Being Realistic About Unmeasured Biases in Observational Studies

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A Version of a Seminar Given at Harvard's HDSI on 7 March 2024

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- Although we always adjust for measured covariates, treated and control groups may nonetheless **differ in terms of covariates that were not measured**.
- **That is**: without random assignment, the probability of treatment may depend upon relevant covariates that were not measured.
- This is **the main source of controversy** in observational studies, and it **organizes the design and analysis** of an observational study.

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- Perhaps surprisingly, **evidence of unmeasured bias** may make an observational study insensitive to larger unmeasured biases.
- The example has **several control groups**, so the logic of several control groups will be briefly discussed.

Some references

- Bahadur efficiency of observational block designs. *J. Am. Statist. Assoc.*, 2024, to appear, doi:10.1080/01621459.2023.2221402.
- Can we reliably detect biases that matter in observational studies? *Statist. Sci.* 2023;38:440-457.
- Sensitivity analyses informed by tests for bias in observational studies. *Biometrics* 2023;79:475-487.
- A second evidence factor for a second control group. *Biometrics* 2023;79:3968-3980.
- Design sensitivity in observational studies. Biometrika 2004;91:153-164.
- *Design of Observational Studies*, 2^{nd} edition, New York: Springer, 2020.
- (with D.B. Rubin) Propensity scores in the design of observational studies for causal effects. Biometrika, 2023;110:1-13.

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- A **sensitivity analysis talks** about unmeasured biases, but it is computed from – it **is a function of – observable data** from observable distributions. Change the observable distributions – change the study design – change the analysis and you change the sensitivity to unmeasured biases.
- **Without guidance from statistical theory** about the previous point, it is easy to make poor decisions in design and analysis, reporting that your results are sensitive to small biases when they are not.

Example: HDL Cholesterol and Light Daily Alcohol

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- Purely as a methodological example, will look at a small corner (and alas less important) corner of this topic, namely whether light daily alcohol consumption increases HDL cholesterol.
- NHANES data are available as `aHDL` in my `weightedRank` package in `R`, and documented in the data appendix to my *Biometrics* 2023;79:475-487 article.

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- Control group B (=former Binge drinker) had a period in their lives when they engaged in binge drinking on most days, but stopped, and currently drinks, if at all, on at most one day a week (i.e., 52 days in the past year). (median 4 drinks/year)

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- Take a moment and think about people in these groups.

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- **Plus** a binary indicator of whether they were in a NHANES subsample that measured methylmercury levels in blood (200 blocks yes, 206 blocks no).

Table: Covariates **Before=Be** and **After=Af** matching, and the remainder that was **Not** matched . D=daily, N=never, R=rarely, B=past binger. All D's were matched.

	Sample Size			Female %			Age			Education		
	Be	Af	Not	Be	Af	Not	Be	Af	Not	Be	Af	Not
D	406	406	0	**34**	34		57	57		**4.1**	4.1	
N	1536	406	1130	**71**	34	84	51	57	50	3.2	3.8	2.9
R	1237	406	831	**72**	34	90	53	56	51	3.4	3.9	3.2
B	914	406	508	**29**	34	25	54	56	53	3.1	3.9	**2.5**

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- **Blocks of size 4 are a better design** (1-treated-to-3-controls), better for example than pairs (even many more pairs). Selection bias is harder to distinguish from a treatment effect in pairs or unmatched comparisons, and easier to distinguish with 1-to-3 blocks. (JASA 2024, Biometrics 2013;69:118-127).

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- **An unaffected outcome, methylmercury**. WHO & CDC say almost all human exposure to methylmercury comes from eating fish/shellfish. Those who have looked for methylmercury in alcoholic beverages haven't found it. Can we use this?

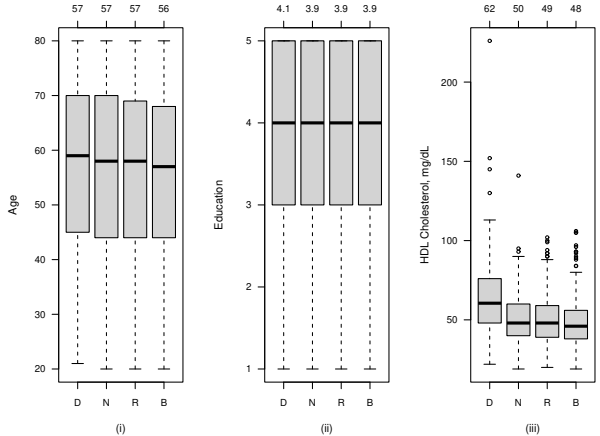

Figure: $I = 406$ matched blocks. Each group is 33.7% female. M-estimates of location are at the top. D = daily drinking, N = never, R = rare, B = formerly a frequent binge drinker. 6 Pairwise Holm comparisons: D-vs-each control, $P \leq 10^{-16}$, each control-vs-control, $P \geq 0.21$.

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- Tests use Friedman or Cochran Q

Table: Blocked comparisons. $\overline{X}$ is the mean, M is the median.

Variable		Alcohol Group				
D=daily, N=never, R=rarely, B=past binge		D	N	R	B	P-value
Ever tried marijuana or hashish?	%	73	9	25	75	0.0000000
Ever tried cocaine, heroin, meth?	%	29	4	4	37	0.0000000
Methylmercury in blood (μg/L)	M	1.12	0.54	0.56	0.56	0.0000008
Been to dentist in past year?	%	67	58	57	48	0.0000006

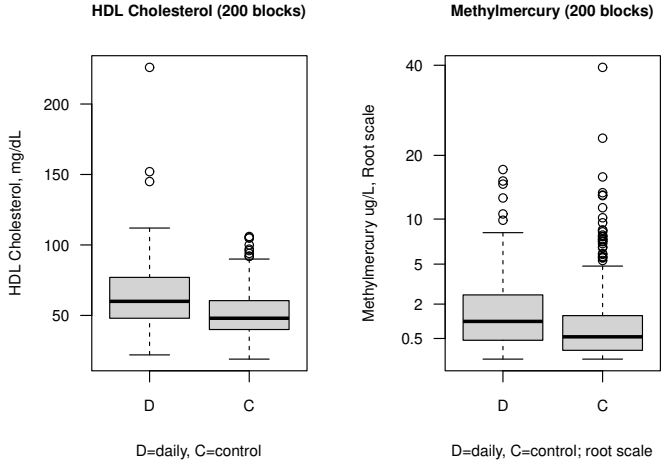

Figure: 200 blocks with methylmercury data. $\sqrt{y}$ scale on right. Control groups are merged.

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- **Covariates**: We also observe a covariate $\mathbf{x}$ and are concerned about unobserved covariates u.
- **Randomized experiment**: Z is determined by a coin flip, perhaps after blocking or matching for some function $\mathbf{h}(\mathbf{x})$. The coin is "fair" in not depending upon $(r_T,\ r_C)$, or more precisely ...

Ignorable Treatment Assignment & Principal Unobserved Covariate

- Treatment assignment is **ignorable given the observed covariates $\mathbf{x}$** if

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- Suppose $0 < \zeta < 1$. **Two key facts follow**. Then, **(i)** treatment assignment is ignorable given $\mathbf{x} \iff e(\mathbf{x}) = \zeta$, and **(ii)** treatment assignment is always ignorable given $\{\mathbf{h}(\mathbf{x}),\, \zeta\}$ for any function $\mathbf{h}(\cdot)$.

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- Importantly, $\zeta = \Pr(Z = 1 \,|\, r_T,\, r_C,\, \mathbf{x})$ is **a function of** $(r_T,\, r_C,\, \mathbf{x})$.

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- Our **worry** is that the **blocking has not controlled the principal unobserved covariate**, ζ, so that $\zeta_{ij} \neq \zeta_{ij'}$ for some i, j.
- **Could happen in any of three ways**: (i) controlling for $\mathbf{h}(\mathbf{x})$ did not control for $e(\mathbf{x})$, (ii) controlling for $\mathbf{h}(\mathbf{x})$ did not control for ζ_{ij} because treatment assignment is not ignorable given $\mathbf{x}$, or (iii) both (i) and (ii).

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- For example, in a randomized block design,

$$\frac{1}{J} = \Pr(Z_{ij} = 1 \,|\, \mathcal{F}, \mathcal{Z})$$

Bias Within Blocks; Introducing θ_{ij}

- Given $\mathcal{F}$, the chance that ij is the only treated individual in block i is the chance that $Z_{ij} = 1$ and $Z_{ik} = 0$ for $k \neq i$

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- So, conditioning on $\sum_{k=1}^{J} Z_{ik} = 1$ says $\Pr\left(Z_{ij} = 1 \,|r_{Tij}, r_{Cij}, \mathbf{x}_{ij}, \sum Z_{ik} = 1\right)$ equals

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  say, where $1 = \sum_{j=1}^{J} \theta_{ij}$ for each i.

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- Sensitivity analysis in terms of the principal unobserved covariate $\zeta = \Pr(Z = 1 \,|\, r_t, r_C, \mathbf{x})$

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- Start with a **collection of closely related statistics**, including familiar and unfamiliar statistics. See how the results vary in this collection.

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- For $J \geq 2$, taking $\varphi(w_i) = 1$ yields the blocked Wilcoxon rank sum test (Lehmann 1975 *Nonparametrics*, §3.3), and taking $\varphi(w) = w$ yields Quade's (1979, JASA) statistic.

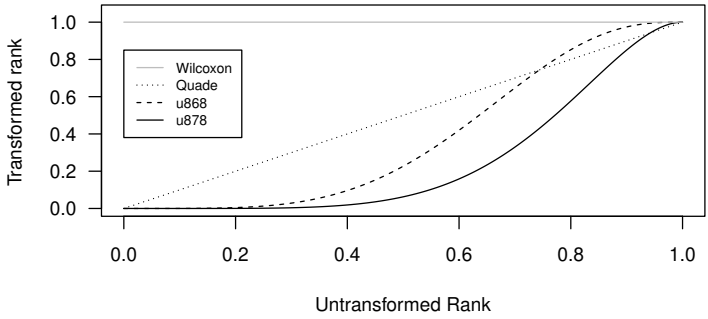

Figure: Four weight functions $\varphi(w)$ of the block ranges.

The Set B_Γ of Biased Treatment Assignments $\boldsymbol{\theta}$

- Define B_Γ as the set of all $\boldsymbol{\theta} = (\theta_{11}, \ldots, \theta_{IJ})$ such that:

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- A **randomized block design** has $\boldsymbol{\theta} = \overline{\boldsymbol{\theta}}$ where $\overline{\theta}_{ij} = 1/J$ or equivalently $\boldsymbol{\theta} \in B_1$.
- The **central problem in an observational block design** is that there is no basis for assuming $\boldsymbol{\theta} \in B_1$. For $\Gamma > 1$, $\boldsymbol{\theta} \in B_\Gamma$ does not identify $\boldsymbol{\theta}$.

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- Reject H_0 if $T \geq t$ where $T = \sum_i \varphi(w_i) \sum_j Z_{ij}\, q_{ij}$ and $\Pr(\mathbf{Z} = \mathbf{z} \,|\mathcal{F}, \mathcal{Z}) = \prod_i \prod_j \theta_{ij}^{z_{ij}}$.

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- For a given $\Gamma \geq 1$, **the max P-value** for $\boldsymbol{\theta} \in B_\Gamma$ is

$$P_\Gamma = \max_{\boldsymbol{\theta} \in B_\Gamma} \sum_{\mathbf{z} \in \mathcal{Z}} \left[\sum_i \varphi(w_i) \sum_j z_{ij}\, q_{ij} \geq t\right] \prod_i \prod_j \theta_{ij}^{z_{ij}}$$

Sensitivity Analysis, Alcohol Example, Comparing 4 Statistics

Table: Upper bounds on one-sided P-values testing no effect of light daily alcohol on HDL Cholesterol. In a column, **bold** is a P-value near 0.05. Hammond's (1964, *JNCI*) study of smoking and lung cancer is sensitive to a bias of $\Gamma = 6$. The choice of test statistic matters.

Γ	Wilcoxon	Quade	U868	U878
1	0.0000	0.0000	0.0000	0.0000
2	0.0000	0.0000	0.0000	0.0000
3.5	**0.0603**	0.0002	0.0000	0.0000
4	0.3478	0.0052	0.0003	0.0001
4.5	0.7401	**0.0447**	0.0028	0.0010
5	0.9429	0.1775	0.0154	0.0050
5.5	0.9926	0.4123	**0.0537**	0.0174
6	0.9994	0.6642	0.1340	**0.0456**

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- Consider the usual Gaussian linear model, additive block effects, constant within block variance σ^2. Estimator is the mean of the treated-minus-average control difference.
- With M 1-to-1 pairs, estimator has variance $2\sigma^2/M$. With I 1-to-3 blocks, estimator has variance $(1 + 1/3)\sigma^2/I$. As far as the standard error goes, M pairs is about the same as I 1-to-3 blocks if $I = (1 + 1/3)M/2$. For $M = 406$ pairs, take $I = 2M/3 \doteq 271$ blocks.

Fair Comparison, Pairs Versus Blocks

Table: Bounds on P-values for the hypothesis of no effect. Last P-value ≤ 0.05 is in **bold**.

	406 1-to-1 Pairs				271 1-to-3 Blocks			
Γ	Wilcoxon	Quade	U868	U878	Wilcoxon	Quade	U868	U878
1	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
2	**0.006**	**0.000**	0.000	0.000	0.000	0.000	0.000	0.000
3.5	0.994	0.233	**0.013**	0.003	**0.044**	0.001	0.000	0.000
4	1.000	0.584	0.064	0.015	0.224	0.008	0.001	0.001
4.5	1.000	0.851	0.182	**0.046**	0.532	**0.045**	0.007	0.004
5	1.000	0.963	0.359	0.106	0.799	0.143	**0.024**	0.014
5.5	1.000	0.993	0.552	0.198	0.937	0.310	0.063	**0.034**
6	1.000	0.999	0.720	0.311	0.985	0.511	0.131	0.069

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$$r_{Tij} = \mu + \beta_i + \tau + \varepsilon_{Tij}, \qquad r_{Cij} = \mu + \beta_i + \varepsilon_{Cij}, \qquad r_{Tij} - r_{Cij} = \tau + \varepsilon_{Tij} - \varepsilon_{Cij},$$

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- **Treated-minus-control pair difference** in block i is $r_{Tij} - r_{Cij'} = \tau + \varepsilon_{Tij} - \varepsilon_{Cij'}$ is symmetric about τ. Numerical work takes $1 = \sqrt{\text{var}(\varepsilon_{Tij} - \varepsilon_{Cij'})}$ and $\tau = 1/2$.

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Can We Understand This Theoretically?

- Suppose that we have some **model that generated the data**, I blocks of size J, one treated individual per block. Let $I \to \infty$.
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- If $\tau \neq 0$, then it is in precisely this sort of case (a so-called **favorable situation**) that you hope to report insensitivity to unmeasured biases. Will you?

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$$\rho_\Gamma = -\lim_{I\rightarrow\infty} \frac{\log(\alpha_{\Gamma I})}{I} \quad \text{so that} \quad \alpha_{\Gamma I} \approx \exp(-I\rho_\Gamma) \text{ as } I \rightarrow \infty.$$

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- The ratio of two Bahadur slopes is the Bahadur (1960) relative efficiency. Better than Pitman efficiency for observational studies because Pitman lets $\tau \rightarrow 0$ as $I \rightarrow \infty$.

Some Design Sensitivities

■ What you saw in the example happens in the limit as $I \to \infty$ for the block model with Normal errors.

Table: Design sensitivity $\widetilde{\Gamma}$ with Normal errors and $\tau = 1/2$ of the standard deviation of a treated-minus-control pair difference. The best result in each situation is in **bold**.

		Wilcoxon	Quade	U868	U878
$J = 2$	Pairs	2.2	3.2	4.2	**5.1**
$J = 4$	1-to-3 Blocks	3.5	4.4	5.2	**5.7**

■ Remember: For $J = 2$, the blocked Wilcoxon statistic is the sign test and Quade's statistic is Wilcoxon's signed rank test.

■ Results for (i) $\tau = 1/3$, (ii) errors with t-distributions with 5 degrees of freedom, and (iii) heterogeneous treatment effects, $\tau = 1/3$ or $2/3$ with probability 1/2, are in R. (2024, JASA).

Table: **Efficiency at** $\Gamma = 2$. Comparing Block Sizes $J = 2$ to $J = 4$ in a sensitivity analysis. Top half is pure block size. Bottom half is block size plus change in test statistic.

Sensitivity Analysis Performed with $\Gamma = 2$				
	$\tau = 1/2$		$\tau = 1/3$	
J	Normal	t_5	Normal	t_5
	U868 compared to U868 at $J = 2$			
2	1.00	1.00	1.00	1.00
3	1.37	1.23	2.14	1.66
4	1.83	1.63	3.07	2.29
	U868 compared to SRS at $J = 2$			
2	1.58	1.26	8.08	3.05
3	2.16	1.55	17.26	5.07
4	2.89	2.04	24.81	6.98

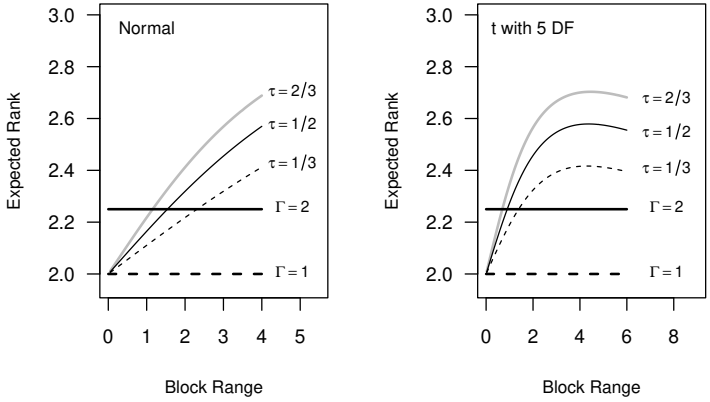

Figure: In 1-to-2 blocks of size $J = 3$, the curves show the expected within block rank — 1, 2, or 3 — conditionally given the within block range. Horizontal lines show maximum expectation with a bias of Γ and no treatment effect.

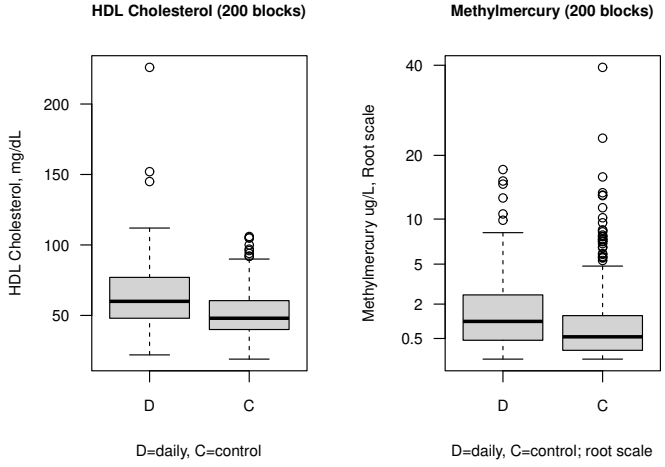

Figure: 200 blocks with methylmercury data. $\sqrt{y}$ scale on right. Control groups are merged.

Unaffected Outcomes

- What should we make of the evidence from methylmercury of biased treatment assignment evident, $\boldsymbol{\theta} \neq \overline{\boldsymbol{\theta}}$, where $\overline{\theta}_{ij} = 1/J, \forall i,j$ and $B_1 = \{\overline{\boldsymbol{\theta}}\}$?

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- In parallel, using the same people in the same blocks, no $\boldsymbol{\theta} \in B_{1.993}$ is plausible if alcohol does not affect methylmercury levels, having been rejected in a 0.05 level test.
- The sensitivity analysis for HDL cholesterol doesn't require amendment, but it does leave us wondering about $\boldsymbol{\theta} \in B_{3.614} - B_{1.993}$; i.e., in $B_{3.614}$ but not in $B_{1.993}$.

Gaps Between Tests for Bias and Sensitivity Analyses

- Part of the boundary of $B_{3.614}$ is troublesome, because there is a $\boldsymbol{\theta} \in B_{3.615}$ that would lead us to accept no effect of alcohol on HDL cholesterol. Call these **troublesome boundary points** $\mathcal{J}$. What does methylmercury say about the troublesome boundary points $\mathcal{J}$?

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- We would like to say: "no $\boldsymbol{\theta} \in \mathcal{J}$ is plausible." That would mean that the HDL cholesterol comparison isn't sensitive at $\Gamma = 3.614$ after all, but only to a larger Γ. If this were true, say that there is **no gap** between the test for bias using methylmercury and the sensitivity analysis for HDL cholesterol.

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- We can **test each of the troublesome** $\boldsymbol{\theta} \in \mathcal{J}$ using the methylmercury data. When we do this, the maximum P-value testing $H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0$ for $\boldsymbol{\theta}_0 \in \mathcal{J}$ is 1.17×10^{-7}.

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- The troublesome biases $\boldsymbol{\theta} \in \mathcal{J}$ are not plausible; so, there is **no gap**, and Γ must be larger than $\Gamma = 3.614$ to explain the higher HDL cholesterol levels of light daily drinkers. The evident bias in methylmercury **strengthened** the causal claim.

Confidence Set for $\boldsymbol{\theta}$; Informed Sensitivity Analyses

- What if we tested all $\boldsymbol{\theta}$'s? Let Θ be the set of all $\boldsymbol{\theta}_0$'s such that: (i) $1 = \sum_{j=1}^{J} \theta_{0ij}$, (ii) $0 \leq \theta_{0ij} \leq 1$, and (iii) the test using methylmercury does not reject $H_0 : \boldsymbol{\theta} = \boldsymbol{\theta}_0$ at the 0.05 level. An infinite set of IJ dimensional $\boldsymbol{\theta}_0$'s.

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- $\Gamma = 3.614$ is $(\Lambda,\ \Delta) = (6,\ 8.7)$, while $\Gamma = 3.82$ is $(\Lambda,\ \Delta) = (6,\ 10.1)$.

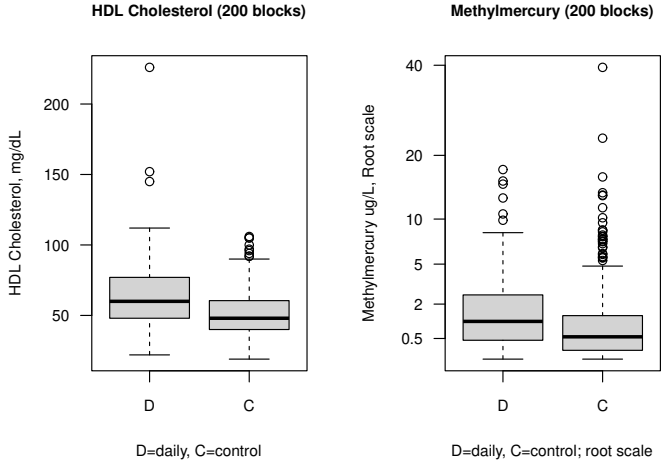

Figure: **Summary**: $\theta \neq \overline{\theta}$ from right. The smallest Γ explaining the right is too small to explain the left. The smallest Γ that explains both sides is larger than the smallest Γ that explains the left.

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- Statistical theory can aid in avoiding mistakes that exaggerate the sensitivity to unmeasured biases. Large mistakes are possible in design and analysis.
- Design sensitivity and Bahadur efficiency of a sensitivity analysis are two tools that guide design and analysis.
- Evidence of biased treatment assignment may increase insensitivity to unmeasured bias.

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- Trivially,

$$\Pr(Z = 1|\zeta) = \mathrm{E}\{\Pr(Z = 1|\mathbf{x}, r_T, r_C, \zeta) \,|\, \zeta\}$$
$$= \mathrm{E}\{\Pr(Z = 1|\mathbf{x}, r_T, r_C) \,|\, \zeta\} = \mathrm{E}(\zeta \,|\, \zeta) = \zeta,$$

  as required to complete the proof.

R Code from `weightedRank`

```
ef2C(hdl3,gamma=4,upsilon = 3.75)$pvals
```

TreatedVSControl1 0.11069568
Control2vsOthers 0.11173143
Combined 0.04667447

```
p1=dwgtRank(hdl3[,1:2],gamma=4,m=8, m1=7, m2=8)$pval
```

```
p2=dwgtRank(hdl3[,3:1],gamma=3.75,alternative="less",m=8,m1=8,m2=8,
range=FALSE,scores=c(1,2,5))$pval
```

```
c(p1,p2)
```

0.1106957 0.1117314

```
sensitivitymv::truncatedP(c(p1,p2))
```

0.04667447

Bahadur Efficiencies for Pairs, $J = 2$

Table: Efficiency of a sensitivity analysis at Γ **vs. U868** with Normal errors and $\tau = 1/2$ of the standard deviation of a treated-minus-control pair difference. The best result is in **bold**.

		Normal Errors, Paired Data, $J = 2$			
		Wilcoxon	Quade	U868	U878
Γ	$\widetilde{\Gamma}$	2.2	3.2	4.2	**5.1**
1		0.72	**1.05**	1.00	0.92
1.5		0.36	0.86	**1.00**	**1.00**
2		0.06	0.63	1.00	**1.11**
3		0.00	0.05	1.00	**1.70**
4		0.00	0.00	1.00	**15.56**

- By definition, efficiency of U868 is 1.00.
- Quade=Wilcoxon's signed rank best at $\Gamma = 1$, but not at $\Gamma = 1.5$.

Bahadur Efficiencies for 1-to-3 Blocks, $J = 4$

Table: Efficiency **relative to U868** with Normal errors and $\tau = 1/2$ of the standard deviation of a treated-minus-control pair difference. The best result is in **bold**.

		Normal Errors, 1-to-3 Blocks, $J = 4$			
		Wilcoxon	Quade	U868	U878
Γ	$\widetilde{\Gamma}$	3.5	4.4	5.2	**5.7**
1		1.08	**1.21**	1.00	0.85
1.5		0.83	**1.11**	1.00	0.89
2		0.58	**1.01**	1.00	0.93
3		0.15	0.76	1.00	**1.04**
4		0.00	0.23	1.00	**1.41**

- Quade's statistic does well for $\Gamma \leq 2$ but falls behind for $\Gamma \geq 3$.