Behavior within a Clinical Trial and Implications for Mammography Guidelines

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U.S. Preventive Services Task Force (USPSTF) 2016 Guidelines for Women in 40's:

"The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years"

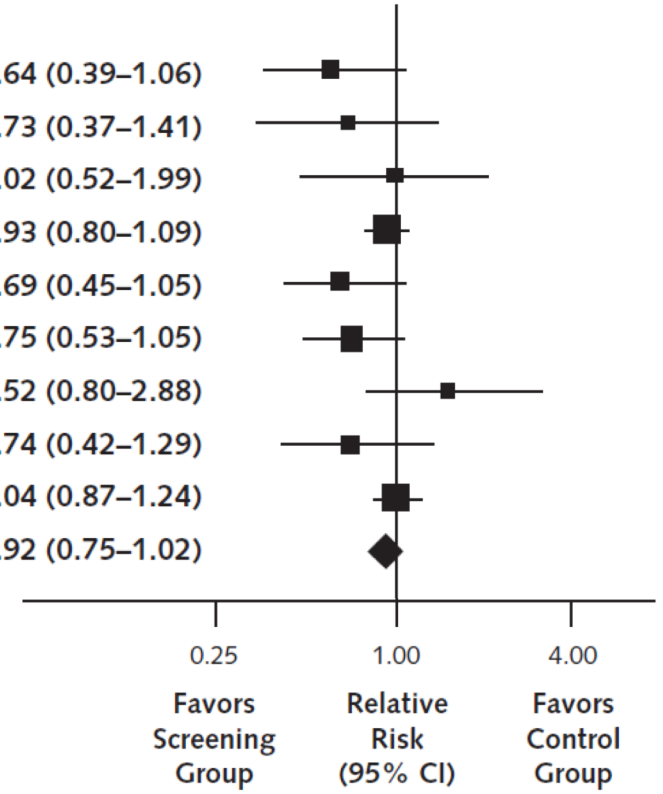
USPSTF 2016 Guidelines Based on RCT's

Annals of Internal Medicine REVIEW

Effectiveness of Breast Cancer Screening: Systematic Review and Meta-analysis to Update the 2009 U.S. Preventive Services Task Force Recommendation

Heidi D. Nelson, MD, MPH; Rochelle Fu, PhD; Amy Cantor, MD, MPH; Miranda Pappas, MA; Monica Daeges, BA; and Linda Humphrey, MD, MPH

Author, Year (Reference)	Trial Name	Mean Follow-up, *y*	Relative Risk (95% CI)
Women aged 39–49 y			
Nyström et al, 2002 (30)*	MMST II	11.2	0.64 (0.39–1.06)
Tabár et al, 1995 (26)	Kopparberg	12.5	0.73 (0.37–1.41)
Tabár et al, 1995 (26)	Östergötland	12.5	1.02 (0.52–1.99)
Moss et al, 2015 (27)	Age	17.5	0.93 (0.80–1.09)
Bjurstam et al, 2003 (25)	Gothenburg	13.8	0.69 (0.45–1.05)
Habbema et al, 1986 (29)	HIP	14.0	0.75 (0.53–1.05)
Nyström et al, 2002 (30)*	Stockholm	14.3	1.52 (0.80–2.88)
Nyström et al, 2002 (30)*	MMST I	18.2	0.74 (0.42–1.29)
Miller et al, 2014 (15)	CNBSS-1	21.9	1.04 (0.87–1.24)
Overall (I^2 = 25%; P = 0.230)			0.92 (0.75–1.02)



CNBSS Consistent with Meta-analysis of RCT's

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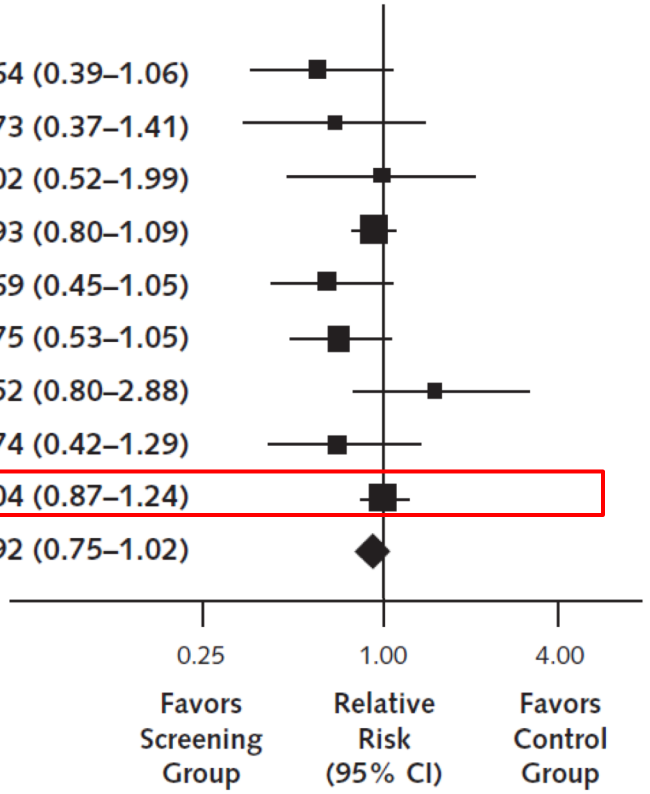
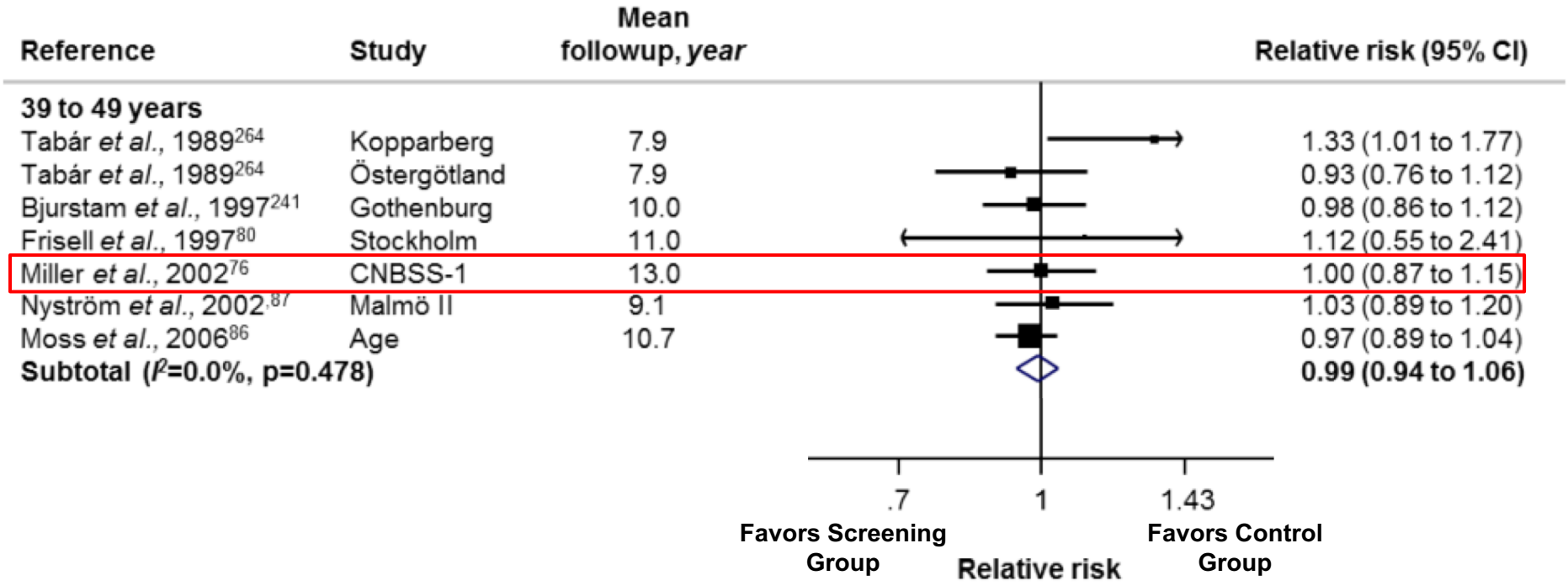


Meta-analysis for All Cause Mortality

Evidence Synthesis
Number 124

Screening for Breast Cancer: A Systematic Review to Update the 2009 U.S. Preventive Services Task Force Recommendation



I Examine Micro Data from the CNBSS

- Canadian National Breast Screening Study
  - 89,835 patients enrolled
  - Patients received mammograms for 4 to 5 years during active study period
  - Recorded mammogram receipt, even in control group
  - Followed patient outcomes from 1980 to 2005 through cancer registry and death records (no attrition)
  - Collected risk factors and demographic data

I Examine Behavior within a Clinical Trial

- Medical literature examines clinical trials
  - See Nelson (2016)
- Economics literature examines mammogram takeup
  - Strumpf, Chai, and Kadiyala (2010)
  - Kadiyala and Strumpf (2011, 2016)
  - Zanella and Banerjee (2016)
  - Buchmueller and Goldzahl (2018)
  - Kim and Lee (2017)

I Examine Behavior within a Clinical Trial

- I show two relationships between biology and behavior in existing clinical trial data by building on LATE and MTE literatures from economics
  - Bjorklund and Moffitt (1987)
  - Imbens and Angrist (1994)
  - Heckman and Vytlacil (1999, 2005, 2007)
  - Vytlacil (2002)
  - Brinch, Mogstad, Wiswall (2015)

I Examine Behavior within a Clinical Trial

"Doing More When You're Running LATE: Applying Marginal Treatment Effect Methods to Examine Treatment Effect Heterogeneity in Experiments." *NBER WP 22363.*

"Extrapolation Using Selection and Moral Hazard Heterogeneity from Within the Oregon Health Insurance Experiment." *NBER WP 24647.*

"How to Examine External Validity Within an Experiment" *NBER WP 24834.*

"Behavior within a Clinical Trial and Implications for Mammography Guidelines." *NBER WP 25049.*

Behavior within a Clinical Trial and Implications for Mammography Guidelines

- **Model**
  - **First Stage: Mammography**
  - Second Stage: Mortality
- Results
  1. Selection Heterogeneity
     - *Women more likely to receive mammograms are healthier*
  2. Treatment Effect Heterogeneity
     - *Women more likely to receive mammograms are more likely to be harmed by them*
- Robustness
- Conclusions

First Stage:

$$V = V_U + (V_T - V_U)D$$
$$V_T - V_U = \mu_D(Z) - \nu_D$$

First Stage:

$$V = V_U + (V_T - V_U)D$$
$$V_T - V_U = \mu_D(Z) - \nu_D$$

Assumptions:

A.1. (Continuity) $F(\cdot)$: absolutely continuous with respect to the Lebesgue measure

First Stage:

$$V = V_U + (V_T - V_U)D$$
$$V_T - V_U = \mu_D(Z) - \nu_D \qquad U_D = F(\nu_D),\ U_D \sim U[0,1]$$

Assumptions:

A.1. (Continuity) $F(\cdot)$: absolutely continuous with respect to the Lebesgue measure

Proof: $\boldsymbol{U_D \sim U[0,1]}$

$$\begin{aligned} F_{U_D}(u) &= P(U_D \le u) \\ &= P(F(\nu_D) \le u) \\ &= P(\nu_D \le F^{-1}(u)) \qquad (F(\cdot) \text{ absolutely continuous by A.1}) \\ &= F(F^{-1}(u)) = u \end{aligned}$$

First Stage:

$$V = V_U + (V_T - V_U)D$$
$$V_T - V_U = \mu_D(Z) - \nu_D \qquad U_D = F(\nu_D),\ U_D \sim U[0,1]$$

Assumptions:

A.1. (Continuity) $F(\cdot)$: absolutely continuous with respect to the Lebesgue measure

A.2. (Independence) (U_D, γ_T) and $(U_D, \gamma_U) \perp Z$

First Stage:

$$
\begin{aligned}
V &= V_U + (V_T - V_U)D \\
V_T - V_U &= \mu_D(Z) - \nu_D \qquad\qquad U_D = F(\nu_D),\ U_D \sim U[0,1] \\
D &= 1\{0 \leq V_T - V_U\} \\
\Rightarrow D &= 1\{U_D \leq P(D = 1 \mid Z = z)\}
\end{aligned}
$$

Assumptions:

A.1. (Continuity) $F(\cdot)$: absolutely continuous with respect to the Lebesgue measure

A.2. (Independence) (U_D, γ_T) and $(U_D, \gamma_U) \perp Z$

Proof: $\boldsymbol{D = 1\{U_D \leq \mathrm{P}(D = 1 \mid Z = z)\}}$

$$
\begin{aligned}
D &= 1\{0 \leq V_T - V_U\} \\
&= 1\{0 \leq \mu_D(Z) - \nu_D\} \\
&= 1\{\nu_D \leq \mu_D(Z)\} \\
&= 1\{F(\nu_D) \leq F(\mu_D(Z))\} && \text{(definition of } F(\cdot) \text{ from A.1)} \\
&= 1\{U_D \leq F(\mu_D(Z))\} && (U_D = F(\nu_D) \text{ by definition}) \\
&= 1\{U_D \leq \mathrm{P}(D = 1 \mid Z = z)\},
\end{aligned}
$$

where the last equality follows from

$$
\begin{aligned}
F(\mu_D(Z)) &= \mathrm{P}(\nu_D \leq \mu_D(Z)) \\
&= \mathrm{P}(\nu_D \leq \mu_D(z) \mid Z = z) && (U_D \perp Z \text{ by A.2}) \\
&= \mathrm{P}(0 \leq \mu_D(Z) - \nu_D \mid Z = z) \\
&= \mathrm{P}(0 \leq V_T - V_U \mid Z = z) \\
&= \mathrm{P}(D = 1 \mid Z = z).
\end{aligned}
$$

First Stage:

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Assumptions:

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A.3. (Instrument Relevance) $\mu_D(Z)$: nondegenerate random variable

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& D = 1\{0 \leq V_T - V_U\} \\
\Rightarrow & D = 1\{U_D \leq P(D=1 \mid Z=z)\} \\
& Z = 0: \quad D = 1\{U_D \leq p_C\}, \quad p_C = P(D=1 \mid Z=0) \\
& Z = 1: \quad D = 1\{U_D \leq p_I\}, \quad p_I = P(D=1 \mid Z=1)
\end{aligned}
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Assumptions:

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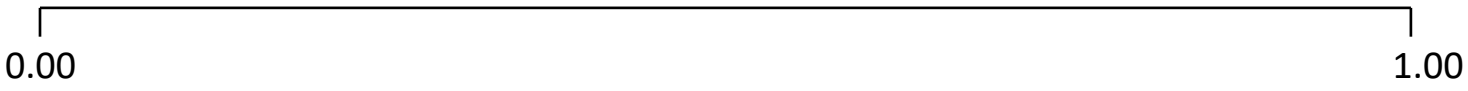

U_D: unobserved net cost of treatment

First Stage:

$$V = V_U + (V_T - V_U)D$$

$$V_T - V_U = \mu_D(Z) - \nu_D \qquad U_D = F(\nu_D),\ U_D \sim U[0,1]$$

$$D = 1\{0 \leq V_T - V_U\}$$

$$\Rightarrow D = 1\{U_D \leq P(D = 1 \mid Z = z)\}$$

$$\boldsymbol{Z = 0:} \quad \boldsymbol{D = 1\{U_D \leq p_C\},} \quad \boldsymbol{p_C = P(D = 1 \mid Z = 0)}$$

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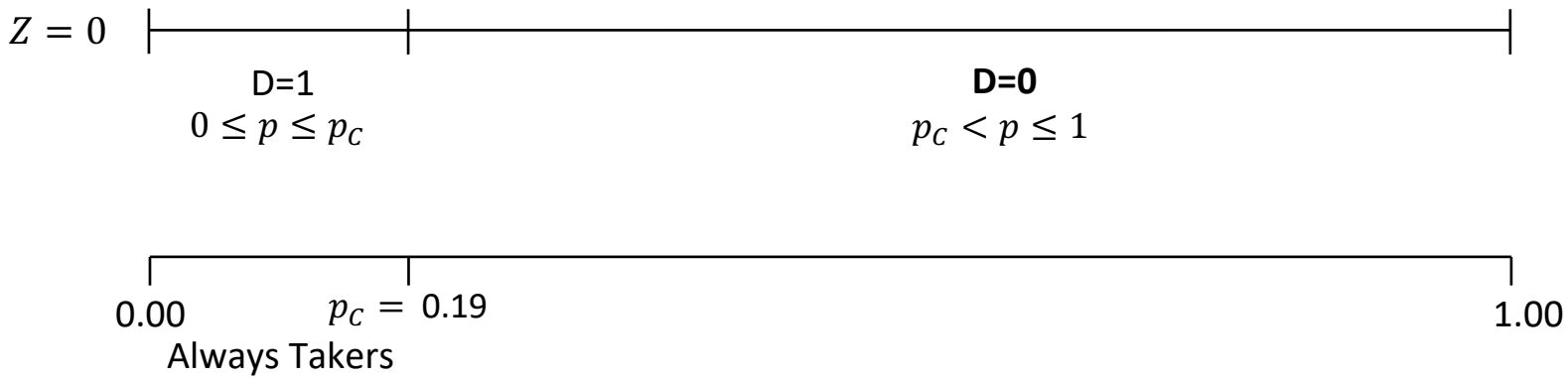

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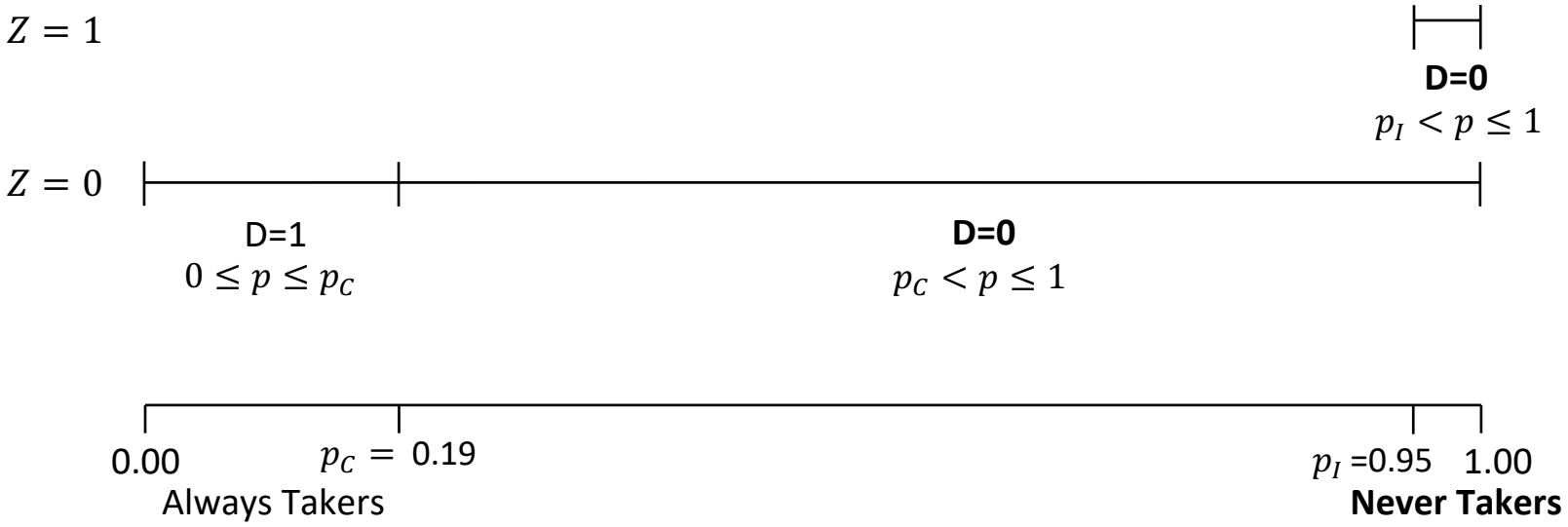

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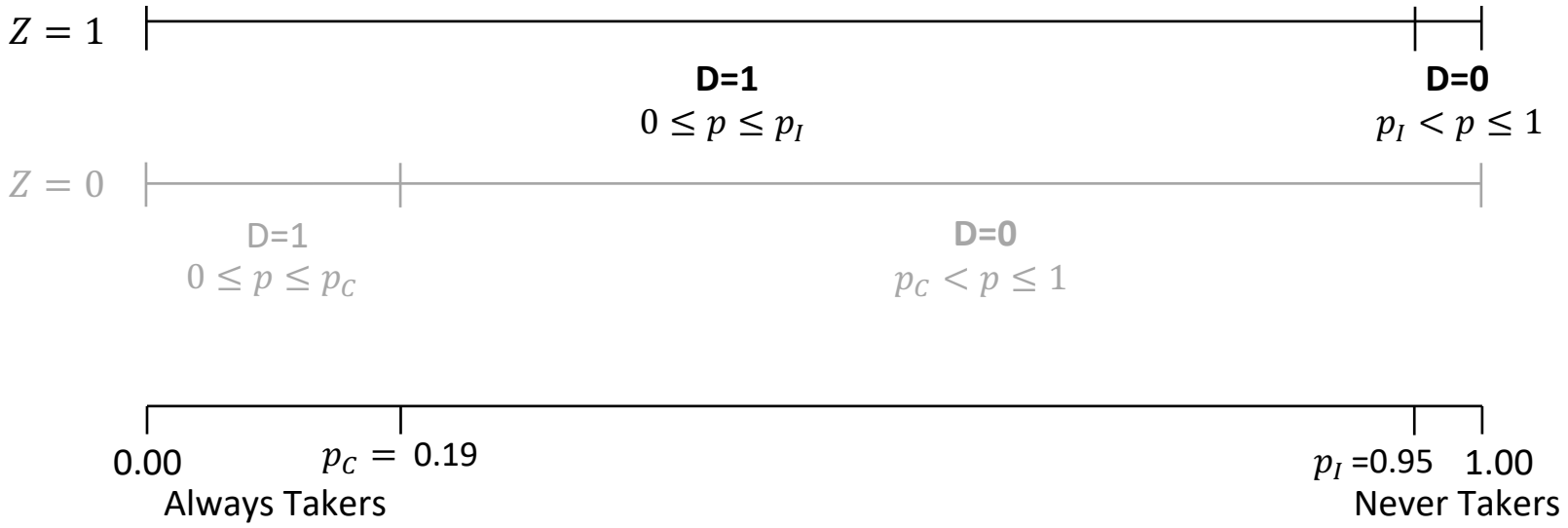

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\end{aligned}
$$

Second Stage:

$$
\begin{aligned}
& Y = Y_U + (Y_T - Y_U)D \\
& Y_T = g_T(U_D, \gamma_T) \\
& Y_U = g_U(U_D, \gamma_U) \qquad\qquad Z \perp (\gamma_T, \gamma_U) \text{ by A.2.}
\end{aligned}
$$

Assumptions (Second Stage):

A.4. (Treated and Untreated) $0 < \mathrm{P}(D=1) < 1$

A.5. (Finite Average Outcomes) $E[Y_T], E[Y_U]$ are finite

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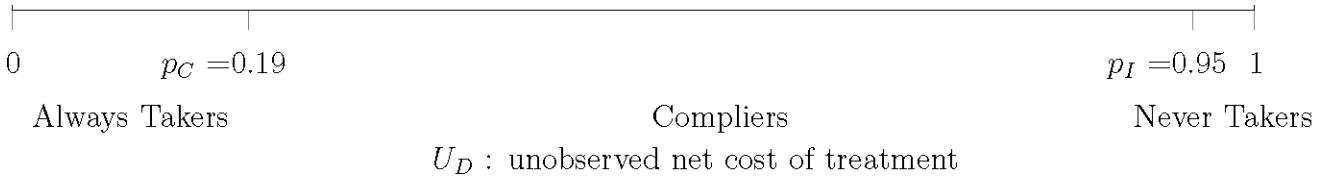
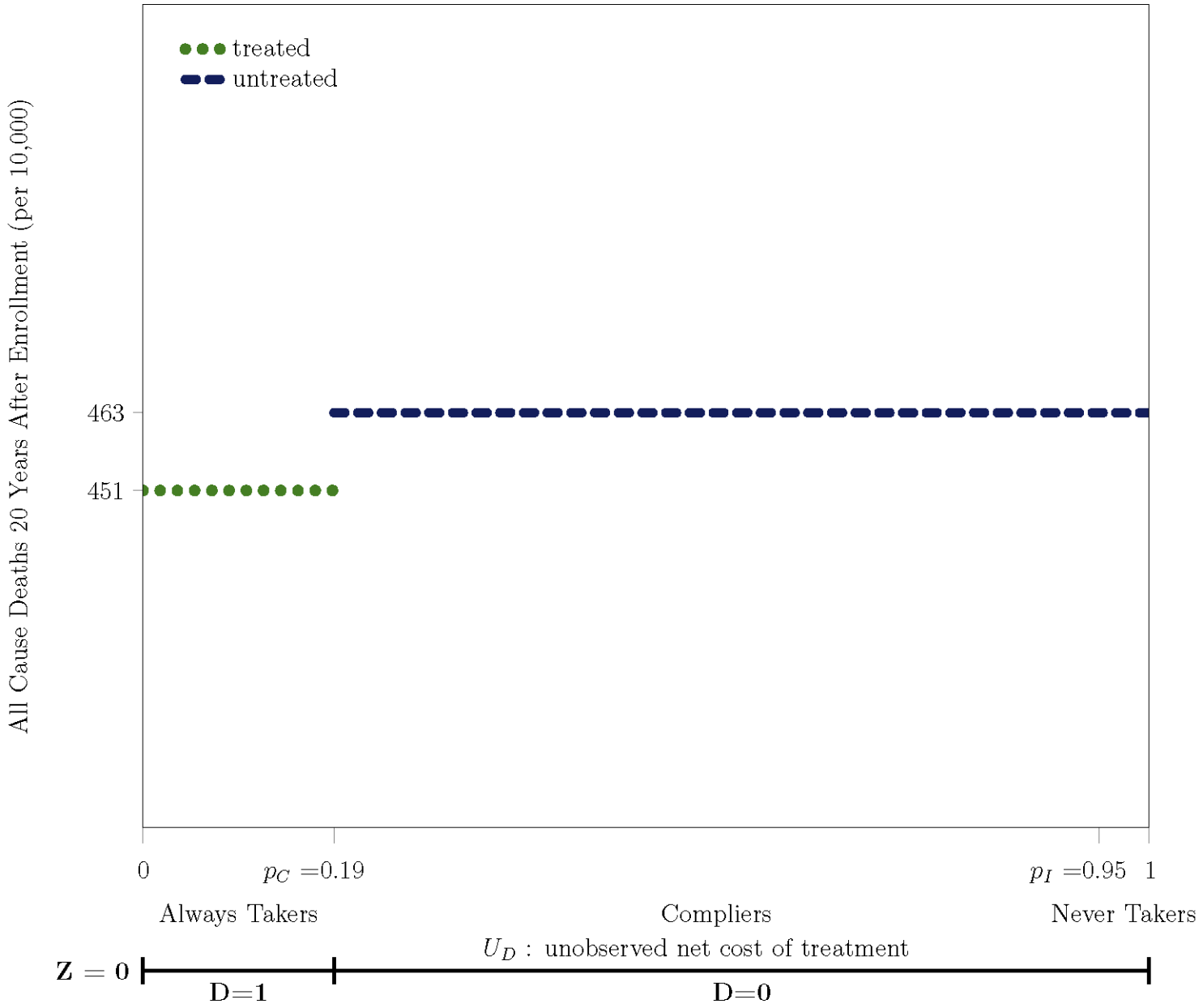
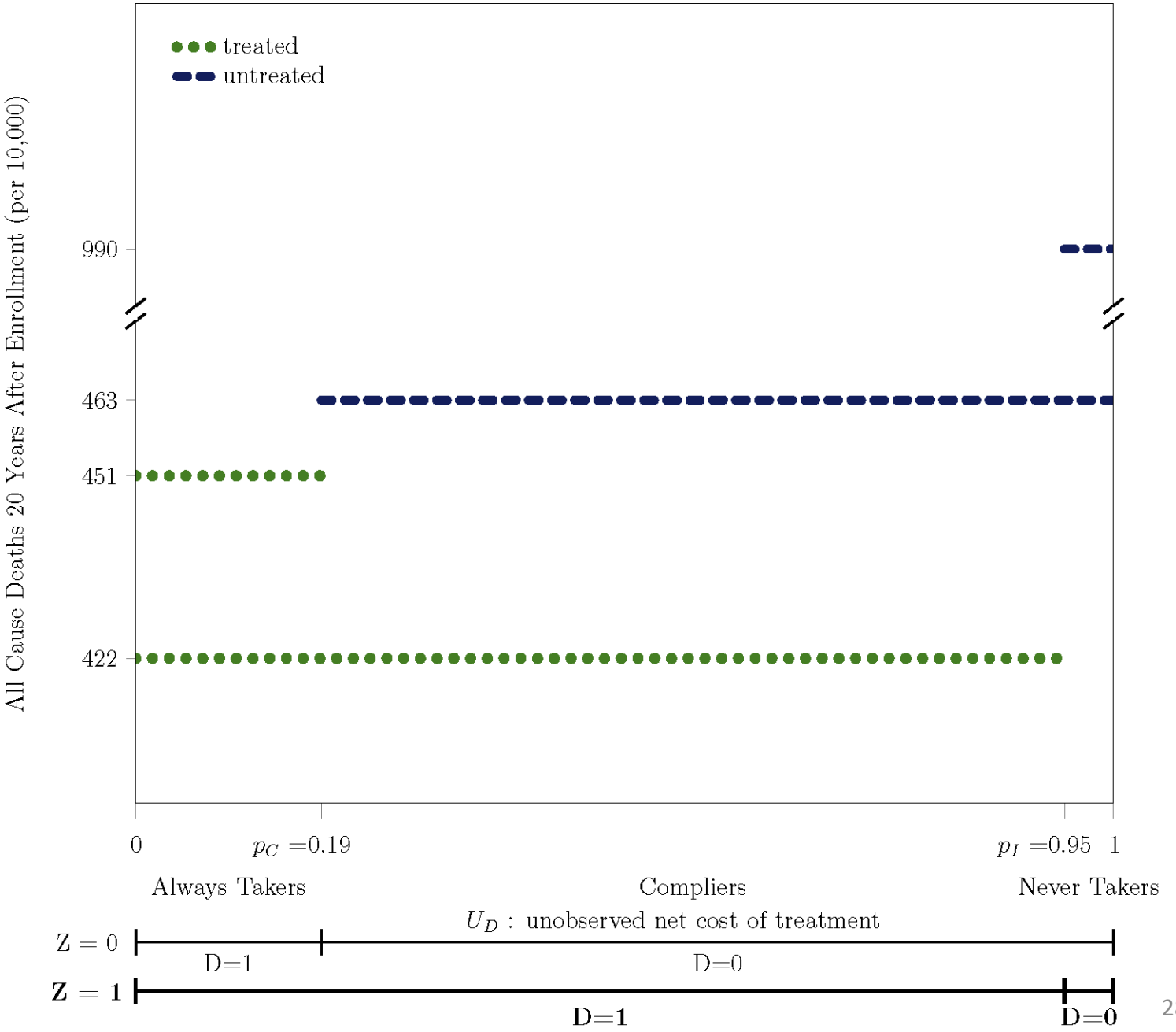
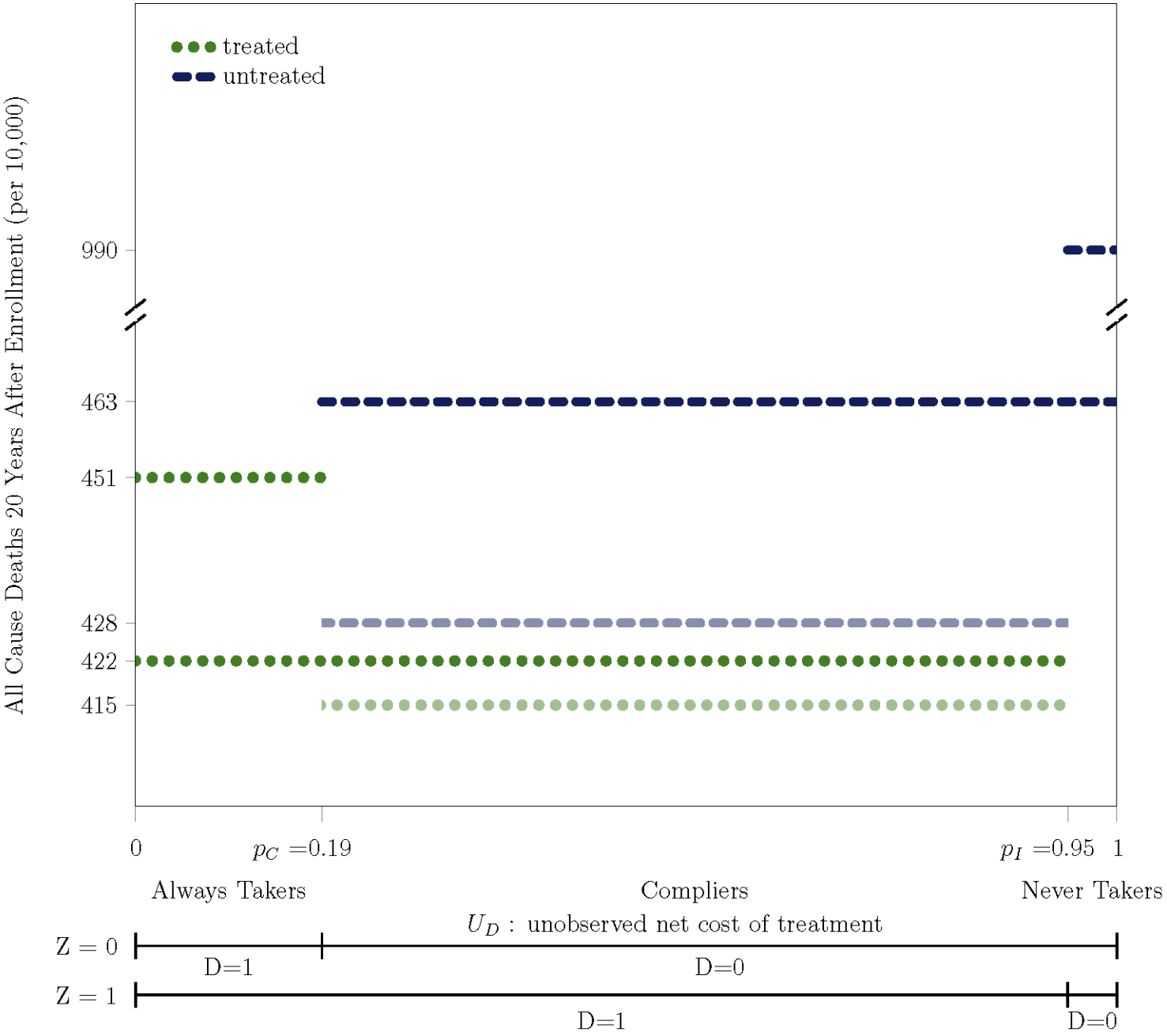



treated
untreated
All Cause Deaths 20 Years After Enrollment (per 10,000)
463
451
0
p_C =0.19
p_I =0.95
1
Always Takers
Compliers
Never Takers
U_D : unobserved net cost of treatment
Z = 0
D=1
D=0


treated
untreated
All Cause Deaths 20 Years After Enrollment (per 10,000)
990
463
451
422
0
p_C =0.19
p_I =0.95
1
Always Takers
Compliers
Never Takers
U_D : unobserved net cost of treatment
Z = 0
D=1
D=0
Z = 1
D=1
D=0


treated
untreated
All Cause Deaths 20 Years After Enrollment (per 10,000)
990
463
451
428
422
415
0
p_C =0.19
p_I =0.95
1
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D=1
D=0
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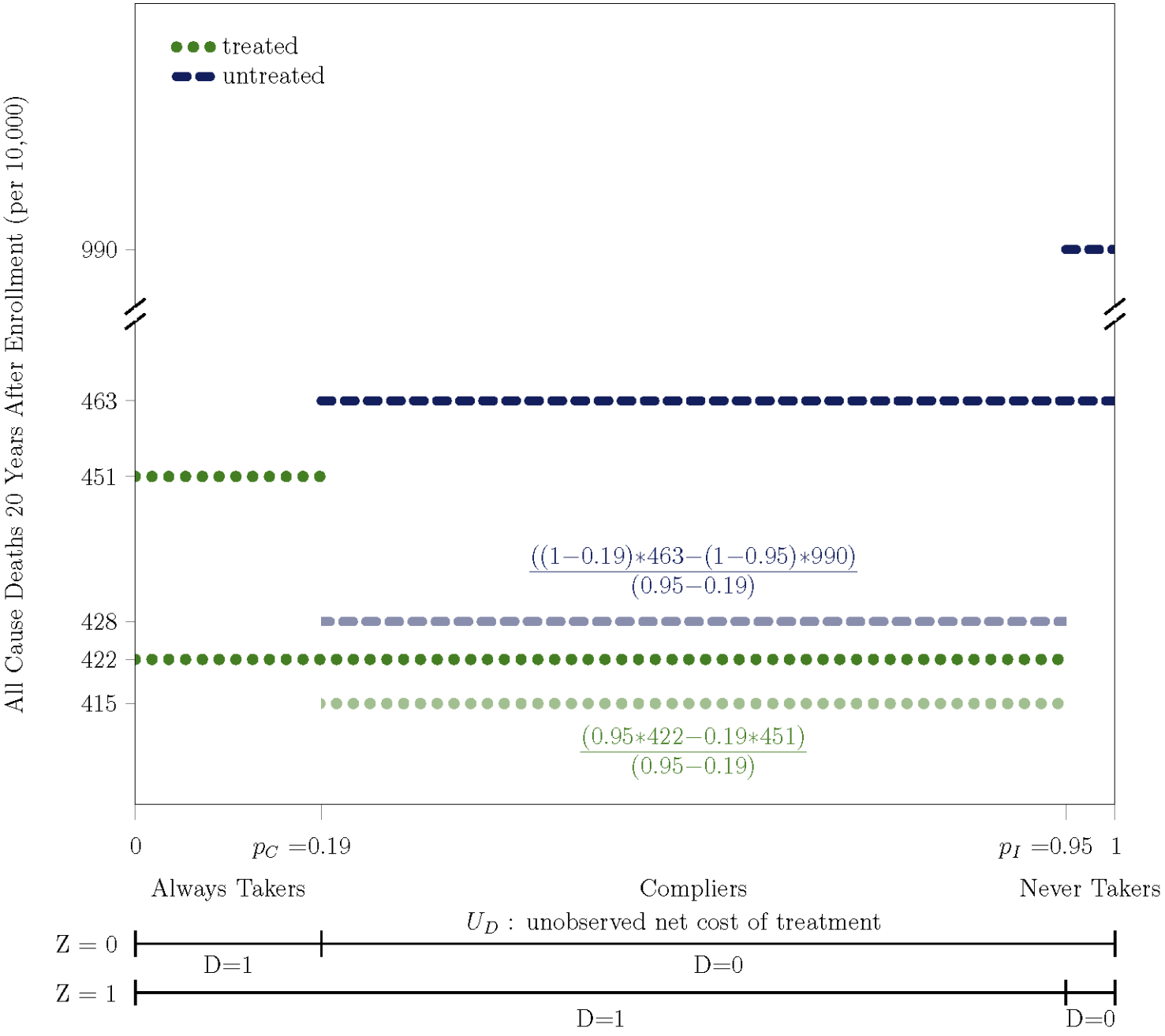
treated
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All Cause Deaths 20 Years After Enrollment (per 10,000)
990
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428
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((1−0.19)∗463−(1−0.95)∗990)
(0.95−0.19)
(0.95∗422−0.19∗451)
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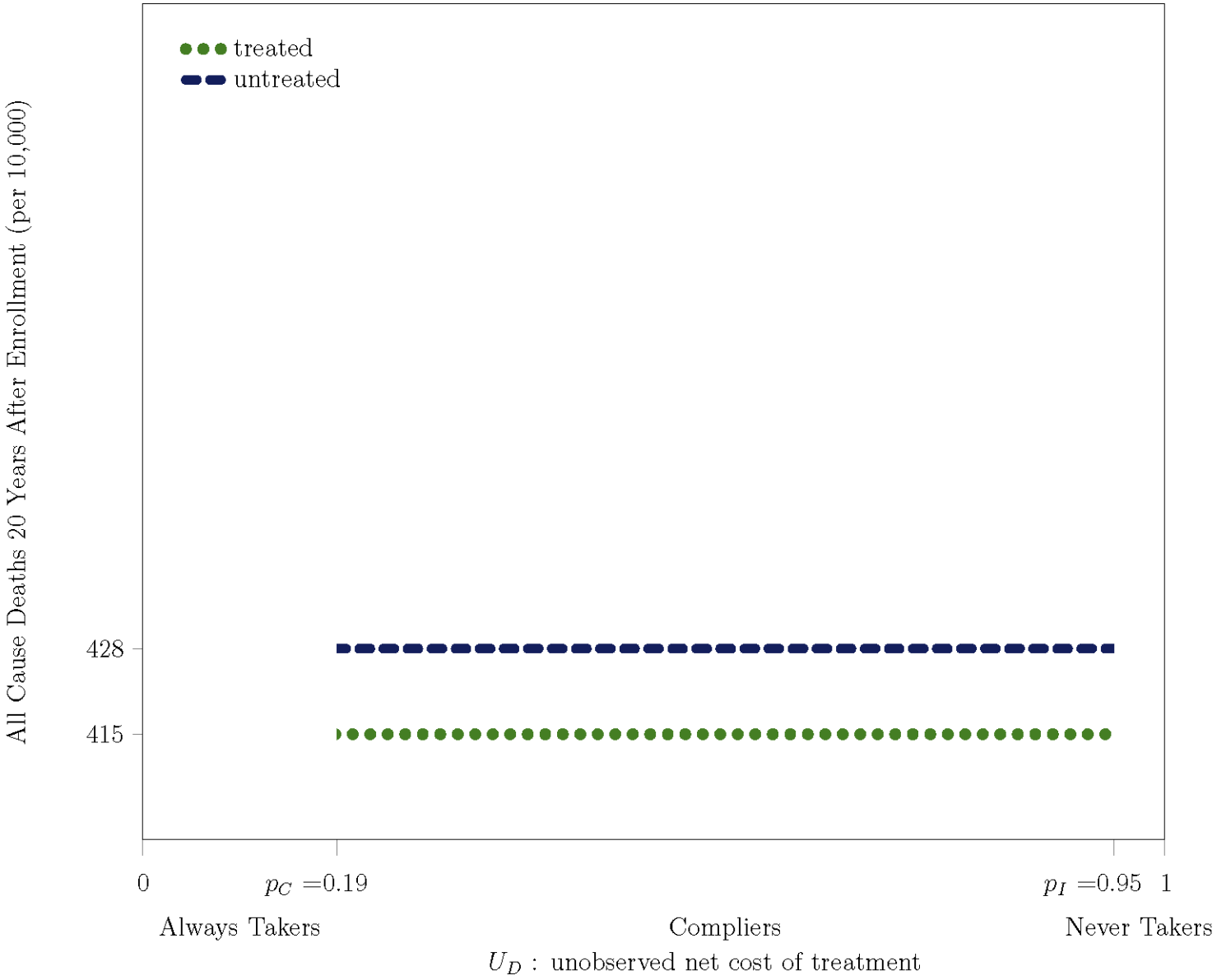
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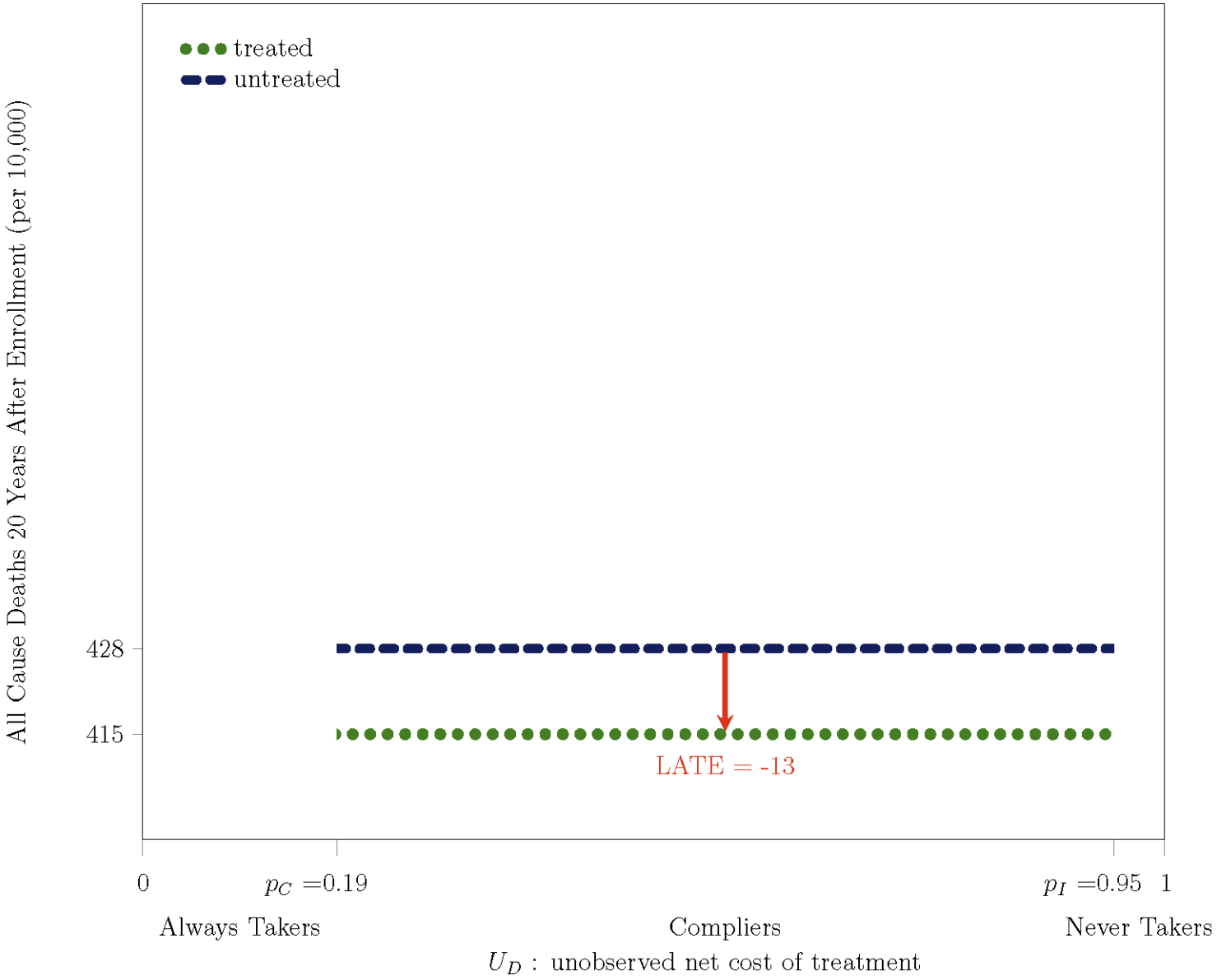
treated
untreated
All Cause Deaths 20 Years After Enrollment (per 10,000)
428
415
LATE = -13
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p_C =0.19
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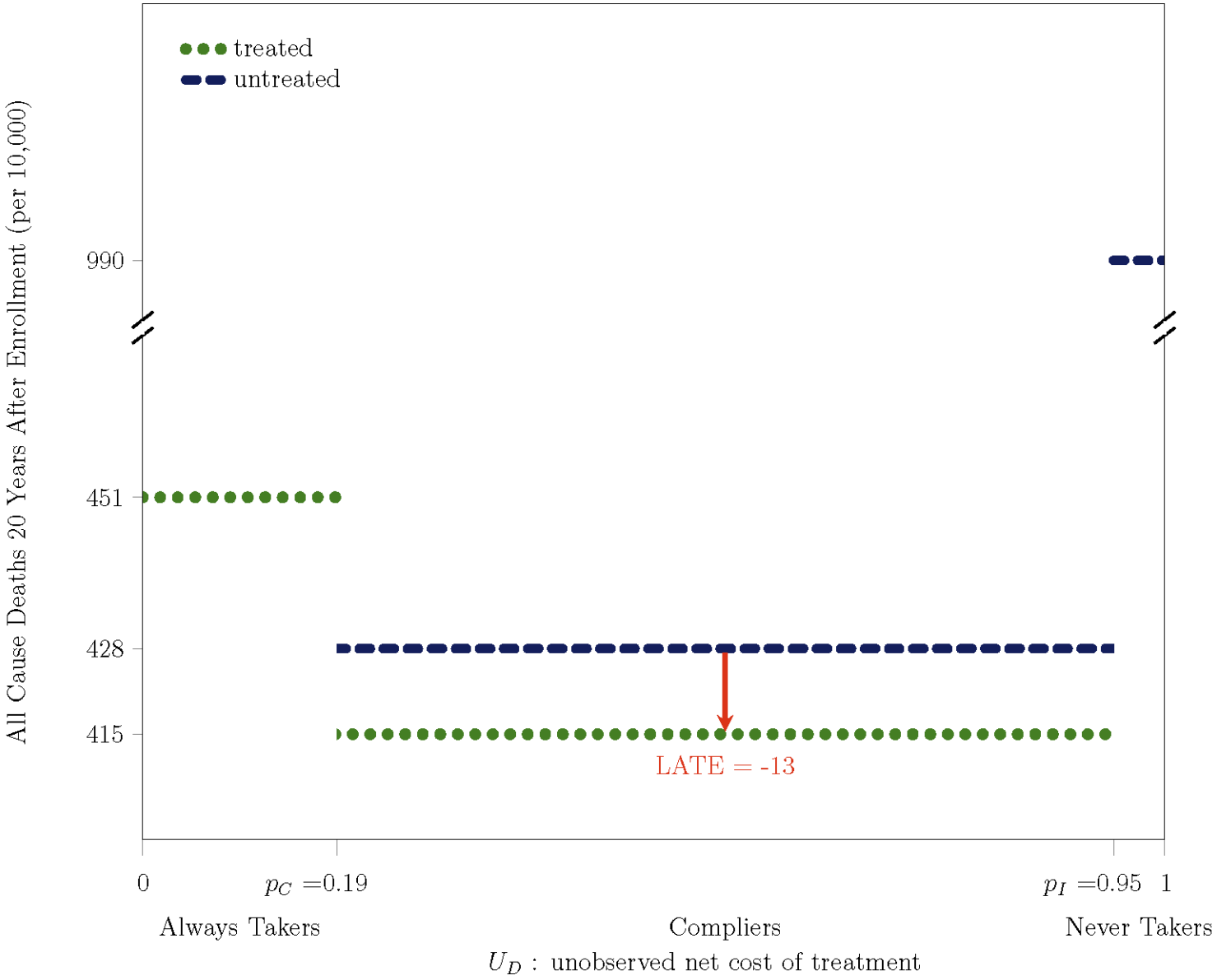
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     - *Women more likely to receive mammograms are more likely to be harmed by them*
- Robustness
- Conclusions

First Stage:

$$
\begin{aligned}
V &= V_U + (V_T - V_U)D \\
V_T - V_U &= \mu_D(Z) - \nu_D \qquad\qquad U_D = F(\nu_D),\ U_D \sim U[0,1] \\
D &= 1\{0 \leq V_T - V_U\} \\
\Rightarrow D &= 1\{U_D \leq P(D=1 \mid Z=z)\}
\end{aligned}
$$

Second Stage:

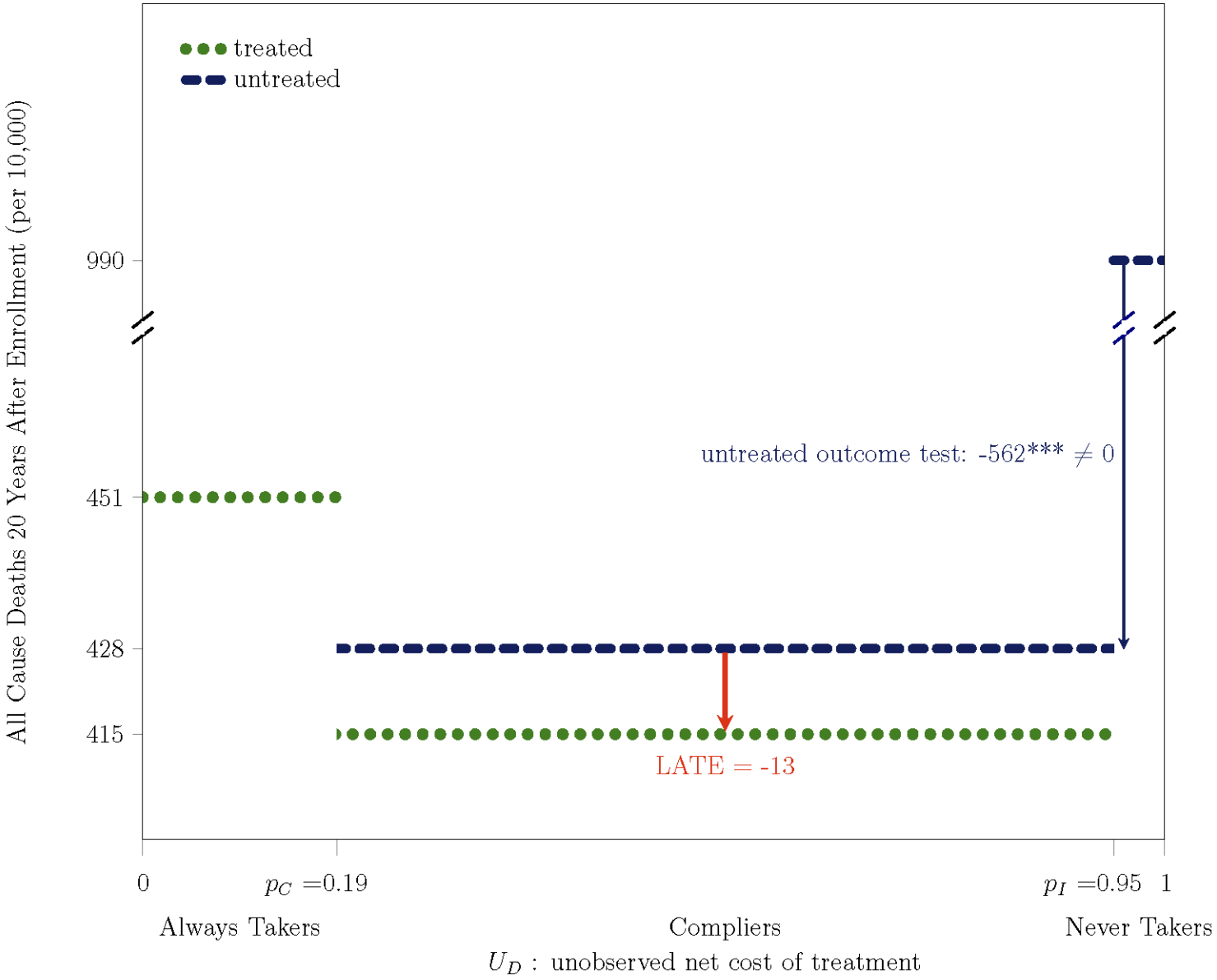
$$
\begin{aligned}
Y &= Y_U + (Y_T - Y_U)D \\
Y_T &= g_T(U_D, \gamma_T) \\
Y_U &= g_U(U_D, \gamma_U) \qquad\qquad Z \perp (\gamma_T, \gamma_U) \text{ by A.2.}
\end{aligned}
$$

Untreated Outcome Test:

$$
\mathrm{E}[Y_U \mid p_C < U_D \leq p_I] - \mathrm{E}[Y_U \mid p_I < U_D \leq 1] = \int_0^1 (\omega(p, p_C, p_I) - \omega(p, p_I, 1))\,\mathrm{MUO}(p)\,\mathrm{d}p
$$

where $\omega(p, p_L, p_H) = 1\{p_L \leq p < p_H\}/(p_H - p_L)$

(Bertanha and Imbens (2014); Guo, Cheng, Lorch, and Small (2014); Black, Joo, LaLonde, Smith, and Taylor (2015); Mogstad, Santos, and Torgovitsky (2018).)


treated
untreated
All Cause Deaths 20 Years After Enrollment (per 10,000)
990
451
428
415
untreated outcome test: -562*** ≠ 0
LATE = -13
0
p_C =0.19
p_I =0.95
1
Always Takers
Compliers
Never Takers
U_D : unobserved net cost of treatment

Behavior within a Clinical Trial and Implications for Mammography Guidelines

- Model
  - First Stage: Mammography
  - Second Stage: Mortality
- **Results**
  1. Selection Heterogeneity
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D &= 1\{0 \leq V_T - V_U\} \\
\Rightarrow D &= 1\{U_D \leq P(D = 1 \,|\, Z = z)\}
\end{aligned}
$$

Second Stage:

$$
\begin{aligned}
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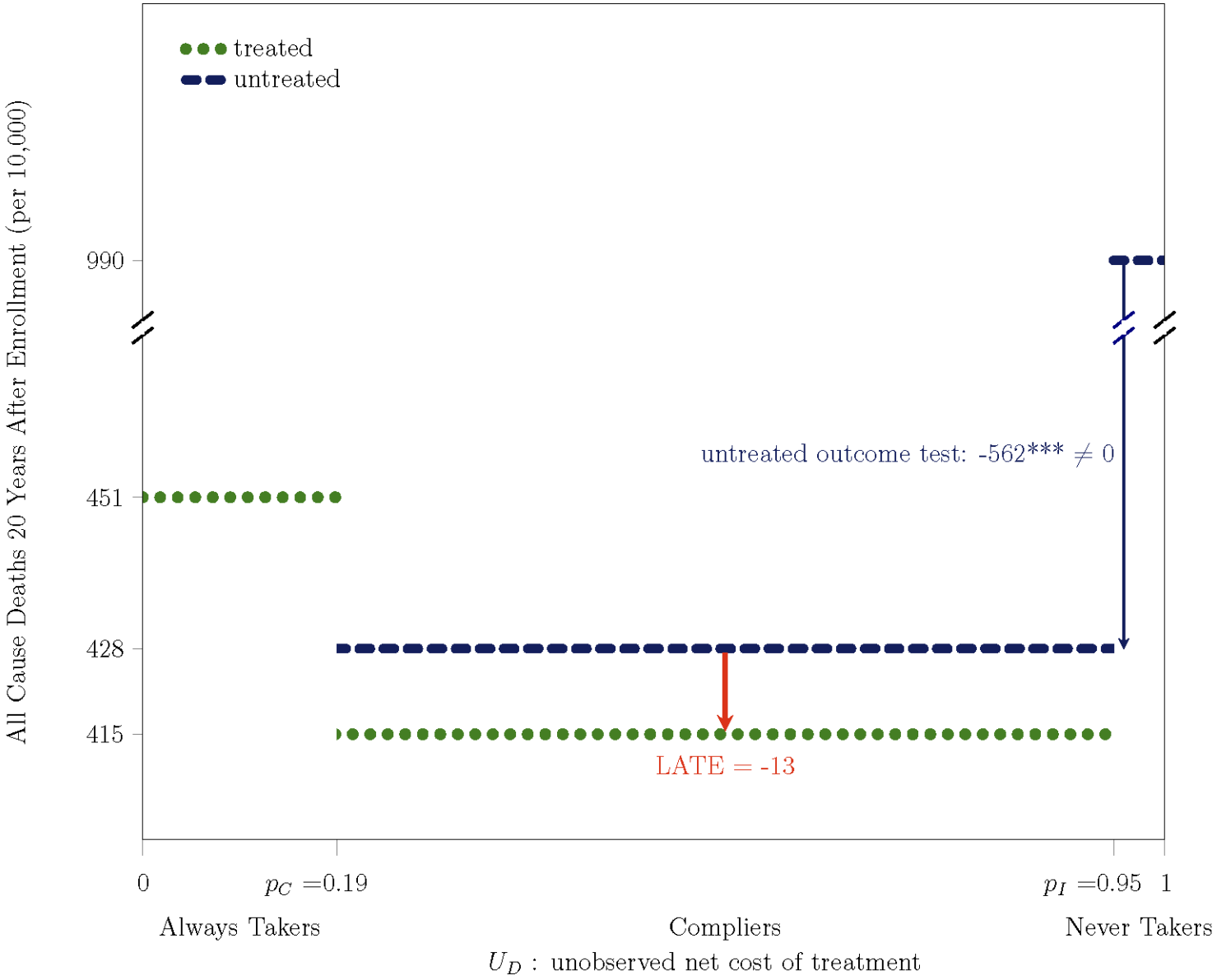
Y_U &= g_U(U_D, \gamma_U) \qquad\qquad Z \perp (\gamma_T, \gamma_U) \text{ by A.2.}
\end{aligned}
$$

Ancillary Assumption - Weak Monotonicity of the MUO Function

For all $p_1, p_2 \in [0,1]$ such that $p_1 < p_2$:
$\mathrm{E}[Y_U \,|\, U_D = p_1] \leq \mathrm{E}[Y_U \,|\, U_D = p_2]$ or $\mathrm{E}[Y_U \,|\, U_D = p_1] \geq \mathrm{E}[Y_U \,|\, U_D = p_2]$

(Brinch, Mogstad, and Wiswall (2017).)


treated
untreated
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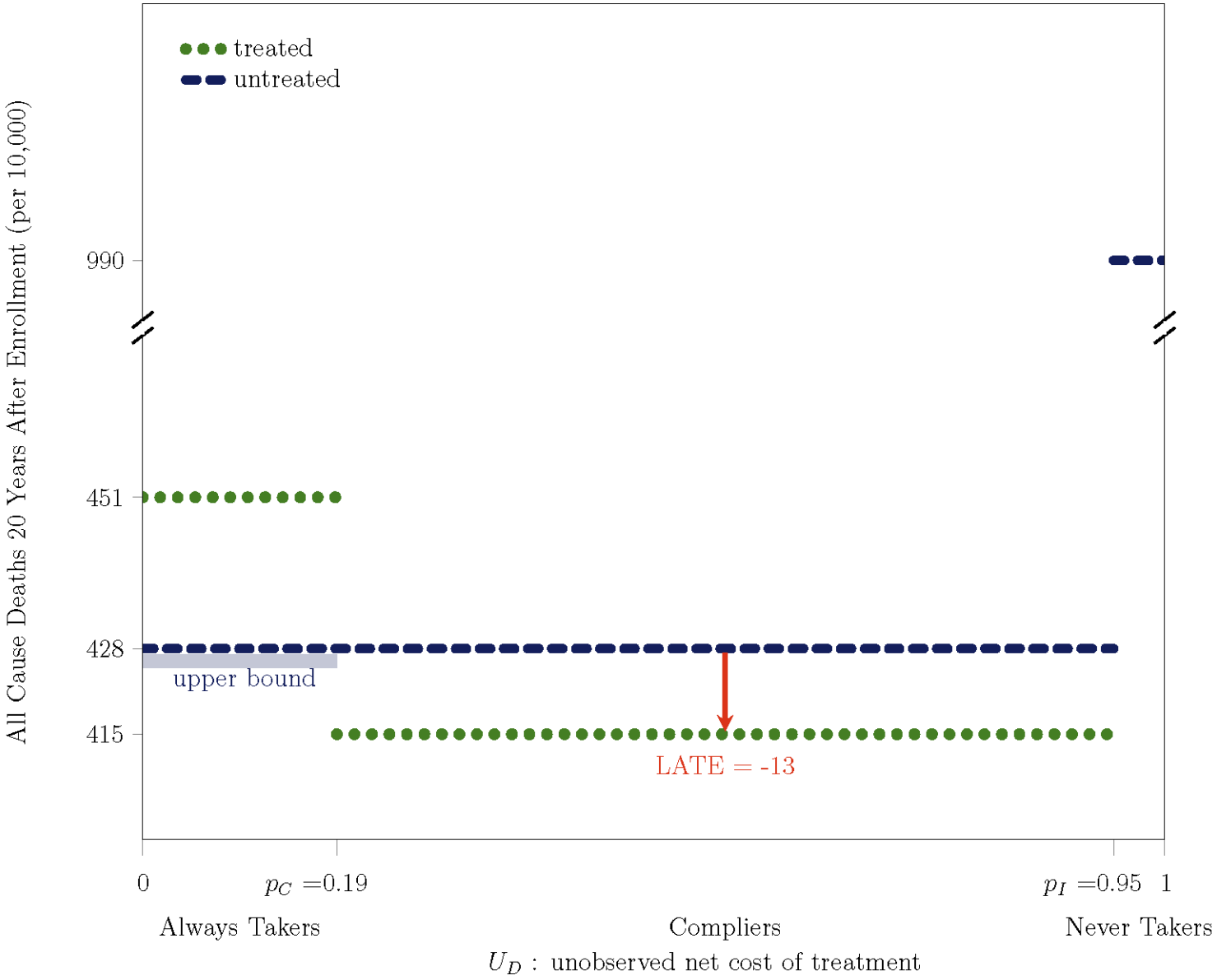
treated
untreated
All Cause Deaths 20 Years After Enrollment (per 10,000)
990
451
428
415
upper bound
LATE = -13
0
p_C =0.19
p_I =0.95
1
Always Takers
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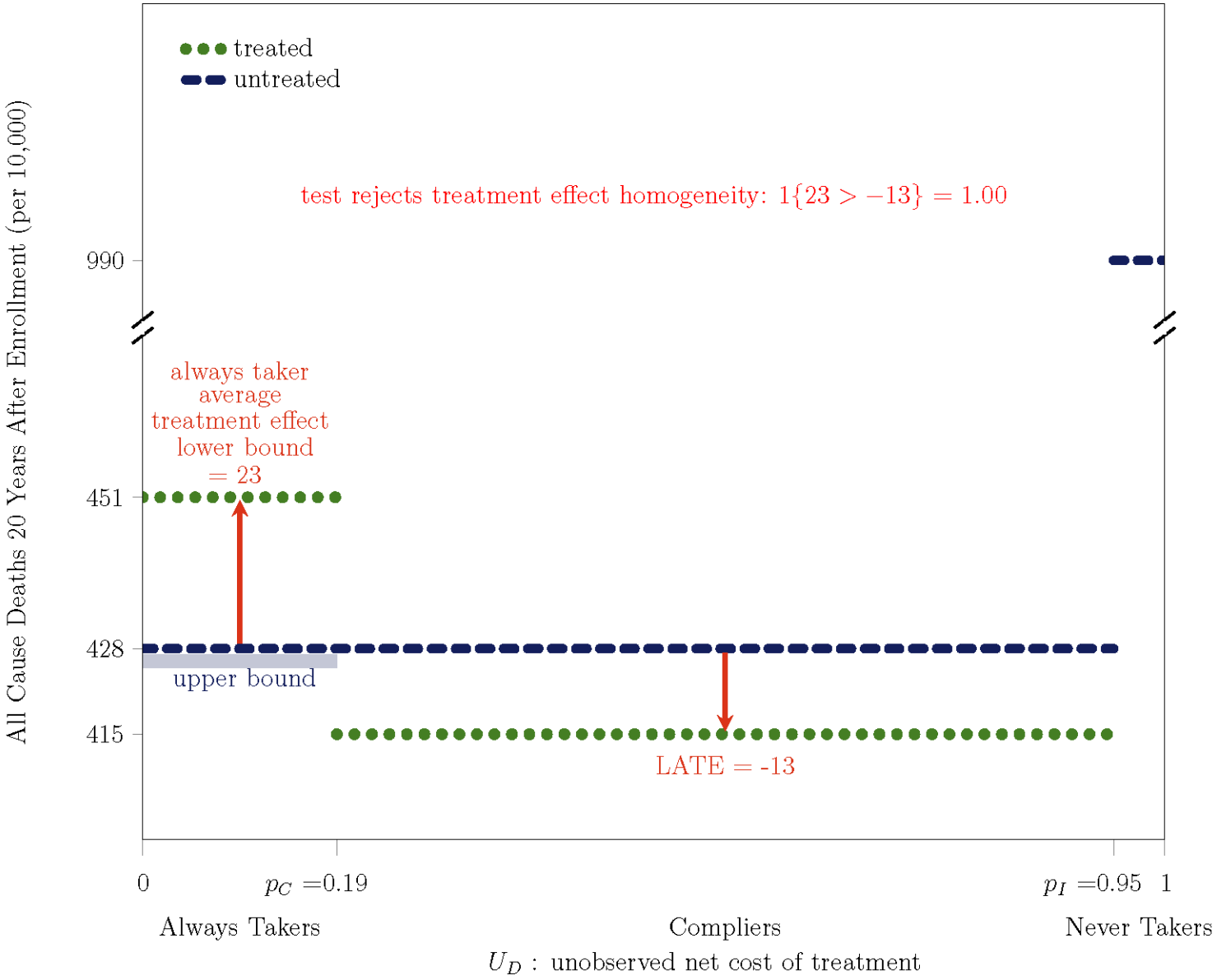

treated
untreated
test rejects treatment effect homogeneity: $1\{23 > -13\} = 1.00$
All Cause Deaths 20 Years After Enrollment (per 10,000)
990
451
428
415
always taker average treatment effect lower bound = 23
upper bound
LATE = -13
0
p_C =0.19
p_I =0.95
1
Always Takers
Compliers
Never Takers
U_D : unobserved net cost of treatment

“I never, though, had a patient whose worry about those side effects came close to her worry about the disease. Being preoccupied with saving one’s life produces a myopia, in which other worries unrelated to one’s possibly imminent death fall away.”

-Brown, New York Times, October 28, 2017

“And so, unable to say whether any particular patient will benefit, we have no choice but to overtreat.”

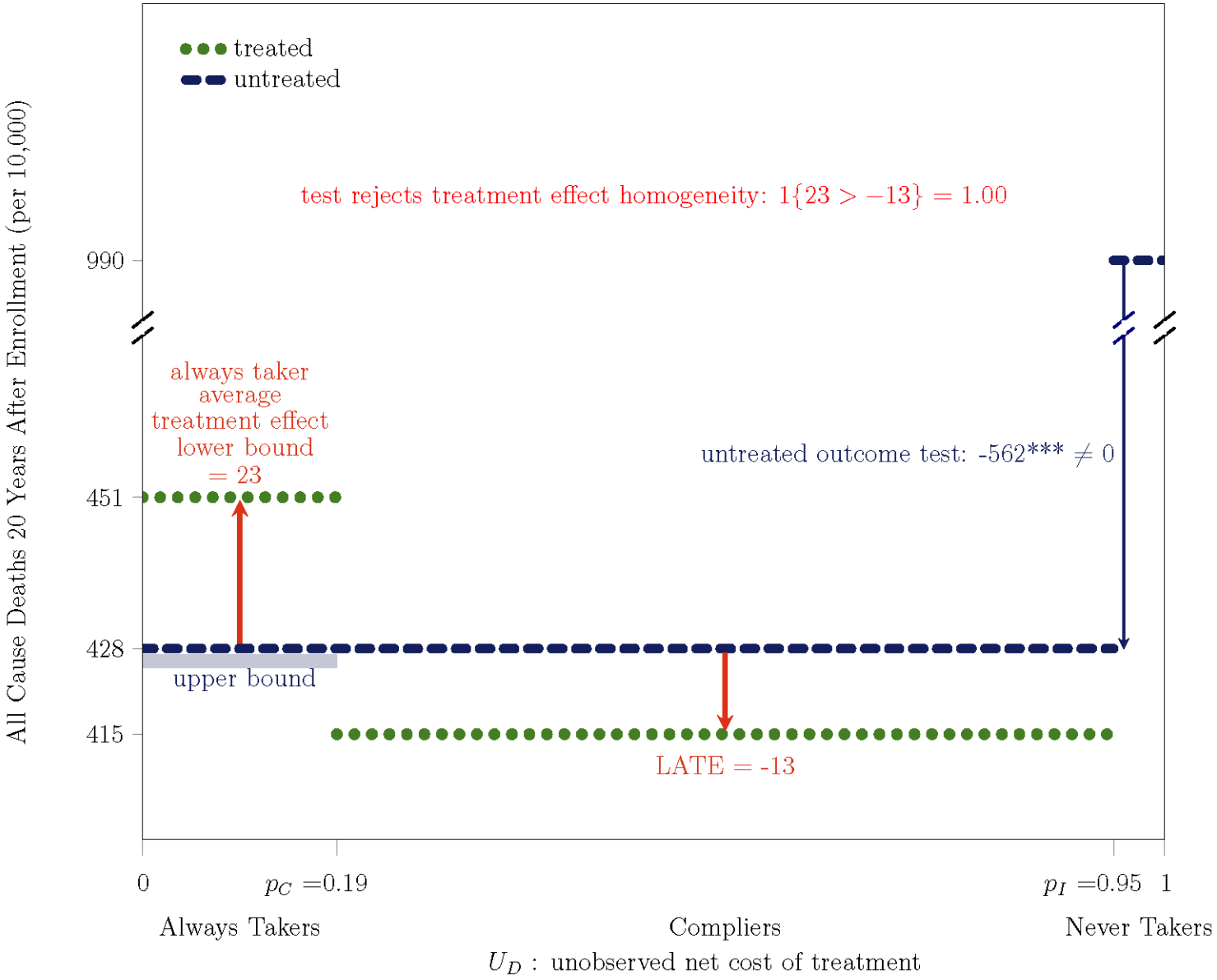
-Mukherjee, New Yorker, September 11, 2017

Baseline Covariates Support Ancillary Assumption

	Means		
	Always Takers	Compliers	Never Takers
Baseline Socioeconomic Status			
University, trade or business school	0.50	0.46	0.39
In work force	0.65	0.64	0.65
Age at first birth	24.28	23.98	23.57
No live birth	0.16	0.15	0.13
Married	0.80	0.81	0.75
Husband in work force / alive	0.81	0.81	0.76
Baseline Health Behavior			
Non-Smoker	0.78	0.75	0.63
Body Mass Index	23.87	24.42	24.48
Used oral contraception	0.74	0.71	0.67
Used estrogen	0.13	0.13	0.15
Mammograms prior to enrollment	0.23	0.13	0.13
Practiced breast self examination	0.47	0.44	0.38

Behavior within a Clinical Trial and Implications for Mammography Guidelines

- Model
  - First Stage: Mammography
  - Second Stage: Mortality
- Results
  1. Selection Heterogeneity
     - *Women more likely to receive mammograms are healthier*
  2. Treatment Effect Heterogeneity
     - *Women more likely to receive mammograms are more likely to be harmed by them*
- **Robustness**
- Conclusions


treated
untreated
test rejects treatment effect homogeneity: $1\{23 > -13\} = 1.00$
All Cause Deaths 20 Years After Enrollment (per 10,000)
990
451
428
415
always taker average treatment effect lower bound = 23
untreated outcome test: -562*** $\neq 0$
upper bound
LATE = -13
0
p_C =0.19
p_I =0.95
1
Always Takers
Compliers
Never Takers
U_D : unobserved net cost of treatment

Main Specification For Comparison

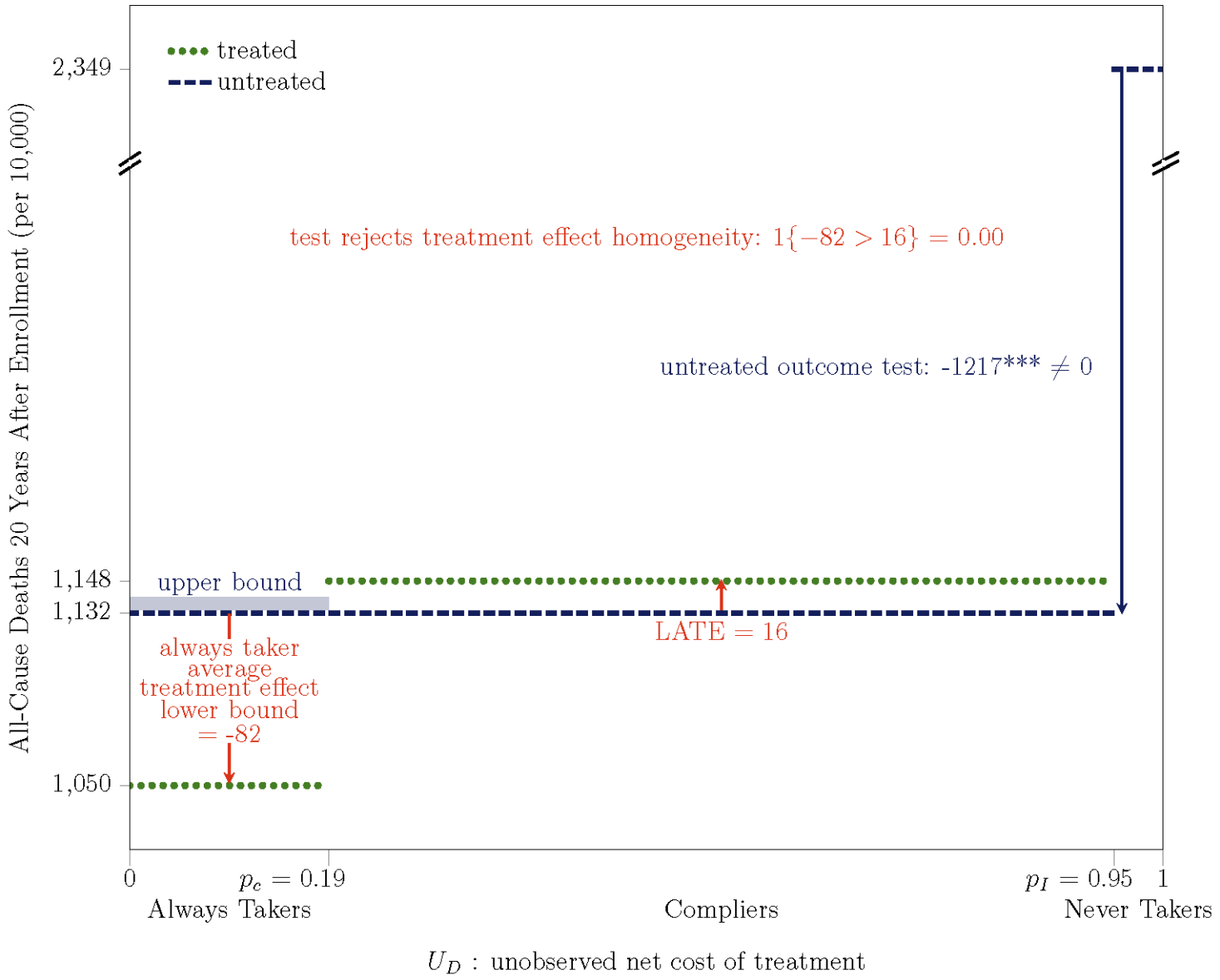
	N	Untreated Outcome Test	Always Taker Average Treatment Effect Lower Bound	LATE	Test Rejects Treatment Effect Homogeneity
Main Specification					
Main Specification	19,505	-562 (147)	23 (59)	-13 (38)	1.00 (0.48)

Results Are Robust Along Many Dimensions

- **Sample Restrictions**
  - **Excluded participants aged 40-49**
  - **All participants aged 40-49**
  - **All participants aged 50-59**
- Definitions of mammography
  - Narrower
  - Broader
- Outcomes
  - Breast cancer mortality
  - Mortality at alternative follow-up lengths

Robust to Alternative Sample Restrictions

	N	Untreated Outcome Test	Always Taker Average Treatment Effect Lower Bound	LATE	Test Rejects Treatment Effect Homogeneity
Main Specification					
Main Specification	19,505	-562 (147)	23 (59)	-13 (38)	1.00 (0.48)
Alternative Sample Restrictions					
All excluded participants aged 40-49 at enrollment	30,925	-759 (135)	60 (39)	27 (40)	1.00 (0.47)
All participants aged 40-49 at enrollment	50,430	-672 (103)	53 (31)	9 (27)	1.00 (0.34)
All participants aged 50-59 at enrollment	39,405	-1,216 (154)	-83 (51)	15 (46)	0.00 (0.26)


treated
untreated
2,349
test rejects treatment effect homogeneity: $1\{-82 > 16\} = 0.00$
untreated outcome test: -1217*** $\neq 0$
1,148
upper bound
1,132
LATE = 16
always taker average treatment effect lower bound = -82
1,050
All-Cause Deaths 20 Years After Enrollment (per 10,000)
0
$p_c = 0.19$
$p_I = 0.95$
1
Always Takers
Compliers
Never Takers
U_D : unobserved net cost of treatment

Results Are Robust Along Many Dimensions

- Sample Restrictions
  - Excluded participants aged 40-49
  - All participants aged 40-49
  - All participants aged 50-59
- **Definitions of mammography**
  - **Narrower**
  - **Broader**
- Outcomes
  - Breast cancer mortality
  - Mortality at alternative follow-up lengths

Robust to Alternative Definitions of Mammography

	N	Untreated Outcome Test	Always Taker Average Treatment Effect Lower Bound	LATE	Test Rejects Treatment Effect Homogeneity
Main Specification					
Mammogram in at least one year after enrollment during the active study period, missing in year = no mammogram in year					
Main specification	19,505	-562	23	-13	1.00
		(147)	(59)	(38)	(0.48)
Narrower Definitions of Mammography					
Mammogram in more than one year after enrollment during the active study period, missing in year = no mammogram in year					
At least two active study period years	19,505	-465	-27	-12	0.00
		(106)	(77)	(35)	(0.49)
At least three active study period years	19,505	-420	56	-12	1.00
		(94)	(145)	(36)	(0.48)
All active study period years	19,505	-225	-135	-15	0.00
		(75)	(138)	(42)	(0.37)
Broader Definition of Mammography					
Mammogram in at least one year after enrollment during the active study period					
Missing in year = mammogram in year	19,505	-776	103	-24	1.00
		(835)	(43)	(69)	(0.43)

Results Are Robust Along Many Dimensions

- Sample Restrictions
  - Excluded participants aged 40-49
  - All participants aged 40-49
  - All participants aged 50-59
- Definitions of mammography
  - Narrower
  - Broader
- **Outcomes**
  - **Breast cancer mortality**
  - Mortality at alternative follow-up lengths

Robust to Alternative Outcomes

	N	Untreated Outcome Test	Always Taker Average Treatment Effect Lower Bound	LATE	Test Rejects Treatment Effect Homogeneity
Main Specification					
Main Specification	19,505	-562 (147)	23 (59)	-13 (38)	1.00 (0.48)
Alternative Outcome					
Breast Cancer Mortality	19,505	-43 (47)	30 (25)	-12 (13)	1.00 (0.43)

Results Are Robust Along Many Dimensions

- Sample Restrictions
  - Excluded participants aged 40-49
  - All participants aged 40-49
  - All participants aged 50-59
- Definitions of mammography
  - Narrower
  - Broader
- **Outcomes**
  - Breast cancer mortality
  - **Mortality at alternative follow-up lengths**

Robust to Mortality at Alternative Follow-Up Lengths: 11-20

Years Since Enrollment	N	Untreated Outcome Test	Always Taker Average Treatment Effect Lower Bound	LATE	Test Rejects Treatment Effect Homogeneity
Main specification: 20	19,505	-562	23	-13	1.00
		(147)	(59)	(38)	(0.48)
19	19,505	-485	50	-13	1.00
		(142)	(58)	(37)	(0.40)
18	19,505	-492	54	-8	1.00
		(139)	(56)	(35)	(0.41)
17	19,505	-456	18	-8	1.00
		(135)	(50)	(33)	(0.48)
16	19,505	-471	15	-16	1.00
		(134)	(46)	(31)	(0.47)
15	19,505	-480	-11	-15	1.00
		(131)	(42)	(31)	(0.50)
14	19,505	-396	-38	-21	0.00
		(121)	(38)	(30)	(0.45)
13	19,505	-365	-30	-24	0.00
		(115)	(36)	(28)	(0.49)
12	19,505	-334	-23	-27	1.00
		(106)	(32)	(27)	(0.50)
11	19,505	-351	-30	-10	0.00
		(105)	(28)	(25)	(0.42)

Robust to Mortality at Alternative Follow-Up Lengths: 1 - 10

Years Since Enrollment	N	Untreated Outcome Test	Always Taker Average Treatment Effect Lower Bound	LATE	Test Rejects Treatment Effect Homogeneity
10	19,505	-306	-41	-15	0.00
		(97)	(25)	(23)	(0.37)
9	19,505	-314	-35	-12	0.00
		(97)	(21)	(20)	(0.36)
8	19,505	-340	-14	-2	0.00
		(97)	(21)	(18)	(0.44)
7	19,505	-351	-15	-6	0.00
		(97)	(18)	(17)	(0.46)
6	19,505	-317	-24	-5	0.00
		(93)	(16)	(15)	(0.33)
5	19,505	-269	-12	-5	0.00
		(86)	(15)	(13)	(0.45)
4	19,505	-218	-3	-9	1.00
		(77)	(14)	(11)	(0.49)
3	19,505	-209	-3	-6	1.00
		(76)	(11)	(9)	(0.50)
2	19,505	-194	-3	-3	1.00
		(67)	(9)	(9)	(0.50)
1	19,505	-55	-5	-5	0.00
		(40)	(5)	(5)	(0.00)

Behavior within a Clinical Trial and Implications for Mammography Guidelines

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  1. Selection Heterogeneity
     - *Women more likely to receive mammograms are healthier*
  2. Treatment Effect Heterogeneity
     - *Women more likely to receive mammograms are more likely to be harmed by them*
- Robustness
- **Conclusions**

U.S. Preventive Services Task Force (USPSTF) 2016 Guidelines for Women in 40's:

"The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between the ages of 40 and 49 years"

U.S. Preventive Services Task Force (USPSTF) "C recommendation"

"The USPSTF recommends selectively offering this service to individual patients based on professional judgment and patient preferences"

Appendix

CNBSS Protocols Varied by Age

- Patients aged 40-49:
  - Intervention group: mammography + physical examination each year for 4-5 years, then return to usual care
  - Control group: usual care
- Patients aged 50-59:
  - Intervention group: mammography + physical examination each year for 4-5 years, then return to usual care
  - Control group: physical examination each year for 4-5 years, then return to usual care

USPSTF Recommendations Differ for Women in 40's and 50's

- The U.S. Preventive Services Task Force (USPSTF) Assigns "grades"
  - "A" and "B" grades fully-covered under ACA
- Different grades for 40's and 50+ (Siu, 2016)
  - "The decision to start screening mammography in women prior to age 50 years should be an individual one. (Grade C recommendation)"
  - "The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. (Grade B recommendation)"