Controls from Principal Stratification and an example from the Baltimore's Needle Exchange Program

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Target of work: partially controlled studies.

In more studies, the treatment is not controllable but other factors are. Example of offering clean needles to users.

- In simple settings, instrumental variables are applicable to estimate treatment effects.
- Instrum. variables not applicable in general settings (e.g., more factors).
- For general settings, principal stratification is applicable (Frangakis and Rubin, 2002).
- Here: case study of Baltimore's Needle Exchange (Frangakis et al., JASA, 2004).

Outline

1. Background on Needle Exchange.
2. Data from Baltimore NEP and Goals.
3. Evaluation using standard stratification.
4. Evaluation using distance and controls from “principal stratification ”.
5. Results.
6. Remarks.

1. Motivation from a Needle Exchange Program.

- Injection drug users (IDUs) are at high risk of HIV
  (e.g., De Jarlais and Friedman, 1988).

- NEPs: sites where IDUs can exchange used for clean needle.
  (e.g., Vlahov et al. 1991; Bastos and Strathdee, 2000).

- Controversy – do NEPs help reduce HIV ?
  (e.g., Bruneau, Franco, and Lamothe, 1997).

2. Data from Baltimore ALIVE + NEP studies; Goals.

(Vlahov et al., 1991; 1997; Strathdee et al., 1998)

- A cohort of injection drug users is followed /6 mos; and given tests for HIV (ALIVE)

- Subjects who visit the NEP give data: names, risk behaviors etc.

- Data here: matched NEP and ALIVE.
  Confidentiality protected.

Goal: Evaluate NEP impact on HIV incidence.

(data continued).

Subject i, semester $t = 1, ..., 12$.

- B_i: 25 baseline risk factors (e.g., injection behaviors).
- $E_{i,t}^{obs}$: 1 if subject exchanges at NEP.
- $Y_{i,t}^{obs}$: 1 if subject gets HIV+ at t.
- $C_{i,t}^{obs}$: 1 if subject gets censored at t.
- $D_{i,t}^{obs}$: distance of subject i from Needle Exchange sites at time t.

Overall:

– Average follow-up: 9 semesters.

– HIV+ incidence: 5/1000 person-semester follow-ups.

– Exchange: 14% person-semester follow-ups.

3. Evaluation of exchange on HIV using standard controls.

- Stratify by observed baseline variables and distance.
- Compare HIV on observed:
  exchangers vs. nonexchangers (standard controls) (see Results).
- Assumes (explicitly/implicitly) exchangers are at same prior risk with nonexchangers.

Problems:

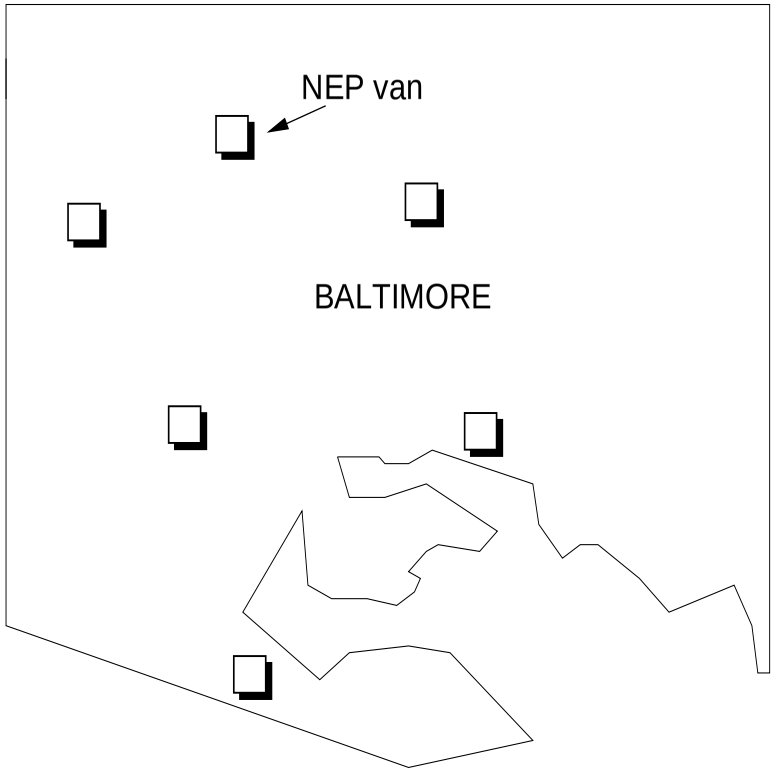
- Exchange is selected by injection users, not by NEP staff.

- Exchangers can be at different unrecorded risk from nonexchangers

.

4. Evaluation using distance and “Principal Stratification”.

- Key Idea: the location (distance) of vans from subjects was controlled by NEP staff, so not subject to selection by injection users.
- Within a large area of prior high risk, vans were placed with no systematic scheme (can be assumed random).

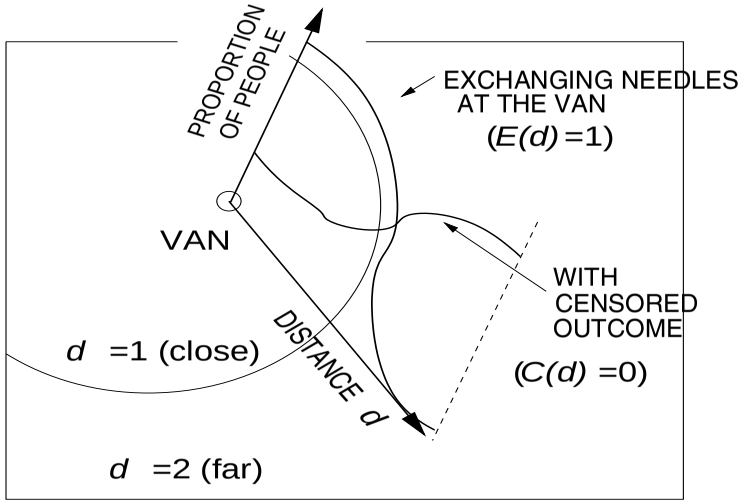


• If distance affects both: (i) exchanging at NEP; and (ii) length of follow-up, then we can use distance to estimate effect of program.

• previous use of distance in other settings: Card (1986), McClellan et al. (1994) as instrumental variable.

• Instrumental vars are not applicable here, because of (i) and (ii) combined (Frangakis and Rubin 1999, Biometrika).

• Use framework of Principal Stratification (Frangakis and Rubin, 2002, BIometrics)



COMBINED UNCONTROLLED FACTORS OF:
(i) EXCHANING NEEDLES; (ii) MEASURED OUTCOME

Examples of literature on potential outcomes and instrumental variables, to address specific applications.

Sommer and Zeger (Stat Med 1991), Robins and Greenland (JASA, 1994), Baker and Lindeman (Stat Med 1994), Angrist, Imbens, and Rubin (JASA 1996), Imbens and Rubin (Ann Statist 1997), Rubin (Statist Med 1998), Robins (Statist Med 1998), Baker (JASA 1998), Frangakis and Rubin (Biometrika 1999), Baker (JASA 2000).

(4 continued) What is Principal Stratification ?

- If for the same subject, i, at semester t, NEP is placed at:

distance d, then	Exchange at NEP is	HIV status is	Censoring is
$d = 1$	$E_{i,t}(1)$	$Y_{i,t}(1)$	$C_{i,t}(1)$
$d = 2$	$E_{i,t}(2)$	$Y_{i,t}(2)$	$C_{i,t}(2)$
...	...	...	...
$d = d_{\text{max}}$	$E_{i,t}(d_{\text{max}})$	$Y_{i,t}(d_{\text{max}})$	$C_{i,t}(d_{\text{max}})$

- Distance of NEP from subject: $D_{i,t}^{obs}$
- Standard stratum: observed exchange $E_{i,t}^{obs} = E_{i,t}(D_{i,t}^{obs})$.

- Principal stratum ($S_i := (E_i(1), ..., E_i(d_{\text{max}}))$) is:
the closest distance to place the NEP beyond which that subject would not exchange at the NEP.

- A principal control of an exposed person is :
a control who is in the same principal stratum as the exposed person.

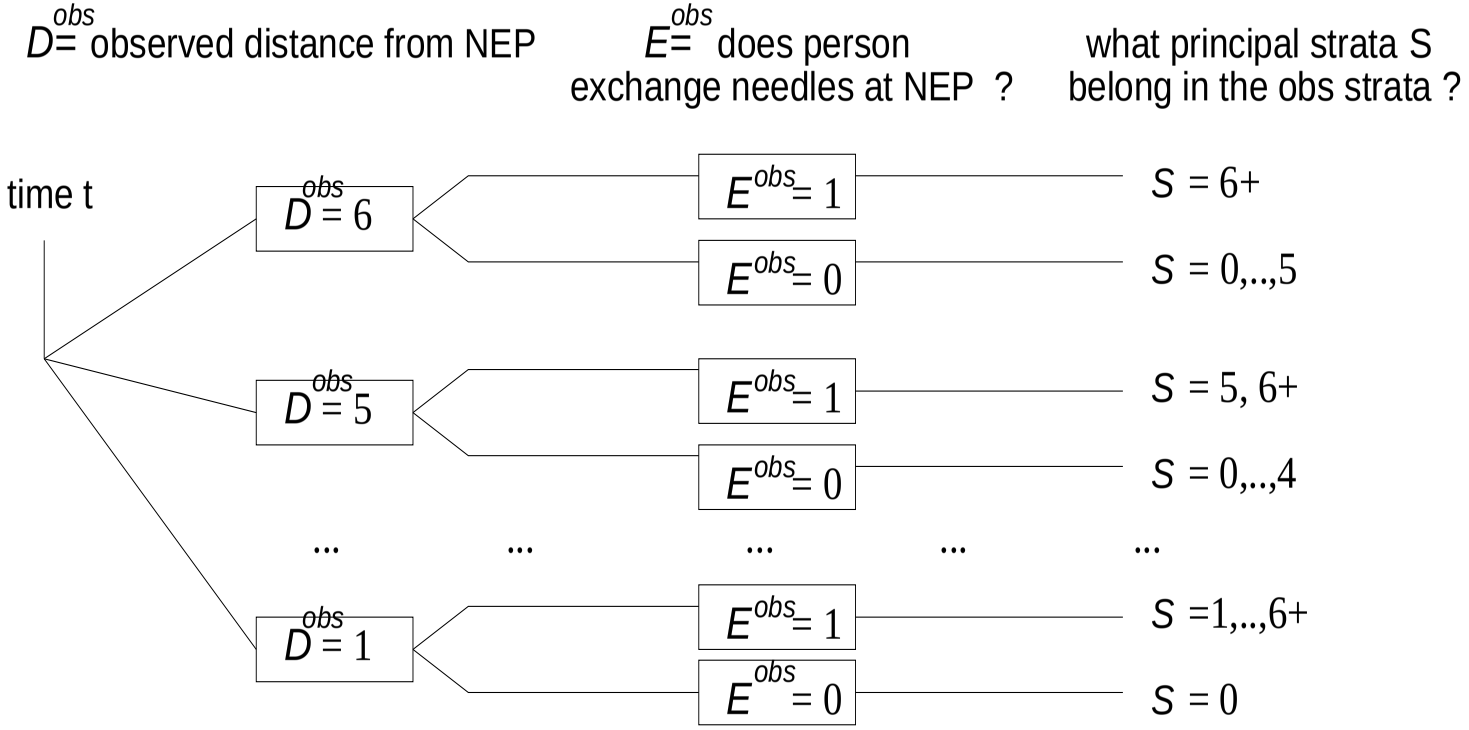
(4 continued) Why is comparison between principal controls and exposed important ?

We can show that under more plausible assumptions, Principal Stratification allows:

- Better definition of the effect of NEP on HIV:
The comparison of principal controls and exposed is experimental.

- Better estimation of the effect of NEP on HIV (addresses selection bias of exchangers using distance).

For these, we need that distance (proximity) encourages exchange
(see next, details in paper).



(B)

(A)

Principal stratum S	what the exchange behavior will be E(d=6)	E(d=5)	E(d=4)	...	E(d=1)
S= 6+ means	1	1	1	...	1
S= 5	0	1	1	...	1
S= 4	0	0	1	...	1
...	...	...			...
S= 1	0	0	0	...	1
S= 0	0	0	0	...	0

(C)

Fraction of people who get HIV, given S

$\lambda(d=6)$ $\lambda(d=5)$ $\lambda(d=4)$ ... $\lambda(d=1)$

λ_{6+} ——————→

λ_5 $\lambda_5 * R_5$ ——————→

λ_4 ——————→ $\lambda_4 * R_4$ ——————→

...

λ_1 ——————→ $\lambda_1 * R_1$

λ_0 ——————→

Evidence that proximity encourages exchange.

Table 1. Percent (%) of subjects exchanging at NEP, at each semester:

(a) For subjects with low baseline risk:

	semester												
Distance	1	2	3	4	5	6	7	8	9	10	11	12	Average
Far	4	5	6	6	6	5	6	4	6	5	7	2	5
Close	8	7	7	8	7	12	12	11	13	13	12	9	10

(b) For subjects with high baseline risk:

	semester												
Distance	1	2	3	4	5	6	7	8	9	10	11	12	Average
Far	16	18	21	19	18	16	14	14	12	14	7	5	14
Close	24	24	24	19	18	19	19	20	21	21	20	16	20

Note: Close = subject $<$ 3 miles from closest NEP site.

5. (a) Results from standard stratification method.

Table 2. Results on exchanging needles at the NEP, and on HIV seroconversion.

	Estimand	Estimate	95% CI
(a)	Odds ratio of HIV seroconversion for one s.d. increase in baseline risk score B:	1.2	(1.1, 1.3)
(b)	Odds ratio of HIV seroconversion for comparing exchangers versus non exchangers, given fixed baseline risk score B:	0.7	(0.3, 1.8)

5 (b). Results from new method (principal stratification).

Table 3. Results on exchanging needles at the NEP, and on HIV seroconversion.

Estimand	Median	95% PI [2]
(a) Odds ratio of higher versus lower principal stratum[1] S for one sd. increase in baseline risk score B:	1.2	(1.1, 1.2)
(b) Odds of HIV seroconversion under fixed exchange, for higher versus lower principal stratum[1] S, given fixed baseline risk score B:	3.3	(1.1, 17.2)
(c) Odds ratio of HIV seroconversion for close versus far distance from the NEP and attributable to needle exchange [3]:	0.1	(0.0, 0.7)

NOTE: (1) A subject's principal stratum is the closest distance to place the NEP beyond which that subject would not exchange at it. (2) Central 95% intervals from the posterior distribution. (3) Conditionally on baseline risk score B and principal stratum S.

6. Remarks.

In NEP:

- Principal stratification points at an 90% decrease in HIV incidence when exchanging.

- Uncertainty is considerable, application of the method to other studies too will be useful.

Generally on controls from principal stratification:

- Estimands and estimation relate more directly to effects of programs.
- Use for improving designs.

Paper:
- http://biosun01.biostat.jhsph.edu/∼cfrangak/papers/nep/nep.pdf