Topics in instrumental variable estimation: structural mean models and bounds

Tom Palmer

MRC CAiTE Centre, School of Social and Community Medicine, University of Bristol, UK

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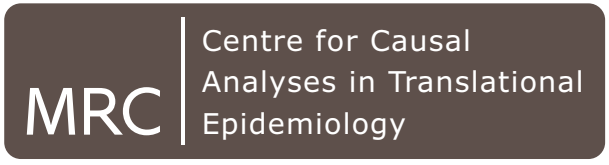
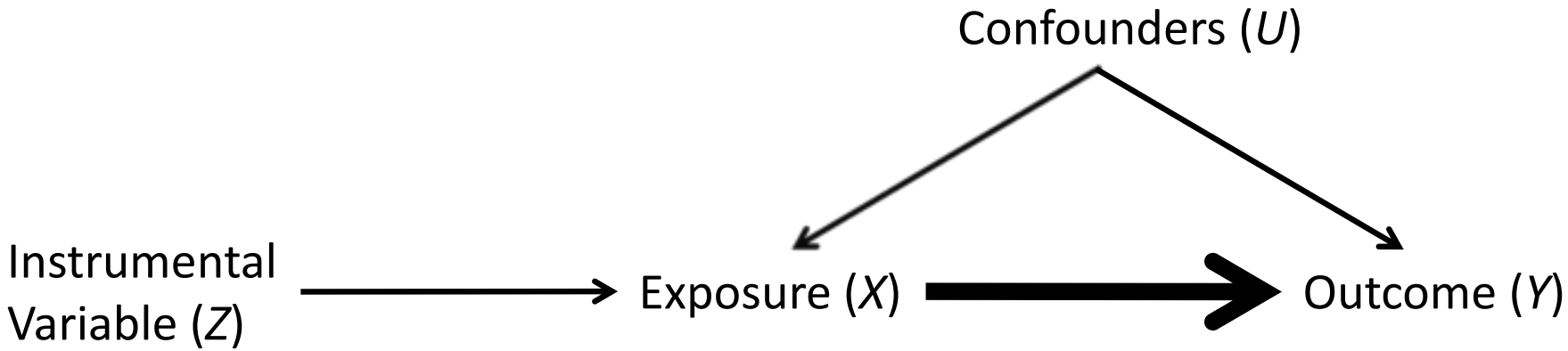


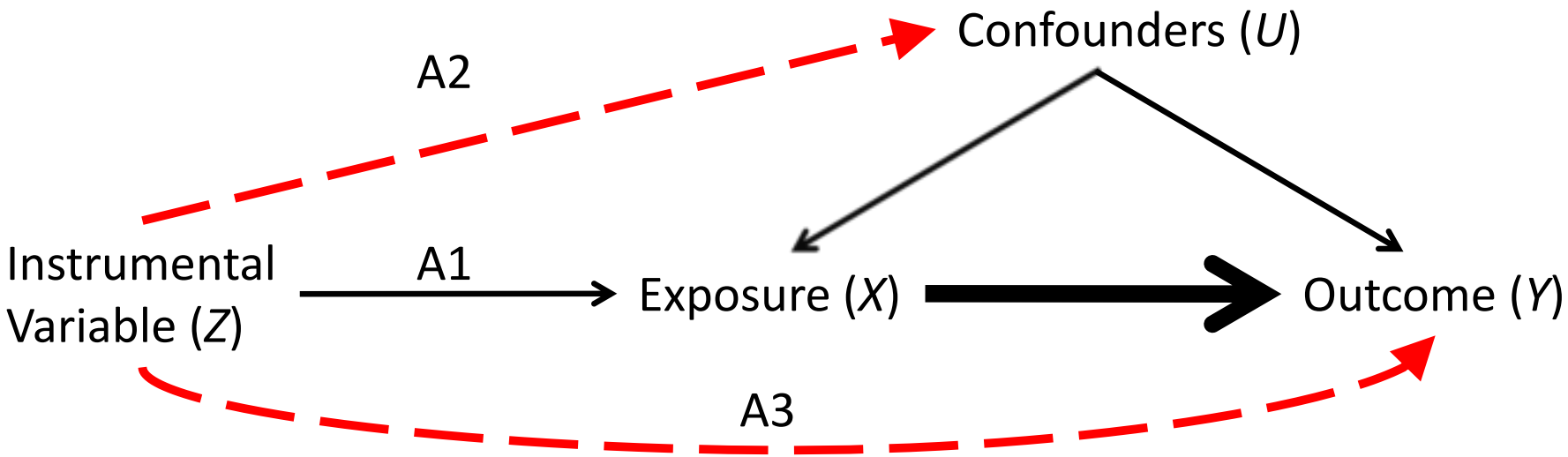
Outline

1. Introduction to instrumental variables
   - Assumptions
   - Applications
     - Mendelian randomization
     - Noncompliance in RCTs
   - Test of presence of effect
   - Estimators: ratio, two-stage least squares
2. Structural mean models
   - Potential outcomes and causal parameters
   - Additive SMM: G-estimation example
   - Multiplicative SMM: estimation with multiple instruments
3. Nonparametric bounds
   - Extensions
   - Limitations
4. Summary

1. Introduction to instrumental variables: Assumptions



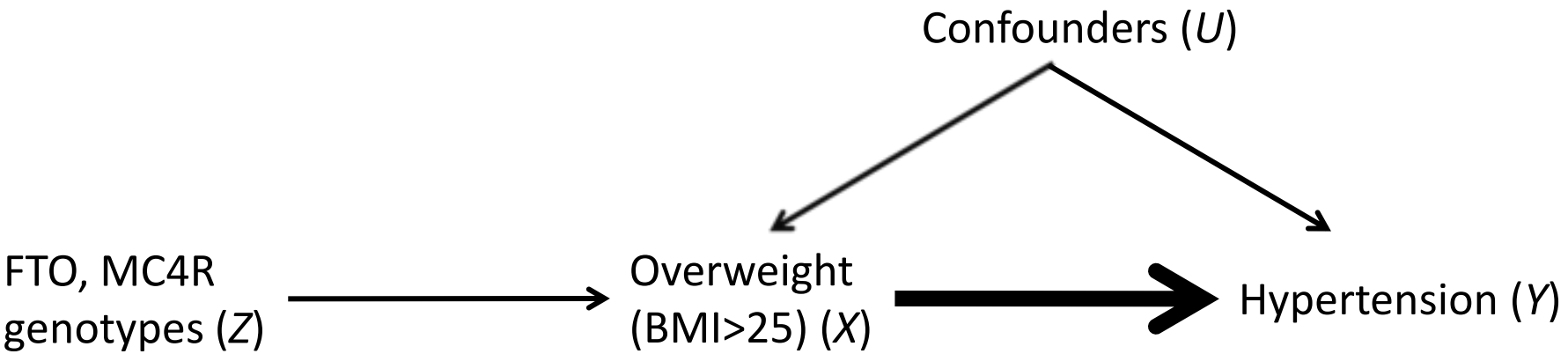
1. Introduction to instrumental variables: Assumptions



A1. Instrumental variable associated with exposure ($Z \not\perp\!\!\!\perp X$)
A2. Instrumental variable independent of confounders ($Z \perp\!\!\!\perp U$)
A3. No direct effect of instrumental variable on outcome
exclusion restriction ($Y \perp\!\!\!\perp Z \mid (X, U)$)

Application: Mendelian randomization

Use of genotypes robustly associated with exposures
(from replicated genome-wide association studies, $P < 5 \times 10^{-8}$)
as instrumental variables (Davey Smith & Ebrahim, 2003)



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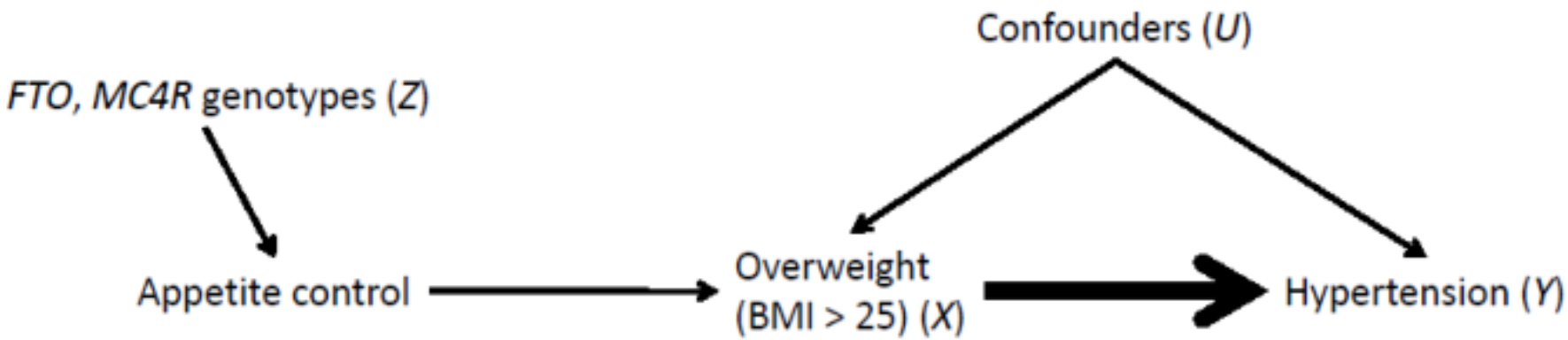
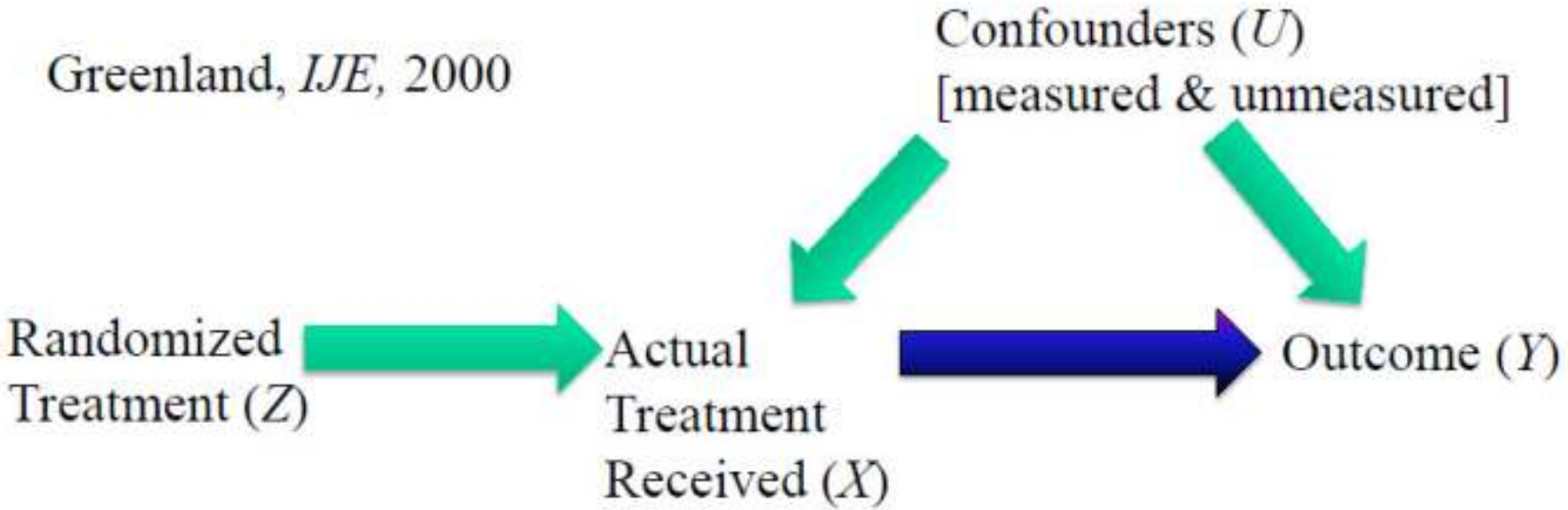


IV does not have to be causal for exposure

Application: randomized controlled trials

Correcting for noncompliance in randomized controlled trials

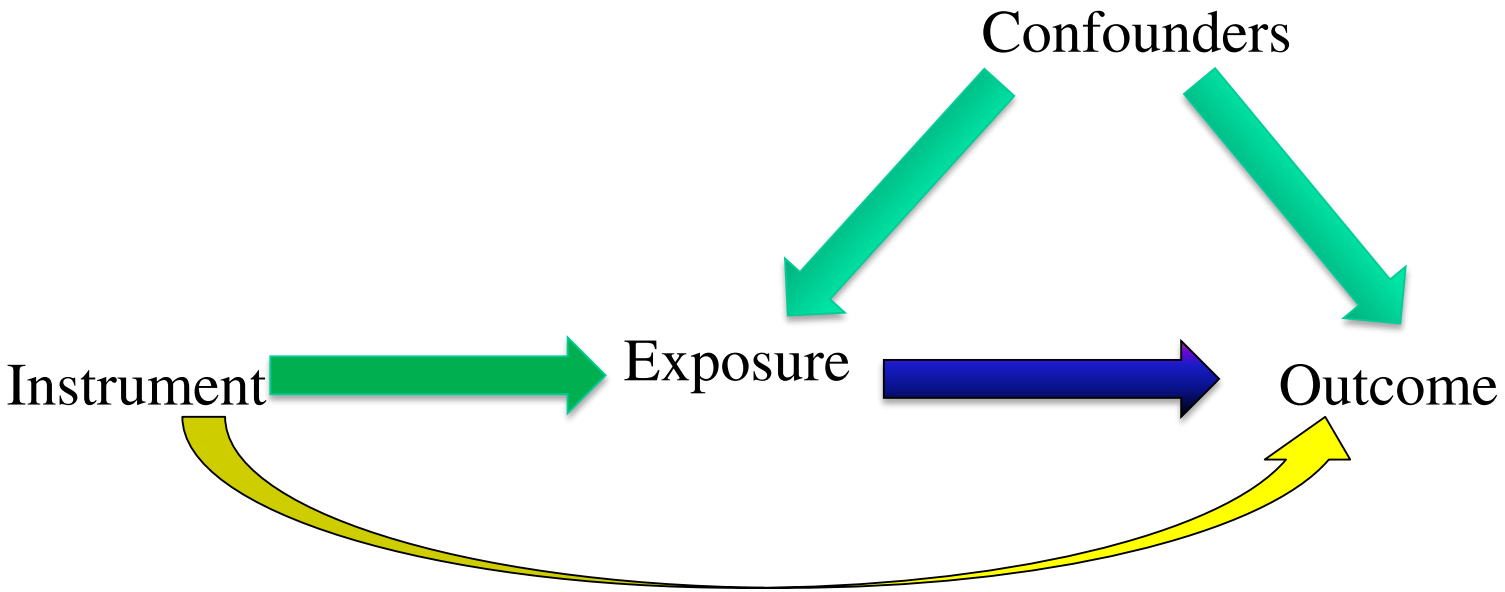


Test of presence of causal effect

If the IV conditions hold, then a test of the

instrument-outcome association

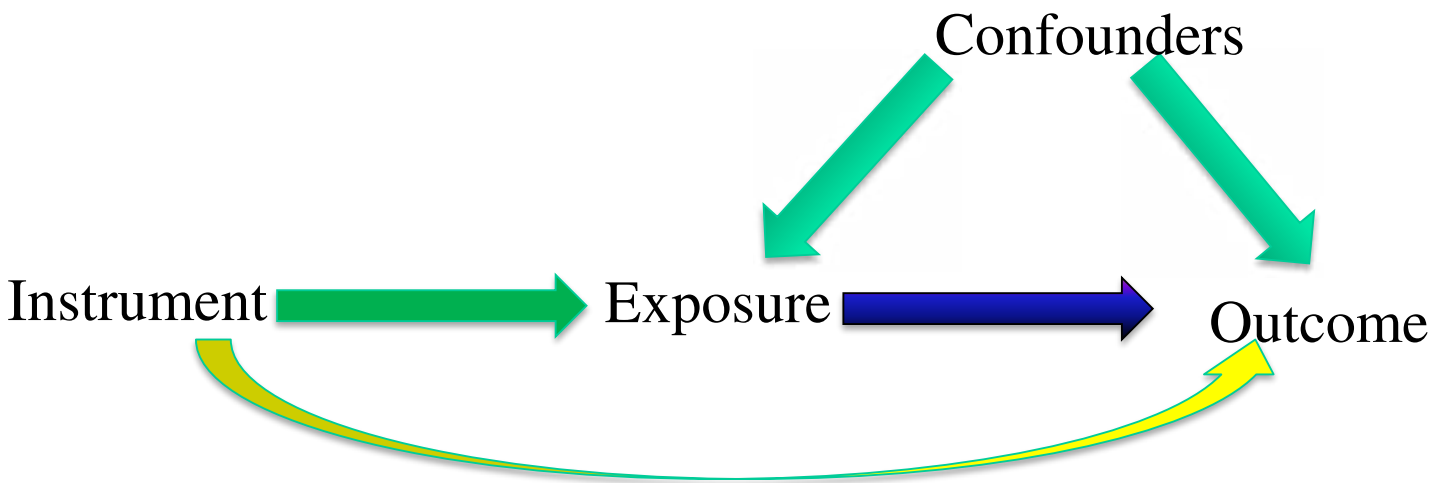
is a test for the presence of a causal effect of exposure on outcome



Ratio estimator

Assumptions: everything linear, binary instrument

$$\text{IV estimate of Exposure on Outcome} = \frac{\text{Instrument-outcome association } (ZY)}{\text{Instrument-exposure association } (ZX)}$$



Standard error & confidence interval from delta-method/Fieller's theorem (Thomas et al. *Ann Epi*, 2007)

Two-stage least squares estimator

Estimation with multiple instruments

Two-stage least squares

$$X = \beta_0 + \beta_{z1}Z_1 + \ldots + \beta_{zn}Z_n$$

Stage 1

- Regress Exposure on instrument/s
- Generate predicted values of exposure

$$\hat{X} = \hat{\beta}_0 + \hat{\beta}_Z Z$$

Stage 2

- Regress Outcome on predicted values of exposure
- (***adjust standard errors***)

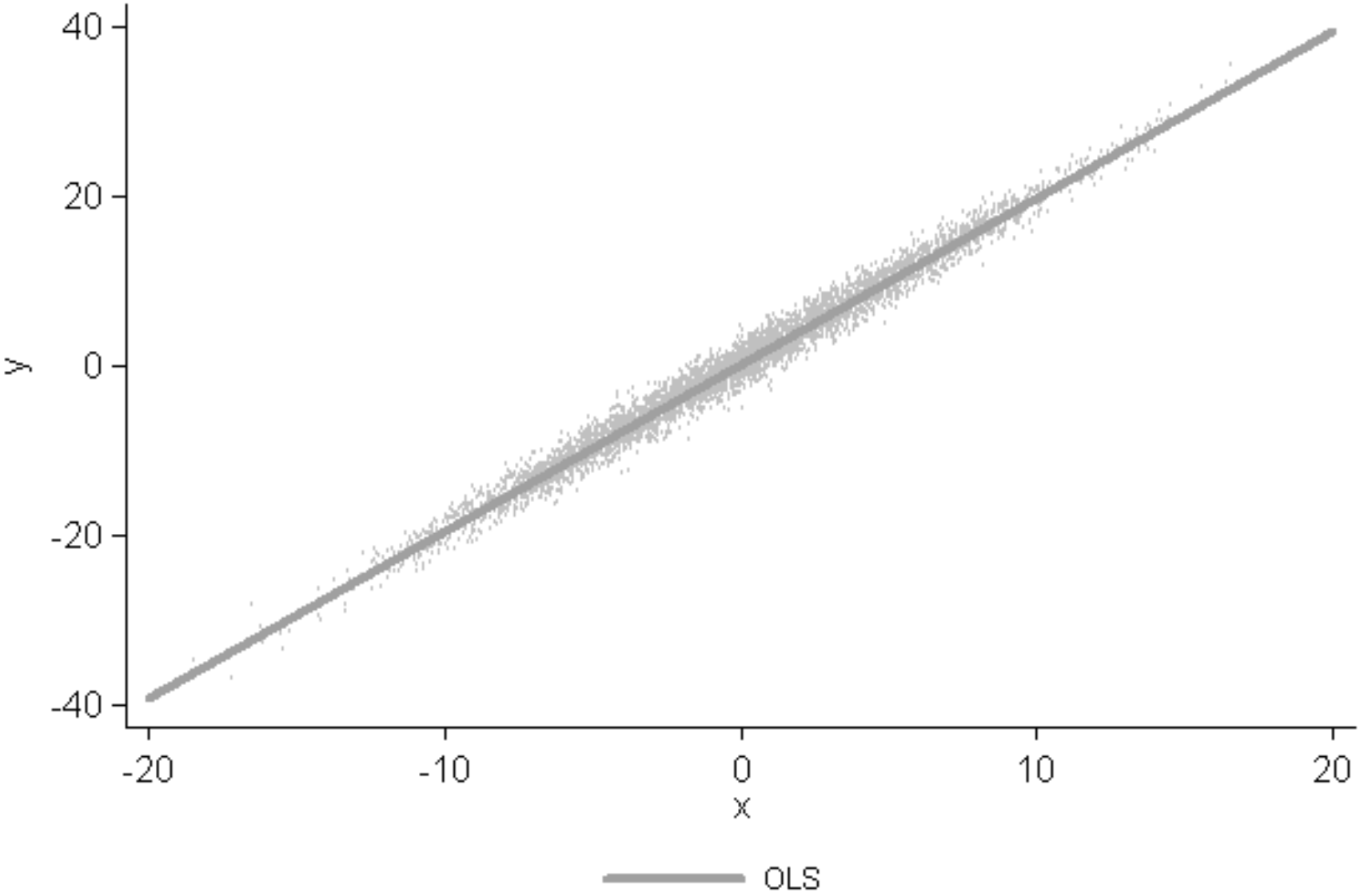
$$Y = \alpha + \beta_{XY}\hat{X}$$

Stata comands: `ivregress`, `ivreg2`

Automatically correct standard errors!!

Binary outcome: parameter = risk difference

Instrument strength example



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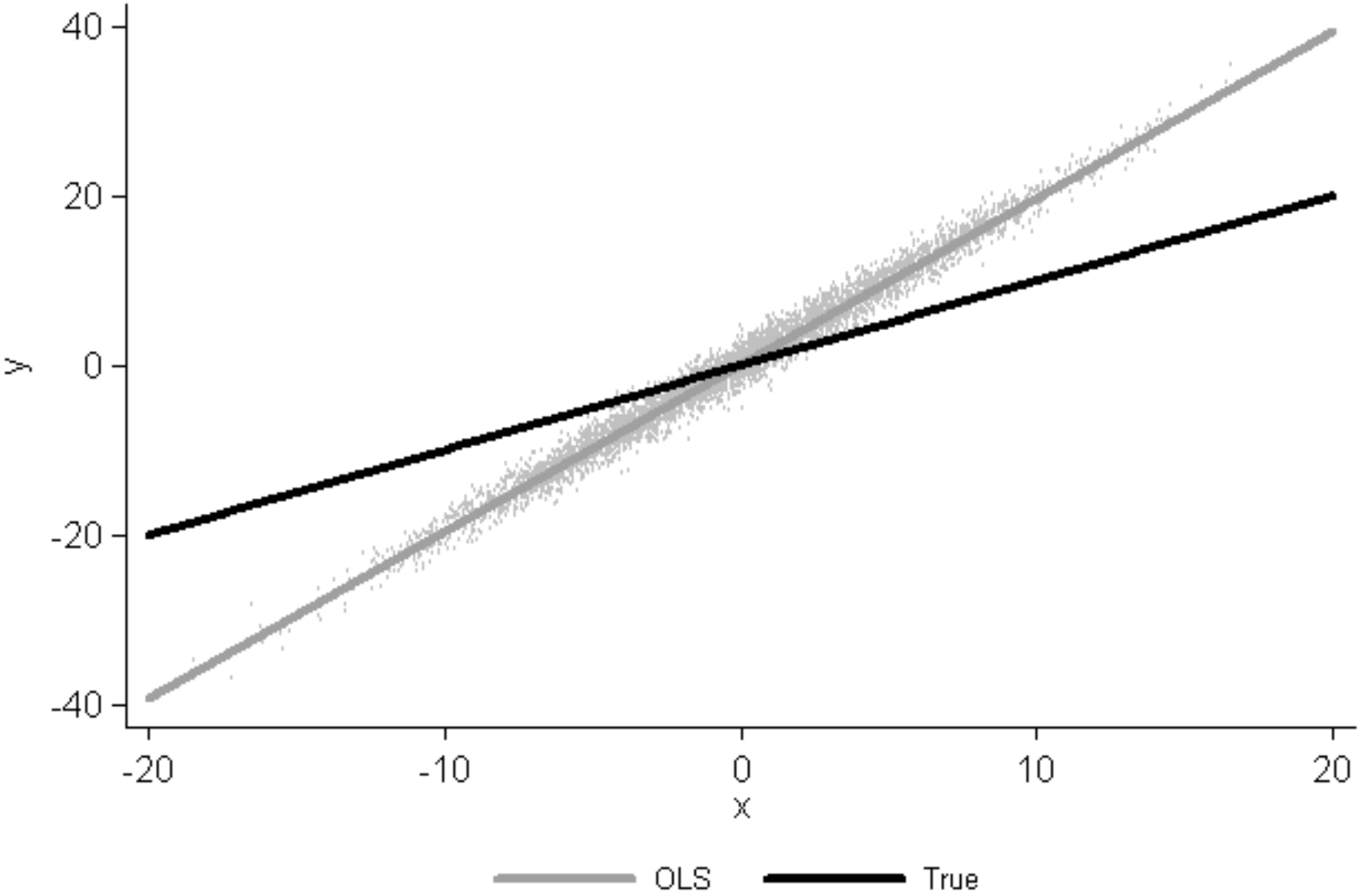

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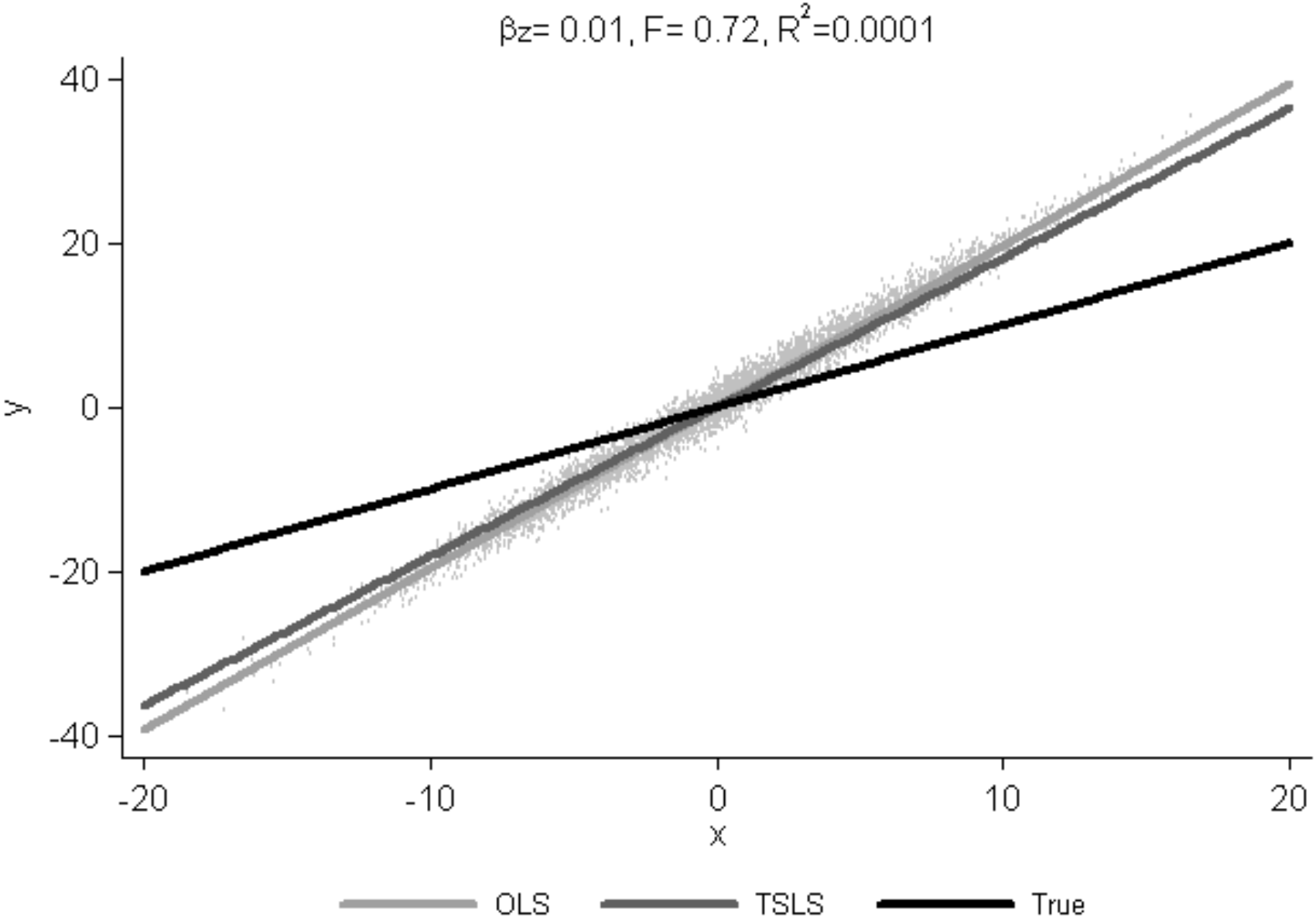

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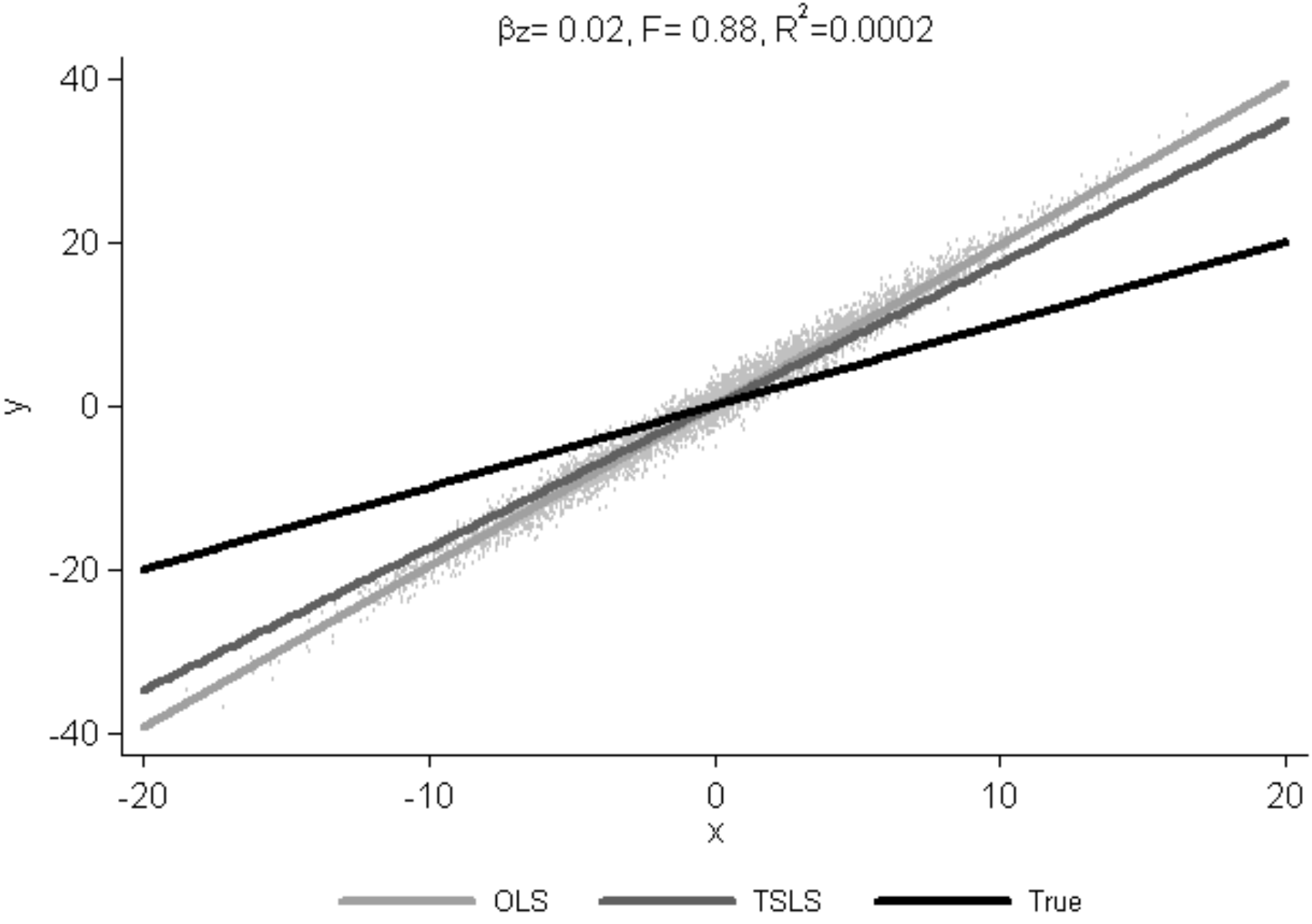

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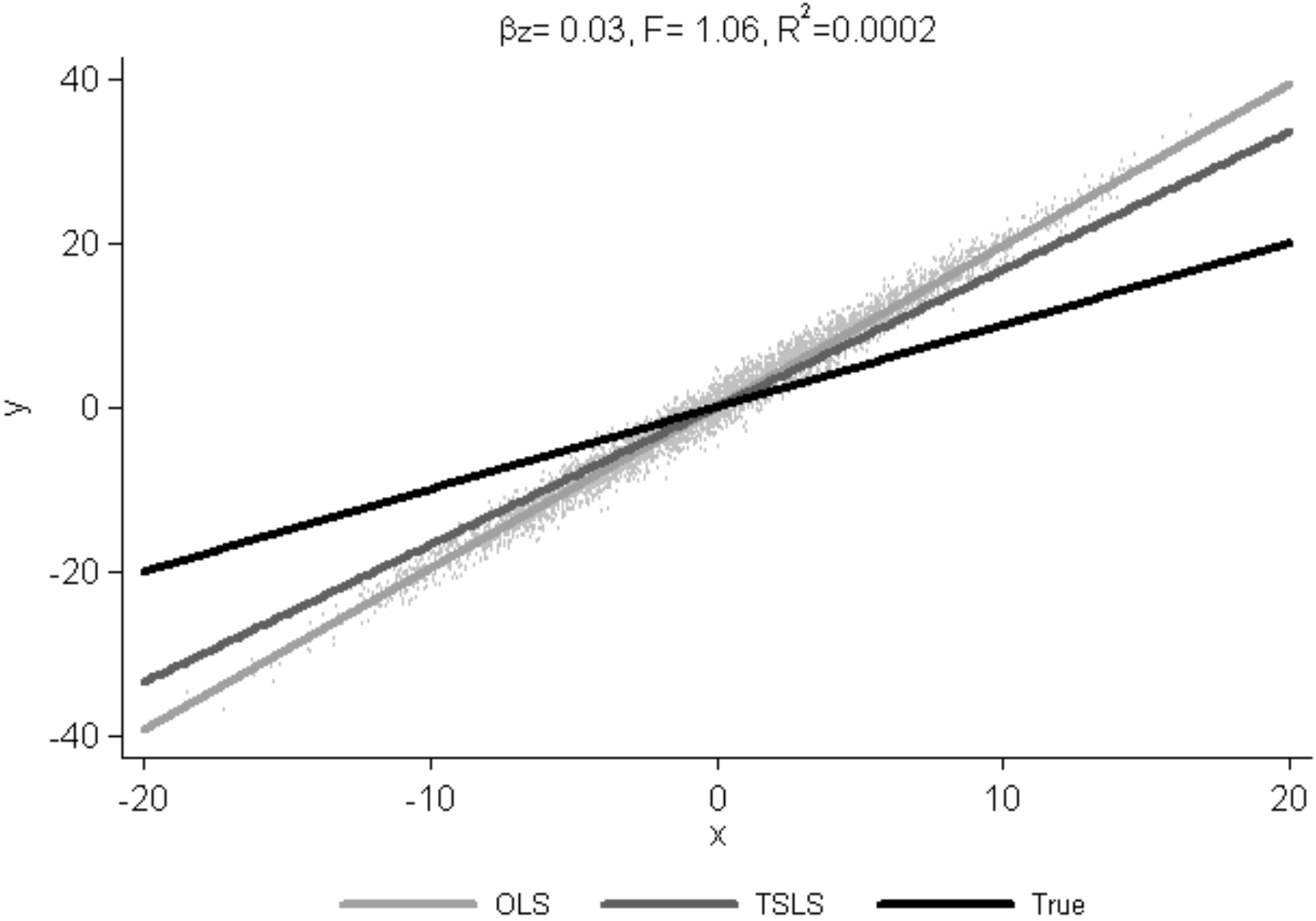

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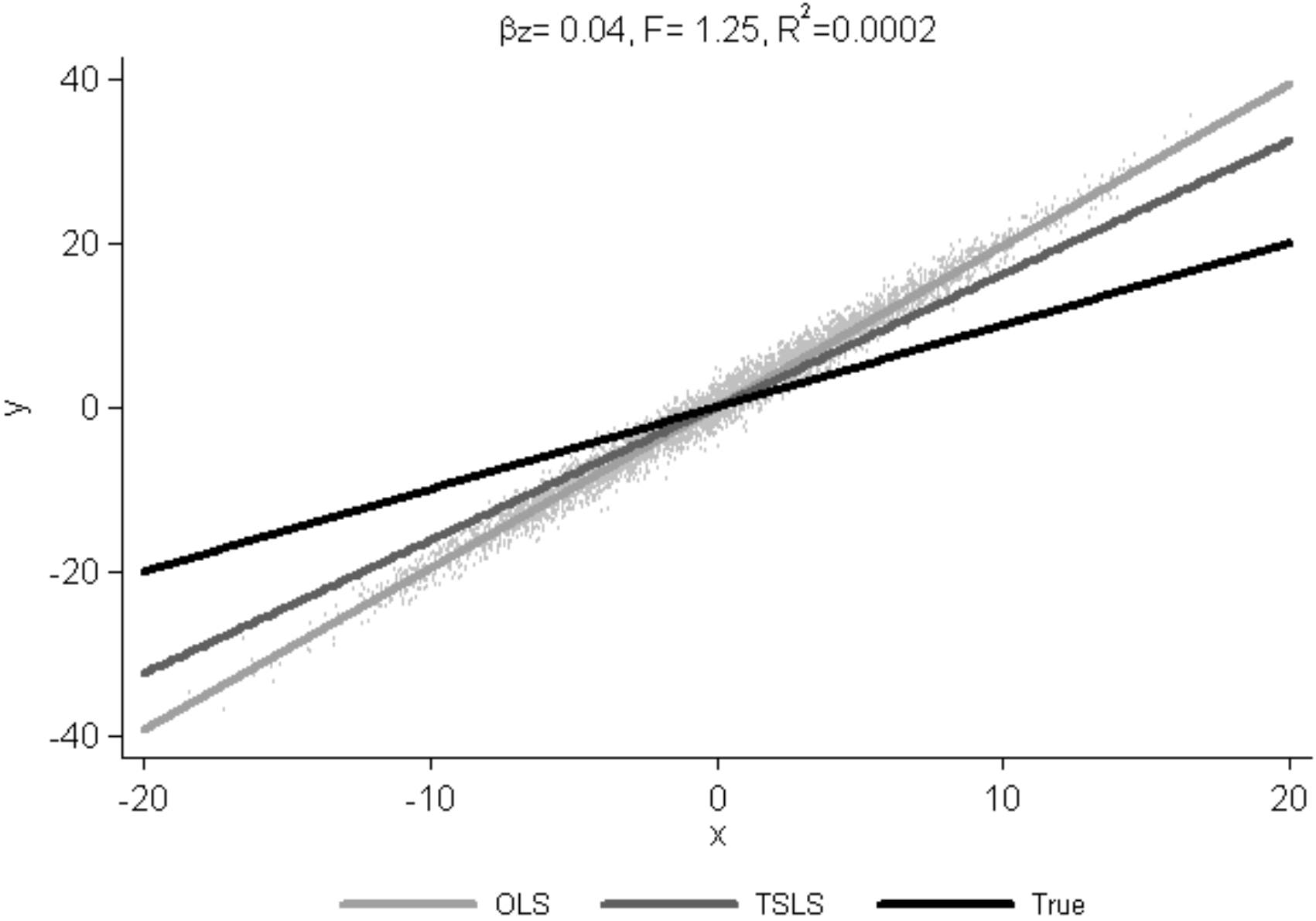

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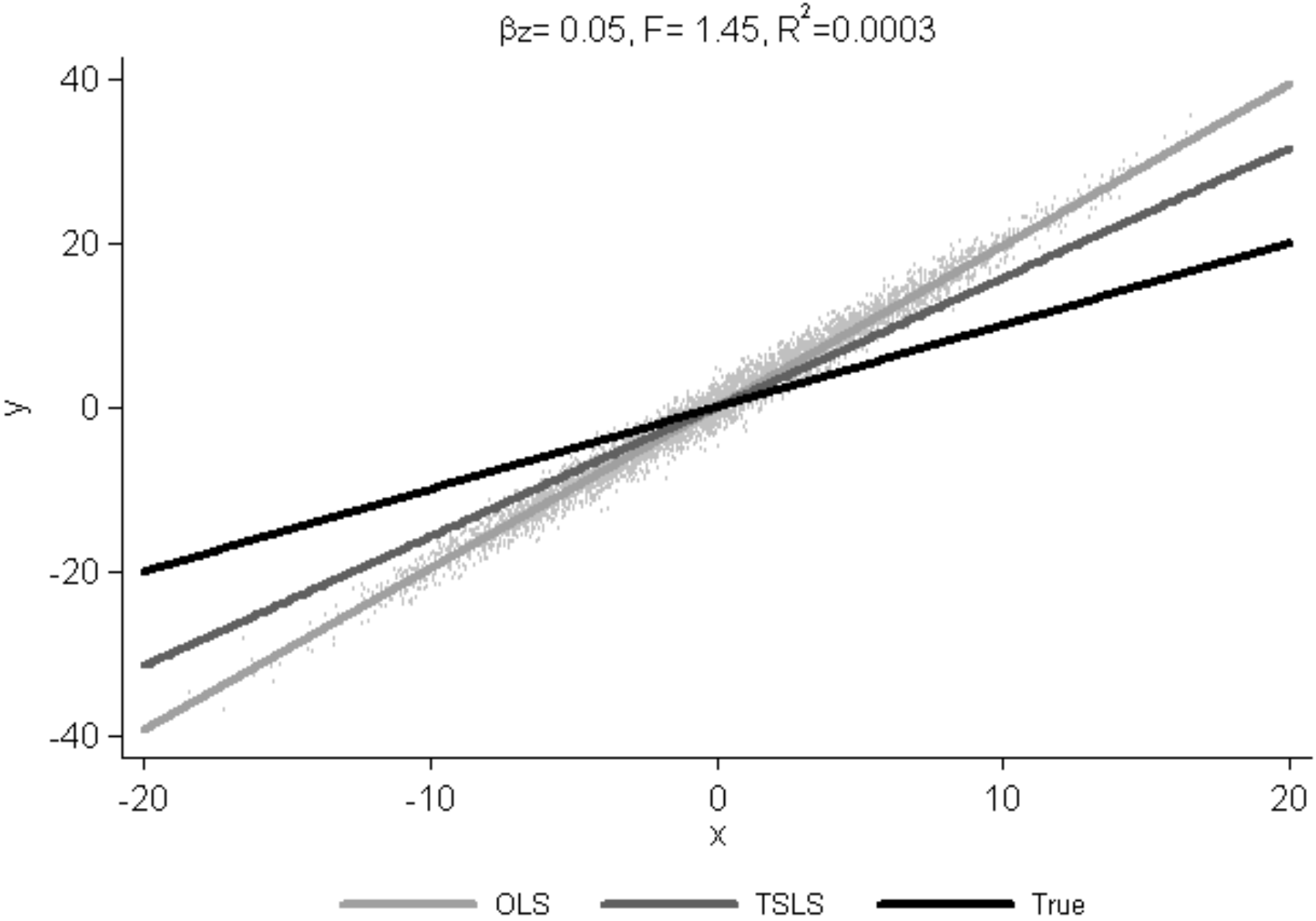

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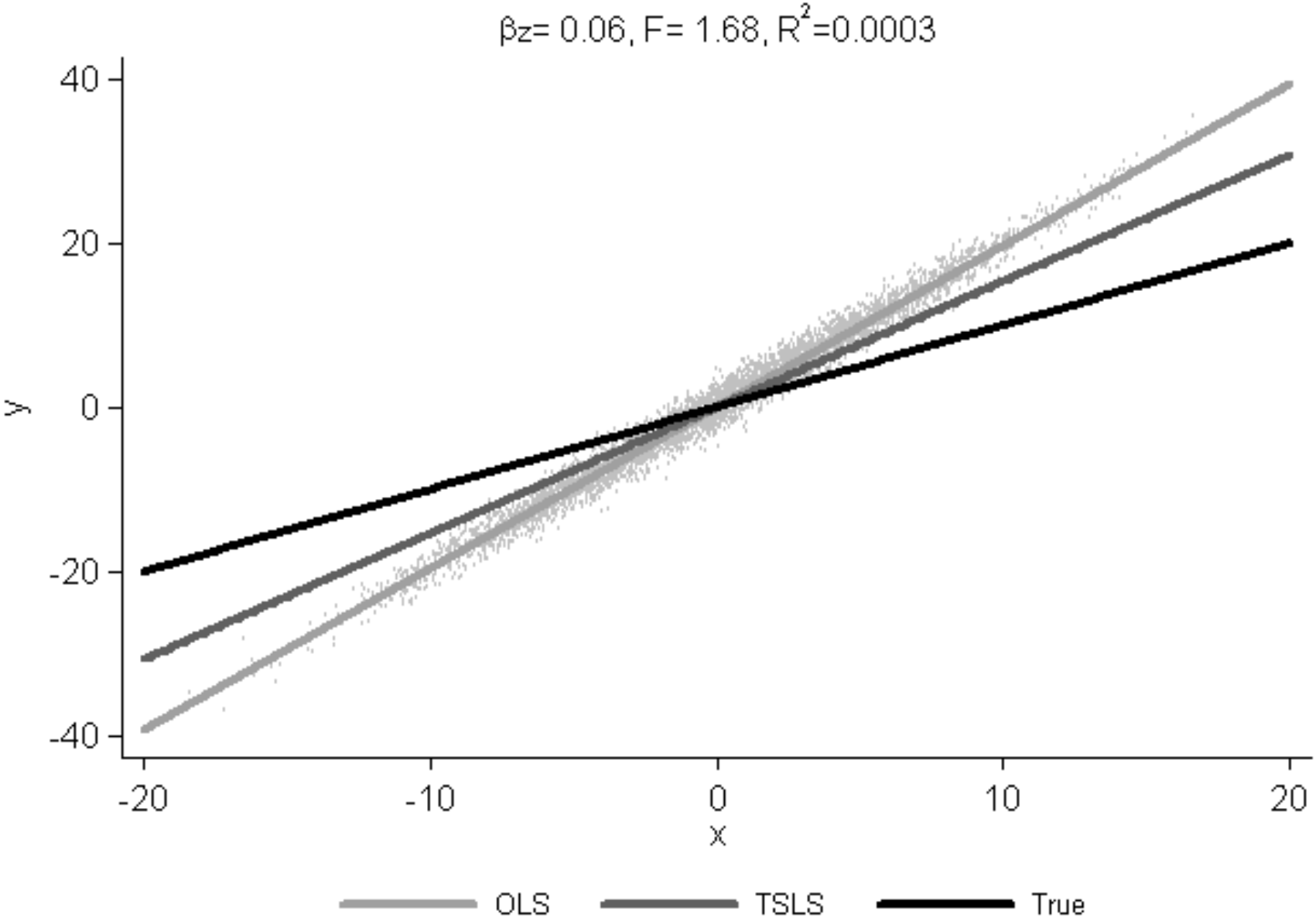

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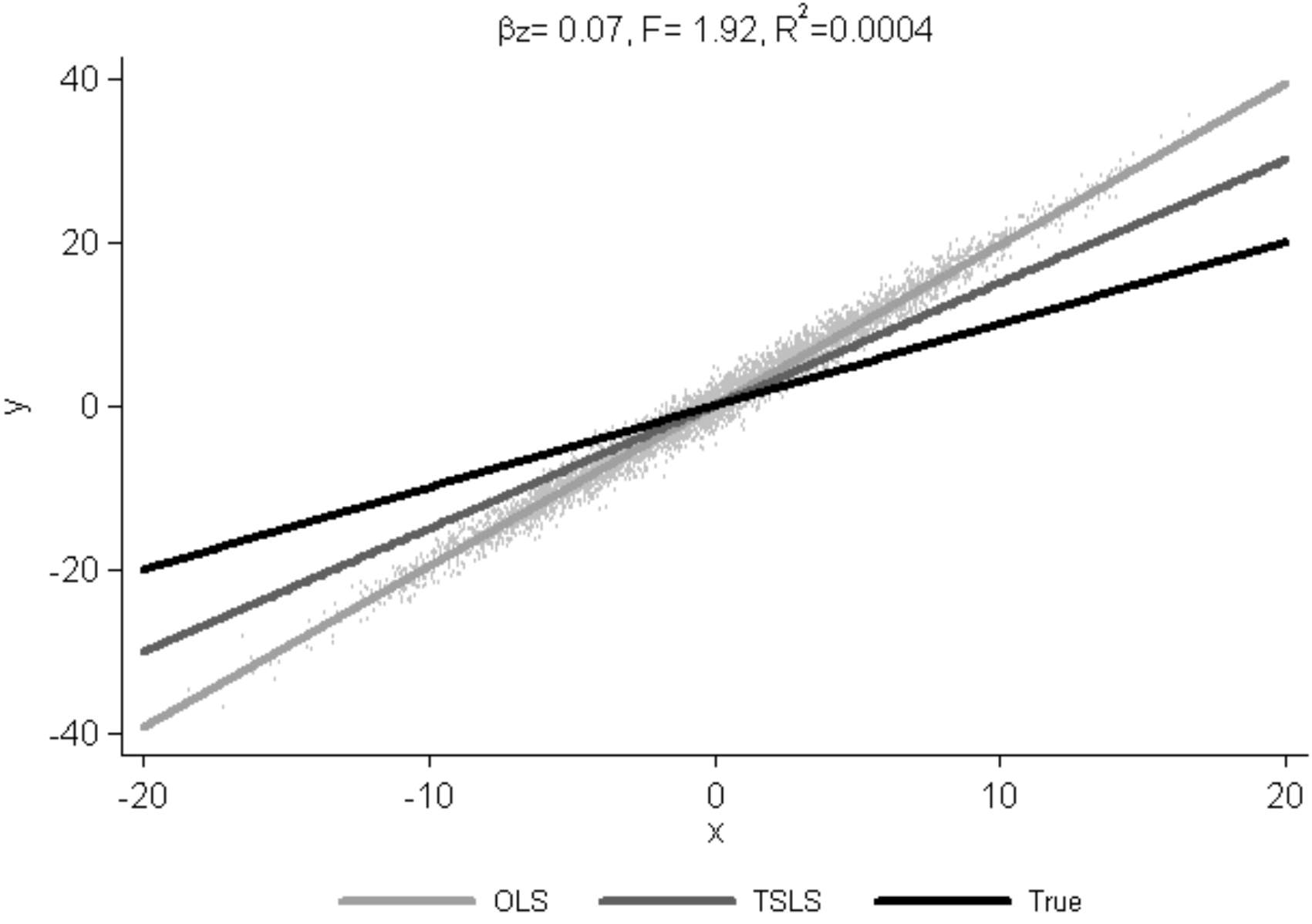

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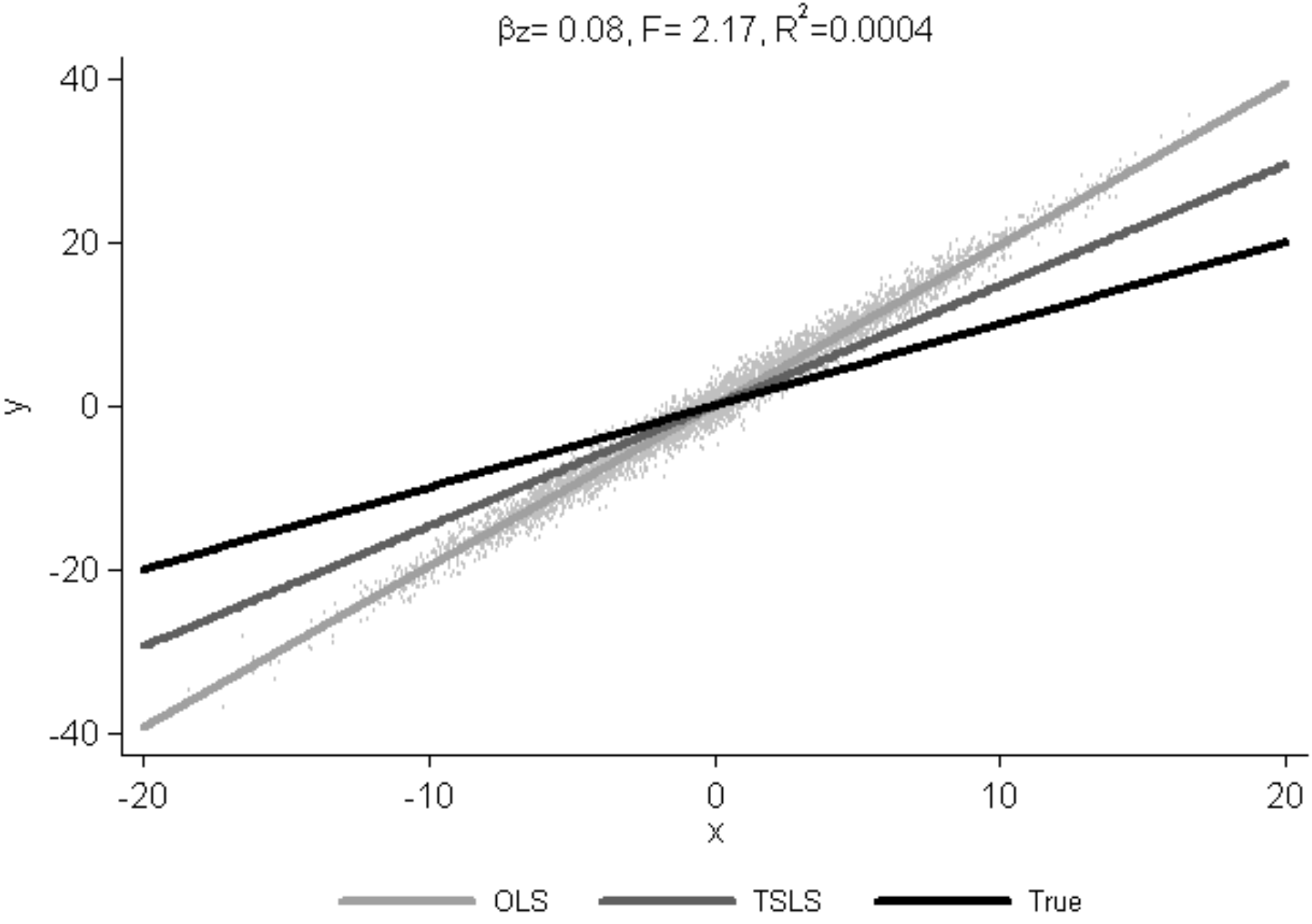

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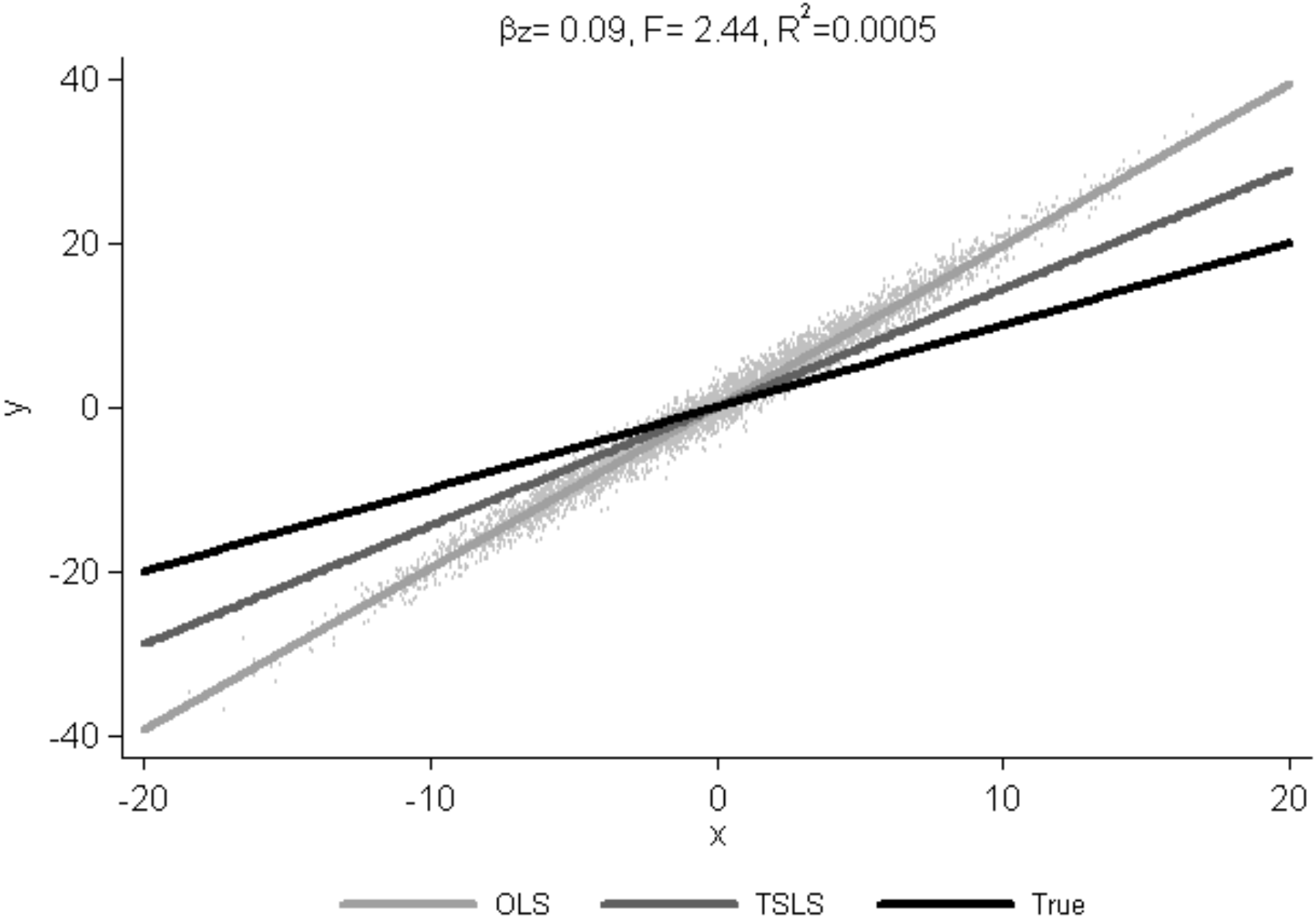

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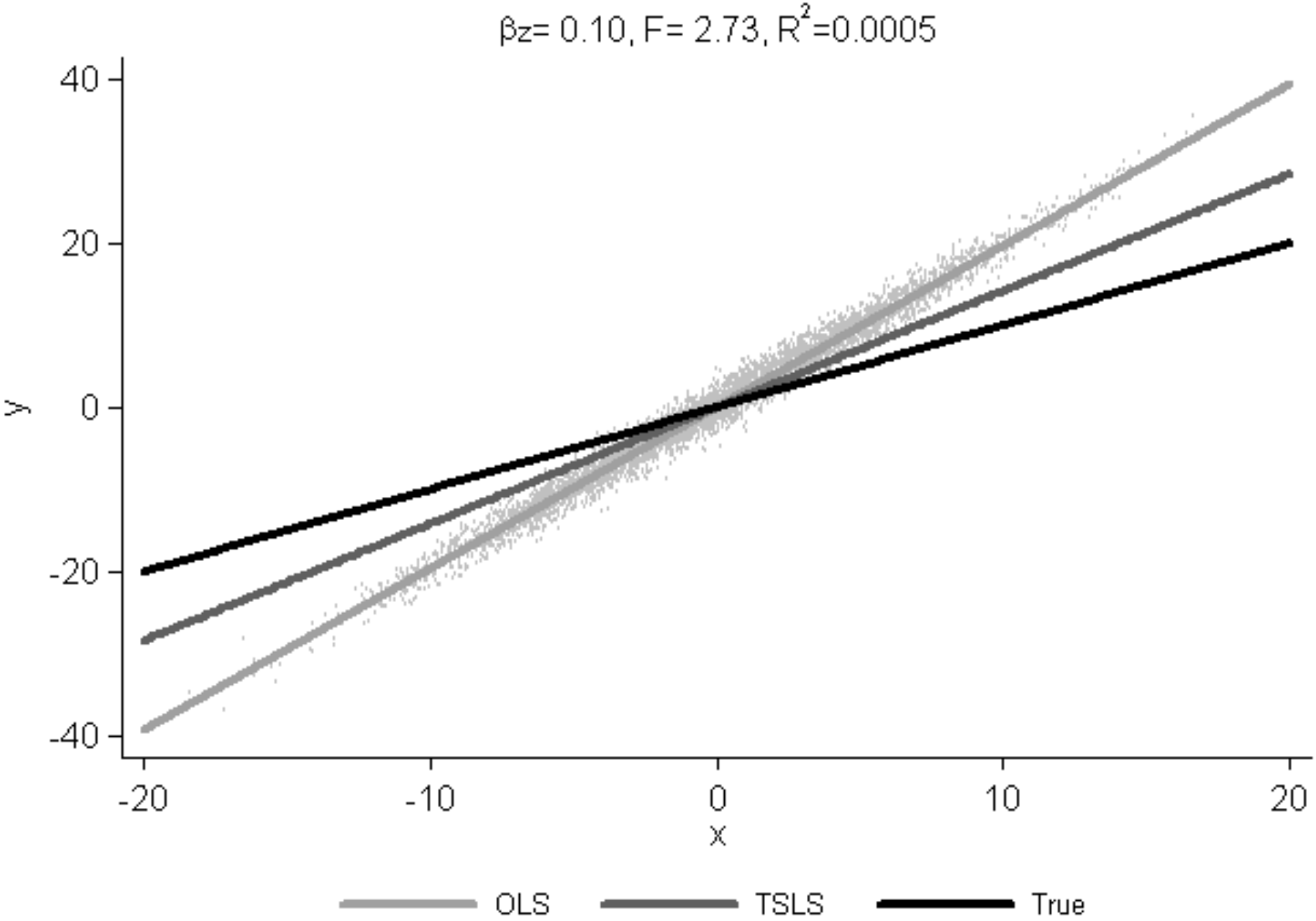

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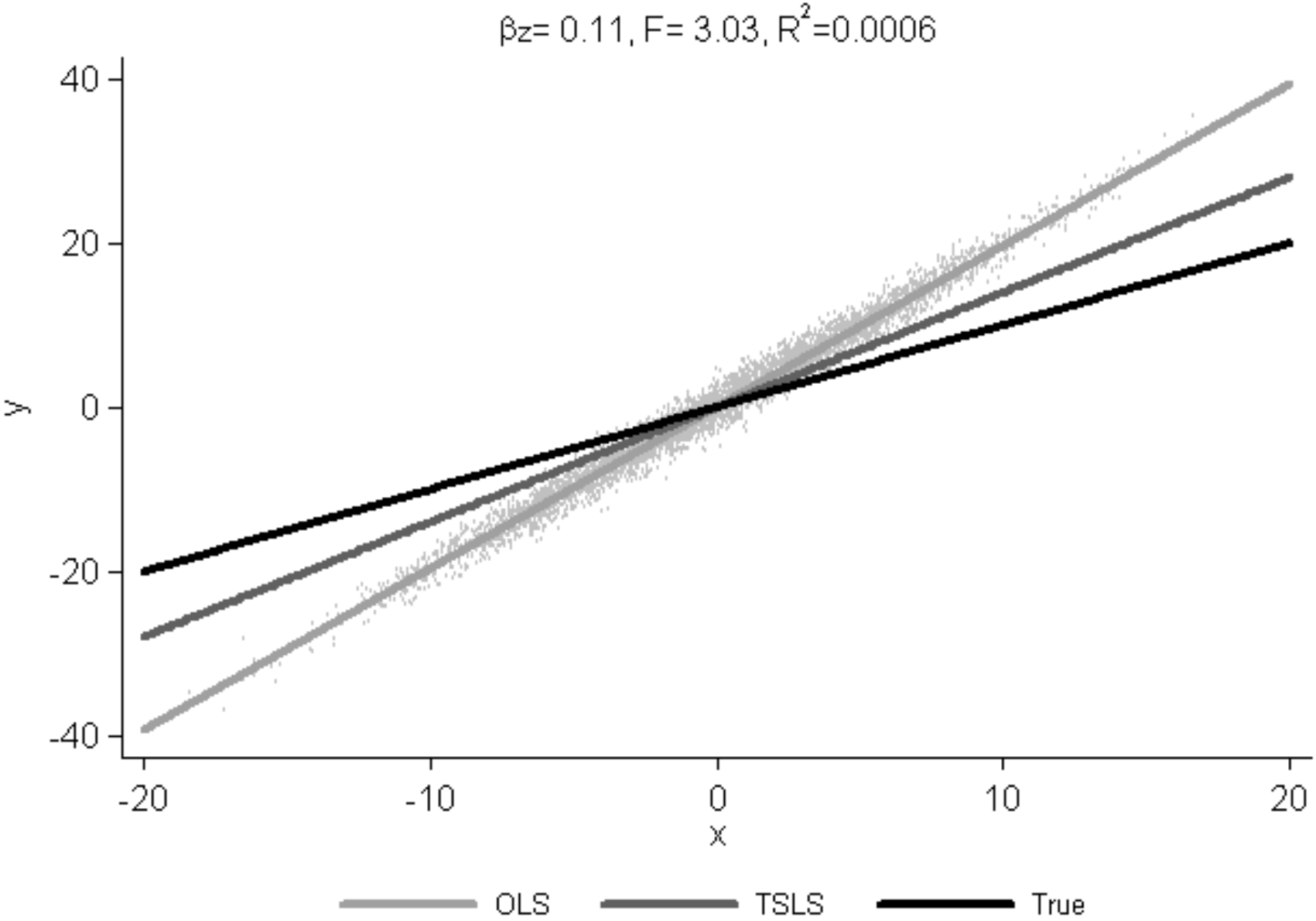

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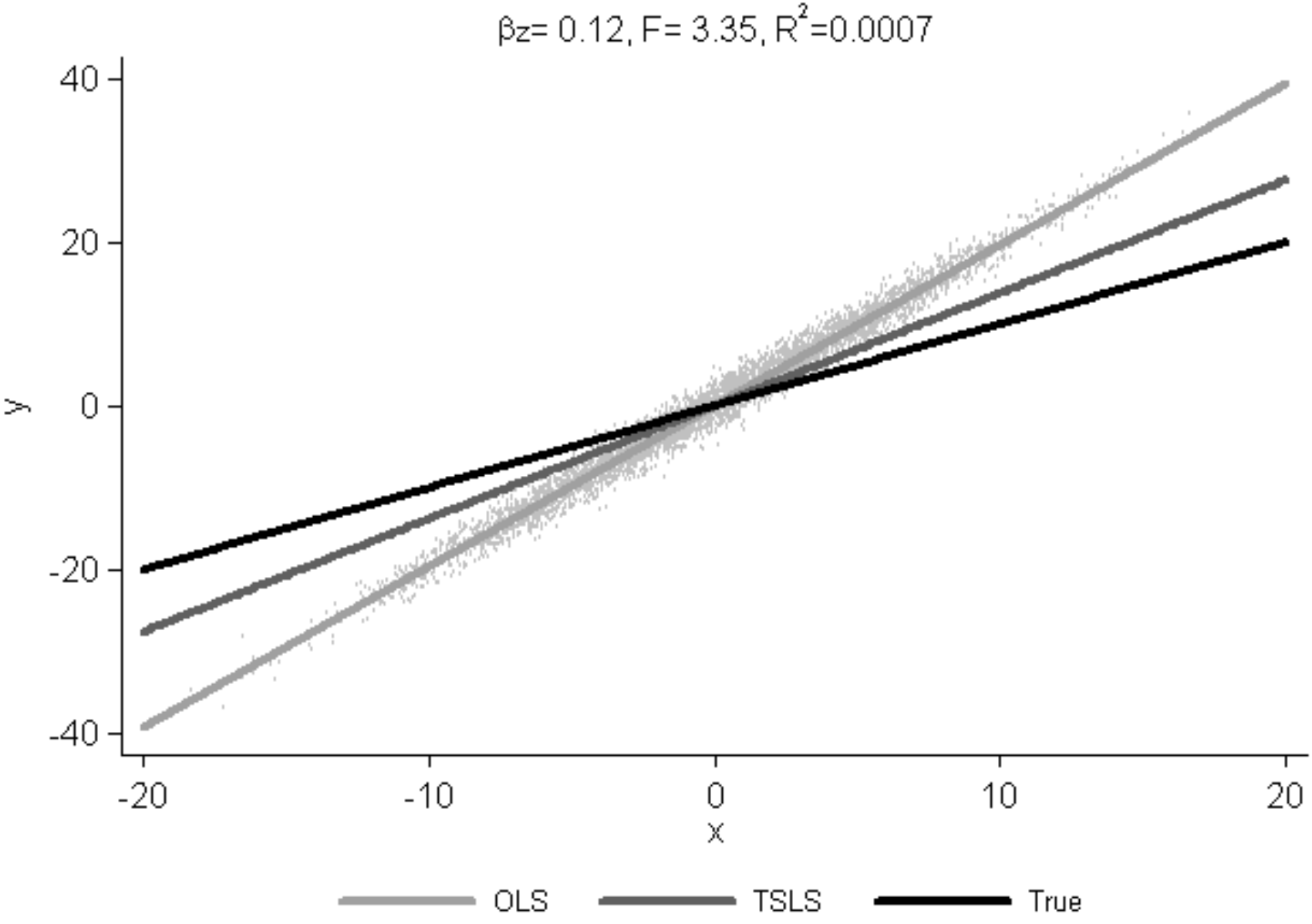

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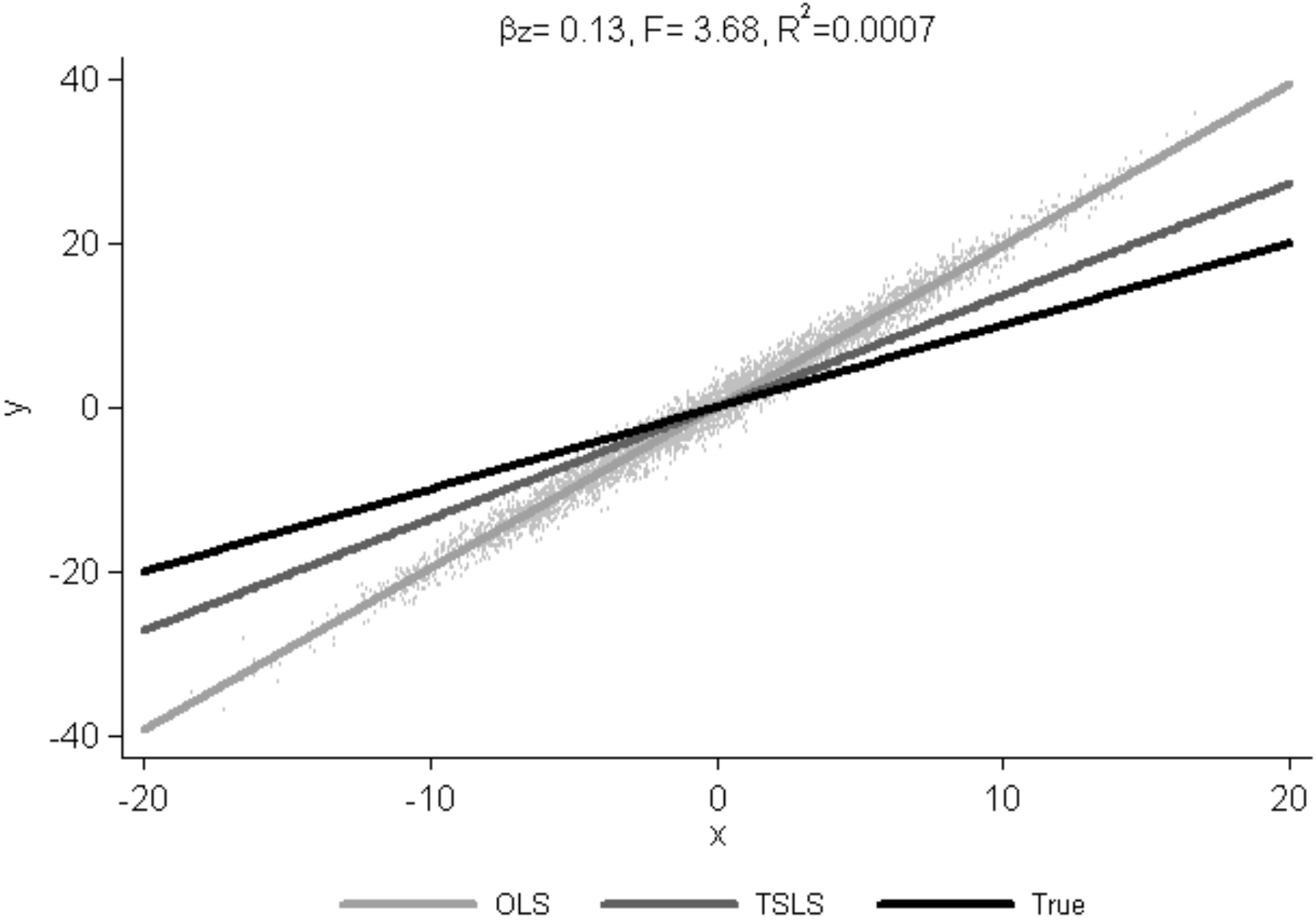

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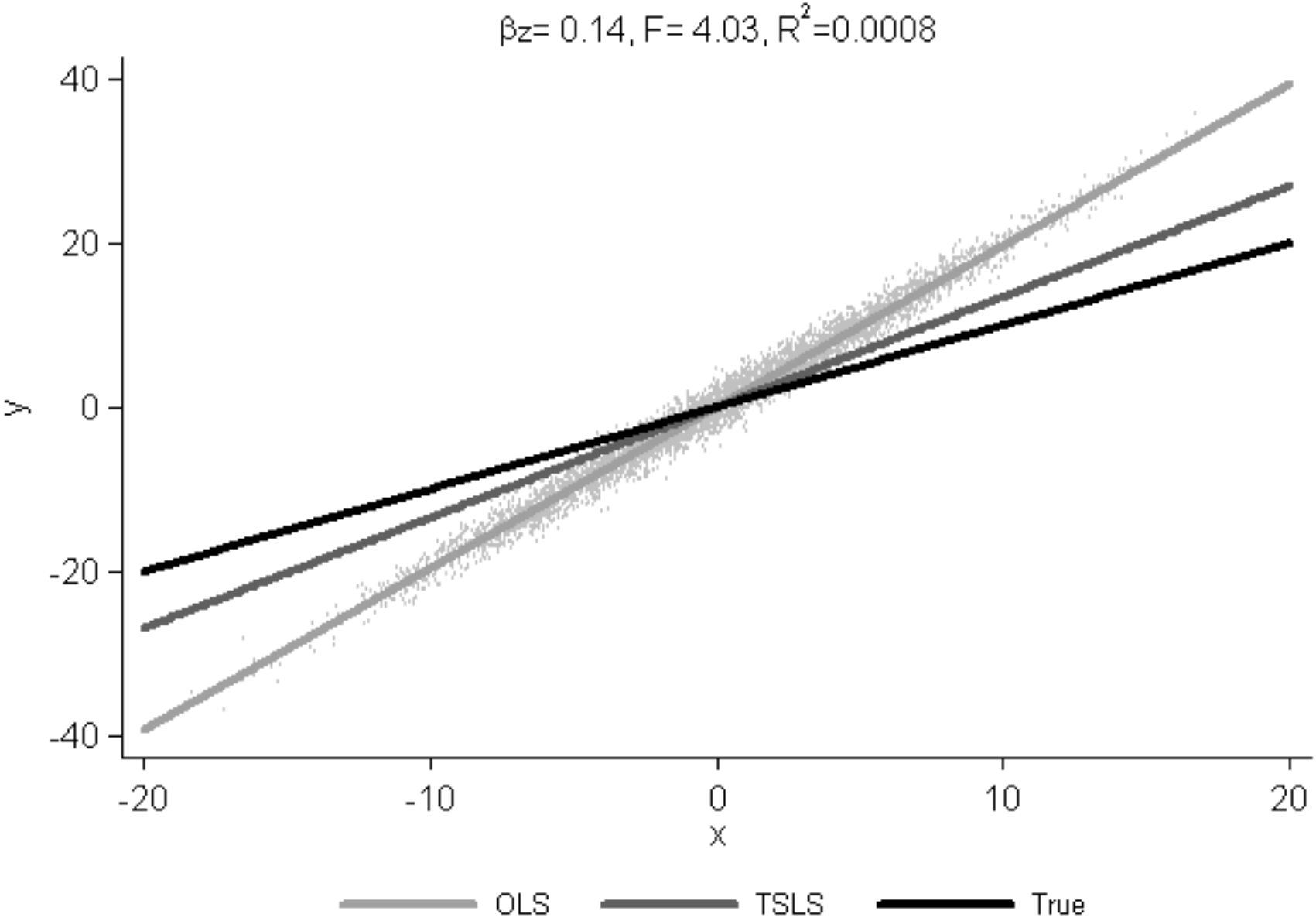

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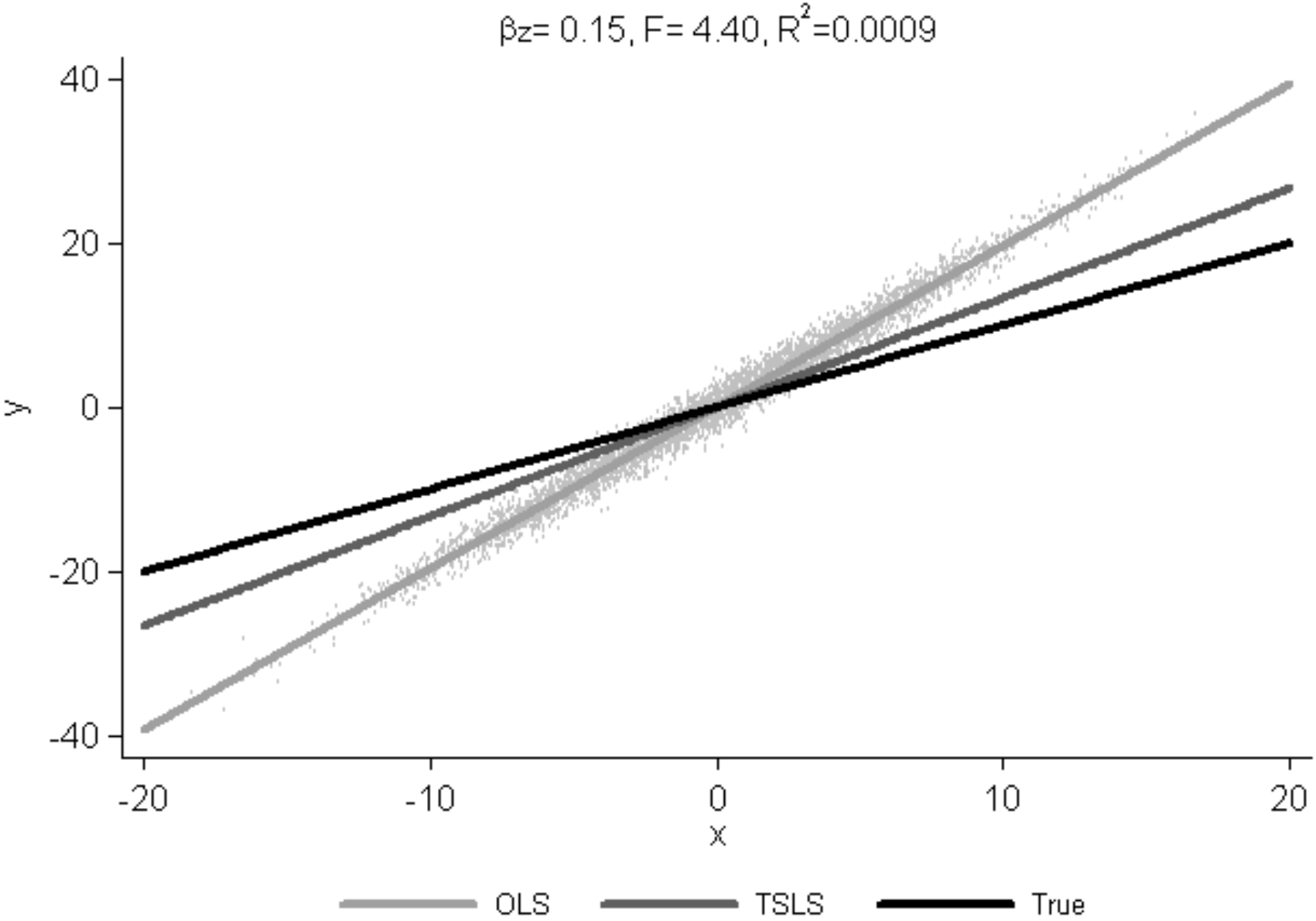

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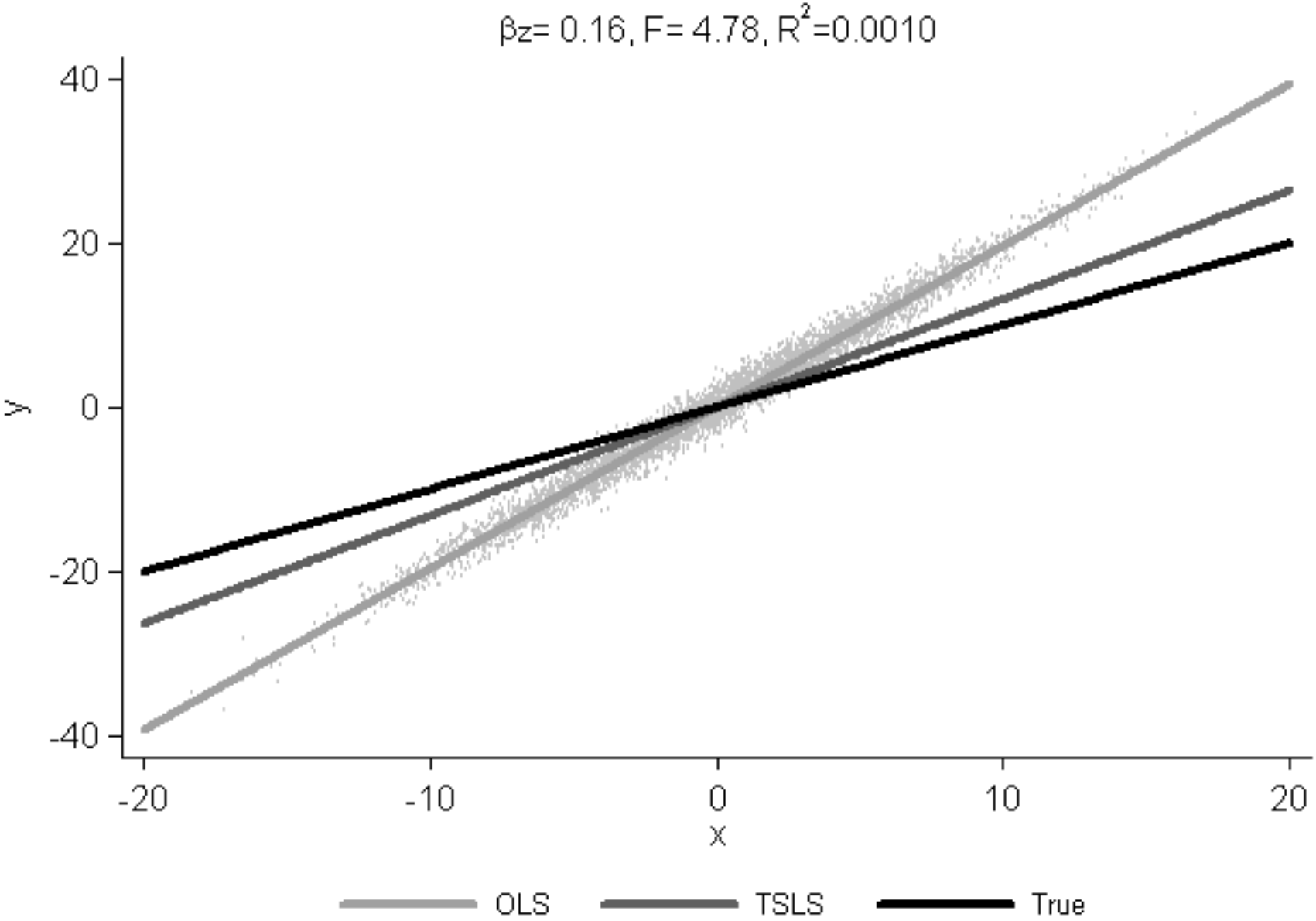

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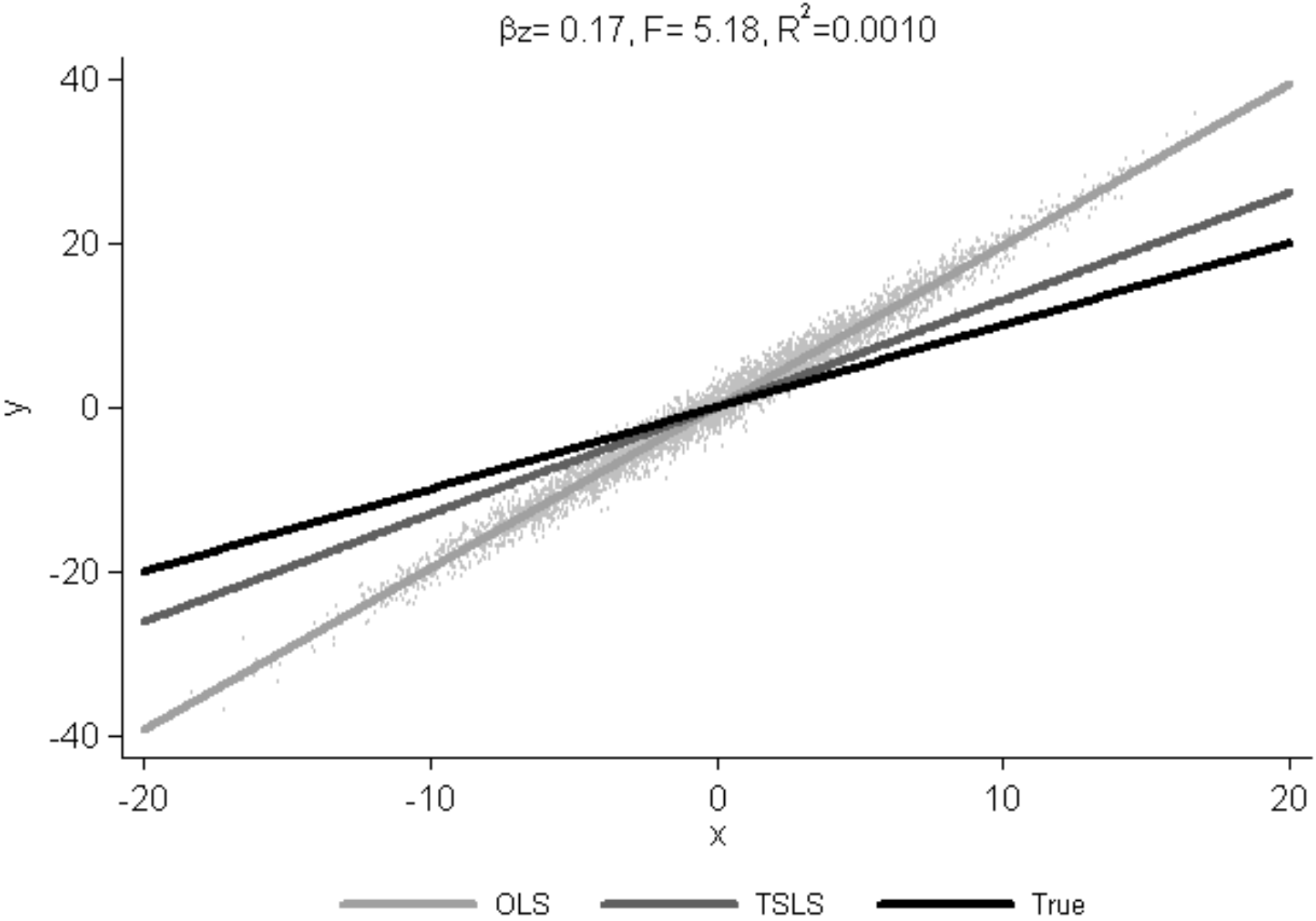

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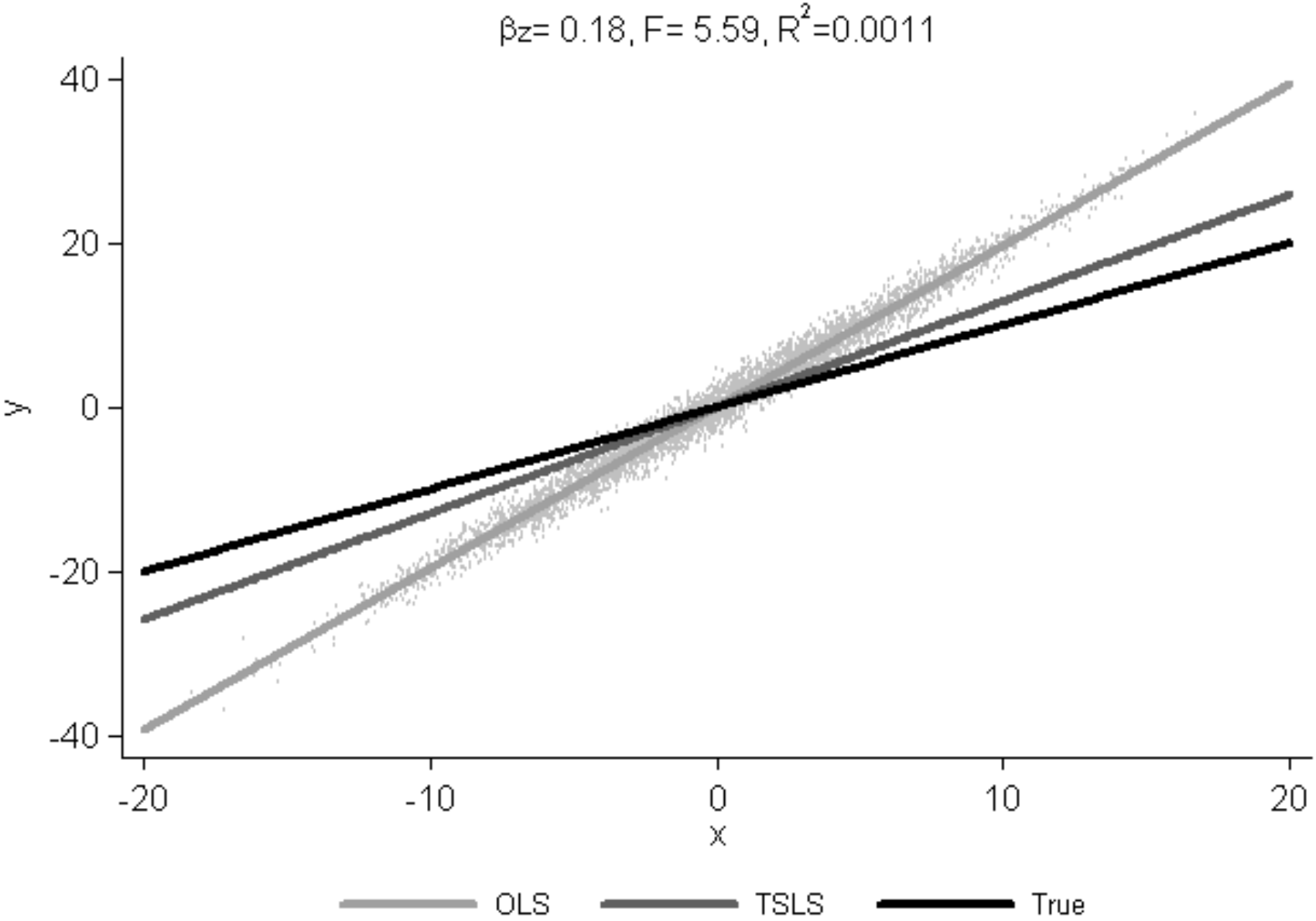

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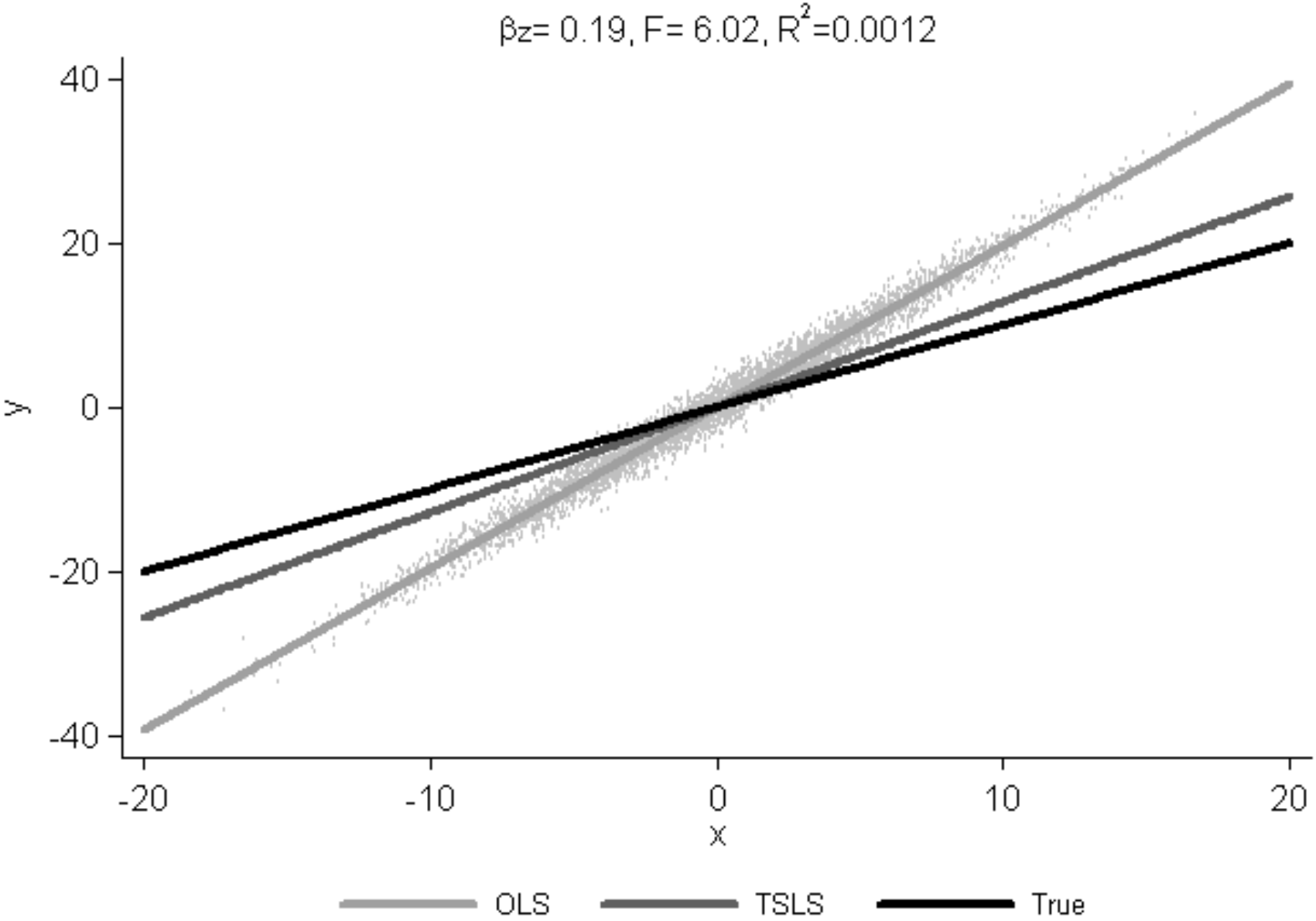

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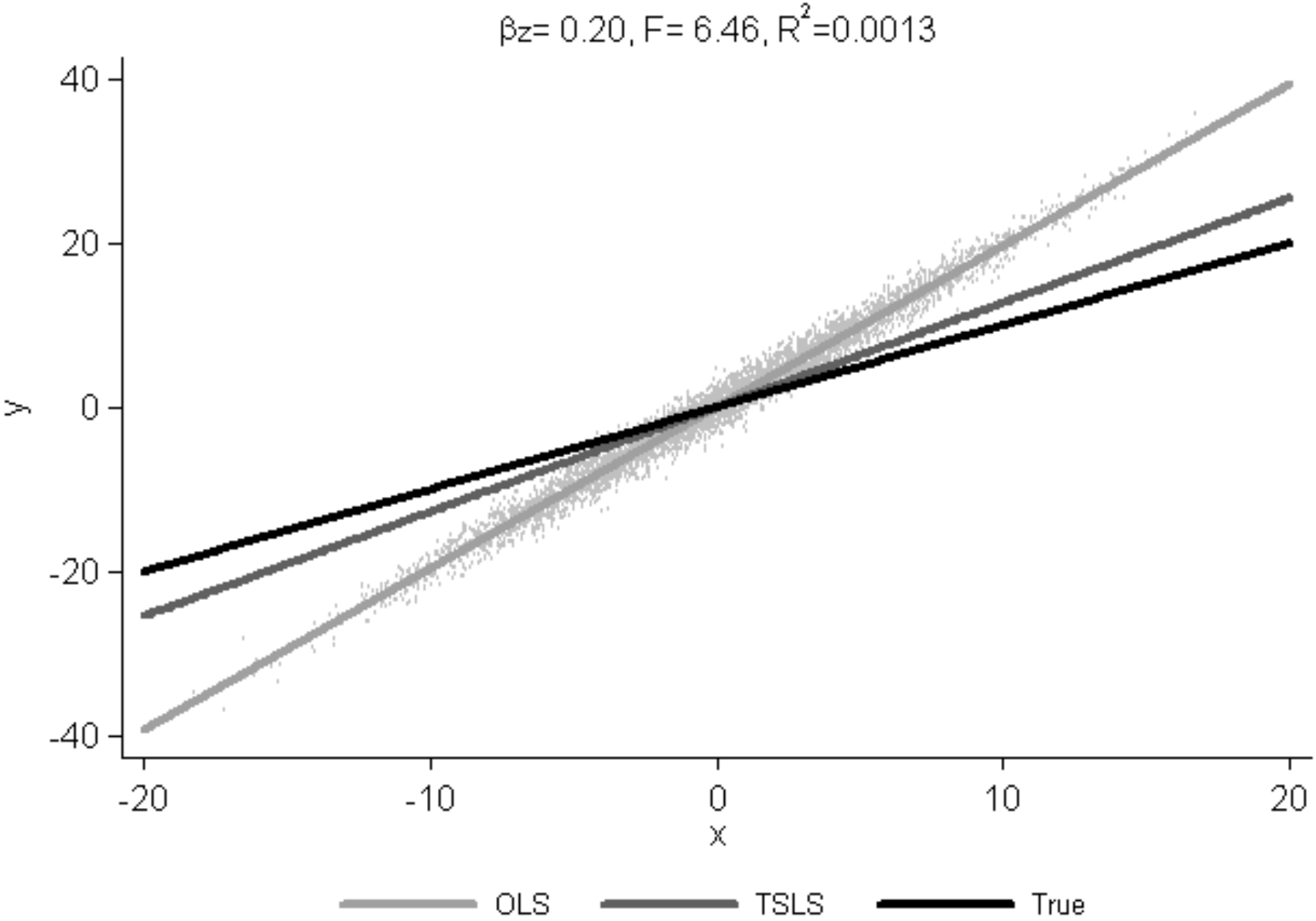

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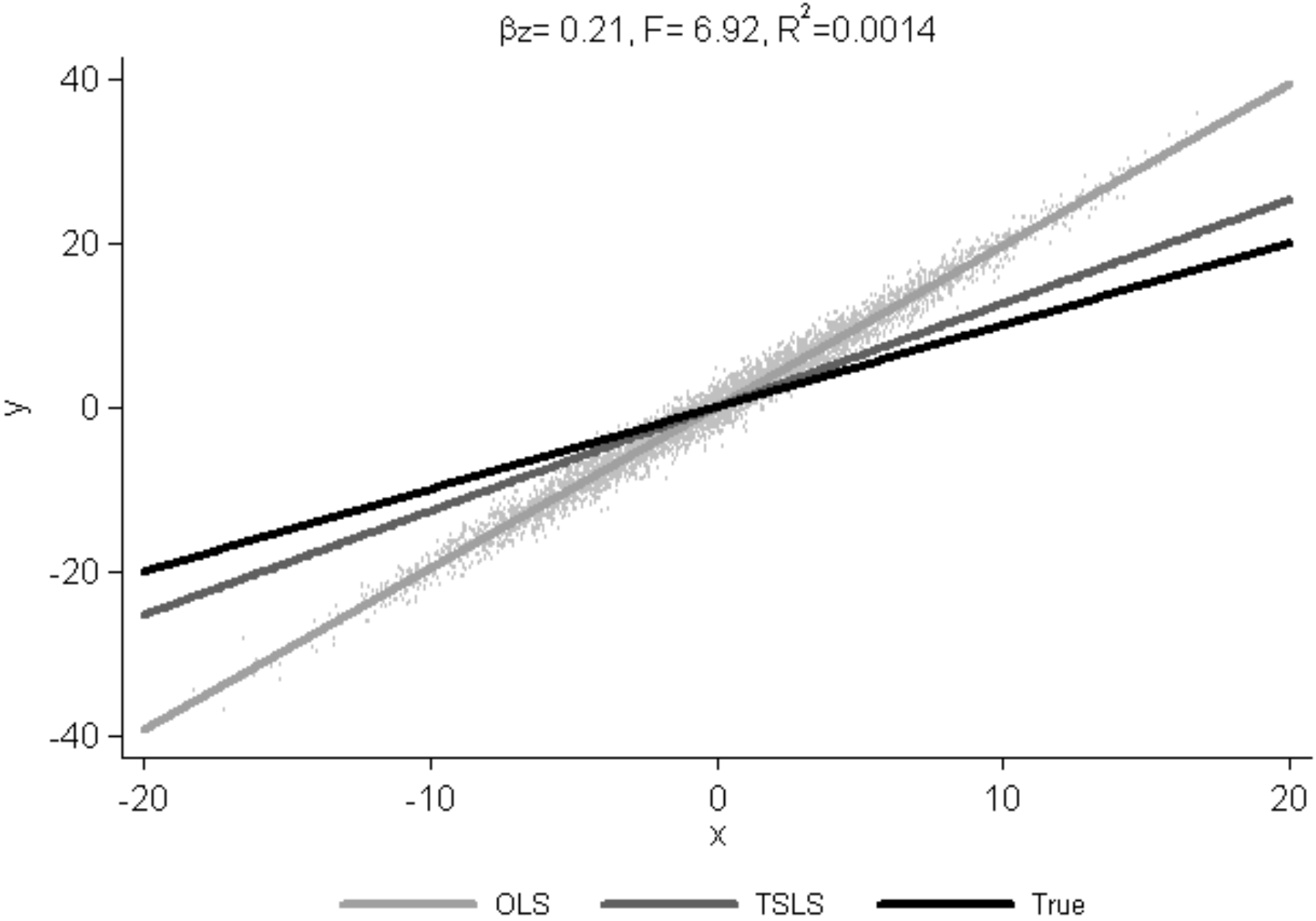

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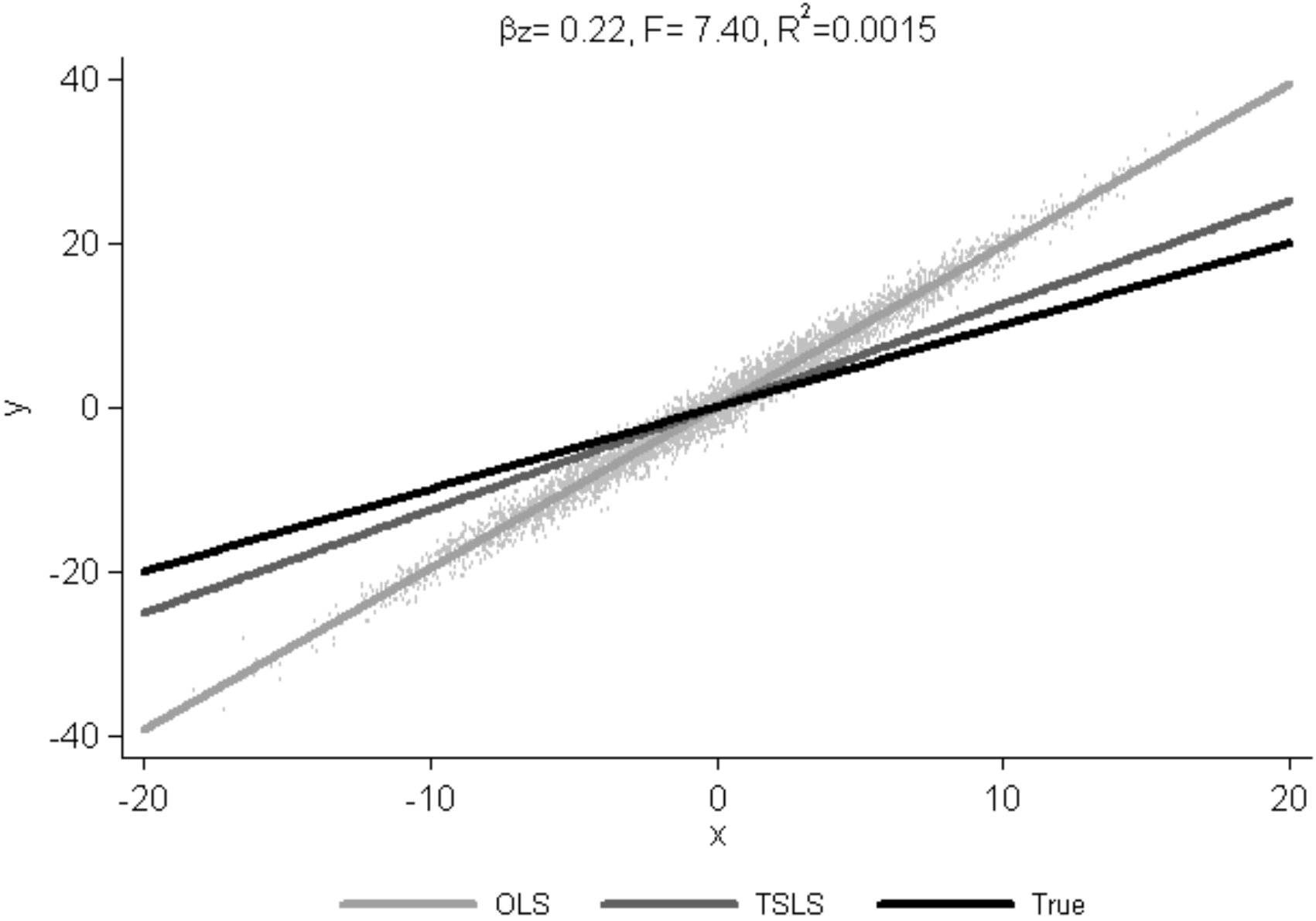

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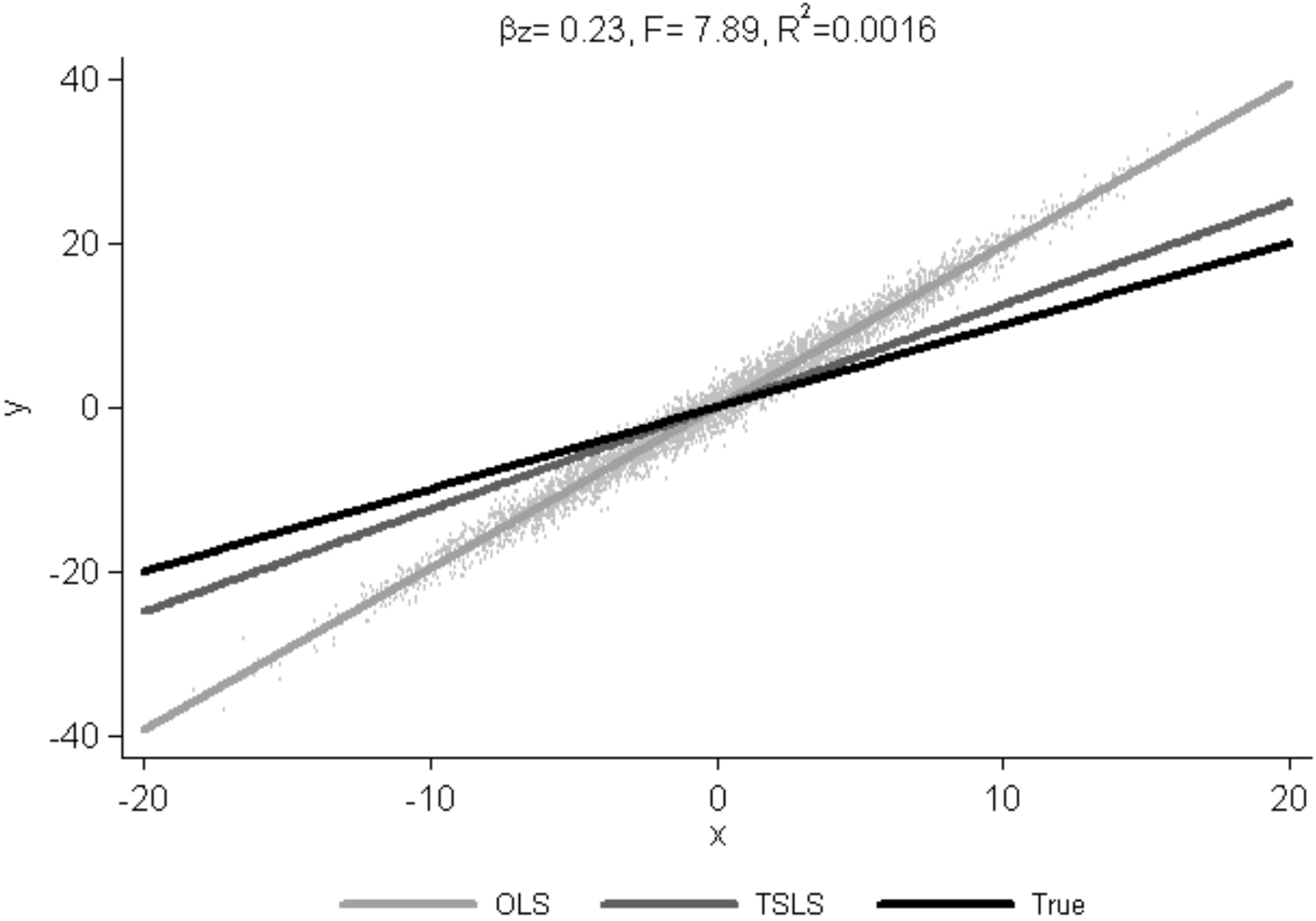

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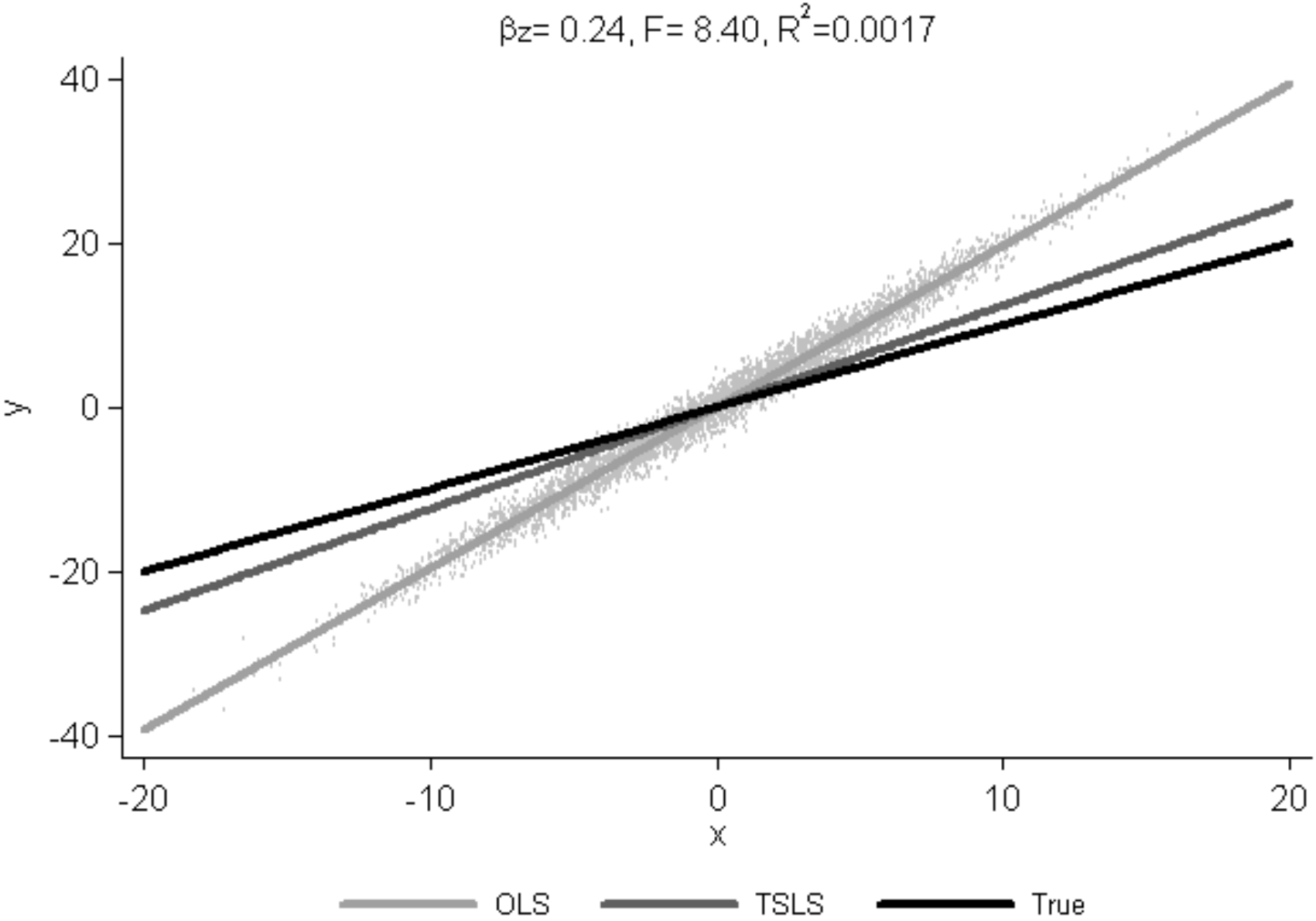

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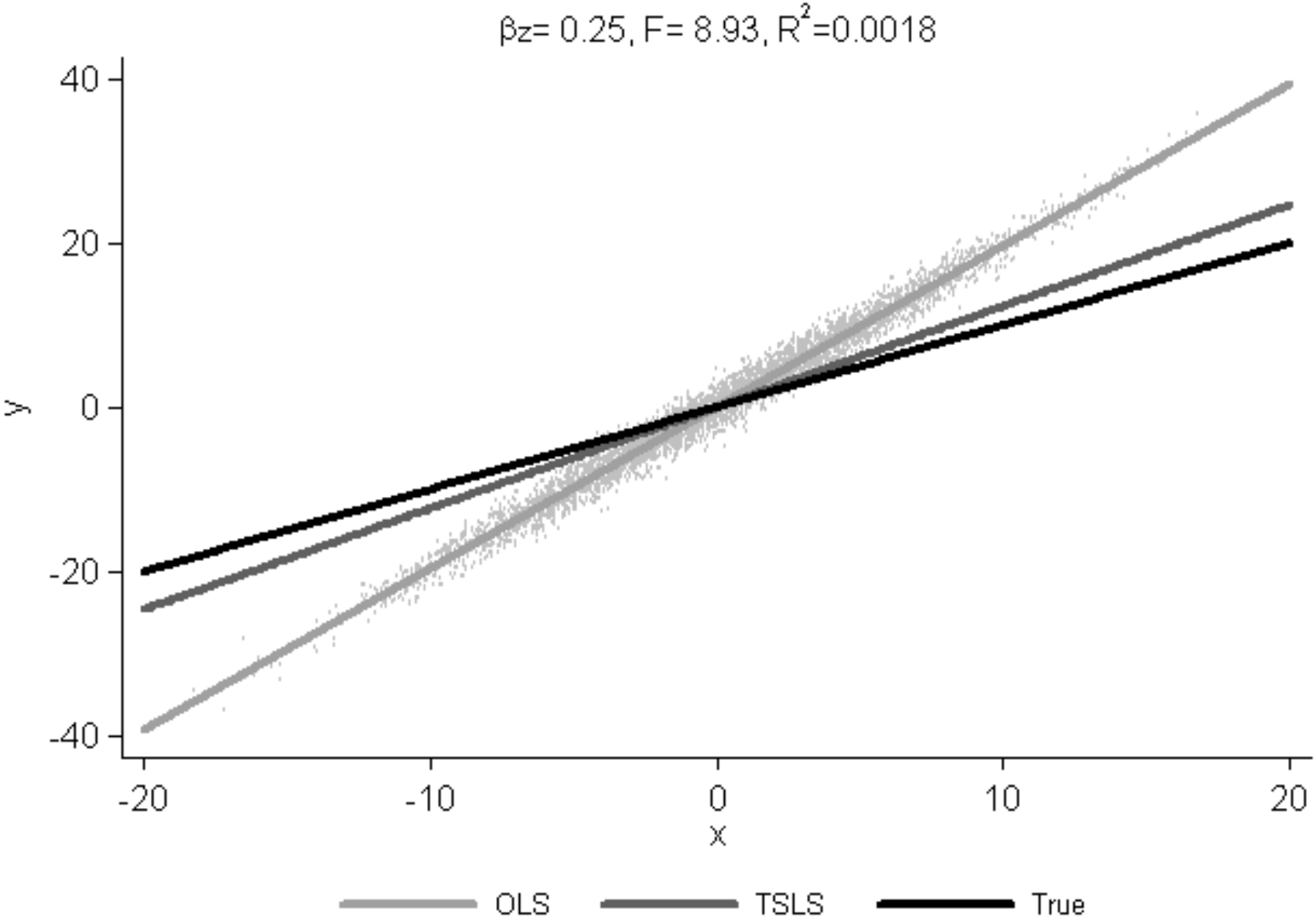

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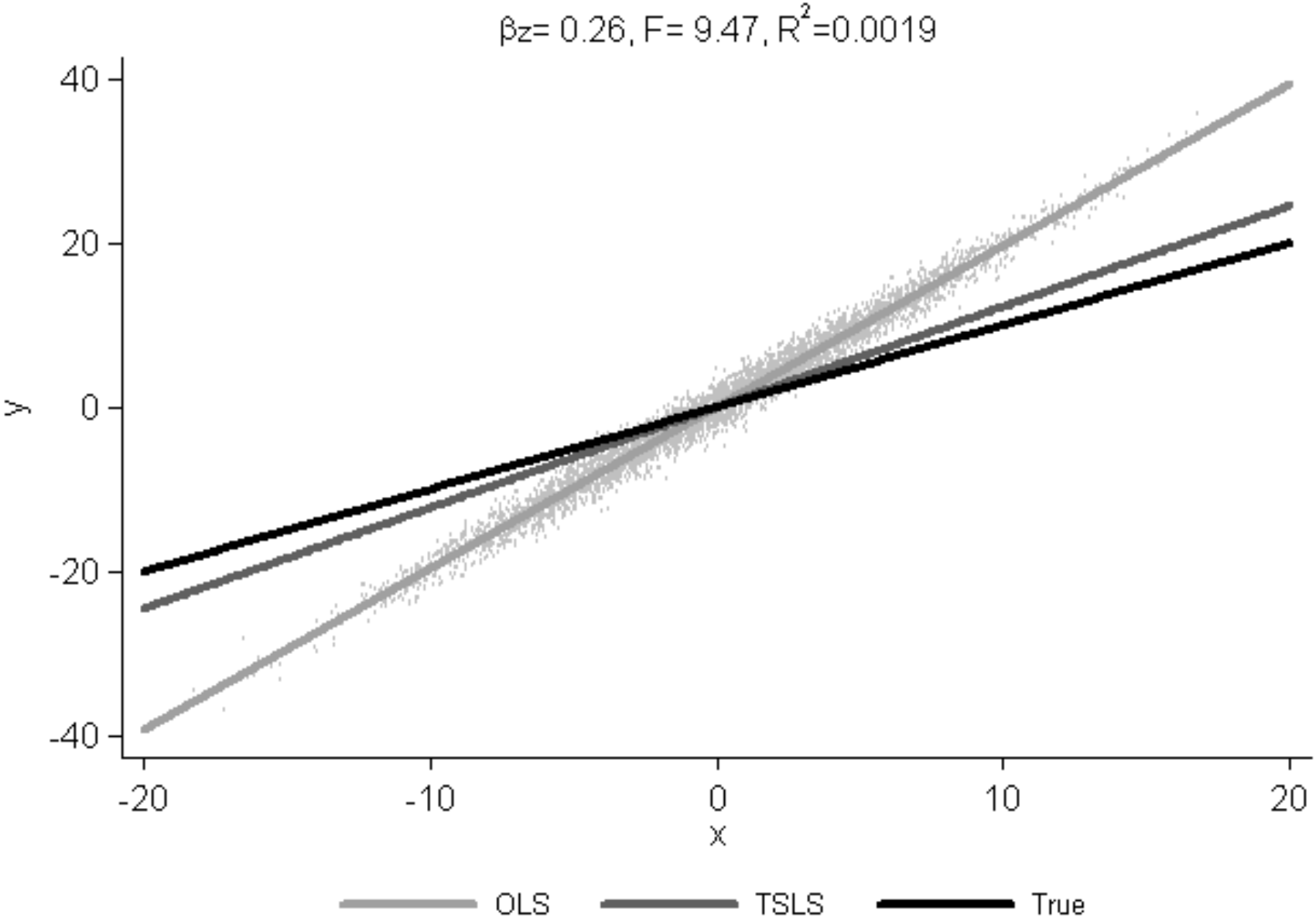

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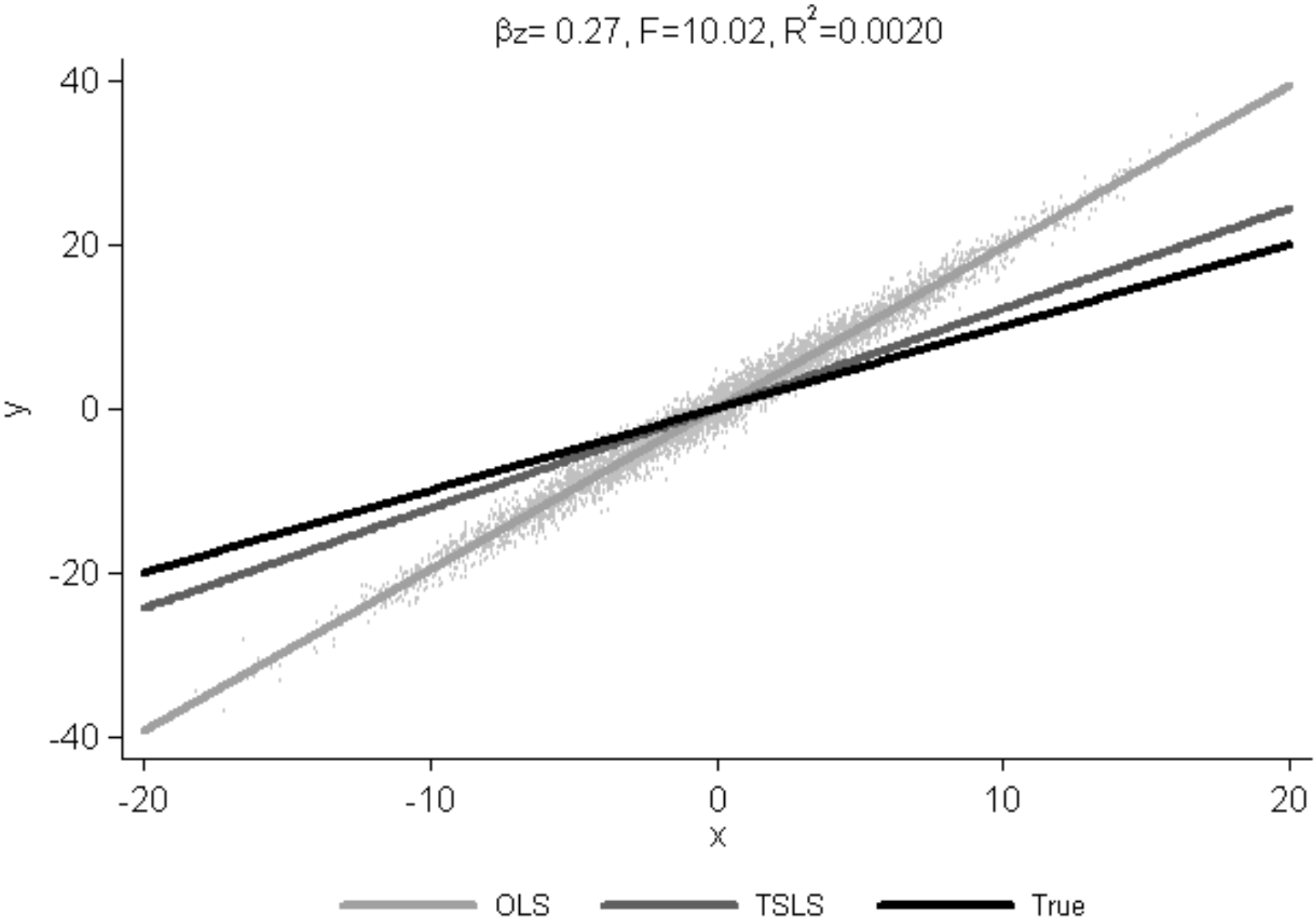

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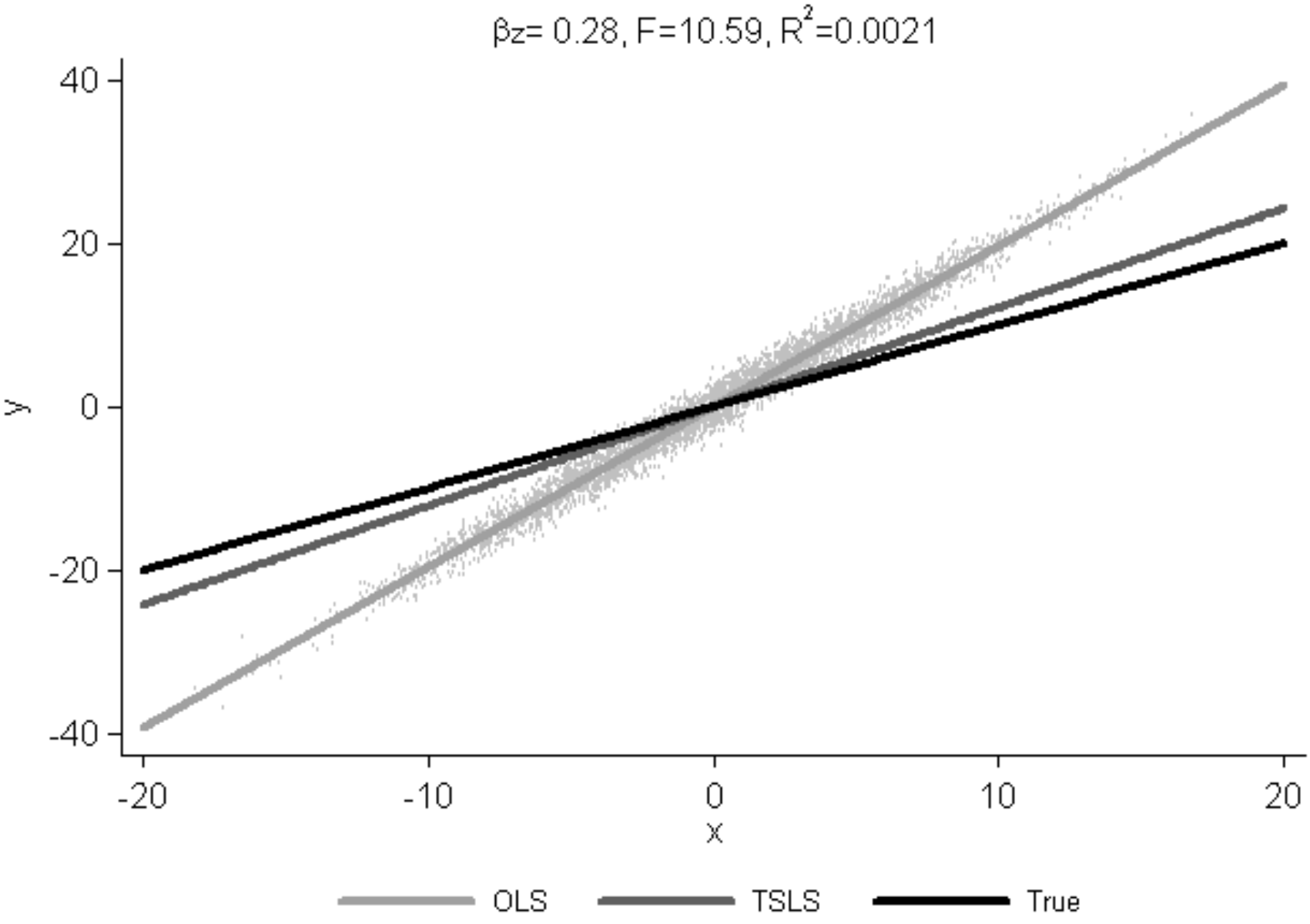

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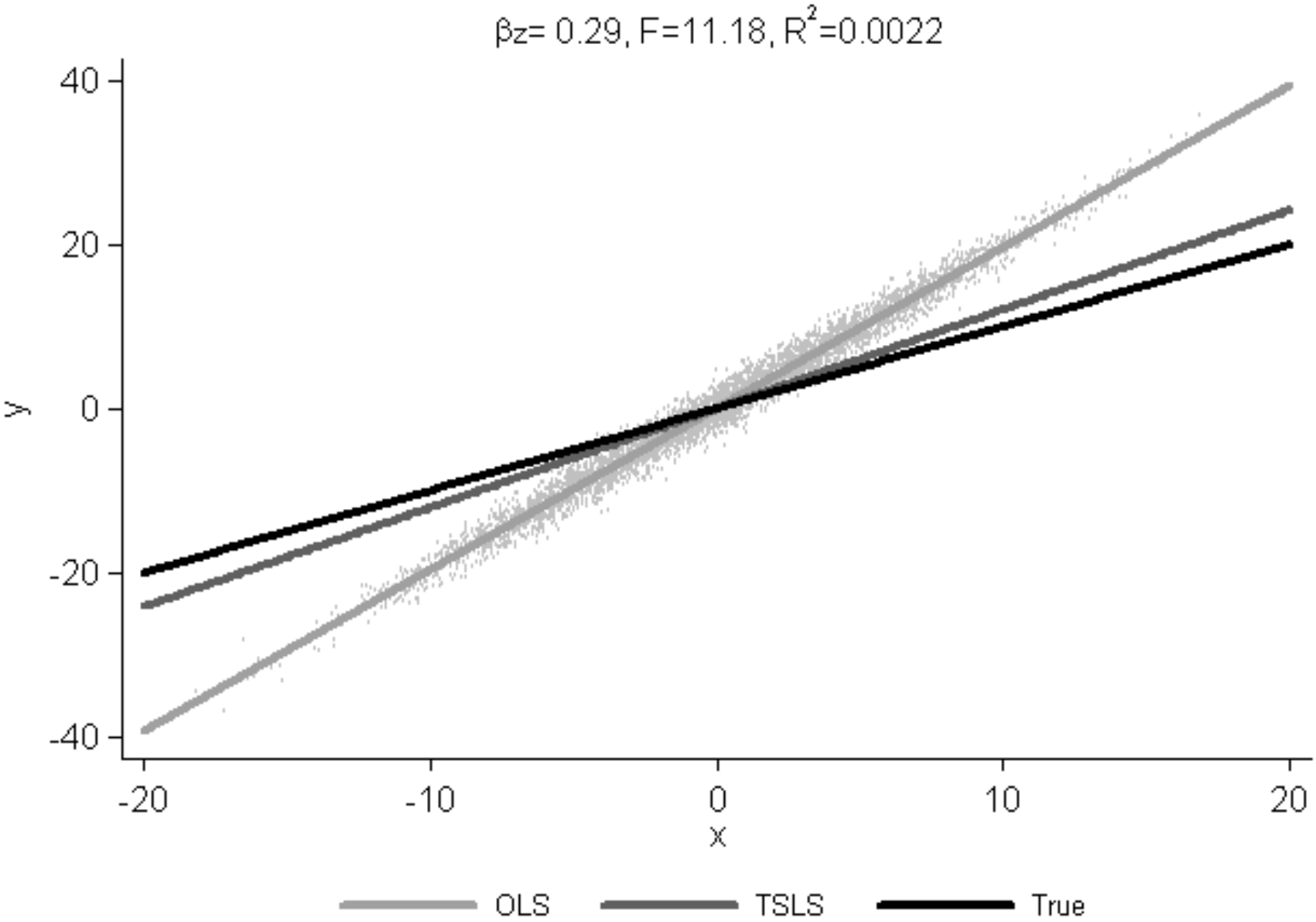

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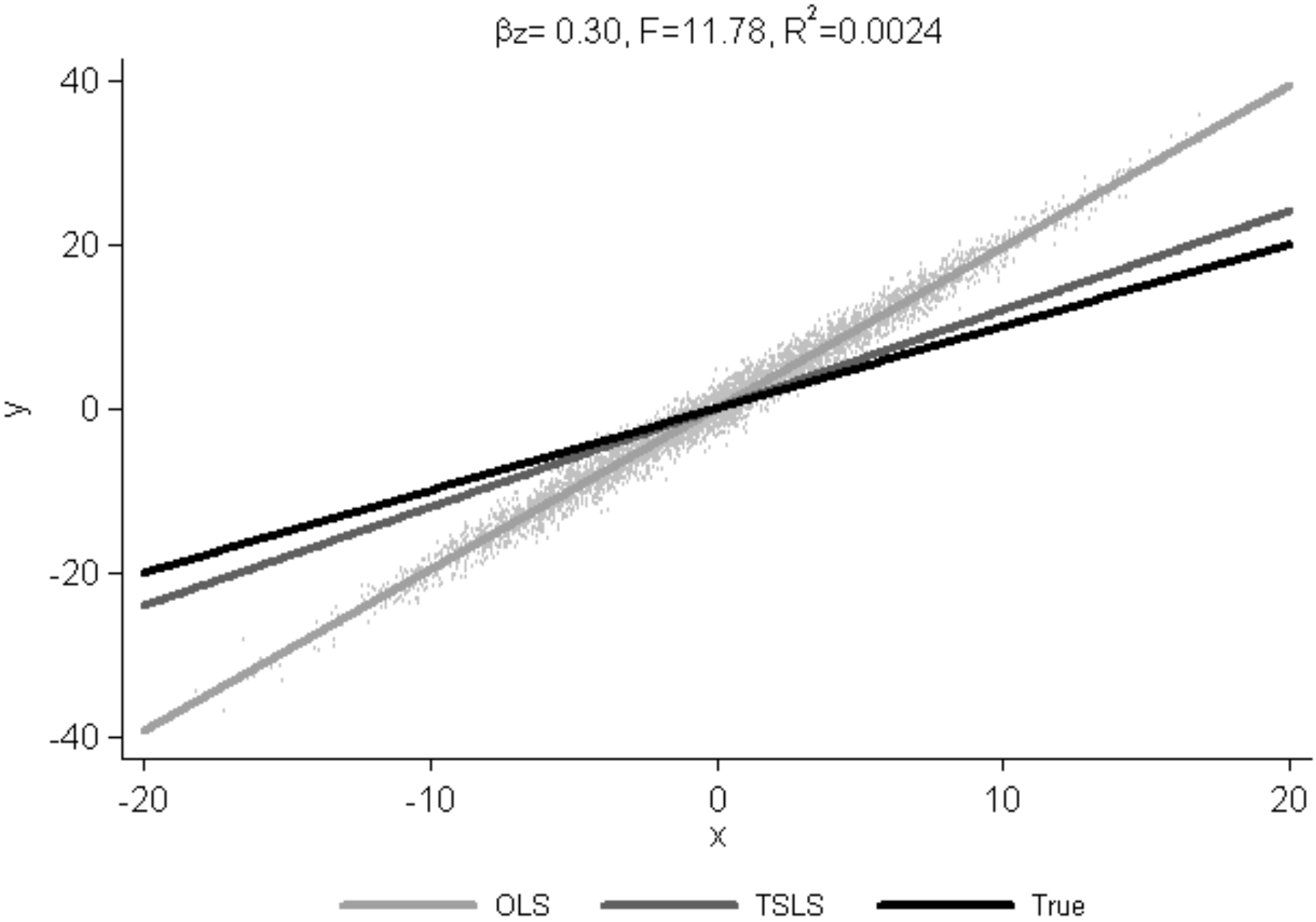
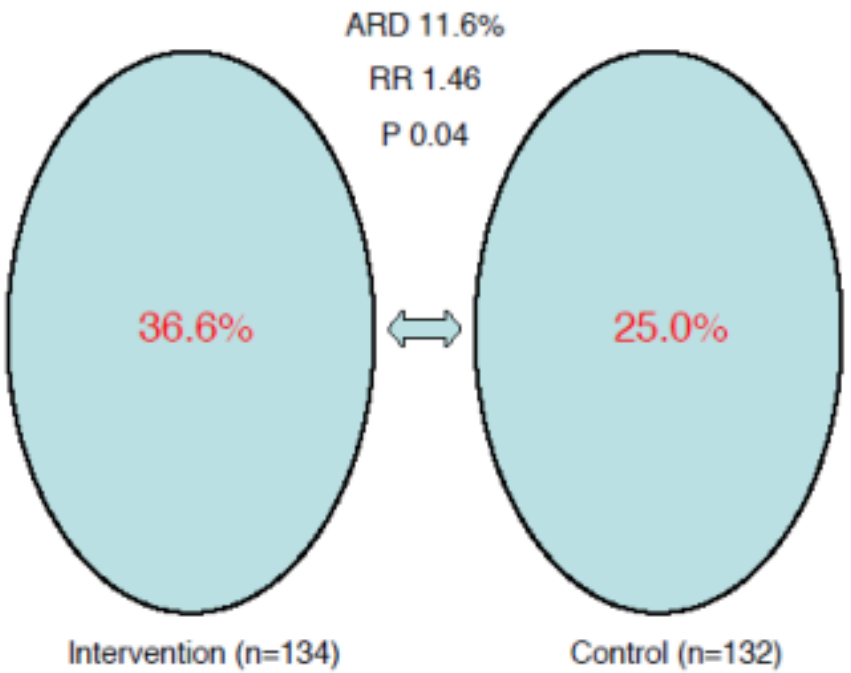


Additive SMM example I

- Ten Have, Elliott, Joffe, Zanutto, & Datto, 2004 266 African American adults with high cholesterol and/or hypertension
- Control: usual care (conventional nutritional info)
- Intervention: usual care + home-based audio tapes
- Outcome: +ve response: beneficial change in cholesterol,
  −ve response: otherwise



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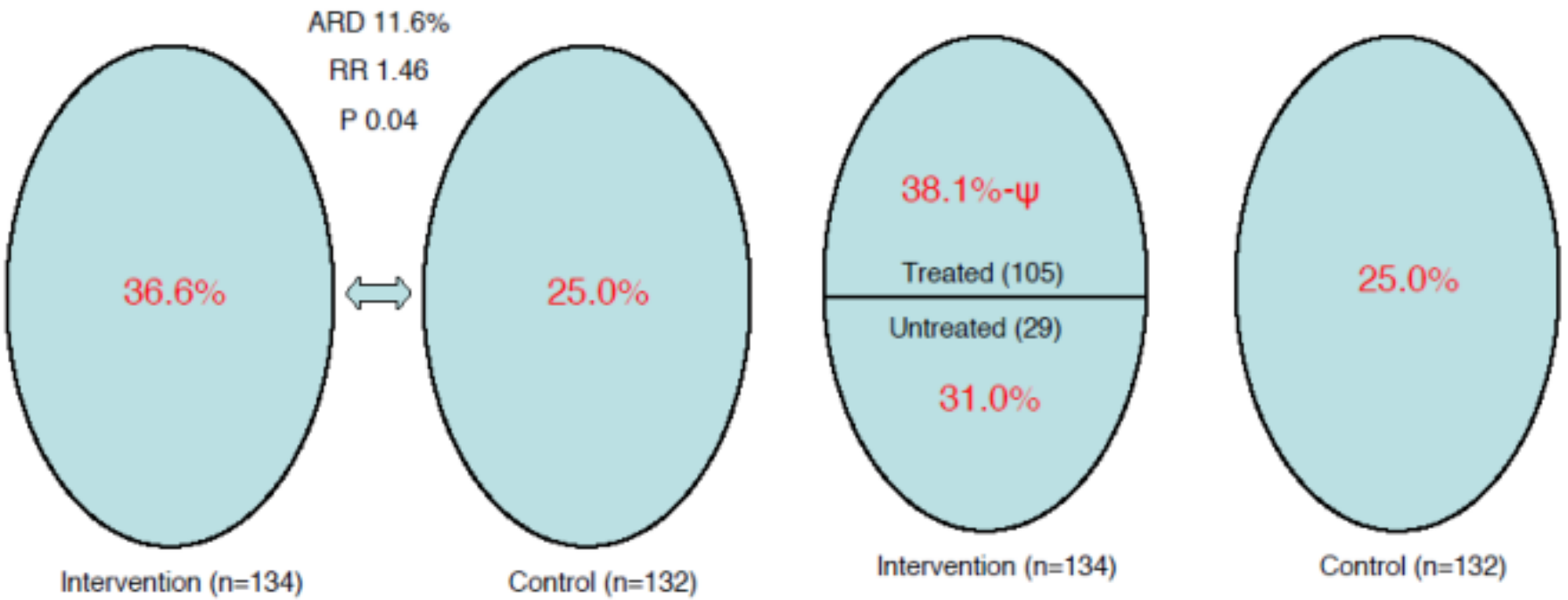
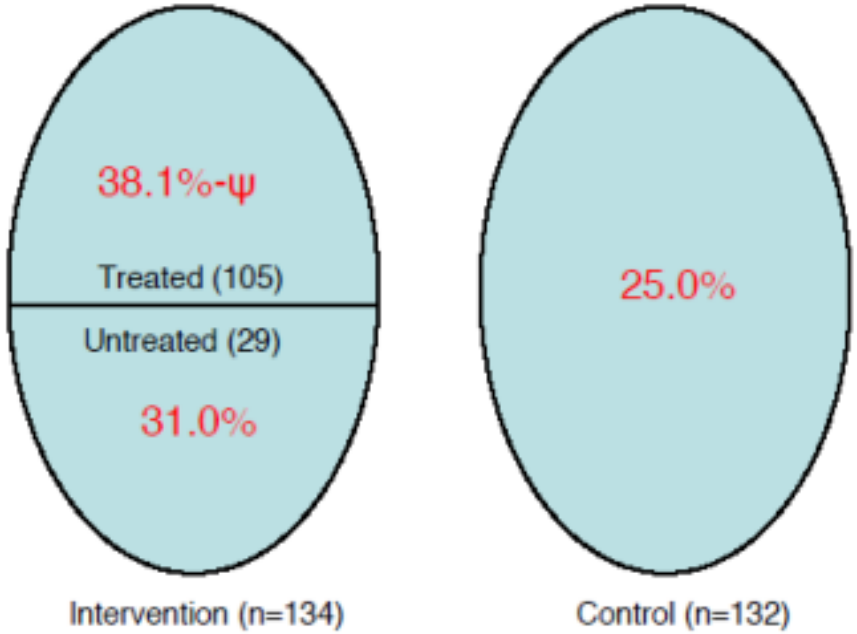
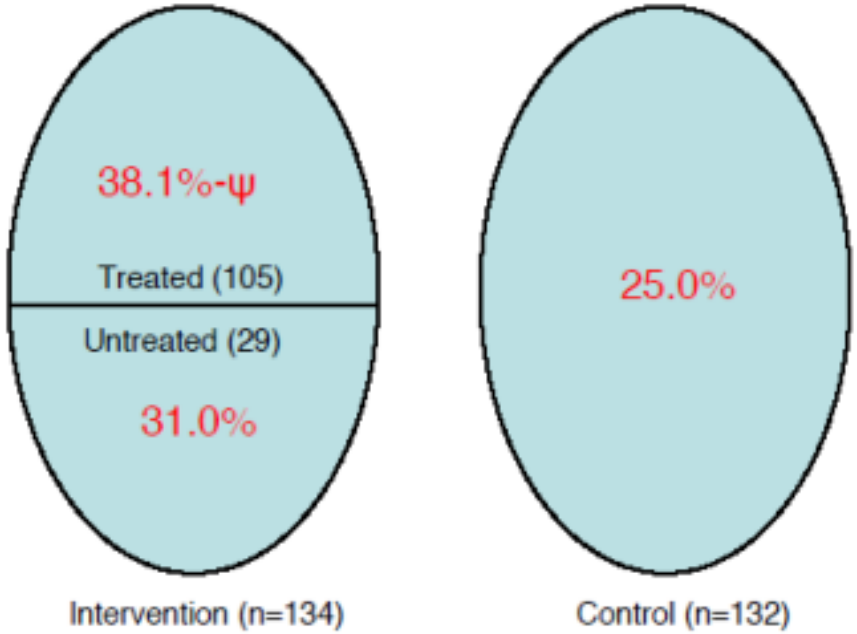


Additive SMM example II



$$\text{Ratio estimate: } \psi = \frac{E(Y|Z=1) - E(Y|Z=0)}{E(X|Z=1) - E(X|Z=0)} = \frac{36.6 - 25.0}{105/134 - 0}$$
$$= 11.6/78.4 = 14.8\% \text{ (95\%CI } 0.8\%, 28.7\%; P = 0.04)$$

Additive SMM example II



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$$= 11.6/78.4 = 14.8\% \text{ (95\%CI } 0.8\%, 28.7\%; P = 0.04)$$

G-estimation: what would have happened if no-one was treated

ASMM estimate: $(38.1 - \psi)(105/134) + 31.0(29/134) = 25.0$

$$\psi = (38.1 \times 105 + 31.0 \times 29 - 25.0 \times 134)/105 = 14.8\%$$

Multiplicative SMM

- Notation: X exposure/treatment, Y outcome, Z instrument, $Y(X = 0)$ exposure/treatment free potential outcome

Robins, Rotnitzky, & Scharfstein, 1999; Hernán & Robins, 2006

$$\log(E[Y|X,Z]) - \log(E[Y(0)|X,Z]) = \psi X$$

$$\frac{E[Y|X,Z]}{E[Y(0)|X,Z]} = \exp(\psi X)$$

ψ : log causal risk ratio

Rearrange: $Y(0) = Y \exp(-\psi X)$

Mutliplicative SMM: estimation with multiple instruments

Under the instrumental variable assumptions (Robins, 1989):

$$Y(0) \perp\!\!\!\perp Z$$
$$Y \exp(-\psi X) \perp\!\!\!\perp Z$$

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$$\text{trick: } Y \exp(-\psi X) - Y(0) \perp\!\!\!\perp Z$$

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Moment conditions

Z=0,1

$$E[(Y \exp(-\psi X) - Y(0))1] = 0$$
$$E[(Y \exp(-\psi X) - Y(0))Z_1] = 0$$

Mutliplicative SMM: estimation with multiple instruments

Under the instrumental variable assumptions (Robins, 1989):

$$Y(0) \perp\!\!\!\perp Z$$
$$Y \exp(-\psi X) \perp\!\!\!\perp Z$$
$$\text{trick: } Y \exp(-\psi X) - Y(0) \perp\!\!\!\perp Z$$

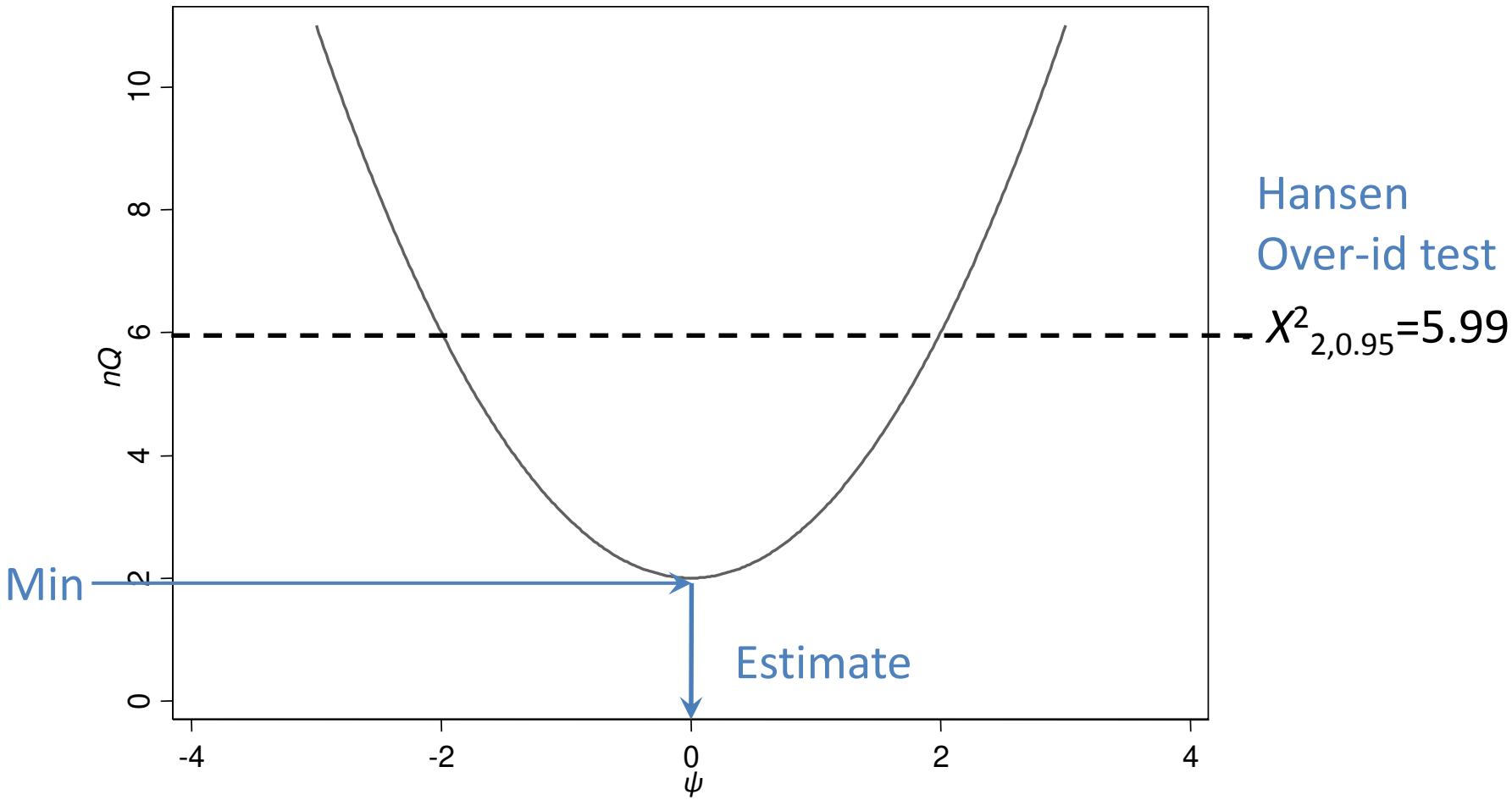
Moment conditions

Z=0,1,2,3 Over-identified

$$E[(Y \exp(-\psi X) - Y(0))1] = 0$$
$$E[(Y \exp(-\psi X) - Y(0))Z_1] = 0$$
$$E[(Y \exp(-\psi X) - Y(0))Z_2] = 0$$
$$E[(Y \exp(-\psi X) - Y(0))Z_3] = 0$$

Generalised Method of Moments

Minimises quadratic form: $Q = m' W^{-1} m$



Implementation in Stata & R

Stata: `gmm` command

```
gmm (y*exp(-1*x*{psi}) - {ey0}), instruments(z1 z2 z3)
```

Implementation in Stata & R

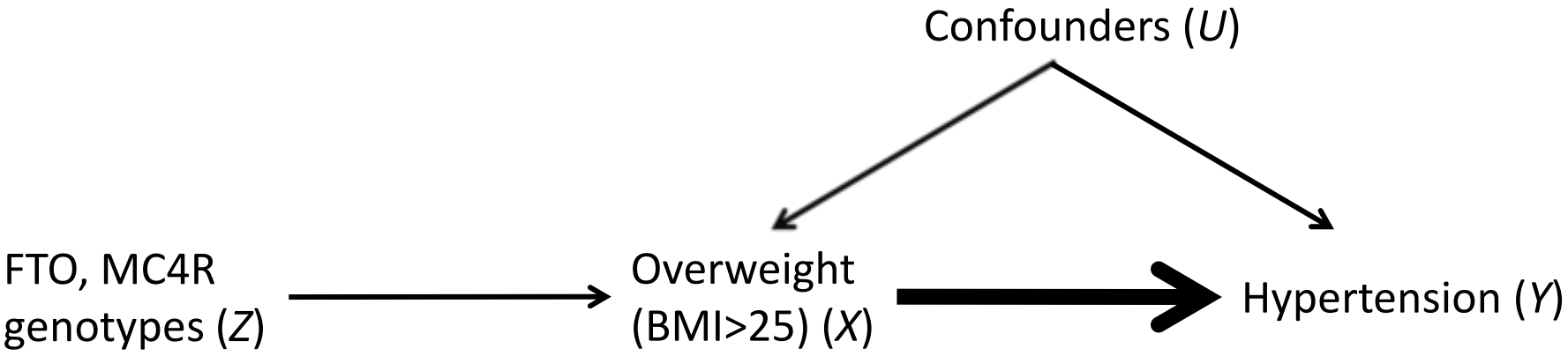
Stata: gmm command

```
gmm (y*exp(-1*x*{psi}) - {ey0}), instruments(z1 z2 z3)
```

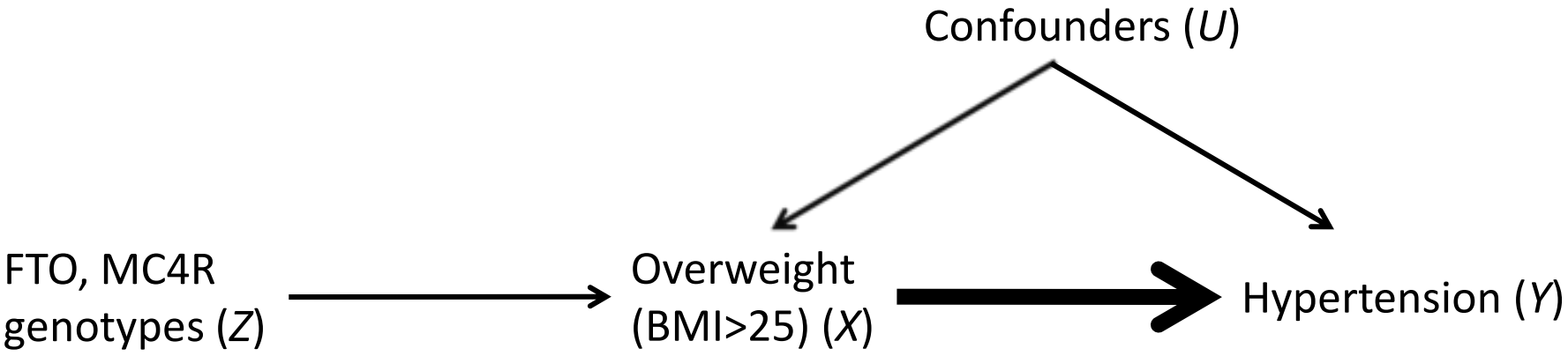
R: gmm package (Chaussé, 2010)

```
library(gmm)
msmmMoments <- function(theta,x){
  # extract variables from x
  Y <- x[,1]; X <- x[,2]; Z1 <- x[,3]; Z2 <- x[,4]; Z3 <- x[,5]
  # moments
  m1 <- (Y*exp(- X*theta[2]) - theta[1])
  m2 <- (Y*exp(- X*theta[2]) - theta[1])*Z1
  m3 <- (Y*exp(- X*theta[2]) - theta[1])*Z2
  m4 <- (Y*exp(- X*theta[2]) - theta[1])*Z3
  return(cbind(m1,m2,m3,m4))
}
fit <- gmm(msmmMoments, data, t0=c(0,0))
```

Copenhagen example descriptive statistics 1



Copenhagen example descriptive statistics 1



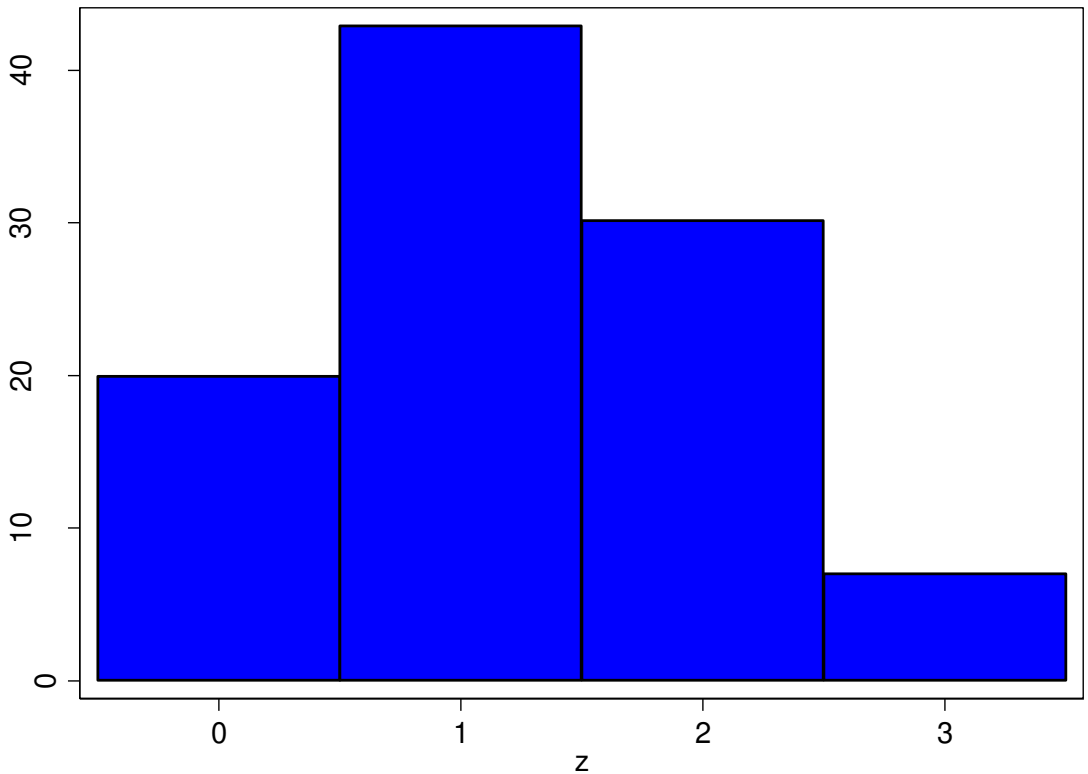
	No Hypertension	Hypertension	Total
Not Overweight	10,066 42%	13,909 58%	23,975
Overweight	6,906 22%	24,642 78%	31,548
Total	16,972 31%	38,551 69%	55,523 χ^2 P<0.001

Risk ratio for hypertension 1.35 (1.32, 1.37)

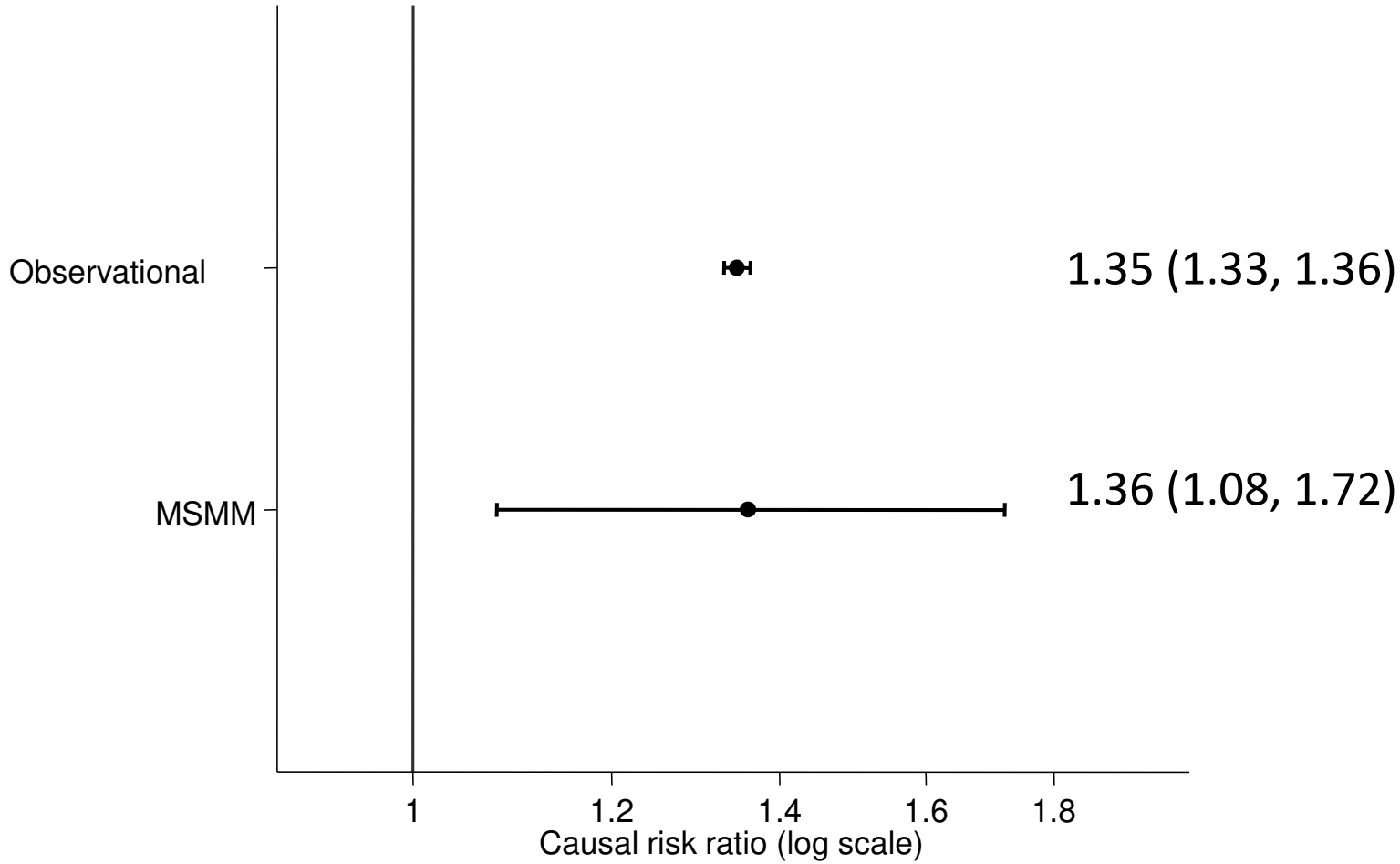
Copenhagen example descriptive statistics 2

Distribution of instrument (Z)

FTO	*MC4R*	*Z*	Freq
0	0	0	0.20
0	1	1	0.15
1	0	1	0.27
1	1	2	0.21
2	0	2	0.09
2	1	3	0.07



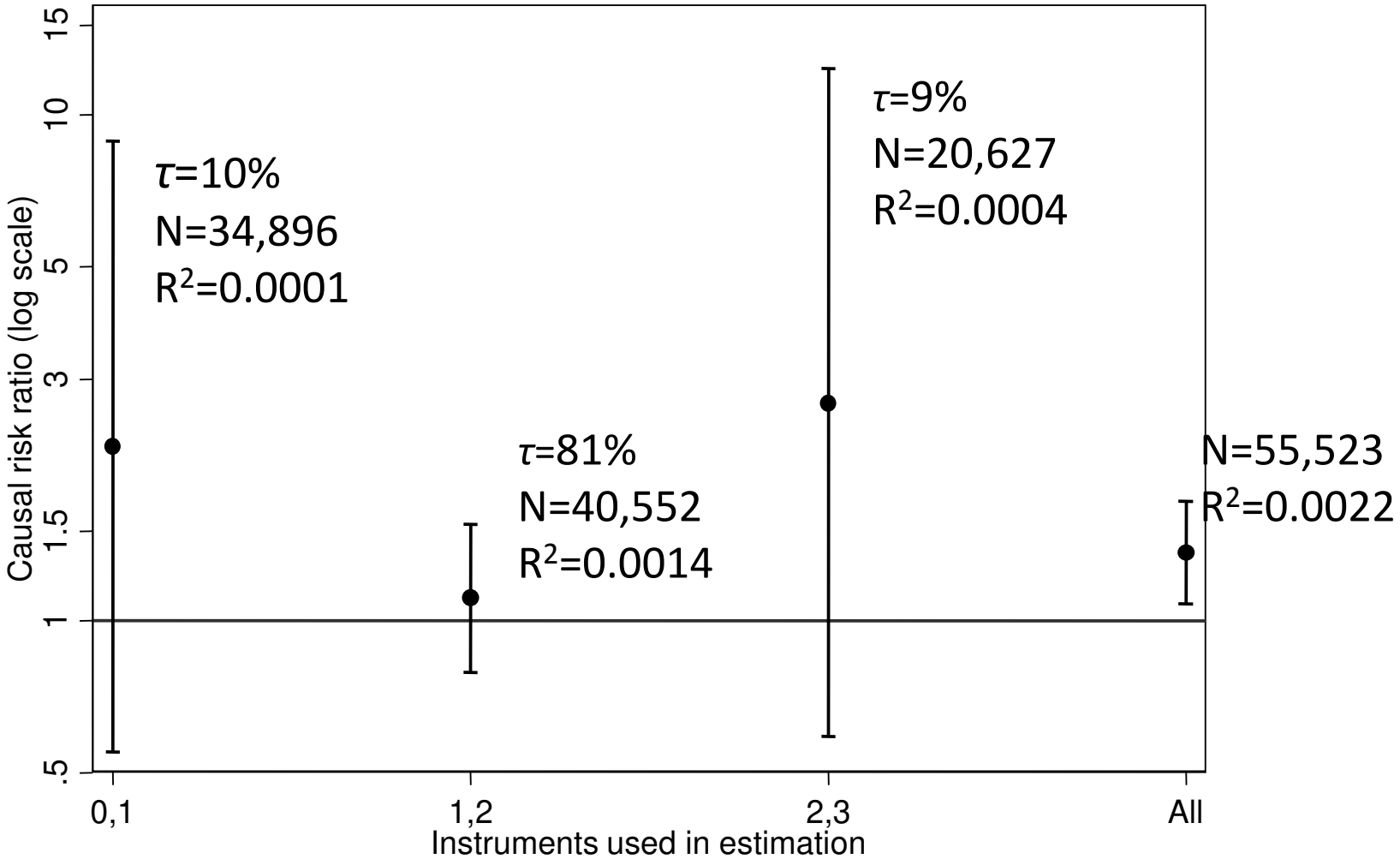
Copenhagen example Multiplicative SMM estimates



MSMM: Hansen over-identification test $P = 0.31$

$\mathrm{E}[Y(0)] = 0.58$ (0.50, 0.65)

Copenhagen example local risk ratios



Check: $(0.10 \times 2.21) + (0.81 \times 1.11) + (0.09 \times 2.69) = 1.36$

3. Nonparametric bounds I

X, Y, Z all binary: IV assumptions–instrumental inequality (Bonet, 2001)

Denote $p_{yx.z} = P(Y = y, X = x \mid Z = z)$

$$\begin{aligned} p_{00.0} + p_{10.1} &\leq 1 \\ p_{10.0} + p_{00.1} &\leq 1 \\ p_{11.0} + p_{01.1} &\leq 1 \\ p_{01.0} + p_{11.1} &\leq 1 \end{aligned}$$

- Not a statistical test
- If fail then the IV assumptions must be violated
- But IV assumptions can be violated without failing the inequalities

Nonparametric bounds II

Bounds on intervention probabilities (Balke & Pearl, 1997):
$P(Y(X=0))$, $P(Y(X=1))$

Bounds on the Average Causal Effect (ACE):
$\text{ACE} = P(Y(X=1)) - P(Y(X=0))$

Nonparametric bounds II

Bounds on intervention probabilities (Balke & Pearl, 1997):

$P(Y(X=0))$, $P(Y(X=1))$

Bounds on the Average Causal Effect (ACE):

$\text{ACE} = P(Y(X=1)) - P(Y(X=0))$

$$\max \left\{ \begin{array}{c} p_{00.0} + p_{11.1} - 1 \\ p_{00.1} + p_{11.1} - 1 \\ p_{11.0} + p_{00.1} - 1 \\ p_{00.0} + p_{11.0} - 1 \\ 2p_{00.0} + p_{11.0} + p_{10.0} + p_{11.1} - 2 \\ p_{00.0} + 2p_{11.0} + p_{00.1} + p_{01.1} - 2 \\ p_{10.0} + p_{11.0} + 2p_{00.1} + p_{11.1} - 2 \\ p_{00.0} + p_{01.0} + p_{00.1} + 2p_{11.1} - 2 \end{array} \right\} \leq \text{ACE} \leq \min \left\{ \begin{array}{c} 1 - p_{10.0} - p_{01.1} \\ 1 - p_{01.0} - p_{10.1} \\ 1 - p_{01.0} - p_{10.0} \\ 1 - p_{01.1} - p_{10.1} \\ 2 - 2p_{01.1} - p_{10.0} - p_{10.1} - p_{11.1} \\ 2 - p_{01.0} - 2p_{10.0} - p_{00.1} - p_{01.1} \\ 2 - p_{10.0} - p_{11.0} - 2p_{01.1} - p_{10.1} \\ 2 - p_{00.0} - p_{01.0} - p_{01.1} - 2p_{10.1} \end{array} \right\}$$

Nonparametric bounds: Example

	$Z=0$		$Z=1$	
	$Y=0$	$Y=1$	$Y=0$	$Y=1$
$X=0$	74	11514	34	2385
$X=1$	0	0	12	9663

Table: Vitamin A supplementation data (Balke & Pearl, 1997).

Nonparametric bounds: Example

	$Z=0$		$Z=1$	
	$Y=0$	$Y=1$	$Y=0$	$Y=1$
$X=0$	74	11514	34	2385
$X=1$	0	0	12	9663

Table: Vitamin A supplementation data (Balke & Pearl, 1997).

	Bounds
Instrumental inequality	`satisfied`
$P(Y(X=0))$	(0.9936, 0.9936)
$P(Y(X=1))$	(0.7990, 0.9990)
Average Causal Effect (risk difference)	(-0.1946, 0.0054)
Causal risk ratio	(0.8042, 1.0054)

TSLS: ACE 0.0032 (95%CI 0.0010, 0.0055)

Nonparametric bounds: Interpretation

- Not same as a confidence interval
- Bounds of [-0.1946, 0.0054]:
  there exists some distribution involving U that yields a true ACE as small as -19.46%, and another that gives a true ACE as large as 0.54%, with both distributions satisfying the IV assumptions and having the same observed marginal frequencies on (X, Y, Z)

Nonparametric bounds: Extensions

- Monotonicity assumption: for all values u of U
  $P(X = 1 \mid Z = 1, U = u) \geq P(X = 1 \mid Z = 0, U = u)$
  gives (slightly) tighter inequalities and bounds
- Extensions for a 3rd instrument category
- Data structures: (X, Z) & (Y, Z) in different samples

Nonparametric bounds: Limitation

Simulate data (N=10,000), two outcomes; both do not fulfil IV assumptions

$$
\begin{aligned}
Z &\sim Bern(0.5), \quad U \sim Bern(0.5) \\
p_X &= 0.05 + 0.1Z + 0.1U, \quad X \sim Bern(p_X) \\
p_1 &= 0.1 + 0.2Z + 0.05X + 0.1U, \quad Y_1 \sim Bern(p_1) \\
p_2 &= 0.1 + 0.05Z + 0.05X + 0.1U, \quad Y_2 \sim Bern(p_2)
\end{aligned}
$$

For Y_1 IV instrumental inequality is not satisfied

Nonparametric bounds: Limitation

Simulate data (N=10,000), two outcomes; both do not fulfil IV assumptions

$$
\begin{aligned}
Z \sim Bern(0.5), \quad U \sim Bern(0.5) \\
p_X = 0.05 + 0.1Z + 0.1U, \quad X \sim Bern(p_X) \\
p_1 = 0.1 + 0.2Z + 0.05X + 0.1U, \quad Y_1 \sim Bern(p_1) \\
p_2 = 0.1 + 0.05Z + 0.05X + 0.1U, \quad Y_2 \sim Bern(p_2)
\end{aligned}
$$

For Y_1 IV instrumental inequality is not satisfied
For Y_2 we get

	Bounds
Instrumental inequality	`satisfied`
$P(Y(X=0))$	(0.1542, 0.2352)
$P(Y(X=1))$	(0.0585, 0.8464)
Average Causal Effect (risk difference)	(-0.1767, 0.6922)

4. Summary

- Instrumental variable assumptions
  - Not fully testable from observational data (as for all causal inf.)
- Applications
  - Mendelian randomization (IV: genotypes)
  - Correct for noncompliance (IV: randomized treatment)
- Test for presence of effect
- Estimators: ratio and two-stage least squares
- Structural Mean Models: G-estimation $Y(0) \perp\!\!\!\perp Z$
- Additive SMM
- Multiplicative SMM
- Review of methods Palmer, Sterne, et al., 2011; Palmer, Lawlor, et al., 2011
- Nonparametric bounds
- Stata command: `bpbounds` Palmer, Ramsahai, Didelez, & Sheehan, 2011

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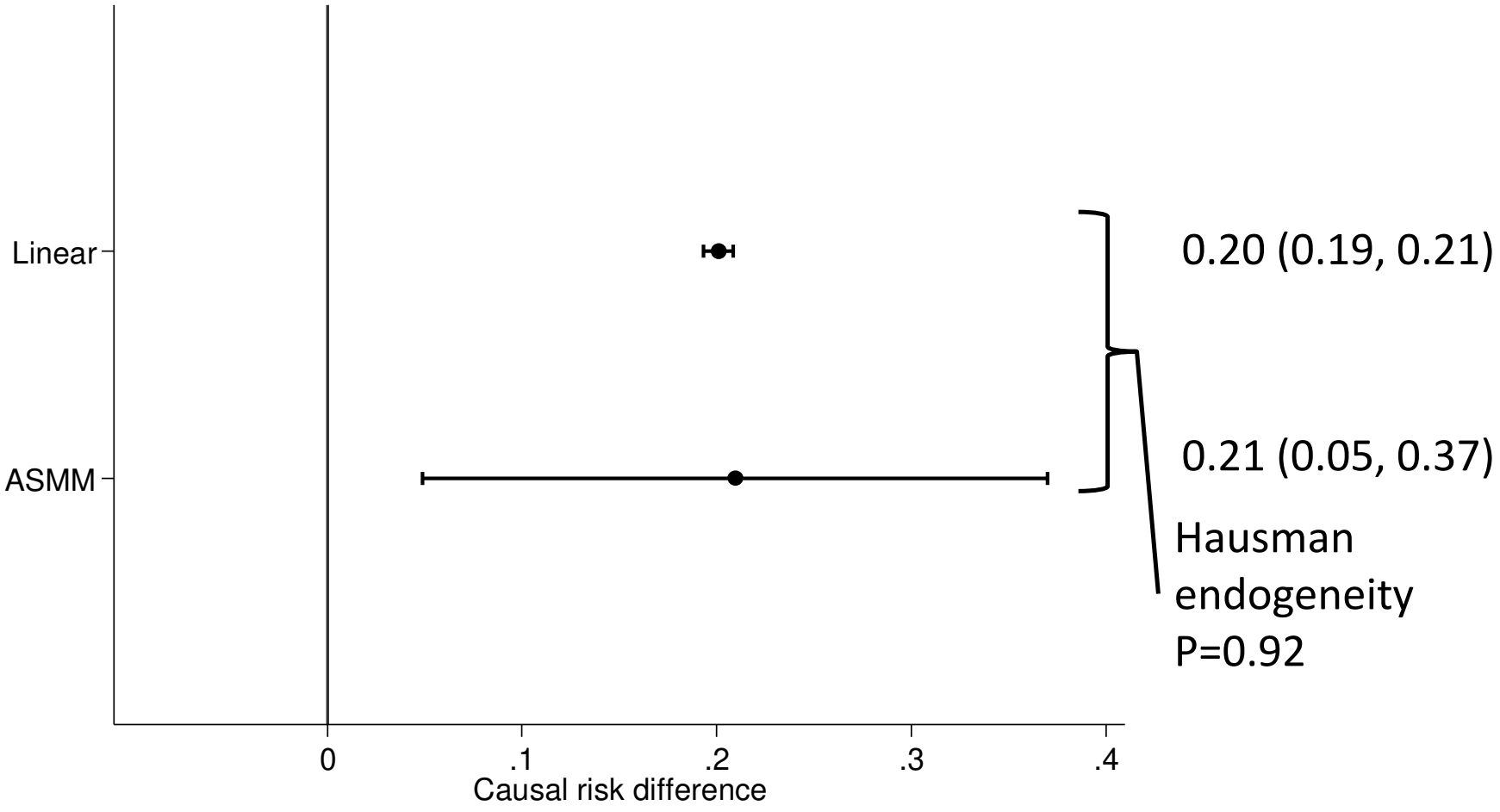
Copenhagen example comparison estimates

	RR (95% CI)	P over-id
MSMM	1.36 (1.08, 1.72)	0.31
$Y - \exp(\psi X) \perp\!\!\!\perp Z$	1.36 (1.07, 1.75)	0.30
Control function	1.36 (1.08, 1.71)	
	OR (95% CI)	P over-id
LSMM two-stage	1.88 (1.75, 2.02)	
LSMM joint	2.87 (1.25, 6.55)	0.29
$Y - \text{expit}(\psi X) \perp\!\!\!\perp Z$	2.69 (1.23, 5.90)	0.30
Control function	2.69 (1.21, 5.97)	

Copenhagen example Additive SMM estimates



MSMM: Hansen over-identification test $P = 0.30$

$\mathrm{E}[Y(0)] = 0.58$ (0.48, 0.67)

(double) Logistic SMM

$\text{logit}(p) = \log(p/(1-p)), \text{expit}(x) = e^x/(1+e^x)$

Goetghebeur, 2010

$$\text{logit}(E[Y|X,Z]) - \text{logit}(E[Y(0)|X,Z]) = \psi X$$

ψ : log causal odds ratio

Rearrange for $Y(0) = \text{expit}(\text{logit}(Y) - \psi X)$

(double) Logistic SMM

$\text{logit}(p) = \log(p/(1-p)), \text{expit}(x) = e^x/(1+e^x)$

Goetghebeur, 2010

$$\text{logit}(E[Y|X,Z]) - \text{logit}(E[Y(0)|X,Z]) = \psi X$$

ψ : log causal odds ratio

Rearrange for $Y(0) = \text{expit}(\text{logit}(Y) - \psi X)$

- Can't be estimated in a single step Robins (1999)
- First stage association model Vansteelandt (2003):
  - (i) logistic regression of Y on X & Z & interactions
  - (ii) predict Y, estimate LSMM using predicted Y

(double) Logistic SMM moment conditions

Association model moment conditions

Logistic regression using GMM

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))1] = 0$$
$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))X] = 0$$
$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))Z] = 0$$
$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))XZ] = 0$$

(double) Logistic SMM moment conditions

Association model moment conditions

Logistic regression using GMM

$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))1] = 0$$
$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))X] = 0$$
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$$E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))XZ] = 0$$

Causal model moment conditions

$$E[(\text{expit}(\text{logit}(\widehat{p}) - \psi X) - Y(0))1] = 0$$
$$E[(\text{expit}(\text{logit}(\widehat{p}) - \psi X) - Y(0))Z] = 0$$

Problem: SEs incorrect - need association model uncertainty

LSMM joint estimation

Joint estimation = correct SEs Gourieroux (1996)

Vansteelandt & Goetghebeur (2003)

$$
\begin{aligned}
E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))1] &= 0 \\
E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))X] &= 0 \\
E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))Z] &= 0 \\
E[(Y - \text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ))XZ] &= 0 \\
E[(\text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ - \psi X) - Y(0))1] &= 0 \\
E[(\text{expit}(\beta_0 + \beta_1 X + \beta_2 Z + \beta_3 XZ - \psi X) - Y(0))Z] &= 0
\end{aligned}
$$

Stata `gmm` command - allows multiple equations - still 1 line of code

Example: causal model SEs $\times 10$

Including covariates

TSLS: include covariates in both stages

GMM: use covariates as instruments for themselves

Including (pre-exposure) covariates in MSMM

$$Y(0) \perp\!\!\!\perp Z|C$$

$$\log(E[Y|X,Z,C]) - \log(E[Y(0)|X,Z,C]) = \psi X + \psi_c C$$

Including covariates

TSLS: include covariates in both stages

GMM: use covariates as instruments for themselves

Including (pre-exposure) covariates in MSMM

$$Y(0) \perp\!\!\!\perp Z|C$$

$$\log(E[Y|X,Z,C]) - \log(E[Y(0)|X,Z,C]) = \psi X + \psi_c C$$

Copenhagen example estimates

Covariates	RR (95%CI)	Over-id P
	1.36 (1.08, 1.72)	0.31
sex	1.36 (1.07, 1.72)	0.39
sex, age	1.35 (1.07, 1.71)	0.58
sex, age, chol	1.33 (1.05, 1.68)	0.49