Addressing Bias from Unmeasured Dispositions in Observational Studies

Paul R. Rosenbaum

November 2016

Basis for the talk

- Rosenbaum, P. R. (2006). Differential effects and generic biases in observational studies. *Biometrika* **93**, 573-586.
- Rosenbaum, P. R. (2013). Using differential comparisons in observational studies. *Chance* **26**, #3, 18-25.
- Zubizarreta, J. R., Small, D. S. and Rosenbaum, P. R. (2014). Isolation in the construction of natural experiments. *Annals of Applied Statistics* **8**, 2096-2121.
- Rosenbaum, P. R. (2017). Biases from general dispositions. Chapter 12 of *Observation and Experiment*, forthcoming.

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- And yet, these biases can be partially, perhaps completely addressed.
- These are generic unobserved biases (aka biases from general dispositions).
- They promote many treatments, not just the treatment that is the focus of your current study.
- Although they invalidate treatment-control comparison, they open up new possibilities for design and analysis.

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- Overadjust for observables to adequately adjust for unmeasured covariates.
- Sensitivity analysis for differential unmeasured biases.

Outline of the talk

- Brief motivation
- Sketch of theory
- Example: NSAIDS and Alzheimer's disease
- Example: Smoking and toxins in the blood
- Example: Seatbelts in car crashes
- Sketch of time-dependent version

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- Is that useful?

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- The mistake is to compare smokers and nonsmokers adjusting for whether you floss your teeth. That underadjusts for the unmeasured disposition.
- It only adjusts for one of the manifestations of the general disposition.
- But people who are not concerned with their health are taking many health related risks.

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- We compare smokers who floss to nonsmokers who don't floss.
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- We overadjust for flossing to adequately adjust for a lack of concern with health.
- Under a simple model, that comparison removes the bias from the general disposition. If that simple model is wrong, a sensitivity analysis can examine differential biases.

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- But perhaps we could use "not having been tested for glaucoma" in place of "not flossing" on the theory that being tested for glaucoma won't cause or prevent periodontal disease.

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- The differential comparison is the comparison of one treatment in lieu of the other, $\left(Z_{si}, Z'_{si}\right) = (1,0)$ to $\left(Z_{si}, Z'_{si}\right) = (0,1)$.

Potential outcomes and treatment assignment probabilities

- Each person si has four potential outcomes for the four potential treatment combinations, $\left(Z_{si}, Z'_{si}\right) = (1,1)$ or $(1,0)$ or $(0,1)$ or $(0,0)$, namely $(r_{11si}, r_{10si}, r_{01si}, r_{00si})$, and we observe one of these; see Neyman (1923) and Rubin (1974).

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- Treatment assignment probabilities: $\pi_{absi} = \Pr\left(Z_{si} = a, Z'_{si} = b \,\middle|\, r_{11si}, r_{10si}, r_{01si}, r_{00si}, x_{si}, u_{si}\right)$ for $a = 0, 1$ and $b = 0, 1$ with $1 = \pi_{11si} + \pi_{10si} + \pi_{01si} + \pi_{00si}$.

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  for $a = 0, 1$ and $b = 0, 1$ with
  $1 = \pi_{11si} + \pi_{10si} + \pi_{01si} + \pi_{00si}$.
- For distinct people in the population, treatment assignments are conditionally independent given $(r_{11si}, r_{10si}, r_{01si}, r_{00si}, x_{si}, u_{si})$.

When is it sufficient to adjust for observed covariates?

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  $1 = \pi_{11si} + \pi_{10si} + \pi_{01si} + \pi_{00si}$.
- Treatment assignment is ignorable given the strata s if $0 < \pi_{absi} = \zeta_{abs} < 1$ varies with s but not with i for $a = 0, 1$ and $b = 0, 1$. (Recall $x_{si} = x_{sj}$ for all s, i, j.)

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- But what if treatment assignment is not ignorable?

Some violations of ignorable assignment with only generic biases

- A Rasch model within each stratum s:

$$\pi_{absi} = \frac{\exp\left\{a\left(\kappa_s + \phi_s u_{si}\right)\right\}}{1 + \exp\left(\kappa_s + \phi_s u_{si}\right)} \times \frac{\exp\left\{b\left(\kappa_s' + \phi_s u_{si}\right)\right\}}{1 + \exp\left(\kappa_s' + \phi_s u_{si}\right)},$$

so π_{absi} varies with u_{si}. Were this model governing treatment assignment, it would not be sufficient to adjust for the strata.

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- A type of bivariate logit model with $1 = \pi_{00si} + \pi_{01si} + \pi_{10si} + \pi_{11si}$ and π_{absi} proportional to

$$\exp\left\{a\kappa_s + b\kappa_s' + ab\kappa_s^* + \phi_s(a+b)u_{si} + \psi_s abu_{si}\right\},$$

  so again treatment assignment is not ignorable given strata s.

Another violation of ignorable assignment with only generic biases

Tversky and Sattath (1979) preference tree with $1 = \pi_{00si} + \pi_{01si} + \pi_{10si} + \pi_{11si}$ and π_{absi} given by:

	$Z + Z'$	(Z, Z')	Prob
$\nearrow$	0	$(0, 0)$	π_{00si}
$\blacksquare \longrightarrow$	1	$(1, 0)$	$\pi_{10si} = \omega_s \varsigma_{si}$
		$(0, 1)$	$\pi_{01si} = (1 - \omega_s)\, \varsigma_{si}$
$\searrow$	2	$(1, 1)$	π_{11si}

where an i subscript indicates a quantity that may depend upon $(r_{11si}, r_{10si}, r_{01si}, r_{00si}, u_{si})$.

A general definition

- Let $\rho_{si} = \pi_{10si} / \pi_{01si}$.

Definition

There are only generic unobserved biases if ρ_{si} varies with s but not with i, that is, if

$$\rho_{si} = \frac{\pi_{10si}}{\pi_{01si}} = \lambda_s \quad (1)$$

for all s, i.

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- There are *differential biases* if (1) is false.

A basic fact: Differential ignorability

- If there are only generic unobserved biases, so $\rho_{si} = \pi_{10si} / \pi_{01si} = \lambda_s$ does not depend upon i, then

$$\Pr\left(Z_{si} = 1 \,|\, Z_{si} + Z_{si}^{'} = L_{si},\, r_{11si},\, r_{10si},\, r_{01si},\, r_{00si},\, x_{si},\, u_{si} \right)$$

$$= \left[\begin{array}{l} 0 \text{ if } L_{si} = 0 \\ \frac{\pi_{10si}}{\pi_{10si}+\pi_{01si}} = \frac{\lambda_s}{1+\lambda_s} \text{ if } L_{si} = 1 \\ 1 \text{ if } L_{si} = 2 \end{array} \right.$$

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$$\Pr\left(Z_{si} = 1 \mid Z_{si} + Z_{si}^{'} = L_{si}, r_{11si}, r_{10si}, r_{01si}, r_{00si}, x_{si}, u_{si}\right)$$

$$= \left[\begin{array}{l} 0 \text{ if } L_{si} = 0 \\ \frac{\pi_{10si}}{\pi_{10si}+\pi_{01si}} = \frac{\lambda_s}{1+\lambda_s} \text{ if } L_{si} = 1 \\ 1 \text{ if } L_{si} = 2 \end{array}\right.$$

- That is, a differential comparison of $\left(Z_{si}, Z_{si}^{'}\right) = (1, 0)$ or $(0, 1)$ has a treatment assignment probabilities that depends only on x_{si} or the strata. Here, $\lambda_s / (1 + \lambda_s)$ is the *differential propensity score*.

A basic fact: Differential ignorability

- If there are only generic unobserved biases, so $\rho_{si} = \pi_{10si} / \pi_{01si} = \lambda_s$ does not depend upon i, then

$$\Pr\left(Z_{si} = 1 \,|\, Z_{si} + Z_{si}^{'} = L_{si},\, r_{11si},\, r_{10si},\, r_{01si},\, r_{00si},\, x_{si},\, u_{si}\right)$$

$$= \begin{bmatrix} 0 \text{ if } L_{si} = 0 \\ \frac{\pi_{10si}}{\pi_{10si} + \pi_{01si}} = \frac{\lambda_s}{1+\lambda_s} \text{ if } L_{si} = 1 \\ 1 \text{ if } L_{si} = 2 \end{bmatrix}$$

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- That is, if there are only generic unobserved biases,

$$\left(Z_{si}, Z_{si}^{'}\right) \perp\!\!\!\perp (r_{11si},\, r_{10si},\, r_{01si},\, r_{00si},\, u_{si}) \,\Big|\, \left(x_{si},\, Z_{si} + Z_{si}^{'}\right)$$

Toy numerical illustration from the Rasch model

Table: 2 treatments, Z and Z'. Unobserved u has two levels, $u = 1$ and $u = 0$, and u predicts each treatment, $Pr(Z = 1 | Z + Z' = 1, u) = 3/4$. but not $(Z, Z') = (0, 1)$ vs. $(1, 0)$.

Unobserved u	Treatment Z	Treatment Z'		Total
High level of unobserved $u = 1$				
$u = 1$		$Z' = 1$	$Z' = 0$	
	$Z = 1$	.675	.075	.750
	$Z = 0$	.225	.025	.250
	Total	0.900	.100	1.000
Low level of unobserved $u = 0$				
$u = 0$		$Z' = 1$	$Z' = 0$	
	$Z = 1$	.375	.125	0.500
	$Z = 0$	.375	.125	0.500
	Total	.750	.250	1.000

Another aspect of the basic fact: Randomization distributions

- If there are only generic unobserved biases, so $\rho_{si} = \pi_{10si}/\pi_{01si} = \lambda_s$ does not depend upon i, then the conditional distribution of $(Z_{s1}, \ldots, Z_{s,n_s})$ given $Z_{s+} = \sum_{i=1}^{n_s} Z_{si}$, $Z'_{s+} = \sum_{i=1}^{n_s} Z'_{si}$ and $\left(Z_{si} + Z'_{si},\ r_{11si},\ r_{10si},\ r_{01si},\ r_{00si},\ x_{si},\ u_{si}\right)$, $i = 1, \ldots, n_s$ is a known permutation/randomization distribution.

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- Conditioning also on Z_{s+} and Z'_{s+} eliminates the unknown nuisance parameter λ_s.
- The conditional distribution does not depend upon u_{si} or on $(r_{11si},\ r_{10si},\ r_{01si},\ r_{00si})$ and is essentially randomized with each stratum s defined by observed covariates.

Randomization distributions, stated more precisely

- $(Z_{s1}, \ldots, Z_{s,n_s})$ given Z_{s+}, Z'_{s+} and $\left(Z_{si} + Z'_{si},\, r_{11si},\, r_{10si},\, r_{01si},\, r_{00si},\, x_{si},\, u_{si}\right)$.
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- Write $W_{si} = 1$ if $Z_{si} + Z'_{si} = 2$, $W_{si} = 0$ otherwise, $W_{s+} = \sum_{i=1}^{n_s} W_{si}$, so there are $Z_{s+} - W_{s+}$ individuals with $\left(Z_{si}, Z'_{si}\right) = (1, 0)$ and $Z'_{s+} - W_{s+}$ individuals with $\left(Z_{si}, Z'_{si}\right) = (0, 1)$.

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- The randomization distribution picks $Z_{s+} - W_{s+}$ individuals with $Z_{si} + Z'_{si} = 1$ at random for $\left(Z_{si}, Z'_{si}\right) = (1, 0)$, the rest receiving $\left(Z_{si}, Z'_{si}\right) = (0, 1)$.

Another aspect of the basic fact: Balancing other treatments

- Suppose I have not 2 but K treatments, Z_{ksi}, $k = 1, \ldots, K$, where Z_{ksi}, $k = 3, \ldots, K$, are not be observed, but they are all promoted by the same generic bias u_{si}.

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- There are many ways a person can express a lack of concern with their health. Each of these ways is another Z_{ksi}.
- Write $\mathbf{P}_{si}$ for all the 2^K potential outcomes.
- Model for treatment assignment is a latent variable model with unmeasured u_{si}:

$$\Pr\left(Z_{ksi} = z_{ksi},\, k = 1, \ldots, K \middle| \mathbf{P}_{si},\, x_{si},\, u_{si} \right)$$
$$= \prod_{k=1}^{K} \psi_{ks}\left(u_{si}\right)^{z_{ksi}} \left\{1 - \psi_{ks}\left(u_{si}\right)\right\}^{1-z_{ksi}}$$
$$\frac{\psi_{1s}\left(u_{si}\right)}{1-\psi_{1s}\left(u_{si}\right)} = \lambda_s \frac{\psi_{2s}\left(u_{si}\right)}{1-\psi_{2s}\left(u_{si}\right)}$$

or an IRT-type model with the first two treatments, Z_{1si} and Z_{2si}, have proportional odds.

Balancing other treatments, continued

- Model repeated

$$\Pr\left(Z_{ksi} = z_{ksi},\ k = 1, \ldots, K \,\middle|\, \mathbf{P}_{si},\ x_{si},\ u_{si}\right)$$

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- Then

$$\left(Z_{1si}, Z_{2si}\right) \perp\!\!\!\perp \left(\mathbf{P}_{si},\, u_{si},\, Z_{3si}, \ldots, Z_{Ksi}\right) \,\Big|\, \left(x_{si},\, Z_{1si} + Z_{2si}\right)$$

so that, by overadjusting for Z_{2si} you have adequately adjusted for the disposition u_{si}.

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- With a little work, one finds that the sensitivity analyses I have proposed for treatment-control comparisons (Rosenbaum 2002, §4) now govern the differential comparison, $(Z_{1si}, Z_{2si}) = (1, 0)$ versus $(0, 1)$.
- The analysis is parallel, but the interpretation has changed: generic biases are entirely removed, and Γ describes the differential bias.

Examples

- An example, more or less, from the literature: NSAIDs and Alzheimer's disease. (Zandi et al. 2002)
- A constructed example from NHANES illustrating some of the technical points.
- An example reconstructed from the literature using recent data: seat belts in car crashes. (L. Evans 1986)
- Time-dependent example about fertility and workforce participation (J. Angrist & W. Evans 1998).

Example 1: NSAIDs and Alzheimer's disease

- There is a theory with persistent but perhaps not conclusive evidence that NSAIDs like ibuprofen (e.g. Advil) reduce the risk of Alzheimer's disease.
- in 't Veld et al. (2002) review some of this evidence and express the following concern:

  "Finally, confounding by indication and contraindication may be important. First, pain perception and expression may be different in those becoming cognitively impaired (53). If either pain perception or expression is impaired in those developing Alzheimer's disease, this impairment may lead to lesser used of NSAIDs and an ostensible protective effect of NSAIDs."

- This describes a generic unobserved bias, one that depresses use of pain relievers.

Example 1: NSAIDs and Alzheimer's disease, continued

- So this is a generic unobserved bias, depressing the use of pain relievers.
- There are, however, popular pain relievers that are not NSAIDs, for instance, acetaminophen (e.g., Tylenol).

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- Zandi et. al. (2002) almost did this analysis, finding that NSAIDs are associated with lower risk of Alzheimer's but non-NSAID pain relievers are not.

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- Zandi et. al. (2002) almost did this analysis, finding that NSAIDs are associated with lower risk of Alzheimer's but non-NSAID pain relievers are not.
- An analysis of this sort addresses the generic bias from a reduced disposition to use pain relievers of all kinds.

Example 2: Smoking as a cause of lead and cadmium in the blood

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- 518 smoker/never-smoker matched pairs

Table: Treatment ($Z = 1$) versus control ($Z = 0$) match of $S = 518$ pairs of a daily smoker and a never smoker from NHANES 2009-2010.

	Treatment Z Smoking	
Covariate	Daily	Never
Age (mean)	43.7	43.2
Female (count)	258	258
$< 2 \times$ Poverty level (count)	326	326
Income/poverty ratio (mean)	2.0	1.9
$<$9th grade (count)	43	43
$\geq$ 9th grade (count)	119	119
High school or equivalent (count)	170	170
Some college (count)	152	152
BA degree or more (count)	34	34
Black (count)	104	104
Hispanic (count)	64	64
Other (count)	350	350

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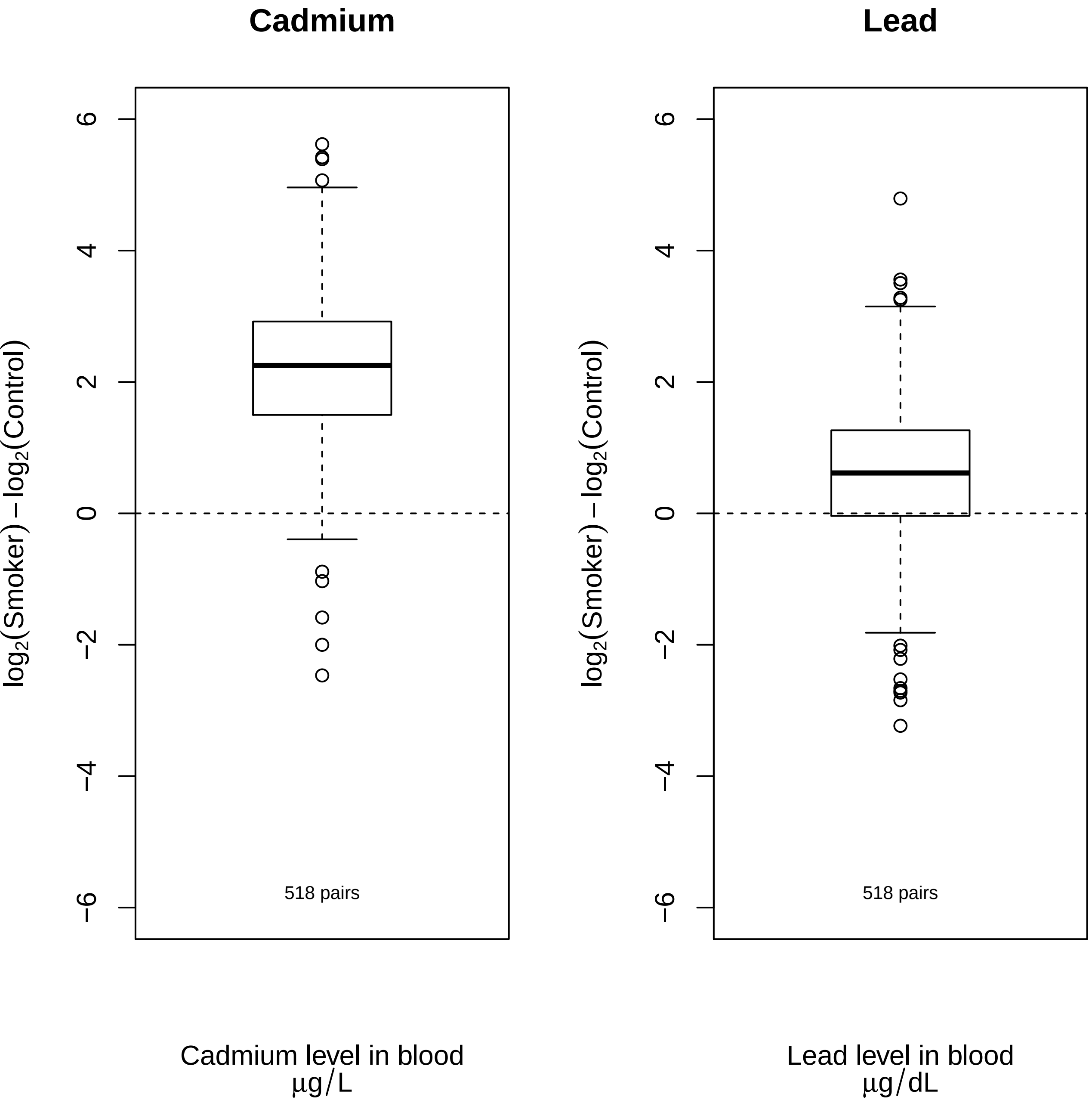
- Will look at 518 smoker-control pair differences.


Cadmium
Lead
log₂(Smoker) − log₂(Control)
6
4
2
0
−2
−4
−6
518 pairs
518 pairs
Cadmium level in blood
µg/L
Lead level in blood
µg/dL

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- Cadmium becomes sensitive at $\Gamma = 64$ or treatment assignment probability in the range $[0.02, 0.98]$ rather than randomization's 0.5.
- $\Gamma = 64$ is equivalent to an unobserved covariate that increased the odds of smoking by ≥ 125 times and the odds of a positive pair difference in cadmium by ≥ 125 times.

Could there be an unobserved covariate strongly associated with smoking?

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- Is this observation a threat to the lead comparison (where $\Gamma = 2.9$)?

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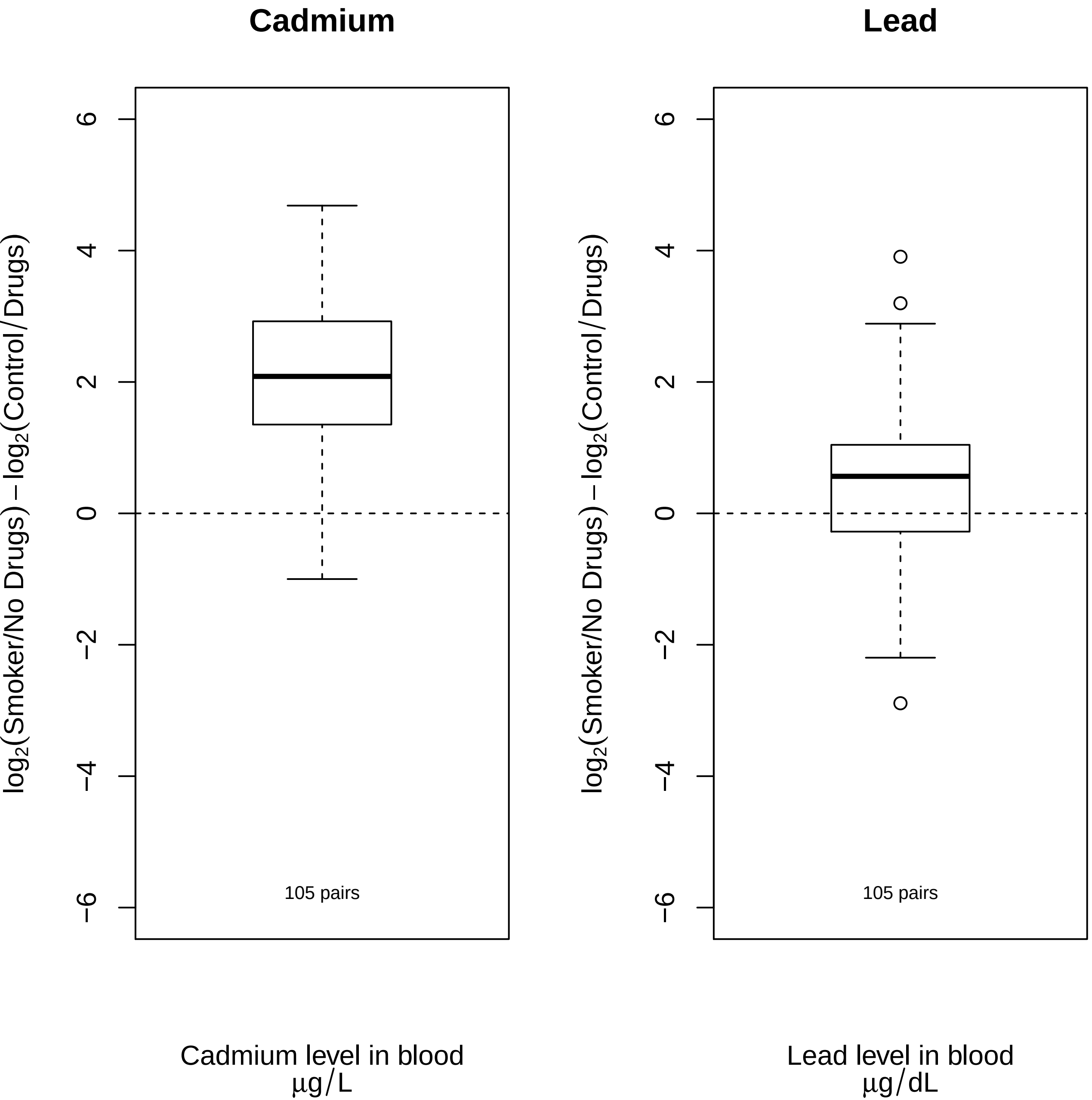
- Smokers who never tried hard drugs to nonsmokers who have tried hard drugs.
- New match with 105 matched pairs, $(1, 0)$ versus $(0, 1)$.

Table: Differential comparison of a smoker who never tried hard drugs $(Z = 1, Z' = 0)$ versus a nonsmoker who has tried them $(Z = 0, Z' = 1)$. $S = 105$ differential pairs.

	(Z, Z')	
Covariate	$(1, 0)$	$(0, 1)$
Age (mean)	43.4	43.1
Female (count)	41	41
$< 2 \times$ Poverty level (count)	44	44
Income/poverty ratio (mean)	1.8	1.6
$<$9th grade (count)	5	5
$\geq$ 9th grade (count)	15	15
High school or equivalent (count)	17	17
Some college (count)	50	50
BA degree or more (count)	18	18
Black (count)	23	23
Hispanic (count)	17	17
Other (count)	65	65



Cadmium
Lead
6
4
2
0
−2
−4
−6
log2(Smoker/No Drugs) − log2(Control/Drugs)
105 pairs
105 pairs
Cadmium level in blood
µg/L
Lead level in blood
µg/dL

Comparison of matched pair differences, conventional versus differential

- Although one analysis removes a bias from a general disposition and the other does not, the results look similar.
- Suggests this general disposition is not a good explanation of the smoker/control difference in outcomes.

Table: Pair differences in $log_2(cadmium)$ and $log_2(lead)$ in 518 conventional smoker-control pairs and in 105 differential pairs of a smoker who never tried hard drugs and a nonsmoker who did try them.

Quantile	10%	25%	50%	75%	90%
Cadmium, Conventional, n=518	0.84	1.50	2.25	2.92	3.59
Cadmium, Differential, n=105	0.66	1.35	2.08	2.92	3.42
Lead, Conventional, n=518	-0.73	-0.04	0.61	1.26	1.94
Lead, differential, n=105	-0.78	-0.28	0.56	1.04	1.64

Balancing another treatment: binge drinking of alcohol

Table: Is alcohol consumption balanced in the basic Z and differential (Z, Z') comparisons? Drinks per day on drinking days, except as noted.

	Smoker/Control, Z		Differential, (Z, Z')	
Alcohol drinks	$Z = 1$	$Z = 0$	$(1, 0)$	$(0, 1)$
<12 per year (%)	12	36	10	9
1-2 per day (%)	31	32	39	41
3-4 per day(%)	28	17	23	22
$\geq$ 5 per day (%)	29	15	28	28
Total (%)	100	100	100	100
Count	385	412	100	94

- Theory says that a differential comparison balances other treatments controlled by the same disposition, whether they are measured or not.

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- The differential comparison for **cadmium** is insensitive to a bias of $\Gamma = 23$.
- $\Gamma = 23$ is an unobserved covariate associated with more than a 45-fold increase in both the odds of treatment and of a positive difference in cadmium.

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- The differential comparison balanced alcohol, while the conventional comparison did not.
- Sensitivity analyses suggest that small to moderate biases cannot explain the conventional comparison, and small to moderate differential biases cannot explain the differential comparison.

Example 3: Seat belts in car crashes

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- A high speed crash while tailgating may involve greater force than a low speed crash with an opportunity to brake.
- Compare belted and unbelted people and you may compare crashes of different severities.

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- Z indicates whether the driver is belted, Z' indicates whether the passenger is belted.
- Interesting, rare, cases are the differential comparisons, $(Z, Z') = (1, 0)$ versus $(Z, Z') = (0, 1)$.

Reconstruct his comparison using 2010-2011 data

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- Range 4 to -4. Here, -4 means the driver was uninjured, passenger died.

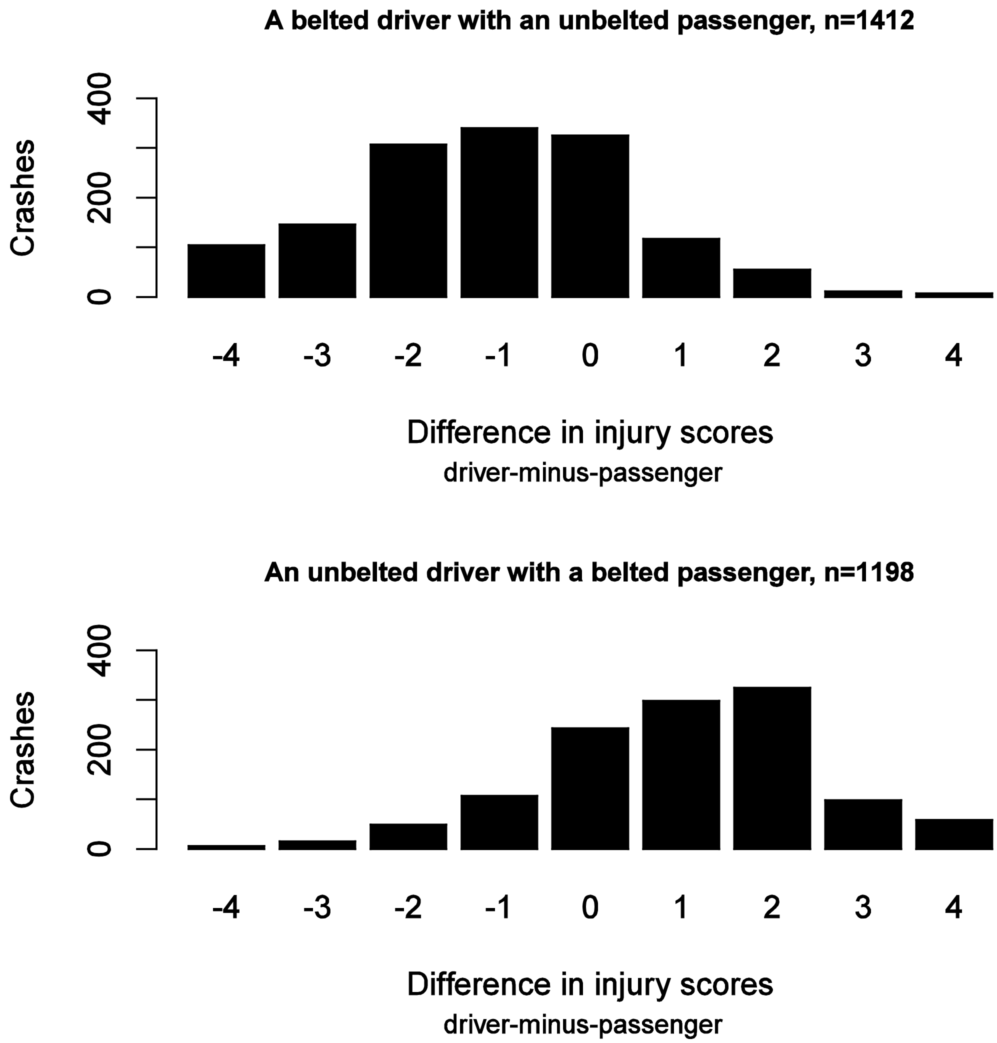

Figure 12.1: Driver-minus-passenger difference in injury scores in crashes from the 2010-2011 Fatal Accident Reporting System in which the driver and front-right passenger were differently belted. Injury scores range from 0=none to 4=death, so: (i) a driver-minus passenger difference of 4 means the driver died and the passenger was uninjured, (ii) a difference of –4 means the driver was uninjured and the passenger died, and (iii) a difference of 0 means the same injury for driver and passenger.

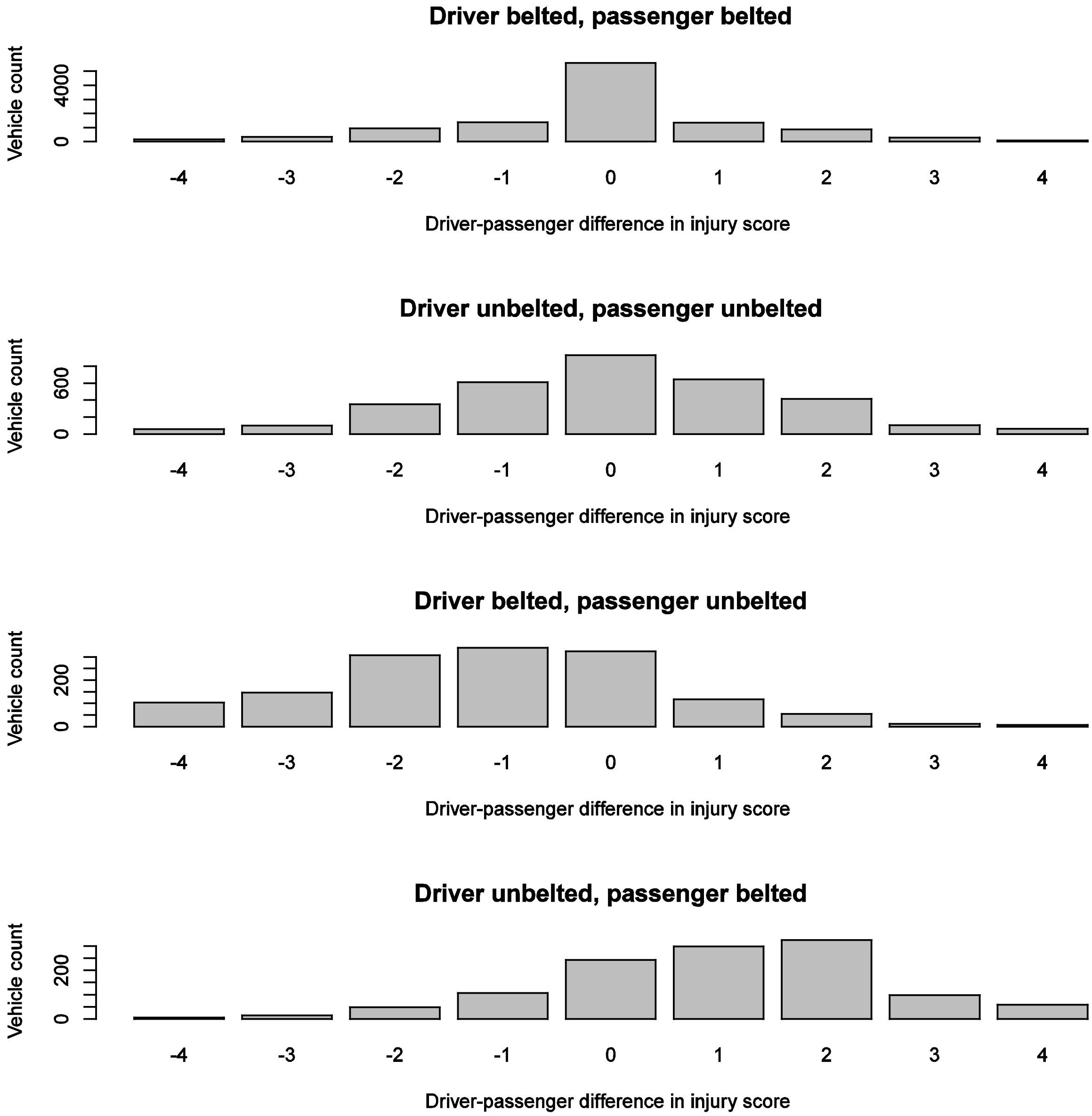

Figure 1: Pair differences in injury scores, driver-minus-passenger, for a driver and a passenger in the same car in FARS 2010-2011, by restraint use. A positive difference indicates the driver suffered more severe injuries than the passenger.

Time-dependent generic biases

- From: Zubizarreta, J. R., Small, D. S. and Rosenbaum, P. R. (2014). Isolation in the construction of natural experiments. *Annals of Applied Statistics* **8**, 2096-2121.

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- Angrist & Evans asked: Does having twins rather than a single child affect workforce participation?
- Idea is that generic unobserved biases affect the timing of pregnancies, but perhaps the twin-versus-single-child treatment is not biased by unobservables conditionally given a pregnancy.

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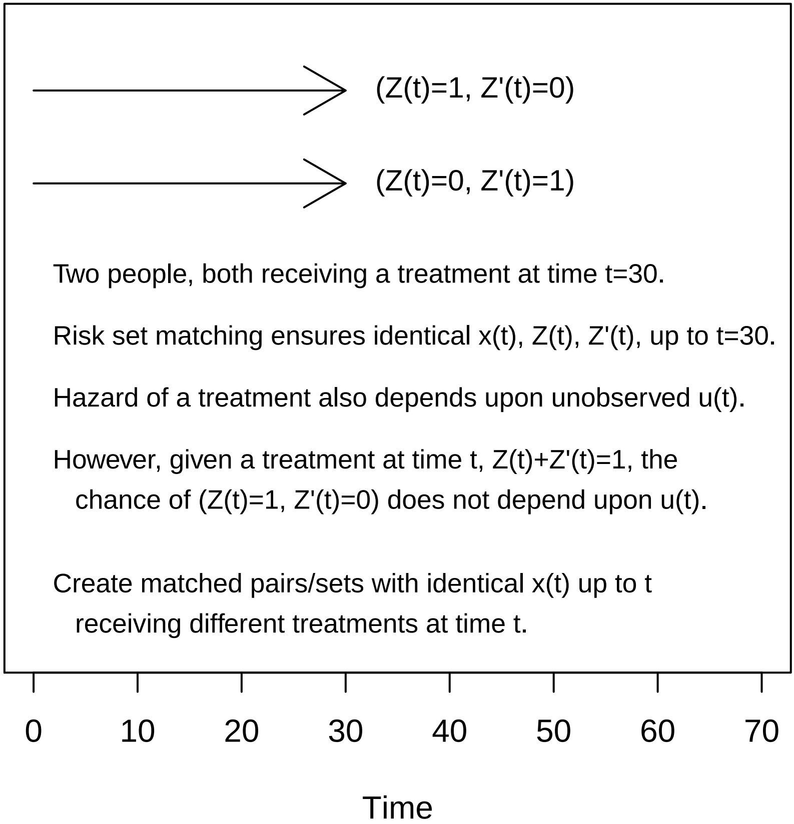
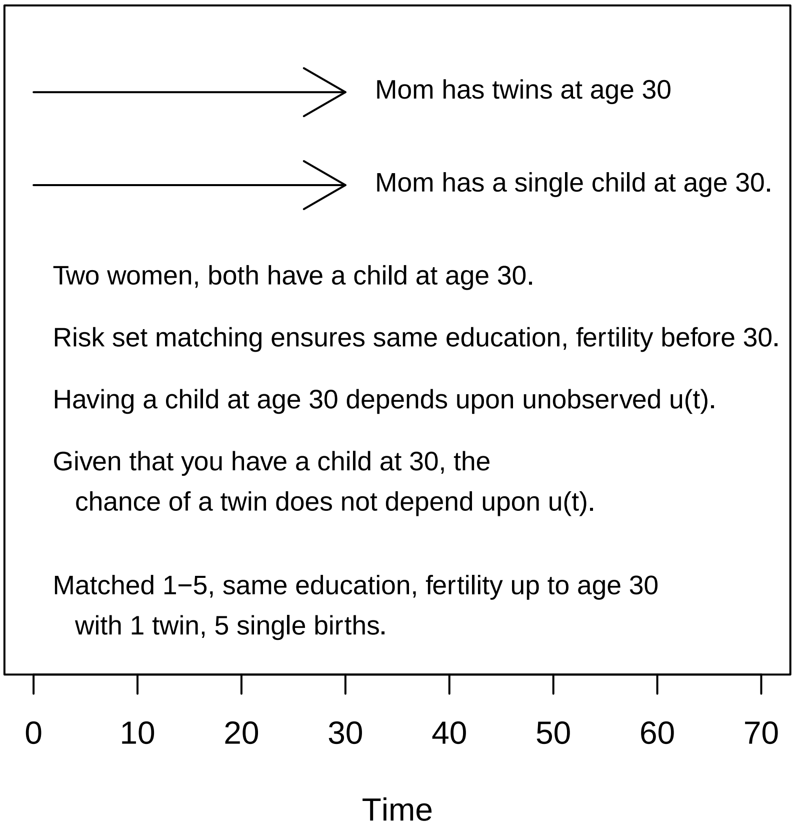
- Timing of treatments is biased by unobservables, but conditionally given that a treatment is received at time t, the assignment of one treatment rather than the other is not biased by unobservables.
- There are only time-dependent generic biases if the hazard of at least one treatment at time t is biased by unobservables, but the ratio of hazards for two different treatments is not biased by unobservables.

Time−dependent Generic Biases



Applied to the Angrist−Evans Data.



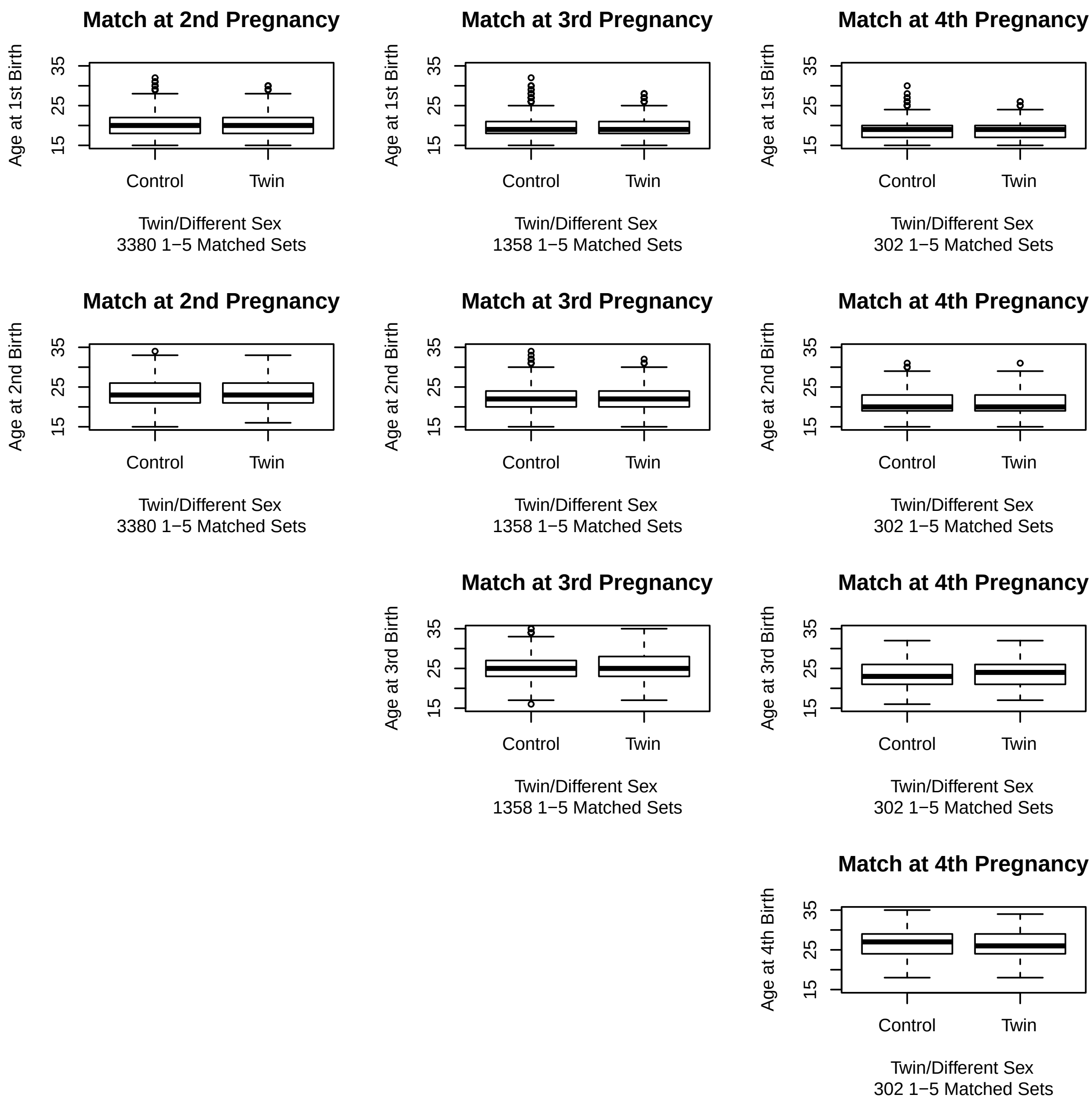


Figure 1: Age at births in 5040 1-5 nonoverlapping matched sets containing 30,240 mothers, specifically 5040 mothers who gave birth to a twin at the indicated pregnancy and 25,200 mothers who had at least one child of each sex by the end of the indicated pregnancy. For 3380 sets matched at the second pregnancy, matching controlled the past, namely age at the first and second births. For 1358 sets matched at the third pregnancy, matching controlled the past, namely age at the first, second and third births. For 302 sets matched at the fourth pregnancy, matching controlled the past, namely age at the first, second, third and fourth births.

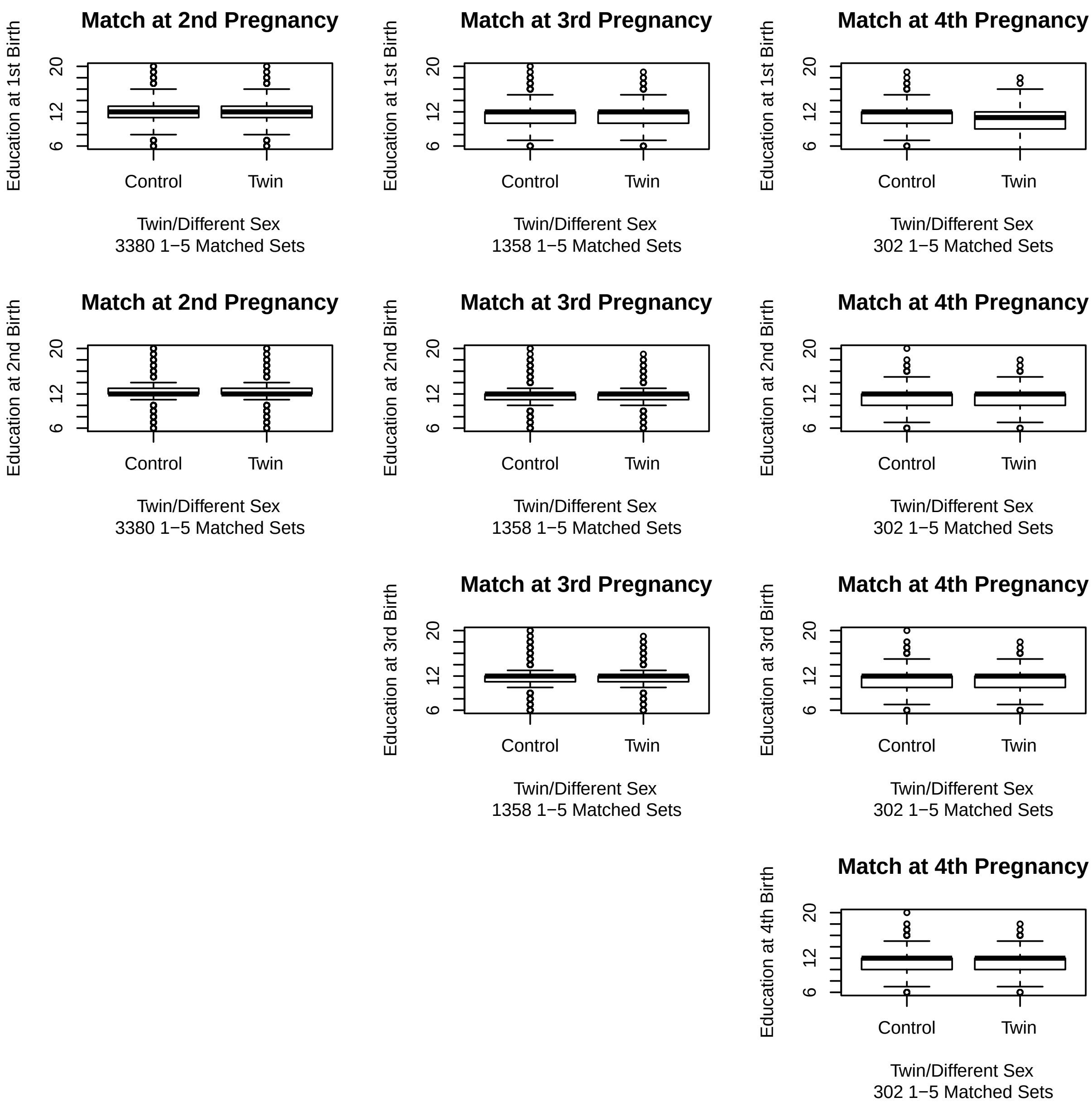


Figure 2: Mother's education at the time of various births in 5040 1-5 nonoverlapping matched sets containing 30,240 mothers, specifically 5040 mothers who gave birth to a twin at the indicated pregnancy and 25,200 mothers who had at least one child of each sex by at the end of the indicated pregnancy. Each match controls the past, not the future. For graphical display in the boxplots, education is truncated at 6 years despite a few values below that.

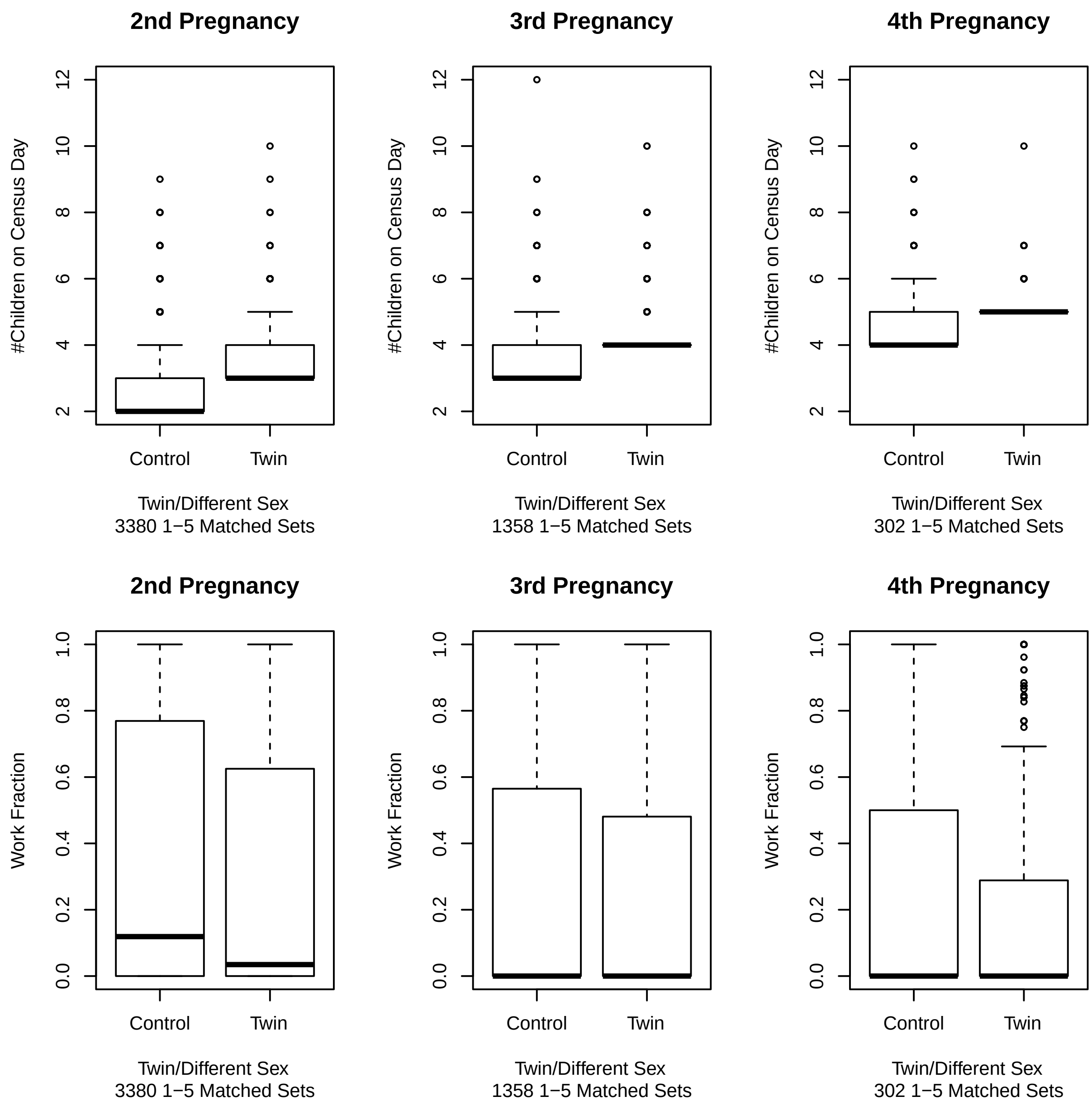


Figure 3: Two outcomes in 5040 1-5 nonoverlapping matched sets containing 30,240 mothers, specifically 5040 mothers who gave birth to a twin at the indicated pregnancy and 25,200 mothers who had at least one child of each sex by at the end of the indicated pregnancy. The upper boxplots indicate the number of children. The lower boxplots indicate the work fraction, defined to be min(hours worked in the previous week, 40) x (weeks worked in the previous year)/(40x52), so a value of 1 is similar to "full time employment."

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- Time-dependent generic biases: hazard of being treated at t that depends upon $u_{si}(t)$, but the relative hazard of different treatments does not.