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Interpretation of the individual effect under treatment spillover

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Some interventions may include important spillover or dissemination effects between study participants [2]. For example, vaccines, cash transfers, and education programs may exert a causal effect on participants beyond those to whom individual treatment is assigned. In a recent paper, Buchanan et al. [3] provide a causal definition of the “individual effect” of an intervention in networks of people who inject drugs. This work builds on a definition of the “direct effect”, randomization design, and framework for causal inference under interference introduced by Hudgens and Halloran [11]. Some researchers have suggested that the “direct effect” may not always have a causal interpretation [7, 13, 15]. In this short note, we discuss the interpretation of the individual effect when a spillover or dissemination effect exists.

Potential outcomes and causal effects defined by Buchanan et al. [3]

Buchanan et al. [3] introduce potential outcome notation for the effect of an intervention on an undesirable outcome (e.g. risk behavior, fatal overdose, HIV infection) among people who inject drugs. Let Y_{ki} be an indicator for that outcome, where $k = 1, \dots, K$ is the cluster, and $i = 1, \dots, n_k$ is the individual within that cluster. Let X_k be an indicator that cluster k is treated, meaning that a single cluster member is the “index” participant who directly receives the intervention. In conformity with the causal inference literature, we use the terms “treatment” and “intervention” interchangeably. Let R_{ki} be the indicator that individual i is the index, with exactly one index individual per cluster. Define the vector of index indicators as $\mathbf{R}_k = (R_{k1}, \dots, R_{kn_k})$. Define the individual potential outcome $Y_{ki}(\mathbf{r}, x)$, where $\mathbf{R}_k = \mathbf{r}$ is the vector of index subject indicators and $X_k = x$ is the group-level treatment indicator. Because $\sum_i R_{ki} = 1$ for all clusters k , the potential outcome notation $Y_{ki}(\mathbf{r}, x)$ reduces unambiguously to $Y_{ki}(r, x)$ where $r = R_{ki}$ indicates that individual i is the index; whenever $R_{ki} = 1$, it is implicit that $R_{kj} = 0$ for $j \neq i$. Buchanan et al. [3] defined the *individual effect* as

$$RD^I = \mathbb{E}[Y_{ki}(1, 1) - Y_{ki}(0, 1)],$$

the *disseminated effect* as

$$RD^D = \mathbb{E}[Y_{ki}(0, 1) - Y_{ki}(0, 0)],$$

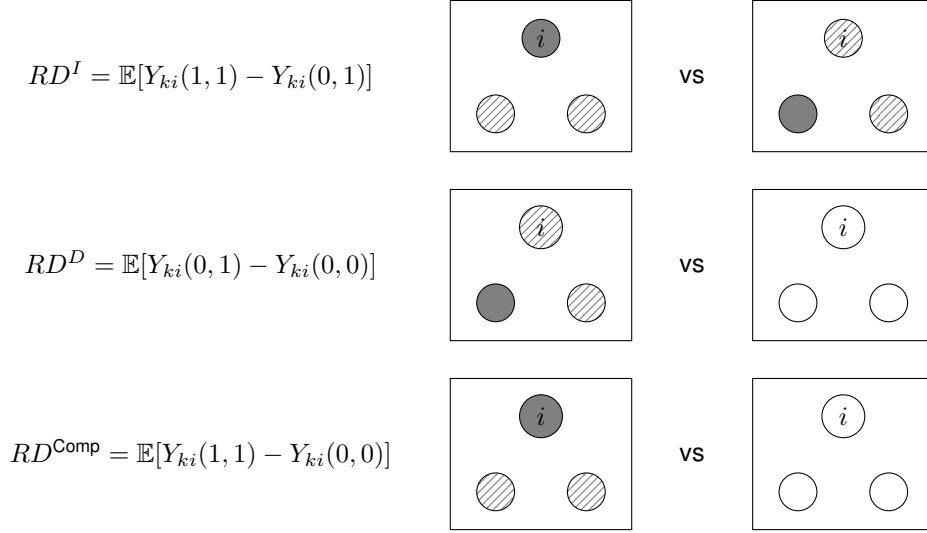


Figure 1. Schematic illustration of the individual, disseminated, and composite effects defined by Buchanan et al. [3] in a cluster of size 3. Cluster k is shown as a rectangle and subjects are shown as circles, with subject i labeled. Gray shading \bullet indicates a treated index subject, and a hatched pattern \textcircled{h} indicates a subject exposed to treatment via dissemination from a treated cluster member. The individual effect RD^I compares the potential outcome of subject i when treated with no dissemination from group members, versus the potential outcome of subject i when untreated with dissemination from the treated index.

and the *composite effect* as

$$RD^{\text{Comp}} = \mathbb{E}[Y_{ki}(1, 1) - Y_{ki}(0, 0)],$$

where expectation is with respect to the potential outcomes of individuals i across clusters k in the study. The composite effect can be written as the sum of the individual and disseminated effects, $RD^{\text{Comp}} = RD^I + RD^D$.

Meaning of the individual effect

The potential outcome notation of Buchanan et al. [3] implicitly encodes two distinct types of exposure to the intervention for subject i in a treated cluster k . First, if subject i is the treated index ($R_{ki} = 1$, $X_k = 1$), then i receives exposure to the intervention via their own treatment, and no disseminated exposure from another cluster member, because no other cluster members can be treated. Second, if subject i is a non-index in a treated cluster ($R_{ki} = 0$, $X_k = 1$), then i receives no direct exposure to the intervention, but receives disseminated exposure from one treated index subject in their cluster. Figure 1 shows how the individual effect RD^I contrasts potential outcomes by changing both of these types of exposures *simultaneously*.

Buchanan et al. [3, Table 1, page 2450] interpret RD^I as the “effect on persons directly receiving an intervention beyond being in an intervention network”. When the outcome is undesirable and $\mathbb{E}[Y_{ik}(0, 0)] \geq \mathbb{E}[Y_{ik}(0, 1)] \geq \mathbb{E}[Y_{ik}(1, 1)]$, RD^I may indeed summarize the additional benefit of being an index, “beyond” that of experiencing disseminated effect. However, this monotonicity relation may not always hold: an intervention with a strong disseminated effect may benefit untreated cluster

members to a greater extent than those who personally receive treatment. In this case, the magnitude of the disseminated effect RD^D would be greater than that of the composite effect RD^{Comp} , and the interpretation of RD^I as the additional benefit of being an index, “beyond” that of experiencing disseminated effect, may not be meaningful.

A hypothetical intervention trial with a strong dissemination effect

One of the most effective interventions for reversing a potentially fatal opiate-related overdose is intranasal or injection administration of naloxone during an overdose. Consider a hypothetical study of clusters of people who inject drugs at risk of fatal opiate overdose, and an intervention that involves dispensing a naloxone kit to one cluster member and training that individual in its administration. The mechanism of action of this intervention in groups induces asymmetry in its effects: overdose involves unconsciousness or incapacitation, so naloxone is rarely self-administered; instead, someone who has it and has been trained in its use can avert another cluster member’s overdose.

Suppose that the outcome of interest is fatal overdose, and treatment involves receipt of a naloxone kit from investigators and training in its use. A subject whose fellow cluster member is treated enjoys a measure of protection against death due to overdose, because the treated subject can use their naloxone kit to reverse their cluster member’s overdose, so $RD^D < 0$. In contrast, the treated subject may derive less benefit from their own treatment because they cannot use their own naloxone kit to reverse their own overdose, except in rare cases [8]. It is possible, but perhaps less likely, that their fellow cluster member not trained by investigators in its use might administer the treated subject’s naloxone kit to the treated subject, should they experience an overdose, implying $RD^D < RD^{Comp} \leq 0$. Clearly treatment is beneficial to any individual whose fellow cluster member receives it, and is either beneficial or ineffective to individuals who only receive it themselves. However, the individual effect is $RD^I = RD^{Comp} - RD^D > 0$, so treatment seems to be harmful to the subject who receives it. Of course, naloxone is not harmful to anyone in this scenario; rather, the “individual effect” contrasts the small (or nonexistent) beneficial effect of individual treatment (RD^{Comp}) against the larger beneficial disseminated effect of treatment (RD^D).

Discussion

The quantity RD^I introduced by Buchanan et al. [3] is a well-defined statistical estimand. However, RD^I may be misleading because it does not measure the effect of the intervention on the individual who would receive it, holding treatment to others constant. Instead, RD^I contrasts the potential outcome of an individual who receives treatment but no disseminated exposure with that of an individual who receives no treatment but disseminated exposure from another subject. When the disseminated effect is large compared to the composite effect, RD^I can be positive (suggesting harm) even when the intervention is beneficial to treated individuals and their fellow cluster members. Buchanan et al. [3, Table 4, page 2455] found a similar pattern in their evaluation of the HPTN 037 trial intervention: the individual effect on any risk behavior RD^I is estimated to be null (ineffective), even though the disseminated and composite effects were estimated to be negative (beneficial). Two additional examples of substantial public health importance could show a similar pattern. Early access to antiretroviral therapy (ART) among HIV positive individuals is known to improve health and helps prevent transmission to HIV-negative partners [5, 6, 9, 10]. Likewise, pre-exposure prophylaxis (PrEP) among HIV negative individuals helps prevent HIV infection in treated individuals [1, 4, 14]. While these interventions

are known to benefit treated individuals, and reduce HIV transmission within groups [12], a trial that computed an “individual effect” by contrasting RD^{Comp} against RD^D might under-estimate the benefit conferred by these interventions to treated individuals.

When might the individual effect RD^I be of scientific interest? First, resource constraints might necessitate a policy in which a single subject (or a fixed number of subjects) is treated per cluster, so a trial design that enforces this constraint may naturally reveal the quantity of interest. Second, RD^I may be of interest to investigators and research subjects because it summarizes the ethical trade-off in benefit or harm experienced by treated versus untreated individuals. In the case of PrEP, these trade-offs might involve the benefit of reduced HIV infection risk for all cluster members, versus potential medication side effects for individuals treated with PrEP [14]. That is, RD^I answers the question, “am I better off being treated or untreated, when someone in my cluster is treated?” If investigators desire a measure of the effect of an intervention on an individual subject while holding disseminated exposure constant, the “composite” effect RD^{Comp} may be a more readily interpretable causal estimand.

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