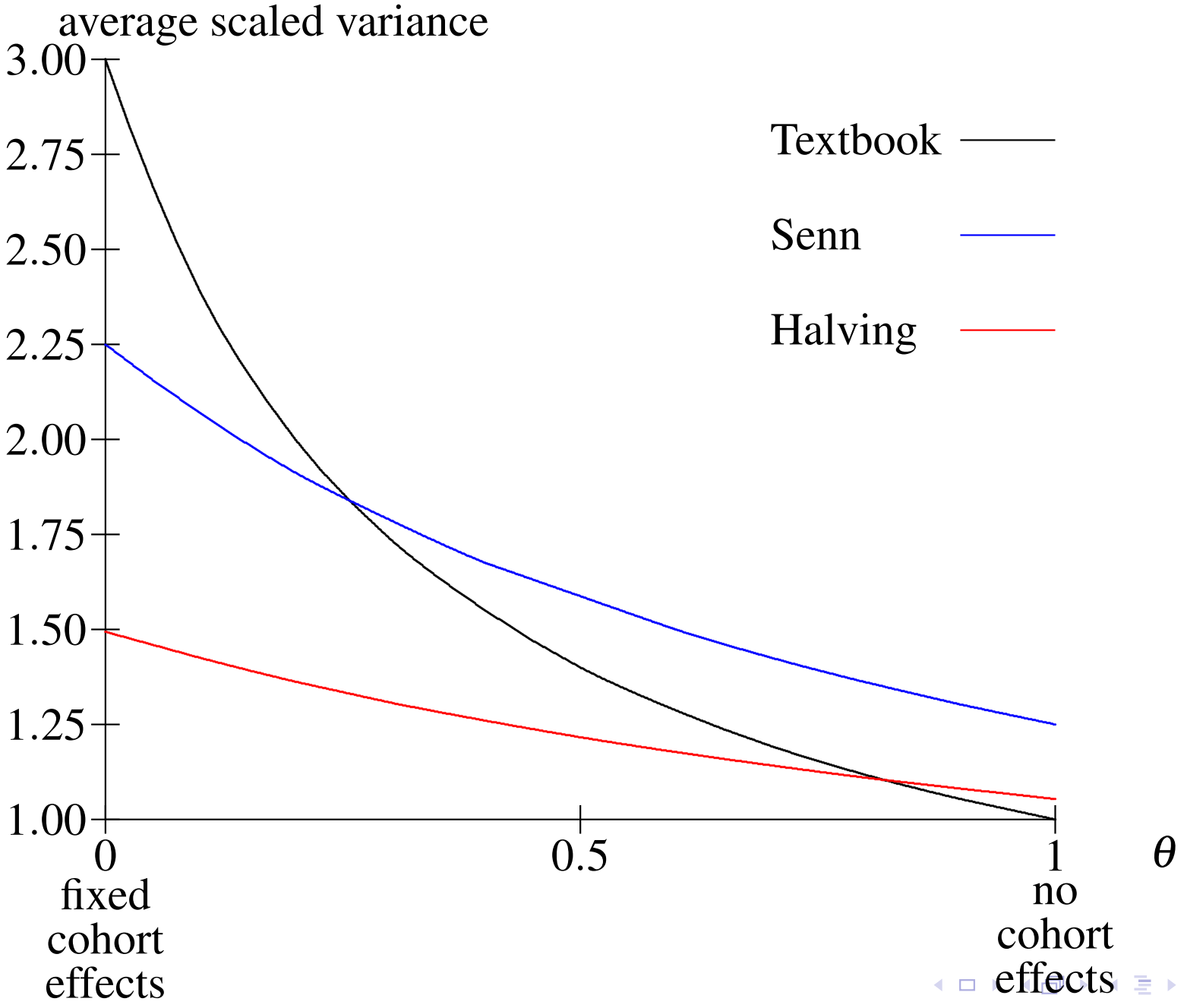
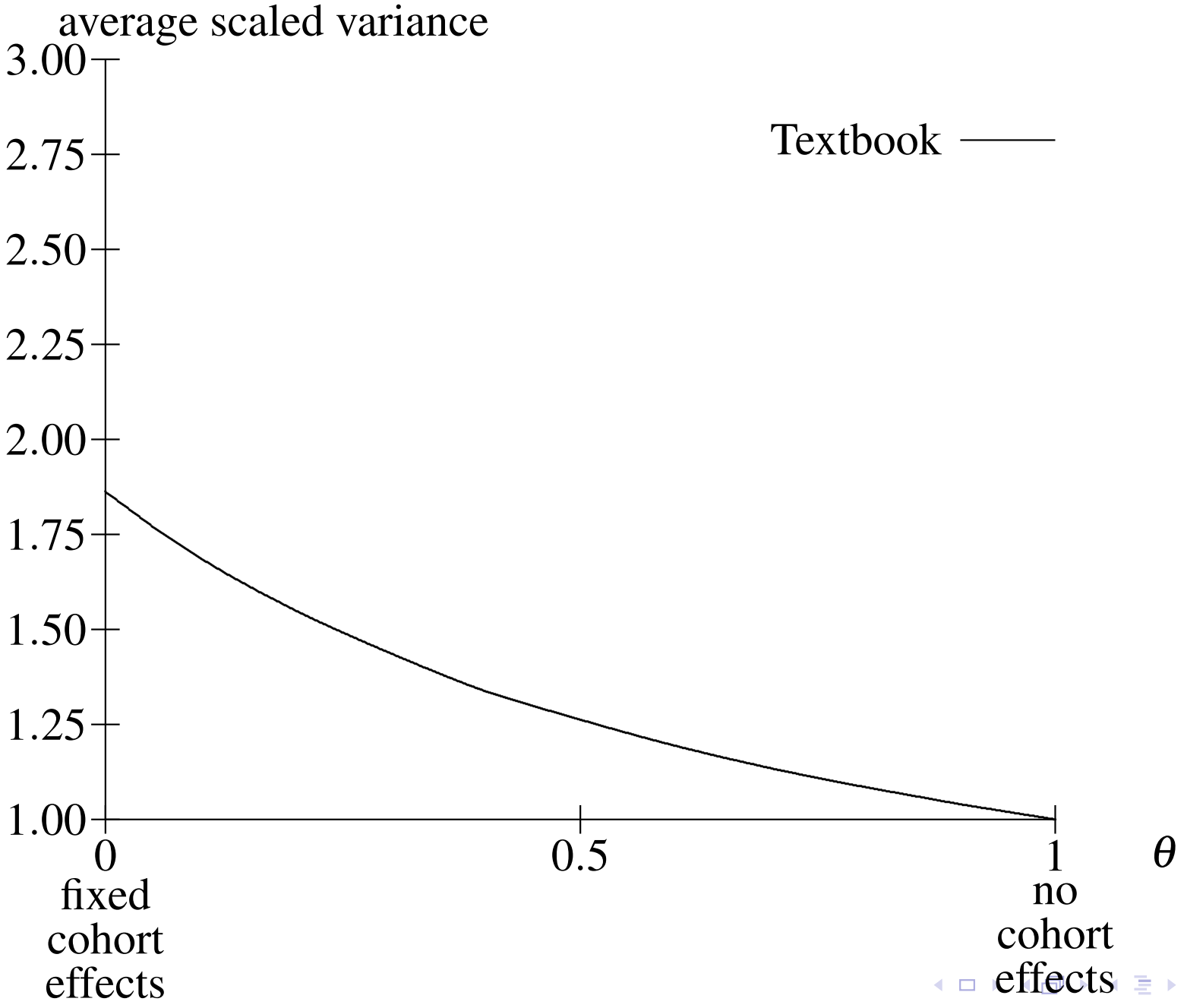


Average scaled variance for 3 doses in 4 cohorts



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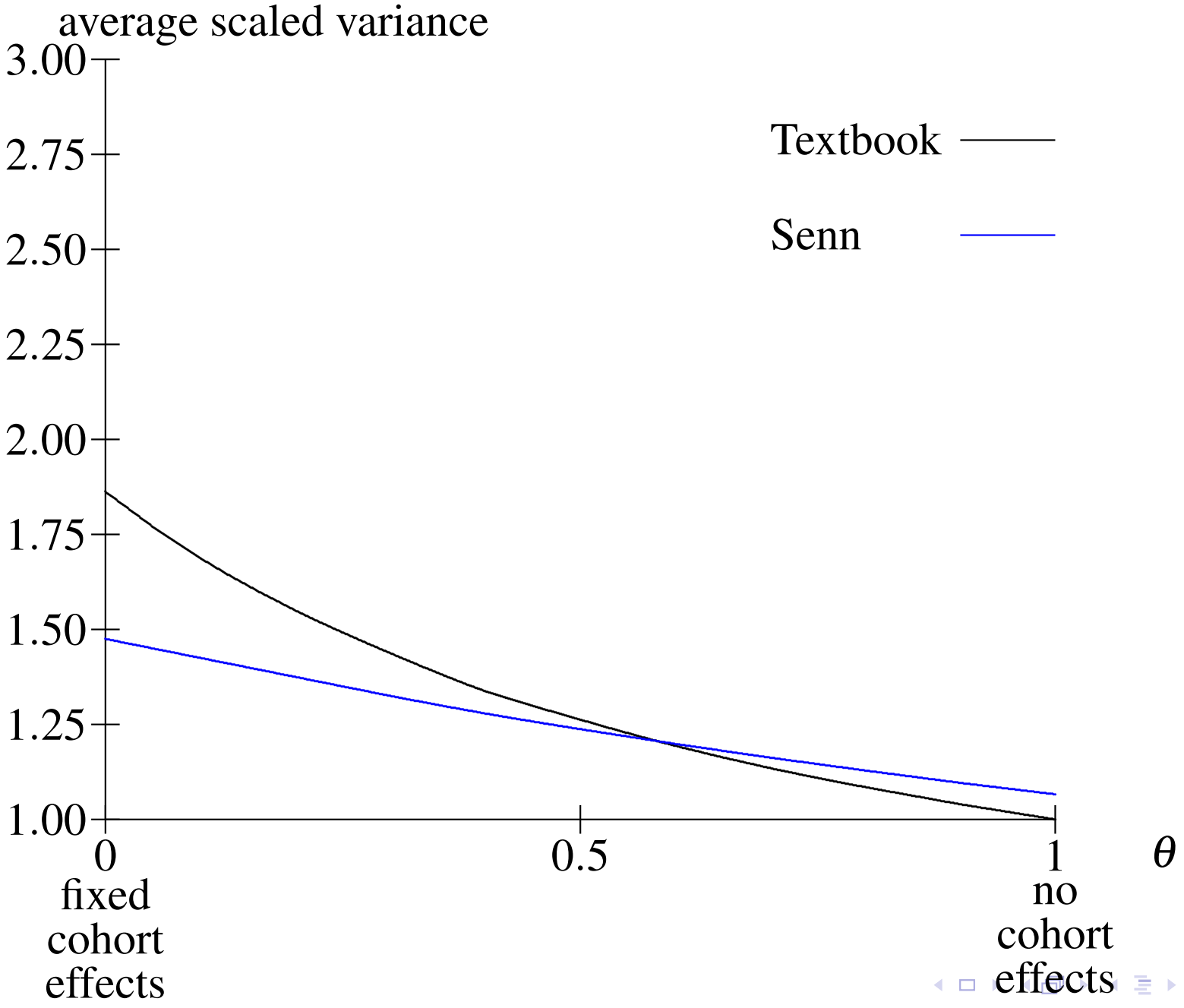

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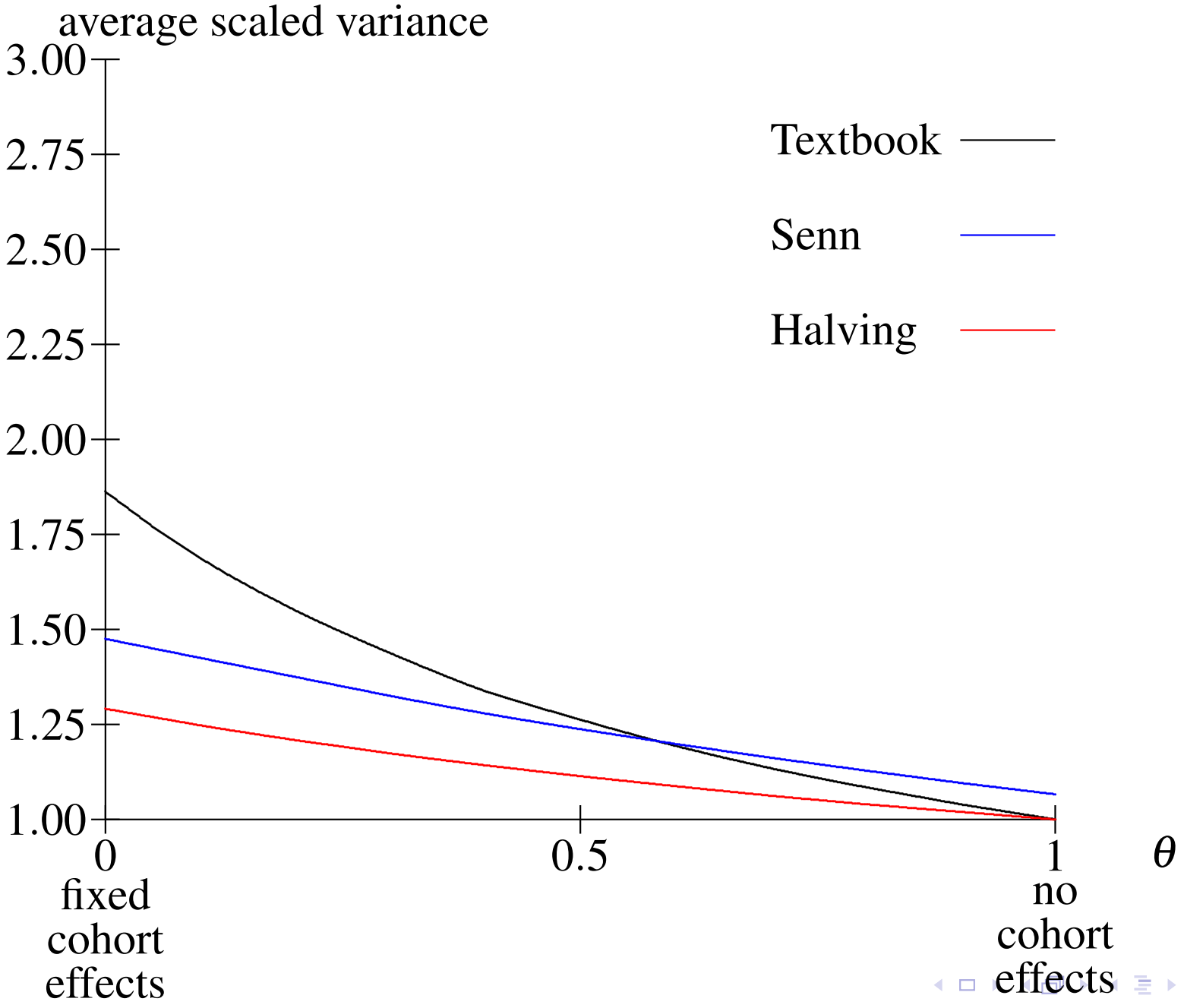

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Both types can be described by the following simple rule:

Principle

In each cohort,
half of the subjects should be distributed (approximately) equally among all the treatments that have been used in any previous cohort; the remaining subjects should be used to make the replication so far as equal as possible by compensating for previous under-replication.

Advantages of the halving designs

- Variance is reduced by a factor of two or more.

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- If the trial has to be stopped early because dose i is harmful, then the previous $i-1$ cohorts form the recommended standard design for $i-1$ doses; if desired, they can be followed by an extra cohort for treatments $0, \ldots, i-1$ only.

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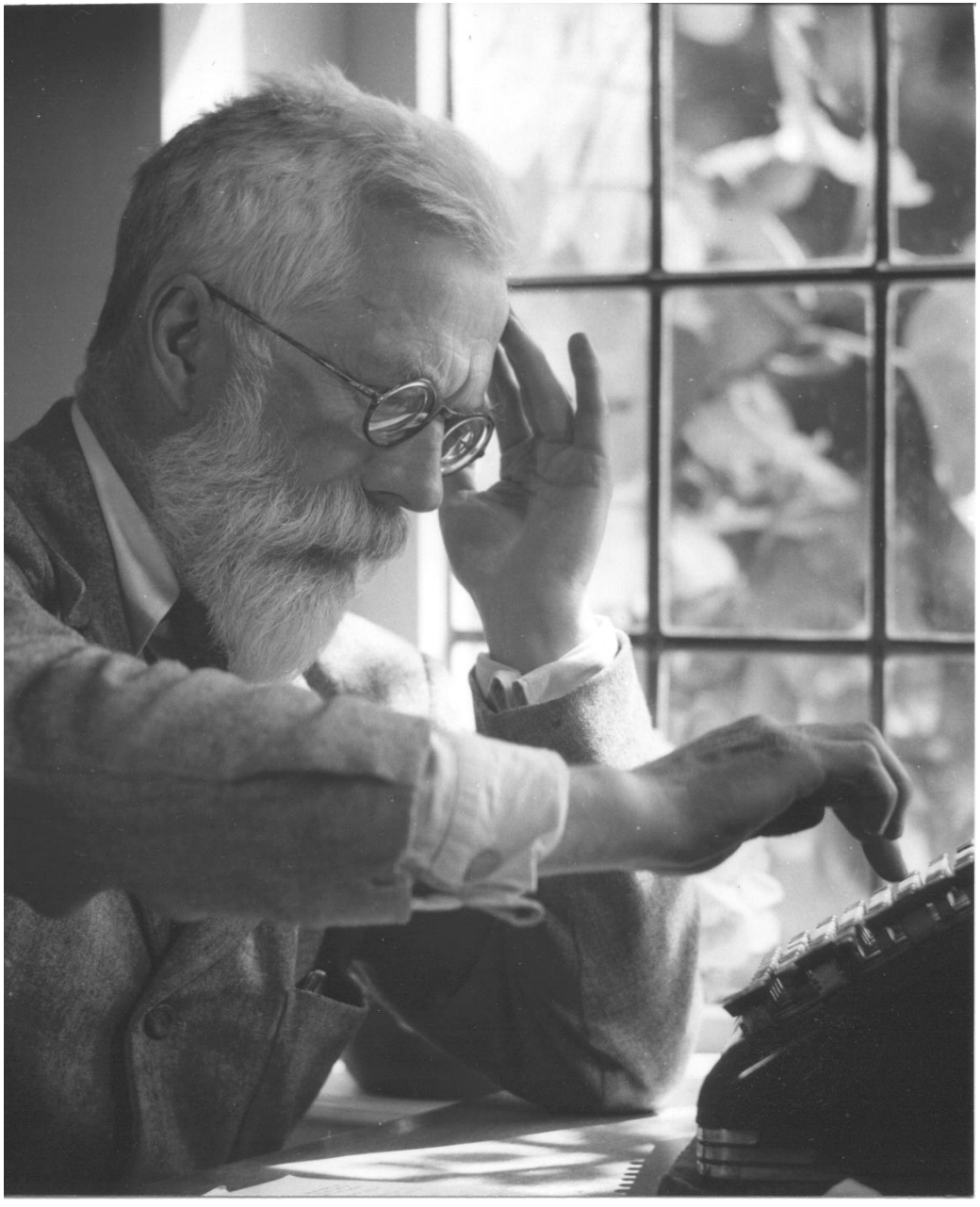
- If the trial has to be stopped early because dose i is harmful, then the previous $i-1$ cohorts form the recommended standard design for $i-1$ doses; if desired, they can be followed by an extra cohort for treatments $0, \ldots, i-1$ only.
- If cohort effects are small and random, the variance is very little more than for the textbook design.

Advantages of the halving designs

- Variance is reduced by a factor of two or more.
- The allocation rule is simple,
  and can be applied to any number of subjects per cohort.
- If the trial has to be stopped early because dose i is harmful, then fewer subjects will have been exposed to dose i than would have been with the textbook design.
- If the trial has to be stopped early because dose i is harmful, then the previous $i-1$ cohorts form the recommended standard design for $i-1$ doses; if desired, they can be followed by an extra cohort for treatments $0, \ldots, i-1$ only.
- If cohort effects are small and random, the variance is very little more than for the textbook design.
- Blinding is more effective than in textbook designs.

R. A. Fisher Memorial Lecture



Applying experience from agricultural field trials to dose-escalation trials in humans.

I hope he would have approved.