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Does Mother Know Best? Treatment Adherence as a Function of Anticipated Treatment Benefit

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Abstract

Background—We describe bias resulting from individualized treatment selection, which occurs when treatment has heterogeneous effects and individuals selectively choose treatments of greatest benefit to themselves. This pernicious bias may confound estimates from observational studies and lead to important misinterpretation of intent-to-treat analyses of randomized trials. Despite the potentially serious threat to inferences, individualized treatment selection has rarely been formally described or assessed.

Methods—The Moving to Opportunity (MTO) trial randomly assigned subsidized rental vouchers to low-income families in high-poverty public housing. We assessed the Kessler-6 psychological distress and Behavior Problems Index outcomes for 2,829 adolescents 4–7 years after randomization. Among families randomly assigned to receive vouchers, we estimated probability of moving (treatment), predicted by pre-randomization characteristics (c-statistic=0.63). We categorized families into tertiles of this estimated probability of moving, and compared instrumental variable effect estimates for moving on Behavior Problems Index and Kessler-6 across tertiles.

Results—Instrumental variable estimated effects of moving on behavioral problems index were most adverse for boys least likely to move ($b=0.93$; 95% CI: 0.33, 1.53) compared to boys most likely to move ($b=0.14$; 95% CI: -0.15 , 0.44; $p=.02$ for treatment*tertile interaction). Effects on

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Conflicts of Interest

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Kessler-6 were more beneficial for girls least likely to move compared to girls most likely to move (-0.62 vs. 0.02 ; interaction $p=.03$).

Conclusions—Evidence of Individualized treatment selection differed by child gender and outcome and should be evaluated in randomized trial reports, especially when heterogeneous treatment effects are likely and non-adherence is common.

Social and pharmacologic treatments may benefit some people but harm others.^{1–5} The Moving To Opportunity (MTO) trial, which randomly assigned volunteer low income families to receive subsidized rental vouchers to move out of public housing, demonstrated qualitative effect modification by child gender and family vulnerabilities.^{1,6} As in most trials, adherence to random assignment was imperfect. Parents, predominantly single mothers, decided whether to move to private market apartments or to remain in their public housing apartments. The expected impact of moving on children presumably influenced mothers' decisions, but it is unknown whether families whose children were most likely to benefit were in fact most likely to move. We call such a process, in which treatment received is associated either positively or negatively with the effects of that treatment, individualized treatment selection. In observational studies, individualized treatment selection is a pernicious type of confounding that arises when a treatment effect modifier also influences treatment received. When an instrumental variable is available, for example from a randomized controlled trial (RCT), individualized treatment selection can be assessed and possible effect heterogeneity can be formally evaluated. Such effect heterogeneity is usually of great substantive interest, because it implies that the optimal treatment differs between individuals. RCTs are often intended to support “scaling up” or universalizing a treatment or policy. If individualized treatment selection occurs, the intention to treat effect estimate can severely misrepresent the effects of such untargeted implementation.

We aim in this paper to formally describe individualized treatment selection and illustrate an approach, related to Peck et al.'s work using propensity score estimates from pre-randomization characteristics,^{7,8} to evaluate individualized treatment selection in MTO. We first contrast individualized treatment selection with conventional confounding, showing why it can lead to false conclusions about population average treatment effects in observational studies or RCTs. We emphasize that randomization does not solve this problem, because even when the population average treatment effect is null, the sharp null (no effect for *anyone* in the sample) may not hold.⁹ We hypothesized that families with children most likely to benefit from moving out of high-poverty public housing were also those most likely to do so.

Conventional confounding compared with individualized treatment selection

The assumption of “no unmeasured confounding” generally requires that counterfactual outcomes under any particular treatment regime are independent of which treatment is actually received. Conventionally, confounding occurs because individuals who would have better outcomes under *any* treatment regime selectively receive one particular treatment. For example, if children with underlying health advantages are more likely to move to high-

socioeconomic status (SES) neighborhoods (vs. lower-SES neighborhoods) than children with health vulnerabilities, the comparison of outcomes for children in high-SES versus low-SES communities will not correspond with the effect of neighborhood SES on health.

We consider a more subtle type of confounding, where treatments have different effects for different people (individual effect heterogeneity), and individuals selectively choose the treatment they anticipate as most beneficial to them personally. For example, some children might have better health responses to high-SES than low-SES neighborhoods, while the health of other children would be best-served by living in low-SES neighborhoods (for example, with less racial harassment and more supportive social networks). If families who would thrive in high-SES neighborhoods selectively move to such communities, while families who would thrive in low-SES areas selectively move to low-SES communities, the contrast in outcomes between children residing in high- and low-SES communities is not necessarily the average causal effect of neighborhood type for all, or any subgroup of, children. This is “confounding by potential effect size”, conceptualizing effect size as an unobserved variable defined for each person prior to exposure. We define each person’s potential effect size as the difference between that individual’s counterfactual outcomes under alternative treatments (similar contrasts define “causal response types”¹⁰).

Individualized treatment selection is only possible if treatment effects differ between people, thus our discussion relates closely to research on heterogeneous treatment effects.^{11,127}

Although health research rarely quantifies this type of confounding formally in RCTs, individualized treatment selection seems plausible for many behavioral or lifestyle exposures. Individuals know whether they are receiving treatment and may have insight into the contexts most beneficial for them personally (or for their children). For example, when choosing a school or residential neighborhood, parents probably carefully consider where their children are most likely to flourish.

Individualized treatment selection may have received so little attention because empirical evaluation of this phenomenon is difficult. Observational studies without instrumental variables cannot distinguish individualized treatment selection from conventional confounding. However, with randomization or another convincing instrumental variable, it may be possible to detect it by identifying subgroups likely to take up the treatment and, within such subgroups, estimating treatment effects.

Counterfactual definitions

Consider a binary exposure X and a continuous outcome Y , with higher values of Y indicating worse health. Denote the counterfactual outcome for person i under treatment x as: $Y_{x,i}$ and let $\mathbf{Y}_{\mathbf{x},i}$ denote the set of counterfactual outcomes of Y under each possible value of X .

A typical definition of confounding is that the probability an individual will receive a particular treatment is associated with that individual’s counterfactual outcome under some treatment:

$$\Pr(X_i=x_i) \neq \Pr(X_i=x_i|Y_{x,i}) \quad (1)$$

Confounding occurs, for example, if some cause of X , say W , also influences either $Y_{x=1}$ or $Y_{x=0}$ or both (figure 1). Individualized treatment selection occurs when the probability an individual will receive a particular treatment is associated with the individual's treatment response. Define each individual's treatment response β_i as the contrast between that person's counterfactual outcome under treatment ($Y_{x=1,i}$) versus no treatment ($Y_{x=0,i}$):

$$\beta_i = Y_{x=1,i} - Y_{x=0,i} \quad (2)$$

Positive β_i thus indicates treatment harms person i , while negative values indicate treatment is beneficial.

Individualized treatment selection implies:

$$\Pr(X_i=x_i|Y_{x=1,i}, Y_{x=0,i}) = \Pr(X_i=x_i|\beta_i) \neq \Pr(X_i=x_i) \quad (3)$$

For example, if treatment selection is advantageous, the probability of treatment uptake is lower among those who would be harmed by treatment than among those who would benefit from treatment:

$$\Pr(X_i=1|\beta_i > 0) < \Pr(X_i=1|\beta_i \leq 0) \quad (4.1)$$

Alternatively expressed we would expect

$$E(\beta_i|X=1) < E(\beta_i|X=0) \quad (4.2)$$

Returning to the causal diagram, if the effect of W on $Y_{x=1}$ differs from the effect of W on $Y_{x=0}$, then W modifies the potential treatment effect and, because W also influences X , this induces individualized treatment selection (figure 2). In other words, if an unobserved factor both influences treatment and modifies the effects of treatment, this implies individualized treatment selection.

If individualized treatment selection is induced by an unobserved factor, the estimate of β from analyses based on measured confounders in an observational study will equal neither the population average treatment effect (see Box 1 for a definition of this and other estimands discussed here), nor any subgroup effect.

Situation 1: Observational study

Consider a hypothetical situation illustrating the bias in estimating the average causal effect in an observational study (see eAppendix 1 for a corresponding simulation in Stata). Define

Was an unobserved treatment effect modifier (and also a confounder), that for simplicity affects $Y_{x=1}$ but not $Y_{x=0}$ (figure 2). We will say:

$$\begin{aligned} E(Y_{x=1} | W=1) &= 1 \\ E(Y_{x=0} | W=1) &= 0 \\ E(Y_{x=1} | W=0) &= -1 \\ E(Y_{x=0} | W=0) &= 0 \end{aligned} \quad (5)$$

Thus treatment harms individuals with $W=1$ ($\beta=1$), and benefits individuals with $W=0$ ($\beta=-1$). Suppose half the population has $W=1$, leading to a population average treatment effect of zero, but people with $W=1$ are less likely to take treatment X than people with $W=0$:

$$\begin{aligned} \Pr(X=1 | W=1) &= 0.4 \\ \Pr(X=1 | W=0) &= 0.6 \end{aligned} \quad (6)$$

Note that $E(\beta_i | X=0) = 0.2 > E(\beta_i | X=1) = -0.2$, consistent with equation (4.2). Under the assumption shown in figure 2 that there are no other confounders, the crude estimate of the effect of X on Y will be -0.2 (calculation shown in Appendix 2 indicating a small benefit of receiving X). However, $E(Y_{x=1} - Y_{x=0} | W=1) = 1$ and $E(Y_{x=1} - Y_{x=0} | W=0) = -1$, and the population average treatment effect $= 0$, so the observational treatment effect estimate does not correspond with the population average treatment effect or the treatment effect in either the subgroup $W=1$ or $W=0$.

So far this seems like typical confounding. We cannot identify the effect of X on Y because an unmeasured factor influences both X and the counterfactual outcomes of Y .^{13–15} Analyses stratified by W will provide correct effect estimates for each group (1 or -1) and averaging or inverse probability weighting based on the prevalence of W will provide the correct population average treatment effect (shown in simulation 1). Individualized treatment selection diverges from typical confounding however, because if W is unmeasured, even an intention-to-treat estimate from an RCT may be non-null when the true population average treatment effect is null.

Situation 2: Randomized trial with imperfect compliance only in the treatment arm

Let Z represent random assignment of treatment X . Assume X is not offered to those in $Z=0$ and X is offered to those in $Z=1$. Although X is *offered* to individuals randomly assigned to $Z=1$, not all of those *offered* X take up the treatment (as illustrated by incomplete treatment adherence in most RCTs). Suppose that when offered X , take-up varies by the unmeasured characteristic W , as above:

$$\begin{aligned} \Pr(X=1 | Z=1, W=1) &= 0.4 \\ \Pr(X=1 | Z=1, W=0) &= 0.6 \\ \Pr(X=1 | W=0, Z=0) &= \Pr(X=1 | W=1, Z=0) = 0 \end{aligned} \quad (7)$$

Appendix 3 provides Stata code simulating data following the rules above. The counterfactuals are as defined above, so the population average treatment effect of X is zero. The intentional-to-treat effect estimate would be -0.1 (eAppendix 2). Thus, although the population average treatment effect is zero, the intention-to-treat estimate is non-zero. Adjusting the intention-to-treat estimate for non-adherence to generate the instrumental variable estimate does not recover the population average treatment effect but rather gives the effect of treatment on the treated

$$(E(Y|Z=1) - E(Y|Z=0)) / (E(X|Z=1) - E(X|Z=0)) = -0.1/0.5 = -0.2. \quad (8)$$

Note this is equivalent to the effect of treatment on the treated only because nobody in the $Z=0$ group could access X and in our hypothetical scenario, W has no effect on $Y_{x=1}$. In other situations with individualized treatment selection, the instrumental variable does not equal the effect of treatment on the treated or the observational effect. Although stratifying on W produces correct β estimates for the effect of X in each stratum, simply adjusting the intention-to-treat regression (i.e. the effect of Z on Y) for W does not change the intention-to-treat estimate from the (non-null) unadjusted intention-to-treat effect.

Thus, even in a situation where the population average treatment effect is null, the intention-to-treat effect estimate may not be null. It is often assumed that in a well conducted and properly analyzed RCT, the intention-to-treat estimate is guaranteed to be null if the average effect of receiving treatment on the outcome is null. However, this guarantee only holds under the sharp null *i.e.*, the effect of receiving treatment on the outcome is null for every individual in the population, or if adherence to assigned treatment is perfect.⁹ Under individualized treatment selection, even if the population average treatment effect is null, the intention-to-treat need not be centered on the null. Similarly, it is often assumed that non-adherence in a trial results in an intention-to-treat effect estimate closer to the null than the effect of receiving treatment. In the context of individualized treatment selection, this is not necessarily the case (eFigure).

We now turn to an empirical example to assess individualized treatment selection, by comparing effect estimates across probability of taking the treatment in the MTO trial. We selected adolescent mental health as an outcome *a priori* because MTO has heterogeneous effects on children's mental health for children with different pre-randomization characteristics,^{1,6,16} and children's mental health and behavioral problems seem especially salient to mothers' move decisions.^{17–19}

Methods

Data

MTO was an RCT in which volunteer families with children were recruited from public housing developments in high-poverty neighborhoods and randomly assigned to a control arm or one of two treatment arms.^{1,20–23} The control group received no further subsidy but could remain in public housing. The “regular section 8” treatment arm received subsidies to rent private market apartments. The “low-poverty neighborhood section 8” also received

rental subsidies, but only if they moved to low-poverty neighborhoods (<10% of the Census Tract living in poverty; participants received housing counseling to help find apartments). We pool the regular section 8 and low-poverty section 8 groups, given previous evidence of similar mental health effects.^{1,16} As a result, the treatment received includes moves from public housing into private market apartments, and moves from very high poverty to a range of lower poverty neighborhoods. Survey data were collected at baseline and interim follow-up (4–7 years after baseline). We use outcomes from MTO Tier 1 Restricted Access Data on 2,829 adolescents randomly assigned from 1994 through 1997 who answered interim surveys in 2002.^{21,23,24} Northeastern University's Institutional Review Board approved this study.

Outcome measures

In 2002, past-month psychological distress was measured by Kessler's K-6 scale,²⁵ which includes 5-option Likert scales ("none of the time" to "all of the time") for six items (so depressed nothing could cheer you up; nervous; restless or fidgety; hopeless; everything an effort; worthless). Past 6-month externalizing behaviors were assessed with 11 items from the Behavior Problems Index,²⁶ such as "I lie or cheat" and "I have a hot temper", ranked from 0 (not true) to 2 (often true). Behavior Problems Index and Kessler-6 scores were estimated with two-parameter binary Item Response Theory models and standardized.²⁵ For both outcomes, higher scores indicate worse outcomes.

Treatment take-up/move

Treatment take-up, corresponding to the treatment variable X in the individualized treatment selection explanation, consisted of using section 8 vouchers offered to the experimental groups to move. All control families were therefore untreated.

Predictors of Take-up

We modeled take-up (among the treatment group only) as a function of all available pre-randomization (baseline) variables, listed in Table 1 and in Figure 3–4 notes.

Analysis

We estimated intention-to-treat effects with linear regression models of randomized assignment predicting mental health. We used random assignment as an instrumental variable in 2-stage least squares models to estimate the effect of take-up on mental health, with adjustment for baseline covariates.¹¹ Sensitivity analyses adjusted only for sex and site produced results similar to covariate adjusted models (eTable).

We then tailored these intention-to-treat and instrumental variable analyses to test for individualized treatment selection. Among families randomly assigned to receive rental vouchers, we use logistic regression to model the probability of take-up as a function of the pre-randomization (baseline) family and child characteristics. We then used this model to predict the probability that each family, treatment, or control would have taken up the voucher if randomized to receive one. For control group families, this was an out-of-sample prediction. This model is not causal: many variables we use to predict take-up may simply proxy for unmeasured determinants of moving. Our goal was to predict take-up; we can

assess the occurrence of individualized treatment selection even if the model is misspecified for causal determinants, provided the model predicts take-up.

We next categorized families in both treatment and control groups into tertiles of probability of take-up (low, moderate, or high). These categories do not reflect actual move status, but rather the probability of moving if, possibly counter to fact, the family was offered a voucher (the variable W above). We then calculate the intention-to-treat and instrumental variable effect estimates within each tertile of probability of take-up, derived from interaction models. To provide evidence of individualized treatment selection, we test whether estimated health effects of treatment were better for children whose families were most likely to move (illustrated by tertile*treatment arm interactions). This assumes that random assignment is a valid instrumental variable for the effect of take-up.⁸ Tertile of take-up was coded using two indicator variables instead of a linear term to allow for greater flexibility of treatment effect estimates. Given documented treatment effect heterogeneity by gender,^{1,16,21} final models included three-way interactions between take-up tertile, treatment group, and gender.

Intention-to-treat estimates can be interpreted as the mental health effects of offering treatment (regardless of take-up). Since, by design, no controls could access treatment, instrumental variable effect estimates can be interpreted as the effect of treatment among compliers and as the effect of treatment on the treated.¹¹ If treatment effects were identical for all individuals (i.e., if effects among compliers and non-compliers were equal, implying no individualized treatment selection), the instrumental variable estimate would represent the population average treatment effect. If individualized treatment selection occurs, these effects likely differ. To test this, we estimate the population average treatment effect, using a weighted instrumental variable in which the weights are equal to the inverse of the probability of take-up. We thus also evaluate individualized treatment selection by comparing inverse probability weighted and unweighted instrumental variable models.

All analyses incorporated sampling weights and accounted for family level clustering of children. We used M-Plus 6.11 (Muthén & Muthén, Los Angeles, CA) for Item Response Theory analyses and STATA 11.0 (StataCorp LP, College Station, TX) for all other analyses.

Results

The treatment take-up model, based on pre-randomization covariates, strongly predicted take-up (positive predictive value=65%, negative predictive value=62%, c-statistic=0.63). Take-up was more common among younger parents who were currently in school or on Aid to Families with Dependent Children (AFDC)/welfare (Table 1) and in smaller households, but did not differ by child gender. Dissatisfaction with neighborhood, confidence in ability to find a new apartment, and history of applying for section 8 also predicted higher likelihood of moving. Take-up differed substantially across sites.

Using predicted probability of take-up from this model, we categorized everyone, including control group families, into three strata: low likelihood of take-up (predicted probability <0.45), moderate likelihood of take-up (probability 0.45–0.61), and high likelihood of take-

up (probability >0.61). Some covariates strongly predicted take-up (Table 2). For example, families with health and developmental vulnerabilities at baseline were disproportionately present in the lowest vs. highest tertile of take-up probability.

The overall effect of the MTO intervention on adolescent boys' mental health was adverse.^{1,16} Our intention-to-treat effect estimates show a graded pattern such that among boys in families least likely to take-up the intervention, the effect of randomization was most harmful, as hypothesized. The intention-to-treat effect estimate on Behavior Problems Index for boys in the lowest probability of take-up group was 0.31 (95% CI: 0.12, 0.50), compared to only 0.09 (−0.12, 0.31) among boys in the group with the highest probability of take-up (Table 3). Many families in MTO did not adhere to the assigned treatment, so the intention-to-treat estimate would not necessarily correspond to the effect of receiving treatment. For this reason, estimates adjusted for adherence (instrumental variable estimates) are more relevant. As expected, patterns in evidence of individualized treatment selection observed with intention-to-treat analyses are reflected even more clearly in instrumental variable estimates: the instrumental variable estimate for boys' Behavior Problems Index in families *least* likely to take the treatment was 0.93 (0.33, 1.53), compared to an instrumental variable estimate of only 0.14 (−0.15, 0.44) for boys' Behavior Problems Index in families *most* likely to take up the treatment ($p=0.02$ for the test of tertile*treatment) (Figure 3, Table 3).

Among boys, patterns for Kessler-6 were similar to Behavior Problems Index, albeit smaller in magnitude. Boys in the lowest tertile of take-up probability had the highest instrumental variable estimate for the effect of moving on Kessler-6 ($b=0.60$; 0.03, 1.17) compared to boys in the highest tertile of take-up probability ($b=0.16$; −0.16, 0.47). There was an inverse gradient of treatment effects on Kessler-6 across tertile for boys, with wide CIs and a non-significant test of tertile*treatment interaction ($p=0.18$).

There was no evidence of individualized treatment selection for girls' Behavior Problems Index, however there was for girls' Kessler-6. Unexpectedly, instrumental variable estimates for Kessler-6 suggest that girls in families least likely to move experienced greater mental health benefits compared to girls in families most likely to move ($b=-0.62$ [−1.09, −0.14] vs. 0.02 [−0.28, 0.32]; interaction term p -value=0.03) (Figure 3).

Our final analyses demonstrate the implications of individualized treatment selection by comparing: (1) instrumental variable estimates of the effect of take-up on mental health, without accounting for individualized treatment selection, and (2) these same instrumental variable analyses, but applying inverse probability weights for treatment (take-up) to account for individualized treatment selection and estimate the population average treatment effect. Estimates of the population average treatment effect (based on inverse probability weighting) were farther from the null for boys for Behavior Problems Index (Figure 4). Without inverse probability weighting, the instrumental variable effect estimate of moving on Behavior Problems Index was 0.39 (0.15, 0.64), but this increased 26% after accounting for treatment selection with inverse probability weighting (instrumental variable $\beta=0.49$; [0.20, 0.79]). Therefore, if the boys least likely to move were forced to move, the adverse effects would have been even larger. Similarly, accounting for individualized treatment

selection increased the estimated population benefit for K6 associated with treating all girls by 36%.

Discussion

We find mixed support for the hypothesis of individualized treatment selection in the MTO trial. While individualized treatment selection occurred for both boys' and girls' mental health outcomes, the results were in different directions. Findings for boys were consistent with our hypothesis: adverse treatment effects on Behavior Problems Index were concentrated among families least likely to move, suggesting that mothers may have correctly anticipated potential harm to their sons when deciding not to move. However, for girls, the opposite pattern emerged: beneficial effects were largest among those least likely to move. Gender of the child, a proven treatment effect modifier in MTO, did not itself predict take-up.

The qualitatively different individualized treatment selection for male and female children was unexpected. Our findings may of course be attributable to chance. We also speculate on three possible substantive explanations. Parents may be less able to assess daughters' mental health.²⁷ Boys are more likely to engage in visible externalizing behaviors, whereas girls more commonly internalize distress.²⁸ Alternatively, parents may prioritize the specific outcomes in our study more for sons than daughters.²⁹ Parents may even prioritize outcomes for their sons over their daughters, given the particular vulnerabilities facing adolescent boys.^{30,31}

Finally, the results may reflect the limitations of our method of evaluating individualized treatment selection, which assumes that random assignment is a valid instrumental variable for treatment. Relaxing this assumption makes individualized treatment selection unidentifiable, but the assumption cannot be proven; the plausibility must be considered on a case by case basis. If randomization influences outcomes via other mechanisms, such as perceptions of empowerment or discrimination through receipt or use of the voucher, such pathways could induce the apparent differences in effects between those who are likely versus unlikely to take up the voucher.

Individualized treatment selection is a potentially serious problem in observational research and randomized trials, but has received remarkably little attention. Prior analyses using methods similar to ours assumed that individualized treatment selection never occurs.^{10,8} In observational data, it is impossible to distinguish between typical confounding (individuals who would have advantageous outcomes regardless of treatment are more likely to be treated) and individualized treatment selection (individuals select treatments of greatest personal benefit). We leveraged MTO's randomization to evaluate individualized treatment selection, yet our approach recovers the population average treatment effect only if there are no unobserved sources of individualized treatment selection. This cannot be proven in real data. Our analyses focused on risk difference effect estimates, because we describe individual-level effects which are easily defined on a linear scale. Individualized treatment selection for non-linear models is an important topic for future research.

Individualized treatment selection may arise in “patient preference” trials, which include patient-elected treatment arms alongside randomized treatment assignment,^{32,33} and behavioral trials, where treatment assignment cannot be masked. Blinding is no guarantee against individualized treatment selection if some treatment side effects cause non-adherence and correlate with the treatment’s efficacy.^{34–36} Although we hypothesized beneficial individualized treatment selection, it is plausible that it is adverse in some situations, when people do not know or act in their own best interest. Health inequalities researchers implicitly invoke adverse individualized treatment selection when speculating that untargeted resources exacerbate inequalities because the most disadvantaged individuals (who would benefit most) are least capable of utilizing the resource.³⁷

Evaluating potential individualized treatment selection is important for assessing observational studies and understanding divergence with randomized trials. Individualized treatment selection has immediate clinical and policy relevance: if individuals naturally choose exposures that are in their own best interest, paternalistic policies that force other options may be harmful. MTO families faced substantial social and financial challenges when moving to low poverty neighborhoods.²¹ Nearly half of MTO families offered vouchers did not move, and many who did move subsequently returned to high-poverty neighborhoods.³⁸ Families may have chosen in their own best interest, albeit within constrained housing options.

In conclusion, we find mixed support for the hypothesis that families who did not take up MTO vouchers acted on accurate predictions that moving would not be in their children’s best interest. Although probability of take-up was associated with estimated treatment effects, patterns differed by child gender. To our knowledge, this is the first empirical assessment of the magnitude of individualized treatment selection. It remains to be seen whether individualized treatment selection is common, but the possibility merits systematic assessment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Box 1**Definition of alternative estimands**

Effect Estimate	Counterfactual Contrast	Description
Population Average Treatment Effect (PATE)	$E(Y_{X=1} - Y_{X=0})$	The difference between an individual's outcome if treated and that same person's outcome if untreated, averaged for everyone in the population. Sometimes this is expressed as $E(Y_{X=1}) - E(Y_{X=0})$, the expected value of the outcome if everyone in the population were given treatment minus the expected value of the outcome if nobody in the population were given the treatment.
Intent to Treat (ITT)	$E(Y Z=1) - E(Y Z=0)$	The difference in expected value of the outcome among those randomized to receive the treatment and those randomized not to receive the treatment. Because Z is randomized, this estimates: $E(Y_{Z=1} - Y_{Z=0})$
Effect of Treatment on the Treated (TOT)	$E(Y_{X=1} - Y_{X=0} X=1)$	The difference between an individual's outcome if treated and that same person's outcome if untreated, averaged across those individuals in the population who were actually treated.

Figure 1. Directed Acyclic Graph (DAG) illustrating confounding

Confounding occurs because an unmeasured trait W influences both X and the counterfactual outcomes of Y (and therefore the actual value of Y). In this DAG, W influences the set of counterfactuals.

Figure 2. Directed Acyclic Graph (DAG) illustrating Individualized Treatment Selection
 Individualized Treatment Selection occurs because an unmeasured trait W that affects X influences different counterfactual outcomes of Y to a different extent. For clarity in a DAG, in this example we show that W influences both X and one of the counterfactual outcomes of Y (if X is set to 1), but has no effect on the other counterfactual outcome of Y (if X is set to 0). Because W has a different effect on each of the two counterfactual outcomes, it also influences β , the effect size of treatment, which is fully determined by the contrast of the two counterfactual values of Y . Under this diagram, the treatment received (X) will be associated with the response to that treatment (β) and Individualized Treatment Selection is expected.

Figure 3. Adherence adjusted treatment effect estimates by predicted probability of take-up, Moving to Opportunity Interim Survey 2002

Estimates were derived using Instrumental Variables analysis with two-stage least square regression. Regression model controls for age, sex, race/ethnicity, parental education, family structure, parent's marital status, parent's employment status, parent's receipt of AFDC/TANF; parent's teen parent status; no teens in household; sibling combination, household size, presence of family health vulnerability/disability, family disability, family experience of victimization, neighborhood/mobility variables (Table 1), and the following interaction terms (treatment*tertile of take-up, treatment*gender, tertile of take-up*gender, and treatment*gender*tertile of take-up). Gender-specific estimates are calculated using post-estimation commands; Estimates are weighted and account for clustering at family level. Instrumental variable estimates for boys' Behavior Problems Index in families least and most likely to take the treatment were 0.93 versus 0.14, respectively ($p=0.02$ for test of interaction). Unexpectedly, instrumental variable estimates for Kessler-6 suggest that girls in

families least likely to move had the greatest benefit compared to girls in families most likely to move ($b=-0.62$ vs. 0.02 ; $p=0.03$ for test of interaction).

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Figure 4. Adherence-adjusted effect estimates with and without inverse-probability of take-up Estimates were derived with instrumental variables analysis using 2-stage least squares regression. Regression model controls for age, gender, race/ethnicity, parental education, family structure, parent's marital status, parent's employment status, parent's receipt of AFDC/TANF, parent's teen parent status, no teens in household, sibling combination, household size, presence of family health vulnerability/disability, family disability, family experience of victimization, neighborhood/mobility variables (Table 1), and treatment*gender interaction term. Gender-specific estimates are calculated using post-estimation commands; estimates are weighted and account for clustering at family level. Note scale change.

Table 1

Adjusted odds of take-up estimated as a function of pre-randomization parent and family characteristics, among treatment group families

		Odds ratio (95% CI)
Parent's age (years)	17–24 (Ref)	1.00
	25–34	0.74 (0.56, 0.98)
	34–44	0.53 (0.38, 0.74)
	45+	0.44 (0.29, 0.65)
Male parent		0.73 (0.41, 1.31)
Hispanic (vs. non-Hispanic)		0.78 (0.63, 0.96)
Education	Less than high school (Ref)	1.00
	GED	1.26 (0.99, 1.61)
	High school diploma	1.10 (0.90, 1.35)
	In School	1.32 (1.05, 1.65)
Family Structure	Never married	0.98 (0.81, 1.20)
	Teen parent	1.19 (0.96, 1.47)
Socioeconomic Status	Employed	1.16 (0.93, 1.45)
	On AFDC (welfare)	1.34 (1.06, 1.69)
Has car		1.24 (0.96, 1.60)
No teens	No teen (ages 13–17) children in core household.	1.09 (0.88, 1.35)
Sibling combination ^a	Girl, girl	1.15 (0.79, 1.66)
	Boy, boy	1.03 (0.71, 1.49)
	Boy, girl	1.09 (0.78, 1.53)
	Girl	0.94 (0.69, 1.28)
	Boy (ref)	1.00
Household size	2	1.75 (1.18, 2.60)
	3	1.17 (0.91, 1.51)
	4	1.13 (0.88, 1.44)
	5+ (ref)	1.00
Health or Developmental Vulnerability	Family level presence of 5 baseline health, developmental, or disability variables: behavior problems, learning problems, school or play difficulties, special medicine or equipment, or someone in HH with a disability	0.89 (0.72, 1.11)
Disability	Household member had a disability	0.98 (0.74, 1.29)
Victimization	Household member victimized by crime during past 6 months	1.12 (0.94, 1.33)
Neighborhood/Mobility Variables	Lived in neighborhood 5 or more years	0.99 (0.81, 1.19)
	Moved more than 3 times in past 5 years	1.12 (0.81, 1.55)
	Very dissatisfied with neighborhood	1.44 (1.20, 1.74)
	Very sure would find an apartment in a different area of the city	1.34 (1.12, 1.59)
	Applied for section 8 voucher before	1.20 (1.01, 1.43)
	Streets very unsafe at night	1.01 (0.84, 1.22)
	No family living in neigh	1.01 (0.84, 1.21)
	No friends living in neigh	1.04 (0.87, 1.25)

		<u>Odds ratio (95% CI)</u>
Neighbor Relationships	Primary or secondary reason for wanting to move was to get away from gangs or drugs	1.16 (0.95, 1.42)
	Primary or secondary reason for moving was to have access to better schools for children	1.15 (0.97, 1.37)
	Chats with neighbors at least once a week	0.88 (0.74, 1.05)
	Respondent very likely to tell neighbor if saw neighbor's child getting into trouble	0.85 (0.72, 1.01)
Site	Baltimore	1.86 (1.38, 2.50)
	Boston	1.23 (0.93, 1.62)
	Los Angeles	3.75 (2.74, 5.14)
	New York	1.17 (0.90, 1.53)
	Chicago (Ref)	1.00

GED: General Educational Development

AFDC: Aid to Families with Dependent Children

Ref: Reference category

CI: Confidence Interval

Estimates weighted for varying treatment random assignment ratios across time. Analyses restricted to sampled adult heads assigned to treatment groups with covariate information (N=2938)

Table 2

Description of the Moving To Opportunity treatment and control group families, by likelihood of take-up estimated as a function of pre-randomization characteristics

Baseline Parent/Family Characteristics	Low likelihood of take-up (bottom tertile)		Moderate likelihood of take-up (middle tertile)		High likelihood of take-up (top tertile)	
	Control	Treatment	Control	Treatment	Control	Treatment
Age (years)						
17–24	2%	2%	16%	13%	30%	31%
25–34	32%	29%	56%	55%	52%	50%
34–44	44%	43%	23%	24%	13%	17%
45+	23%	26%	5%	7%	4%	2%
Male	4%	3%	3%	2%	1%	1%
Hispanic	37%	39%	33%	30%	20%	22%
Education						
Less than high school	38%	44%	38%	34%	35%	35%
GED	16%	12%	22%	20%	23%	22%
High school diploma	33%	34%	35%	41%	37%	40%
Missing	12%	11%	5%	5%	5%	3%
In School	7%	8%	18%	15%	23%	27%
Never married	51%	50%	63%	62%	76%	73%
Teen parent	15%	18%	23%	23%	37%	35%
Employed	22%	26%	29%	27%	25%	26%
Socioeconomic Status						
On AFDC (welfare)	62%	64%	75%	74%	86%	86%
Has car	11%	12%	16%	15%	20%	24%
No teens	44%	39%	67%	64%	77%	76%
Sibling combination ^a						
Girl, girl	14%	14%	15%	16%	14%	18%
Boy, boy	17%	19%	16%	16%	17%	14%
Boy, girl	31%	30%	38%	36%	34%	29%
Girl	16%	13%	13%	14%	17%	18%
Boy	13%	13%	14%	13%	15%	17%
Missing	9%	11%	4%	6%	3%	5%
Household size	10%	12%	22%	21%	29%	32%
2						

Baseline Parent/Family Characteristics	Low likelihood of take-up (bottom tertile)		Moderate likelihood of take-up (middle tertile)		High likelihood of take-up (top tertile)	
	Control	Treatment	Control	Treatment	Control	Treatment
3	35%	30%	29%	31%	31%	29%
4	24%	26%	24%	23%	19%	20%
5+	31%	32%	25%	24%	20%	18%
Health or Developmental Vulnerability	43%	48%	35%	33%	25%	25%
Family level presence of 5 baseline health/ disability variables: behavior problems, learning problems, school or play difficulties, special medicine or equipment, or someone in HH with a disability						
Disability	23%	24%	15%	15%	11%	9%
Victimization	31%	34%	43%	43%	50%	51%
Household member had a disability Household member victimized by crime during past 6 months						
Lived in neighborhood 5 or more years	68%	71%	63%	59%	53%	52%
Moved more than 3 times in past 5 years	7%	5%	10%	8%	14%	13%
Very dissatisfied with neighborhood	29%	26%	47%	50%	64%	65%
Very sure would find an apartment in a different area of the city	28%	26%	42%	49%	65%	66%
Applied for section 8 voucher before	40%	35%	42%	41%	50%	46%
Streets very unsafe at night	37%	37%	49%	48%	65%	63%
No family living in neigh	65%	64%	66%	63%	63%	67%
No friends living in neigh	36%	34%	41%	40%	48%	47%
Primary or secondary reason for wanting to move was to get away from gangs or drugs	70%	71%	76%	74%	88%	84%
Primary or secondary reason for moving was to have access to better schools for children	36%	37%	49%	52%	55%	58%
Chats with neighbors at least once a week	60%	58%	53%	51%	48%	45%
Respondent very likely to tell neighbor if saw neighbor's child getting into trouble	64%	60%	53%	55%	53%	49%
Baltimore	5%	4%	12%	14%	27%	27%
Boston	35%	31%	22%	25%	11%	12%
Los Angeles	2%	1%	9%	9%	37%	37%
New York	32%	36%	31%	28%	13%	13%
Chicago	26%	28%	25%	25%	12%	11%

GED: General Educational Development

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AFDC= Aid to Families with Dependent Children
N=4248 families

Estimates are weighted for varying treatment assignment ratios across time. Percentages reported are column percentages.

Treatment effects by predicted likelihood of take-up, Moving To Opportunity Interim Survey, 2002

Table 3

	Effect estimate by tertile of likelihood of treatment take-up ^a			Interaction coefficient		
	Low likelihood of take-up (bottom tertile) ^b	Moderate likelihood of take-up (middle tertile) ^b	High likelihood of take-up (top tertile) ^b	Low*Treatment Group	Moderate*Treatment Group	P-value
<i>Intention-to-Treat (ITT)^c</i>	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)	b (95% CI)	
Boys BPI	0.31 (0.12, 0.50)	0.14 (−0.08, 0.35)	0.09 (−0.12, 0.31)	0.21 (−0.07, 0.50)	0.04 (−0.26, 0.34)	0.78
Girls BPI	−0.03 (−0.21, 0.15)	−0.07 (−0.30, 0.16)	0.04 (−0.14, 0.23)	−0.08 (−0.33, 0.18)	−0.11 (−0.40, 0.18)	0.46
Boys K6	0.20 (0.01, 0.38)	0.10 (−0.13, 0.33)	0.11 (−0.11, 0.33)	0.09 (−0.20, 0.38)	−0.01 (−0.32, 0.31)	0.96
Girls K6	−0.25 (−0.45, −0.06)	−0.06 (−0.28, 0.16)	0.02 (−0.19, 0.22)	−0.27 (−0.55, 0.01)	−0.07 (−0.37, 0.22)	0.62
<i>Adherence adjusted (Treatment-on-Treated, TOT)^c</i>						
Boys BPI	0.93 (0.33, 1.53)	0.26 (−0.16, 0.67)	0.14 (−0.15, 0.44)	0.79 (0.12, 1.45)	0.11 (−0.39, 0.62)	0.66
Girls BPI	−0.08 (−0.52, 0.36)	−0.13 (−0.56, 0.31)	0.06 (−0.21, 0.33)	−0.14 (−0.66, 0.38)	−0.19 (−0.70, 0.32)	0.46
Boys K6	0.60 (0.03, 1.17)	0.19 (−0.24, 0.62)	0.16 (−0.16, 0.47)	0.44 (−0.20, 1.09)	0.03 (−0.50, 0.57)	0.90
Girls K6	−0.62 (−1.09, −0.14)	−0.11 (−0.52, 0.30)	0.02 (−0.28, 0.32)	−0.64 (−1.20, −0.07)	−0.13 (−0.63, 0.37)	0.61

BPI: Behavior Problems Index

K6: Kessler 6

CI: Confidence Interval

N=2829

^aIndicator variables created for tertile of take-up^bSubgroup specific estimates are calculated using post-estimation commands; Estimates are weighted and account for clustering at family level^cRegression model controls for age, sex, race/ethnicity, parental education, family structure, parent's marital status, parent's employment status, parent's receipt of Aid to Families with Dependent Children, parent's teen parent status, no teens in household, sibling combination, household size, presence of family health vulnerability/disability, family disability, family experience of victimization, neighborhood/mobility variables (Table 1), and the following interaction terms (treatment*tertile of take-up, treatment*gender, tertile of take-up*gender, and treatment*gender*tertile of take-up). "Low" indicates the lowest tertile of take-up, while "Moderate" indicates the middle tertile of take-up (compared to highest tertile, reference).