

# Measurement error and missing data

Killing two birds with one stone

**Ruth Keogh**

Department of Medical Statistics  
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**On Behalf of TG4 Measurement Error and Misclassification**

LONDON  
SCHOOL of  
HYGIENE  
& TROPICAL  
MEDICINE



# Measurement error and misclassification

**Laurence Freedman**

**Victor Kipnis**

Hendriek Bozhuizen

Raymond Carroll

Veronika Deffner

Kevin Dodd

Paul Gustafson

Ruth Keogh

Helmut Kuechenhoff

Pamela Shaw

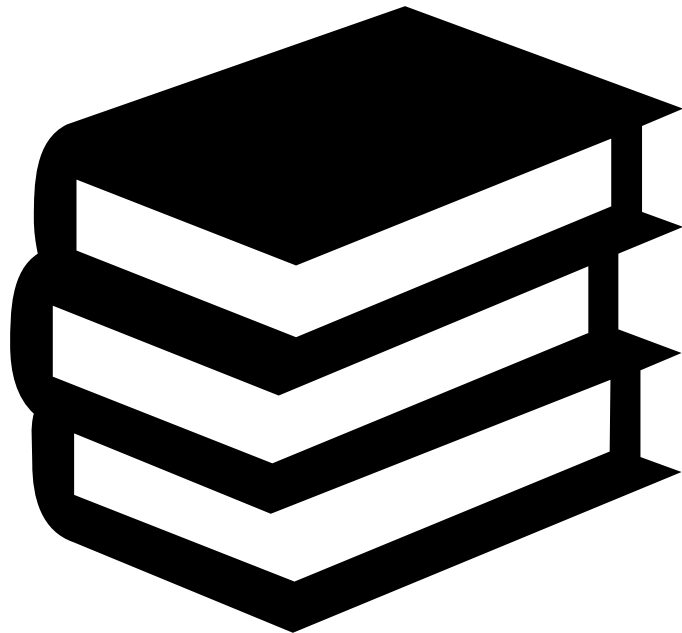
Anne Thiebaut

Janet Tooze

Michael Wallace



## What are people saying and doing about measurement error?



We surveyed the literature in four areas :

- Nutritional intake cohort studies
- Physical activity cohort studies
- Air pollution cohort studies
- Dietary intake distributions

# Literature survey: N=81

What percentage of studies mentioned measurement error as a potential problem?

What percentage of studies used methods to mitigate the impact of measurement error?

What percentage of studies categorized their main exposure?

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80% (N=65)

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80% (N=65)

What percentage of studies used methods to mitigate the impact of measurement error?

6% (N=5)

What percentage of studies categorized their main exposure?

# Literature survey: N=81

What percentage of studies mentioned measurement error as a potential problem?

80% (N=65)

What percentage of studies used methods to mitigate the impact of measurement error?

6% (N=5)

What percentage of studies categorized their main exposure?

88% (N=71)

# Literature survey: observations

- Most of those who mentioned error as a problem made an incomplete/incorrect claim
  - Many stated that their estimates could only be attenuated by measurement error
  - Some claimed no bias in associations but for spurious reasons



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- Most of those who mentioned error as a problem made an incomplete/incorrect claim
  - Many stated that their estimates could only be attenuated by measurement error
  - Some claimed no bias in associations but for spurious reasons
- Most studies categorized the continuous exposures
  - Common belief: categorization will reduce impact of measurement error
  - Categorizing can actually make things worse

Epidemiologic analyses with error-prone exposures: review of current practice and recommendations.

Shaw et al. *Annals of Epidemiology* 2018; 28: 821-828.

Measurement error is often neglected in medical literature: a systematic review.

Brackenhoff et al. *Journal of Clinical Epidemiology* 2018; 98: 89-97.

Five myths about measurement error in epidemiologic research.

van Smeden, Lash, Groenwold. DOI 10.17605/OSF.IO/MSX8D.

<https://osf.io/msx8d/>

## **STRATOS guidance document on measurement error and misclassification of variables in observational epidemiology**

### **Part 1 – basic theory and simple methods of adjustment**

Ruth H Keogh, Pamela A Shaw, Paul Gustafson, Raymond J Carroll, Veronika Deffner, Kevin W Dodd, Helmut Küchenhoff, Janet A Tooze, Michael P Wallace, Victor Kipnis, Laurence S Freedman

### **Part 2 – more complex methods of adjustment and advanced topics**

Pamela A Shaw, Paul Gustafson, Raymond J Carroll, Veronika Deffner, Kevin W Dodd, Ruth H Keogh, Victor Kipnis, Janet A Tooze, Michael P Wallace, Helmut Küchenhoff, Laurence S Freedman

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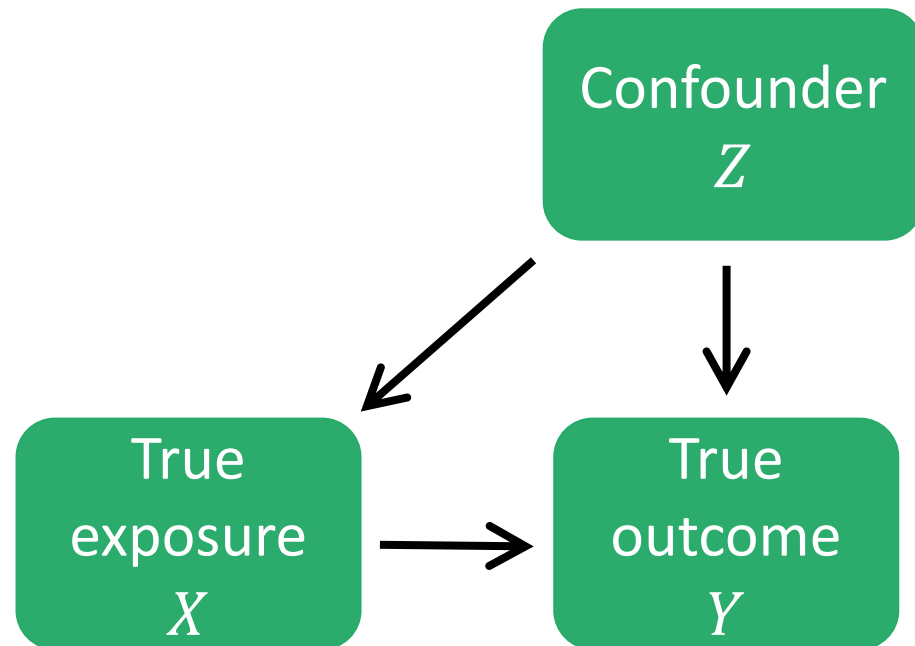


Jonathan Bartlett, University of Bath

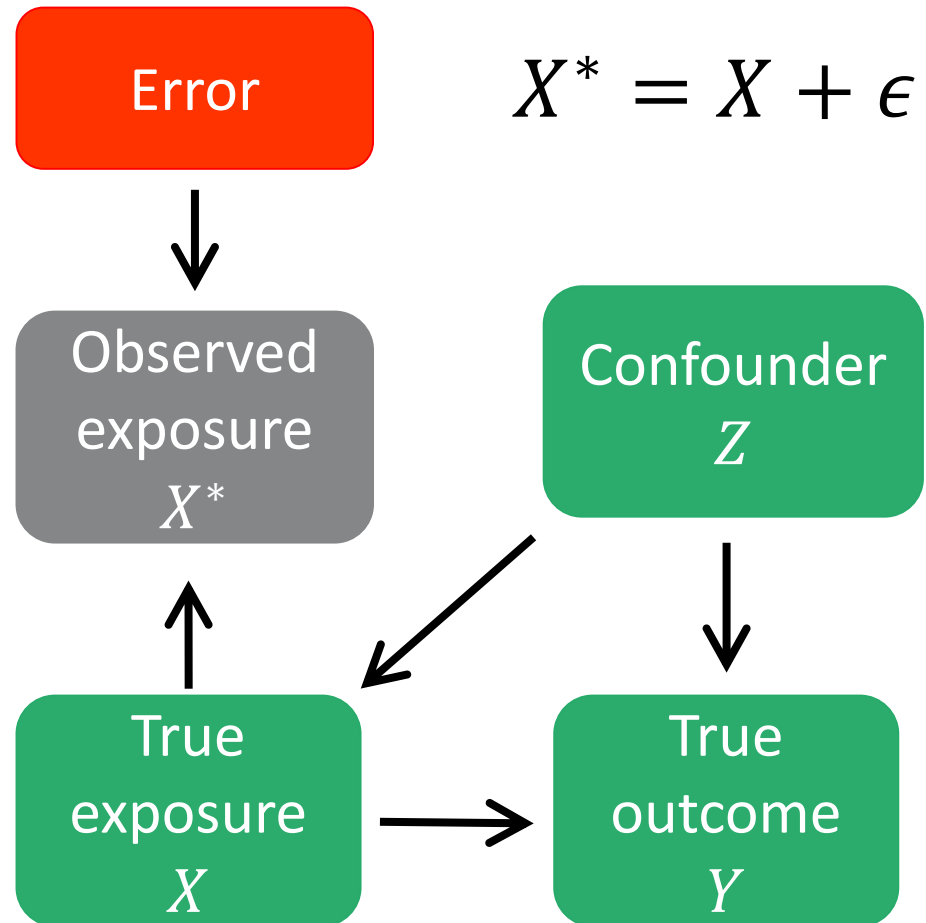
Christen Gray, IQVIA



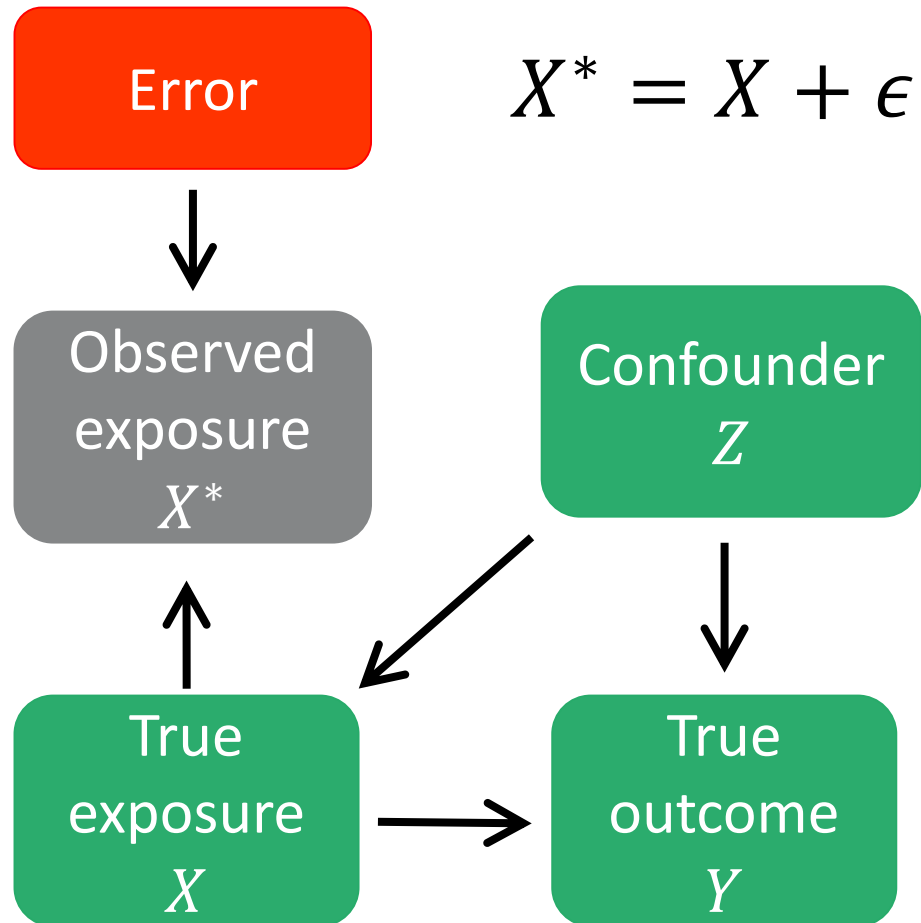
# Notation and set-up



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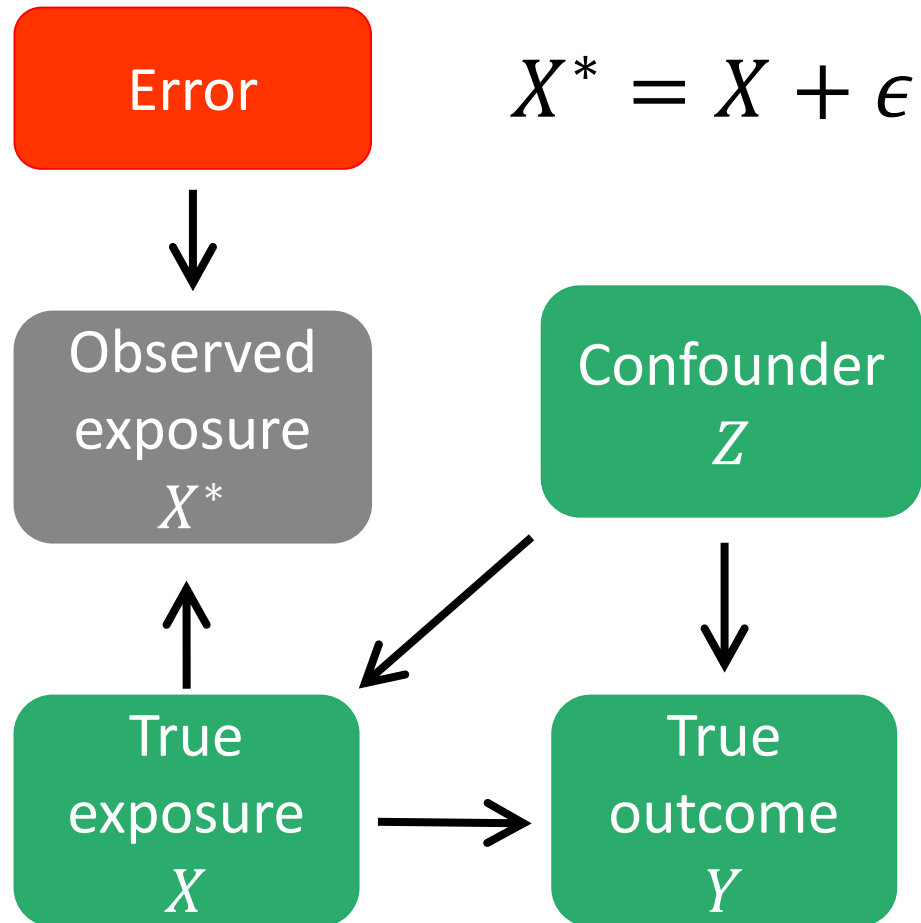


True outcome model: Using  $X$

$$Y = \beta_0 + \beta_X X + \beta_Z Z + e$$



# Notation and set-up



True outcome model: Using  $X$

$$Y = \beta_0 + \beta_X X + \beta_Z Z + e$$

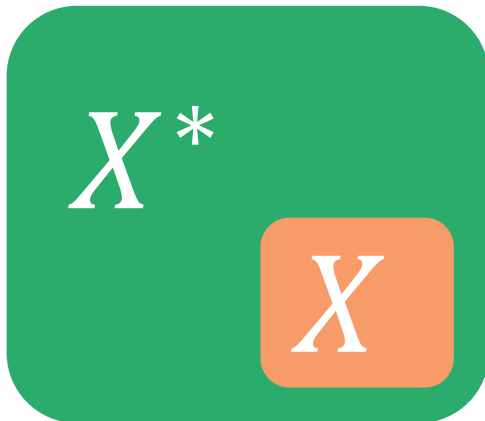
Naive outcome model: Using  $X^*$

$$Y = \beta_0^* + \beta_X^* X^* + \beta_Z^* Z + e$$

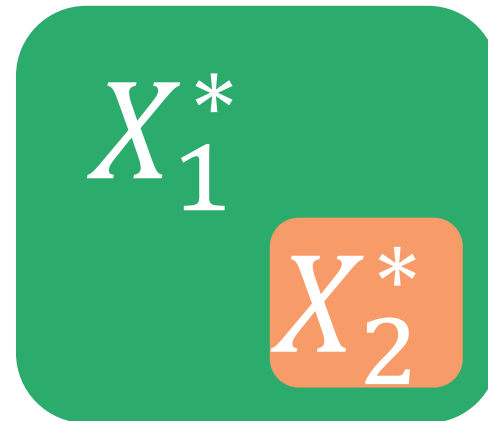
# Ancillary studies

To do something about the impact of measurement error in our analysis, we need to know the form and extent of the error

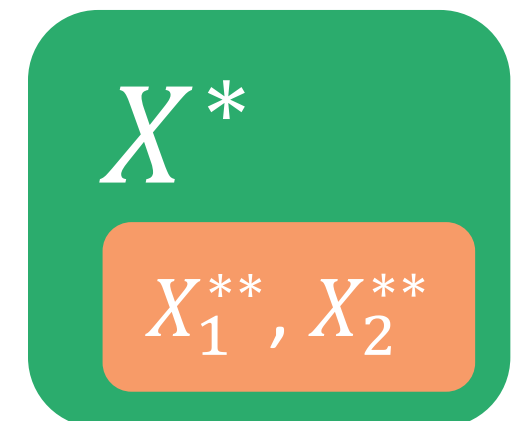
## Validation study



## Replicates study



## Calibration study



# Motivating example: NHANES data

- Association between systolic blood pressure (SBP) and deaths due to cardiovascular disease (CVD)
- Adjusted for sex, age, smoking status, diabetes
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## Challenges

- SBP is error-prone
- Missing data in smoking status

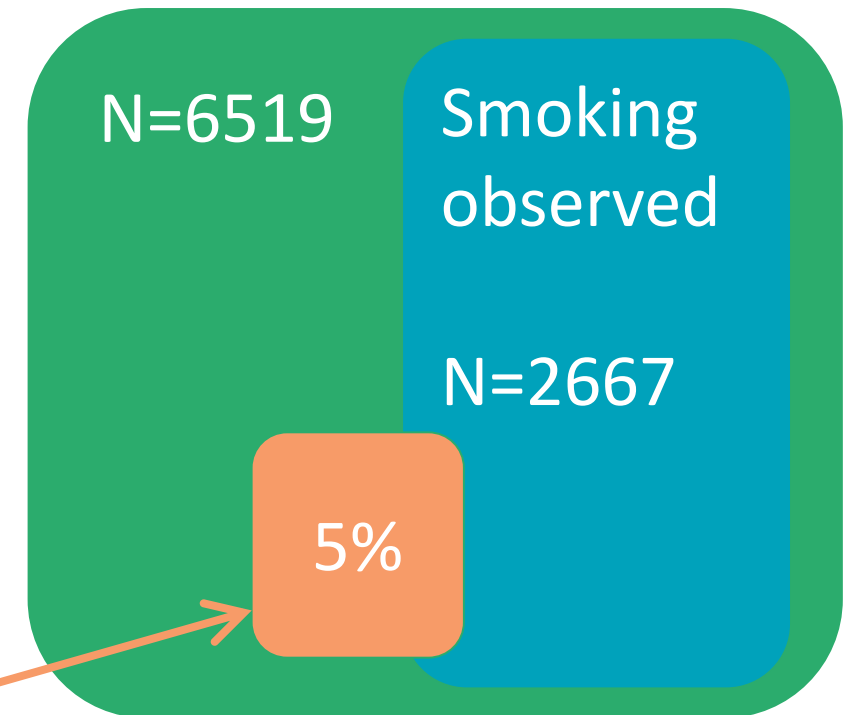
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Replicate SBP measurement



# Regression calibration

Obtain an estimate of  $E(X|X^*, Z)$  using the ancillary study and use in the outcome regression model:

$$Y = \beta_0 + \beta_X E(X|X^*, Z) + \beta_Z Z + e$$

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## Limitations

- Requires non-differential error assumption
- Requires an approximation for non-linear outcome models
- How do we accommodate missing data as well?

# Multiple imputation (MI)

- Very popular method for handling missing data
- Measurement error can be viewed as a missing data problem – the ‘truth’ is missing



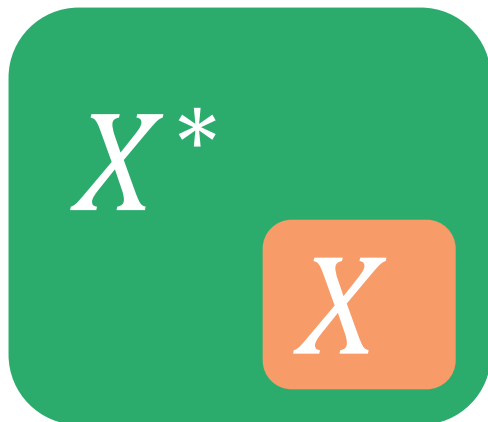
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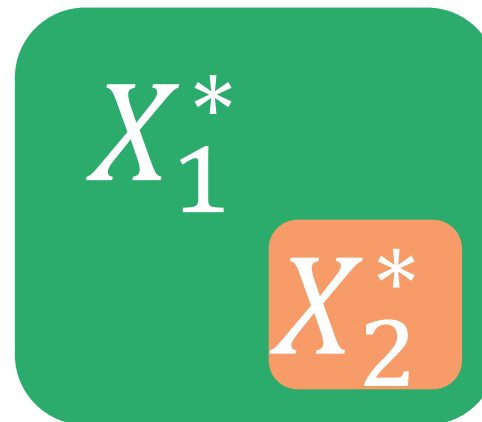
...for some people

...for everyone!

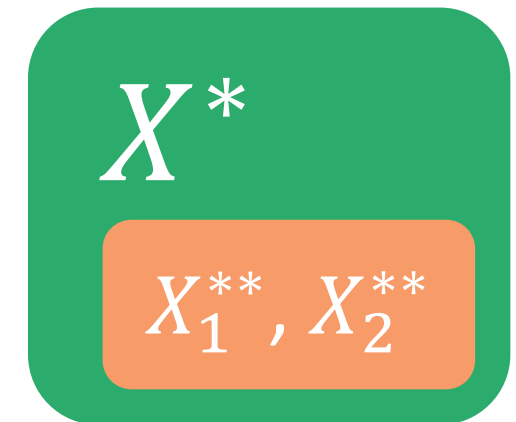
Validation study



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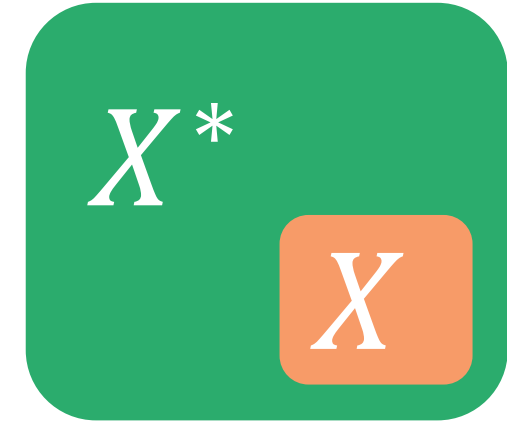


# Multiple imputation (MI)

**Cole SR, Chu H and Greenland S.** Multiple-imputation for measurement-error correction. *Int J Epidemiol* 2006; 35: 1074–1081.

1. For individuals with  $X$  missing, draw a value  $X$  from  $X|X^*, Z, Y$
2. This gives a complete imputed data set
3. Fit the outcome model using the imputed data
4. Repeat for  $M$  imputed data sets
5. Pool the results using Rubin's Rules

Validation study



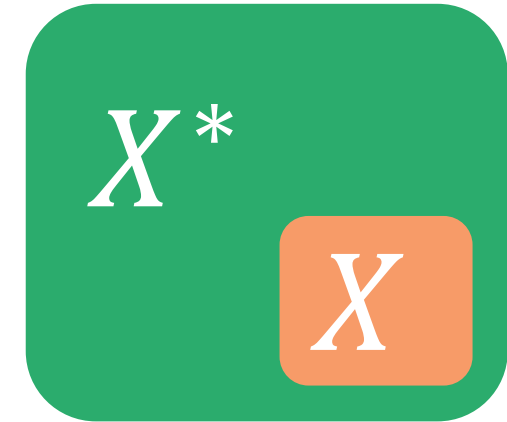
# Multiple imputation (MI)

In the validation situation we benefit from the huge missing data literature on MI.

**Carpenter & Kenward.** Multiple imputation and its application. New York: Wiley. 2013

**Sterne et al.** Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009; 338: b2393

Validation study



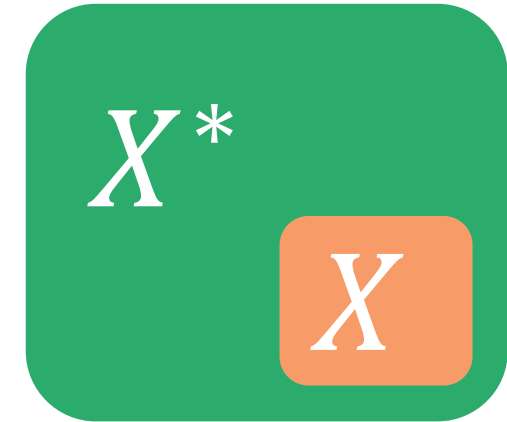
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Validation study



## Software

R: mice, smcfcs

Stata: mi impute, smcfcs

SAS: PROC MI

# Multiple imputation (MI)

**Freedman et al.** A comparison of regression calibration, moment reconstruction and imputation for adjusting for covariate measurement error in regression. *Stat Med* 2008; 27: 5195–5216.

**Keogh & White.** A toolkit for measurement error correction, with a focus on nutritional epidemiology. *Stat Med* 2014; 33: 2137-2155.

## Calibration study

$X^*$

$X_1^{**}, X_2^{**}$

## Replicates study

$X_1^*$

$X_2^*$

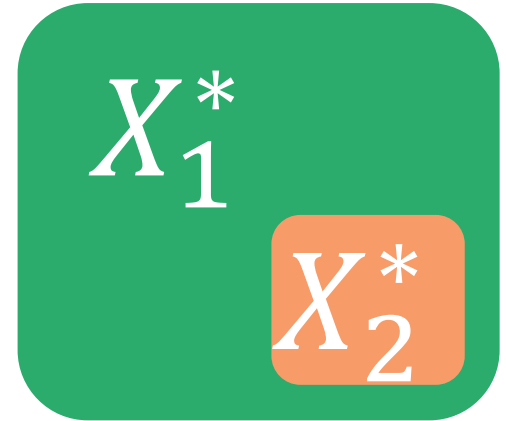
# Multiple imputation (MI)

## The difficult step of MI

1. For individuals with  $X$  missing, draw a value  $X$  from  $X|X_1^*, X_2^*, Z, Y$

- We need to e.g. assume a multivariate normal distribution for  $X, X_1^*, X_2^*|Z$
- This gives form of  $p(X|X_1^*, X_2^*, Z, Y)$

Replicates study



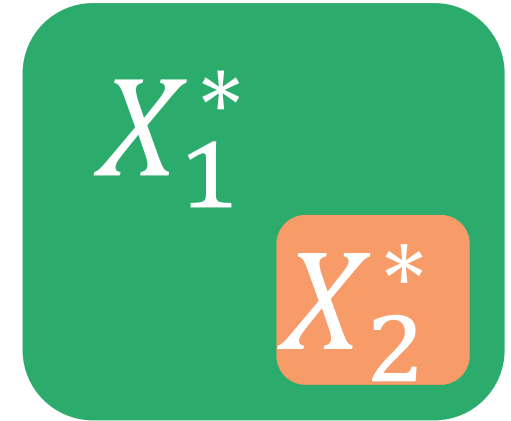
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- We need to assume a distribution for  $X, X_1^*, X_2^*|Z$ , e.g. multivariate normal
- This gives form of  $p(X|X_1^*, X_2^*, Z, Y)$
- This approach is not very flexible
- There is no software and it is not very easy to implement

## Replicates study



# A more flexible MI approach

In general it is difficult to know what is the form of  $X|X_1^*, X_2^*, Z, Y$

- There are non-linear terms in the model

$$Y = \beta_0 + \beta_X X + \beta_Z Z + \beta_{X^2} X^2 + e$$

- The outcome model is not a linear regression

$$h(t|X, Z) = h_0(t) e^{\beta_0 + \beta_X X + \beta_Z Z}$$



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**Meng.** Multiple-imputation inferences with uncongenial sources of input. *Statistical Science* 1994; 9: 538-558.

**Bartlett et al.** Multiple imputation of covariates by fully conditional specification: Accommodating the substantive model. *Stat Meth Med Res* 2015; 24: 462-487.

# A more flexible MI approach

Instead of trying to specify  $X|X_1^*, X_2^*, Z, Y,$

...we specify

$Y|X, Z$  and  $X|Z$  and

the measurement error model

## Basic idea

1. Propose a potential imputed value for  $X$  from  $X|X_1^*, X_2^*, Z$
2. Use a rejection sampling procedure to accept or reject the value as being from the target distribution  $X|X_1^*, X_2^*, Z, Y$
3. The acceptance/rejection rule is a function of the outcome model

**Substantive model compatible full conditional specification  
(SMCFCS)**

# A more flexible MI approach

## Application for measurement error correction

- Validation study: we can use it directly
- Replicates: we extended the method to the setting of replicates

**Keogh & Bartlett.** Measurement error as a missing data problem. Handbook of Measurement Error and Variable Selection. 2019. Forthcoming.

**Bartlett & Keogh.** smcfcs: Multiple imputation of covariates by substantive model compatible fully conditional specification. 2019.

[https://github.com/ruthkeogh/meas\\_error\\_handbook](https://github.com/ruthkeogh/meas_error_handbook)

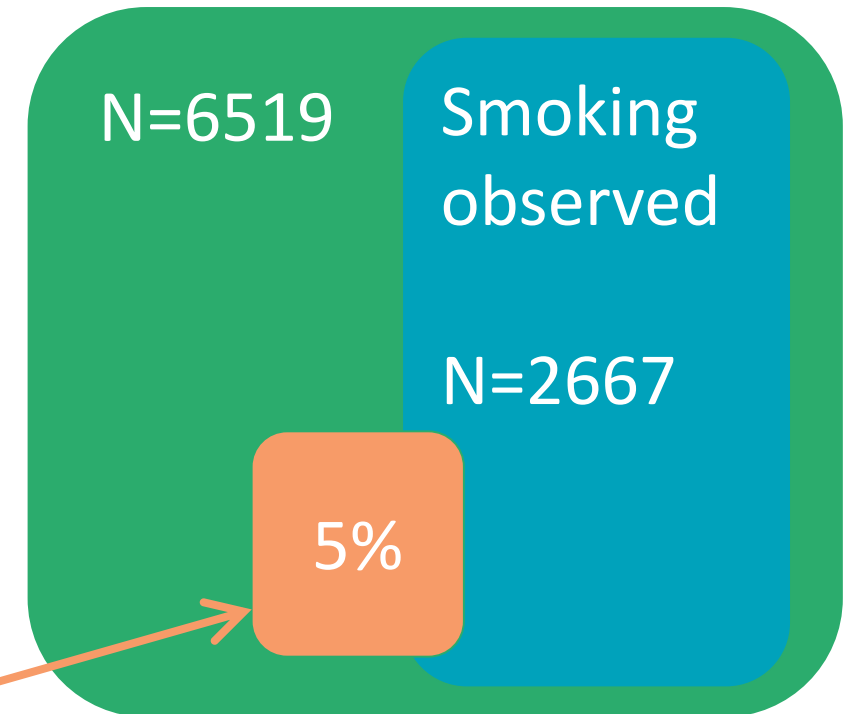
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- Adjusted for sex, age, smoking status, diabetes
- Analysis method: Cox regression

## Challenges

- SBP is error-prone
- Missing data in smoking status

Replicate SBP measurement



# Motivating example: NHANES data

## First ignoring missing data.....

| Covariate | Naïve analysis       | Regression calibration | Multiple imputation  |
|-----------|----------------------|------------------------|----------------------|
| SBP       | 0.085 (0.014, 0.157) | 0.114 (0.011, 0.222)   | 0.120 (0.020, 0.219) |
| Male      | 0.49 (0.30, 0.67)    | 0.49 (0.32, 0.68)      | 0.49 (0.30, 0.67)    |
| Age       | 0.88 (0.77, 0.99)    | 0.87 (0.76, 0.99)      | 0.88 (0.77, 0.99)    |
| Smoker    | 0.26 (0.07, 0.46)    | 0.26 (0.07, 0.45)      | 0.26 (0.07, 0.46)    |
| Diabetes  | 0.50 (0.29, 0.72)    | 0.50 (0.28, 0.72)      | 0.50 (0.29, 0.72)    |

# Motivating example: NHANES data

## Accounting for missing data as well...

| Covariate | Naïve analysis       | Regression calibration | Multiple imputation  | Multiple imputation 2 |
|-----------|----------------------|------------------------|----------------------|-----------------------|
| SBP       | 0.085 (0.014, 0.157) | 0.114 (0.011, 0.222)   | 0.120 (0.020, 0.219) | 0.104 (0.035, 0.173)  |
| Male      | 0.49 (0.30, 0.67)    | 0.49 (0.32, 0.68)      | 0.49 (0.30, 0.67)    | 0.46 (0.35, 0.56)     |
| Age       | 0.88 (0.77, 0.99)    | 0.87 (0.76, 0.99)      | 0.88 (0.77, 0.99)    | 1.04 (0.97, 1.11)     |
| Smoker    | 0.26 (0.07, 0.46)    | 0.26 (0.07, 0.45)      | 0.26 (0.07, 0.46)    | 0.26 (0.09, 0.43)     |
| Diabetes  | 0.50 (0.29, 0.72)    | 0.50 (0.28, 0.72)      | 0.50 (0.29, 0.72)    | 0.69 (0.56, 0.83)     |



N=2667

N=6519

# Summary

- We commonly face more than one ‘data quality’ challenge at the same time
- Multiple imputation (and fully Bayesian approaches) enable us to ‘easily’ tackle measurement error and missing data together
- The smcfcs package in R facilitates this

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**Bartlett & Keogh.** Bayesian correction for covariate measurement error: A frequentist evaluation and comparison with regression calibration. *Stat Meth Med Res* 2016; 27: 1695-1708.



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