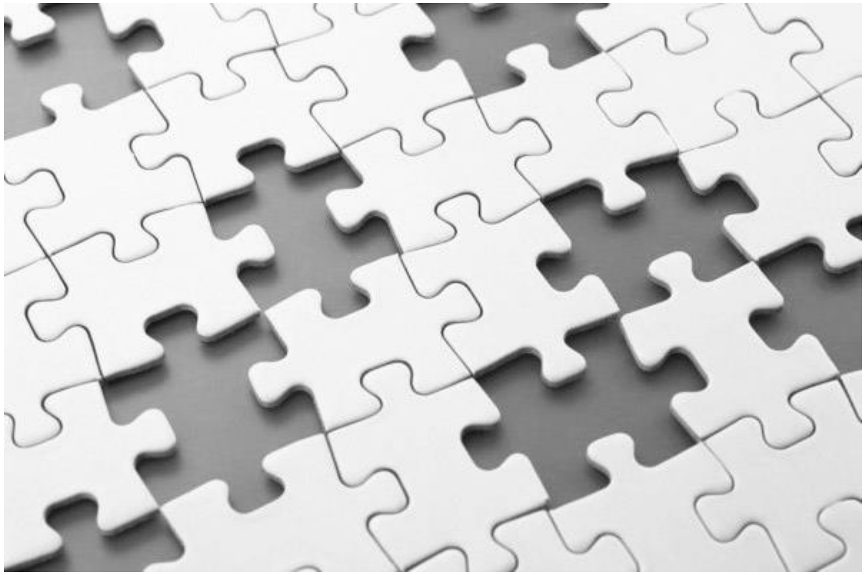
Missing data and multiple imputation



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Primary Care & Population Health

Today

- Missing data
- Different methods to deal with missing data
- Multiple imputation (MI) of missing data

What do we mean by missing data?

- Missing values are observations/records which were:
  - Never collected
  - Lost by accident
  - Wrongly collected and so deleted

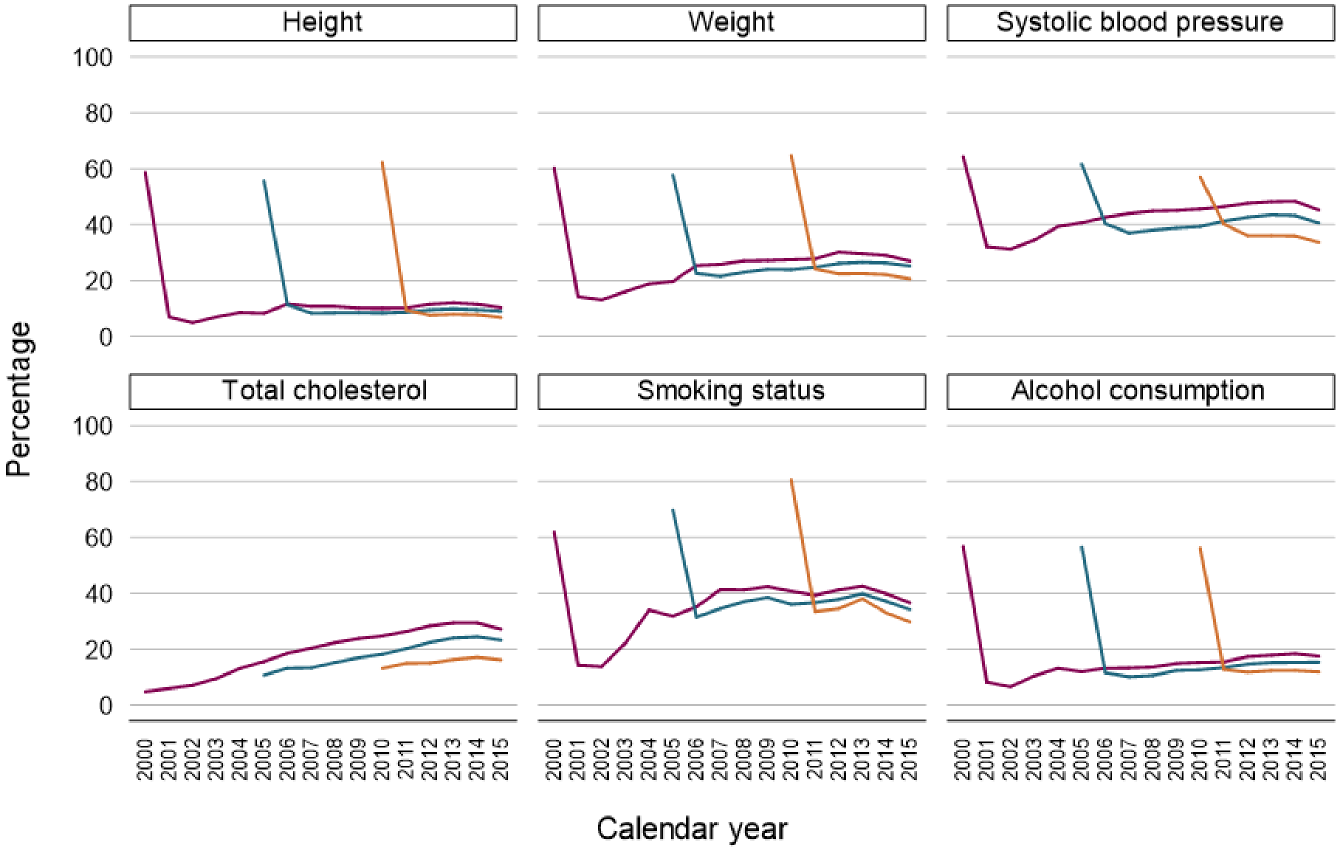
- Missing data can be in outcomes, explanatory variables or covariates

Missing data in electronic health records

Health indicators

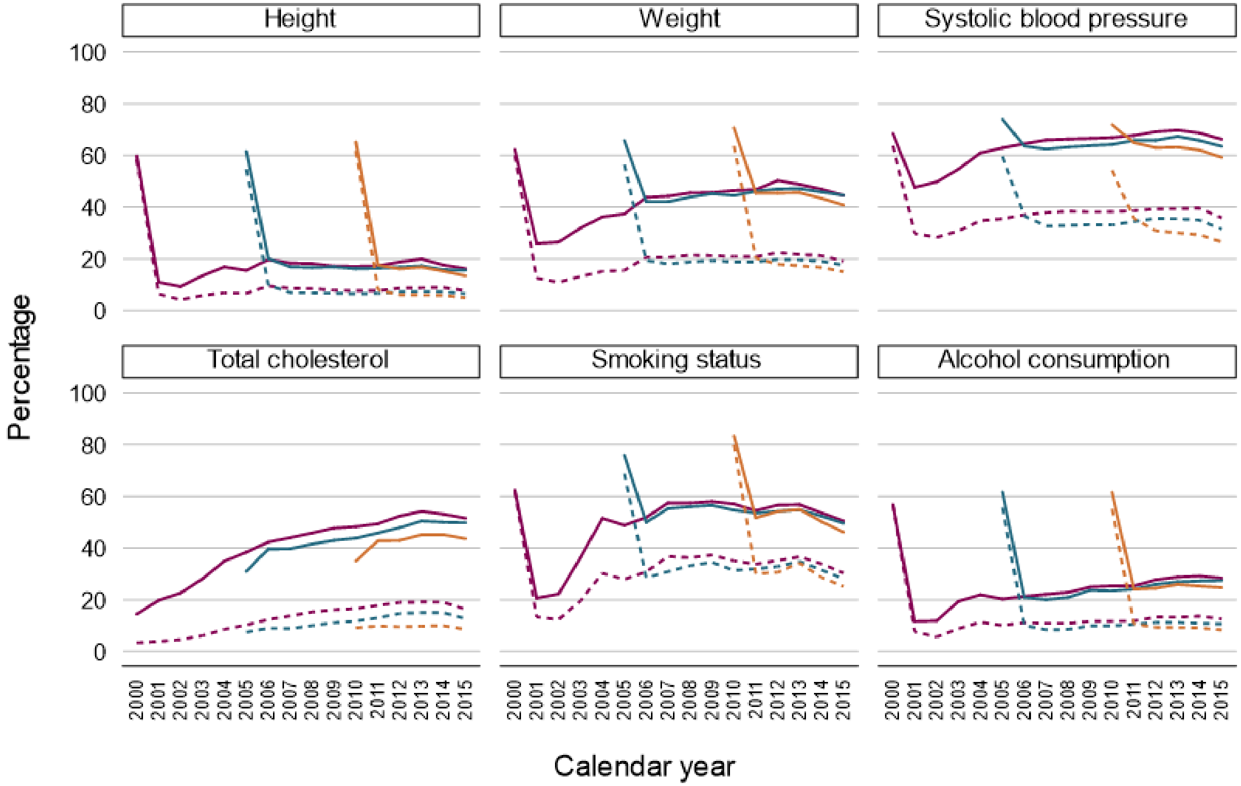
- Blood pressure
- Weight
- Height
- Smoking
- Alcohol
- Cholesterol

Recording of health indicators – 3 cohorts



Petersen et al.(2019) **Health indicator recording in UK primary care electronic health records: key implications for handling missing data.**

People with diabetes are more likely to have health indicators recorded



Solid line - diabetes; dashed line - no diabetes

Data can be missing in different ways….

The scale is broken

- Missing Completely at Random (MCAR): Missingness of Y is independent of Y and X.

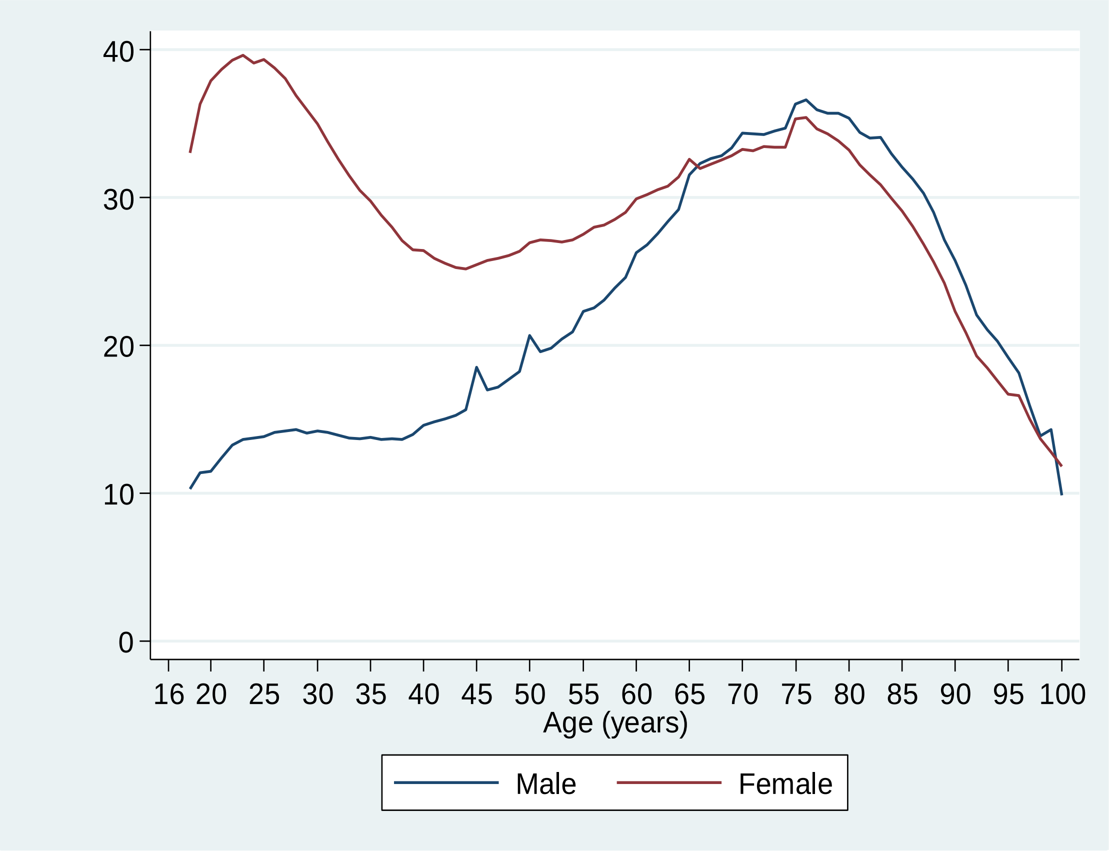
More younger women have weight measured than younger men

- Missing at Random (MAR): Missingness of Y is independent of Y *given* X.

Only those with **high** weight have weight recorded

- Missing Not at Random (MNAR): Missingness of Y is depending on Y, even after conditioning on X.

Recording of weight by age and gender



What kind of missingness??

How do I know if data are MAR, MCAR or MNAR?

- We can exclude that data are missing completely at random (MCAR)
- Important to understand dataset
- Tricky to demonstrate whether data are MAR or MNAR
  – Compare mean or % to external data sources
  – E.g. Health Survey for England

Ad hoc methods

- *Ad hoc* = a method that is proposed for convenience
- Sometimes *ad hoc* methods are fine, but not always

Different types of ad-hoc methods

- Exclude variables with incomplete records
- Complete case analysis
- Create missing data category
- Mean imputation
- Regression imputation

Exclude variable with incomplete records

- Sometimes we have no other options
  - High proportion of missing data
- Analysis may be biased
  - If variable is a strong confounder

Complete case analysis

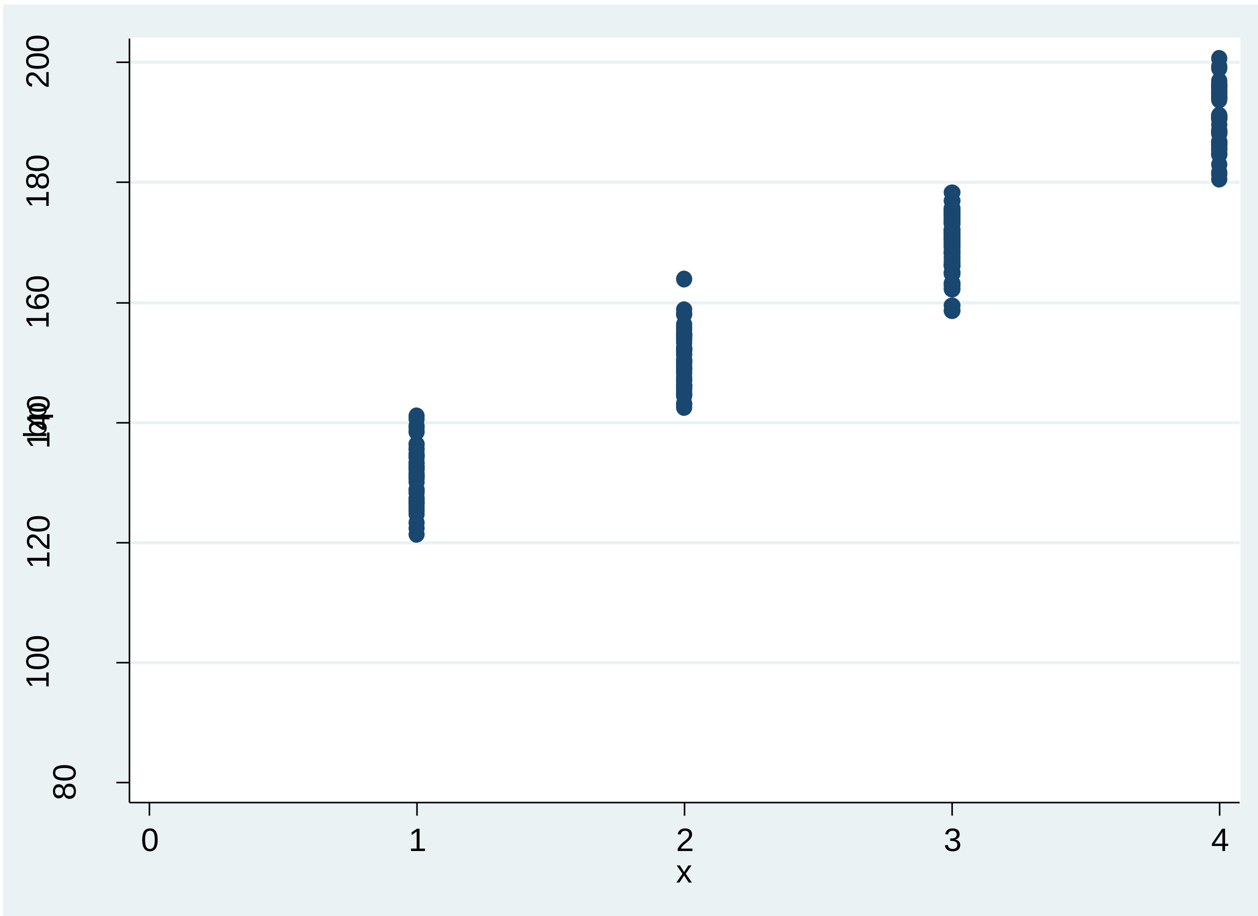
- Reduce sample size = reduce precision of results ☹
- Make assumption
  - Complete cases represent full dataset

- May be OK if some situations
  - Data missing completely at random
  - Small proportion of missing data
  - If missingness is not associated with outcome

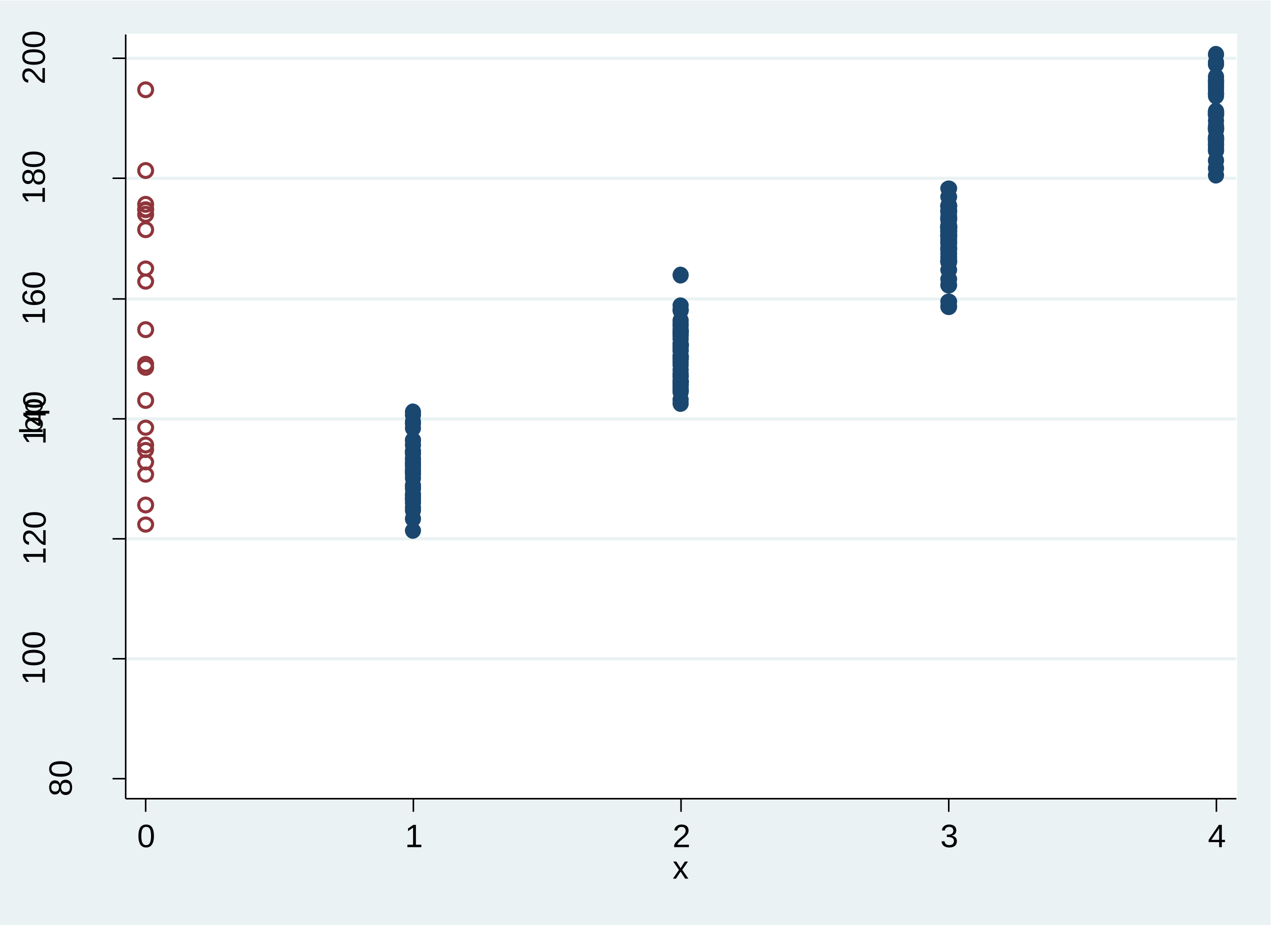
- **Create missing data category**

  - Mixed bag – results not meaningful ☹
  - Severe bias can arise, in any direction
  - Variable will not correctly adjust for confounding

Missing data category



Missing data category



Some real data…

- Cardiovascular risk in people with severe mental illnesses
- Sample of 42,213 people
- Risk factors:
  - Age
  - Sex
  - Smoking
  - Diabetes
  - Blood pressure
- All variables have missing data

Risk of cardiovascular diseases in 42,213 people - Complete case analysis

	Complete case	
	N=3,736	
	Hazard ratio (95% CI)	P
Age, years (per unit increase)	1.05 (1.04 to 1.06)	<0.001
Sex: Females v males	1.19 (0.86 to 1.66)	0.3
SBP, mmHg (per unit increase)	1.94 (1.33 to 2.82)	0.001
Diabetes: Yes v no	1.19 (0.82 to 1.71)	0.4
Smoking: Never	1	
Ex	1.77 (1.23 to 2.53)	0.002
Current	1.56 (1.07 to 2.28)	0.02

SBP: systolic blood pressure

Mean imputation

- Impute average values for missing data

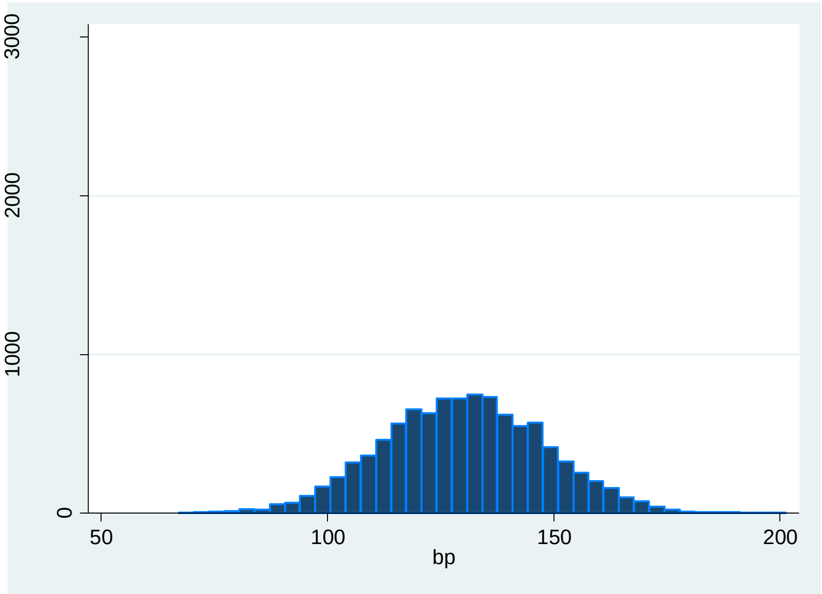
- For example replace all missing systolic blood pressure values with 140 mmHg

Issues with mean imputation

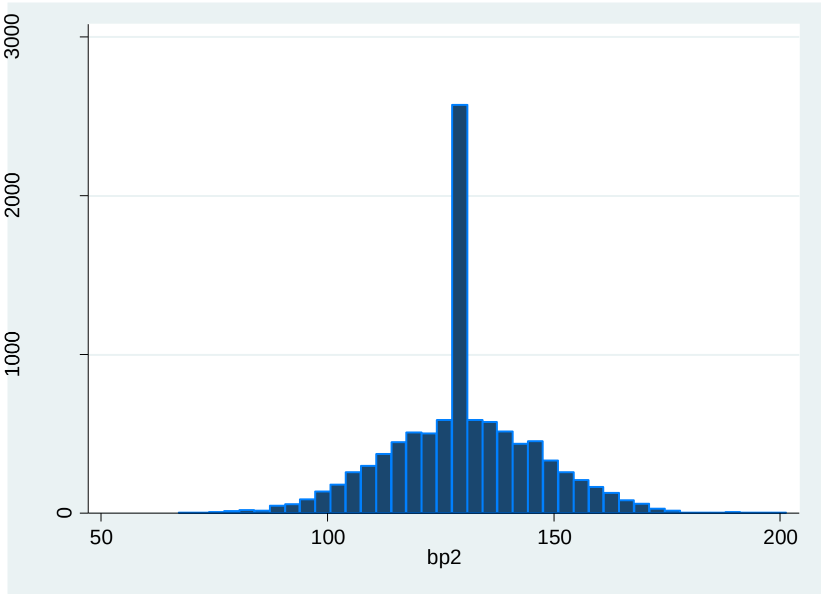
Systolic Blood pressure 10 000 observation

20 % missing = 130 mmHg

Mean = 130 Variance = 319



Mean = 130 Variance = 256



Regression Imputation

- Fit a regression model
- Use all information available in existing data
- Provides a 'best guess'

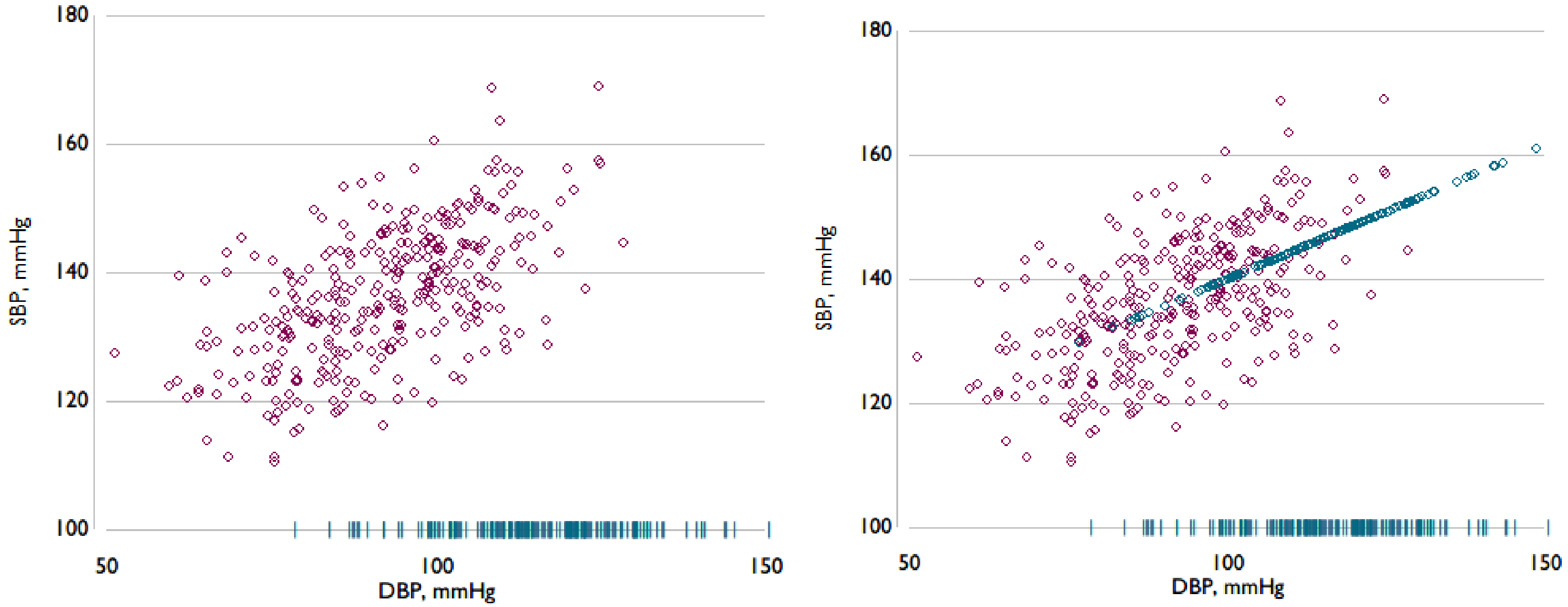
Health indicators

- Blood pressure
- Cholesterol
- Weight
- Height
- Smoking
- Alcohol

Predictors

- Age
- Gender
- Social deprivation
- Ethnicity
- Diseases/illness
- Medication

Regression imputation



What is the problem?

Regression imputation

- Just ONE estimate - do not account for uncertainty of the missing data ☹
- Creates datasets with too small variation ☹
  - (too narrow confidence intervals)
- Bias results

Multiple imputation

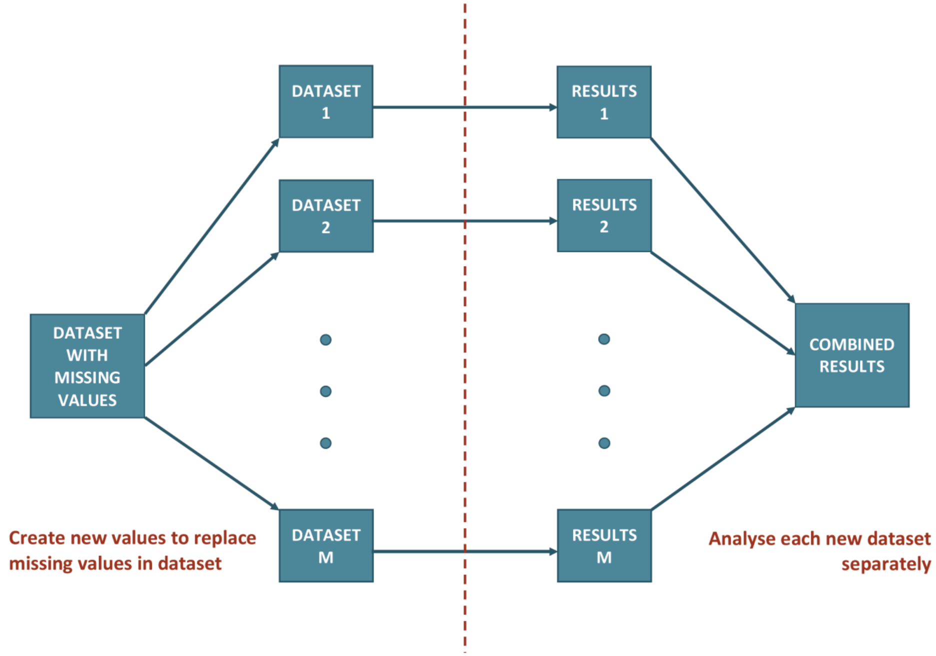
- Builds on regression modelling
- Replace missing values with ‘plausible’ values
  - Based on distribution of observed values
  - Include randomness to reflect uncertainty

Multiple imputation (MI) involves three steps

- **Step 1:** Create *multiple* imputed datasets
  - We will never know the *true* values of the missing data
  - Set of values – not just a single value
- **Step 2:** Analyse each dataset separately
- **Step 3**: Combine results of *m* analyses using ‘Rubin’s rule’

Multiple imputation (MI) of missing data

- Builds on regression imputation – three stages



- Implemented in SAS, Stata, R

Rubin’s rule

- Combine results from individual analysis
  - Overall point estimate is just the average

- Variance estimate
  - Within imputation variance
  - Between imputation variance

- For details see White IR, Royston P, Wood AM (2011).

An example of multiple imputation of a single variable

	Original data	
ID	Y	X
1	1.1	3.4
2	1.5	3.9
3	2.3	2.6
4	3.6	1.9
5	0.8	2.2
6	3.6	3.3
7	3.8	1.7
8	**?**	0.8
9	**?**	2.0
10	**?**	3.2

Multiply imputed data

	Original data Imp 1		Imp 2	Imp 3	Imp 4	
ID	Y	X	Y X	Y X	Y X	Y X
1	1.1	3.4	1.1 3.4	1.1 3.4	1.1 3.4	1.1 3.4
2	1.5	3.9	1.5 3.9	1.5 3.9	1.5 3.9	1.5 3.9
3	2.3	2.6	2.3 2.6	2.3 2.6	2.3 2.6	2.3 2.6
4	3.6	1.9	3.6 1.9	3.6 1.9	3.6 1.9	3.6 1.9
5	0.8	2.2	0.8 2.2	0.8 2.2	0.8 2.2	0.8 2.2
6	3.6	3.3	3.6 3.3	3.6 3.3	3.6 3.3	3.6 3.3
7	3.8	1.7	3.8 1.7	3.8 1.7	3.8 1.7	3.8 1.7
8	**?**	0.8	**0.2** 0.8	**0.8** 0.8	**0.3** 0.8	**1.3** 0.8
9	**?**	2.0	**1.7** 2.0	**2.4** 2.0	**1.8** 2.0	**3.5** 2.0
10	**?**	3.2	**2.7** 3.2	**2.5** 3.2	**1.0** 3.2	**1.7** 3.2

So far

- Missing data mechanisms
- Different ad-hoc methods to deal with missing data
- Multiple Imputation of a single variable
- Now we will touch on multiple imputation of multiple variables

FCS Multiple Imputation

- 5 variables with missing data Y1, Y2, Y3, Y4, Y5
- Breaks the problem down into individual regression models

  f(Y1|Y1(obs), Y2, Y3, Y4, Y5, x1, x2)

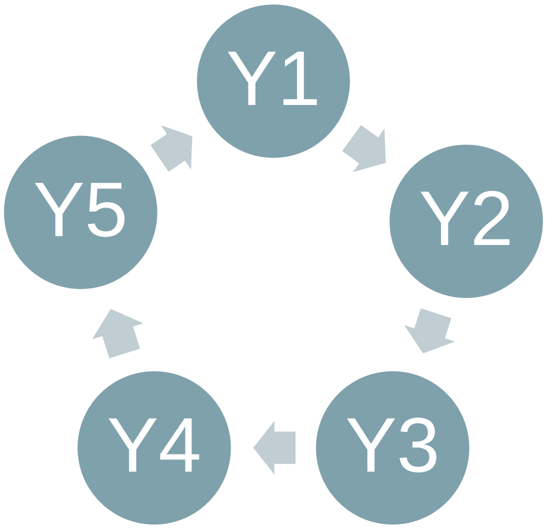
  f(Y2|Y1, Y2(obs),Y3, Y4, Y5, x1, x2)

  f(Y3|Y1, Y2, Y3(obs), Y4, Y5, x1, x2)

  …..
- Each is a model for a single variable
- Logistic, linear model…

FCS Multiple Imputation

- Combine thousands of regression models



FCS Multiple Imputation

We need to think….

A few things to consider before doing MI

- Why are the data missing?
- What variables may explain missing data?
  - Age, gender, deprivation, diseases, drug treatment

- Clear idea of your analysis model (the analyses that you will perform *after* MI)
  - Outcome
  - Any interactions, non-linear relationships

Example from the real world - QRisk

BMJ

RESEARCH

Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study

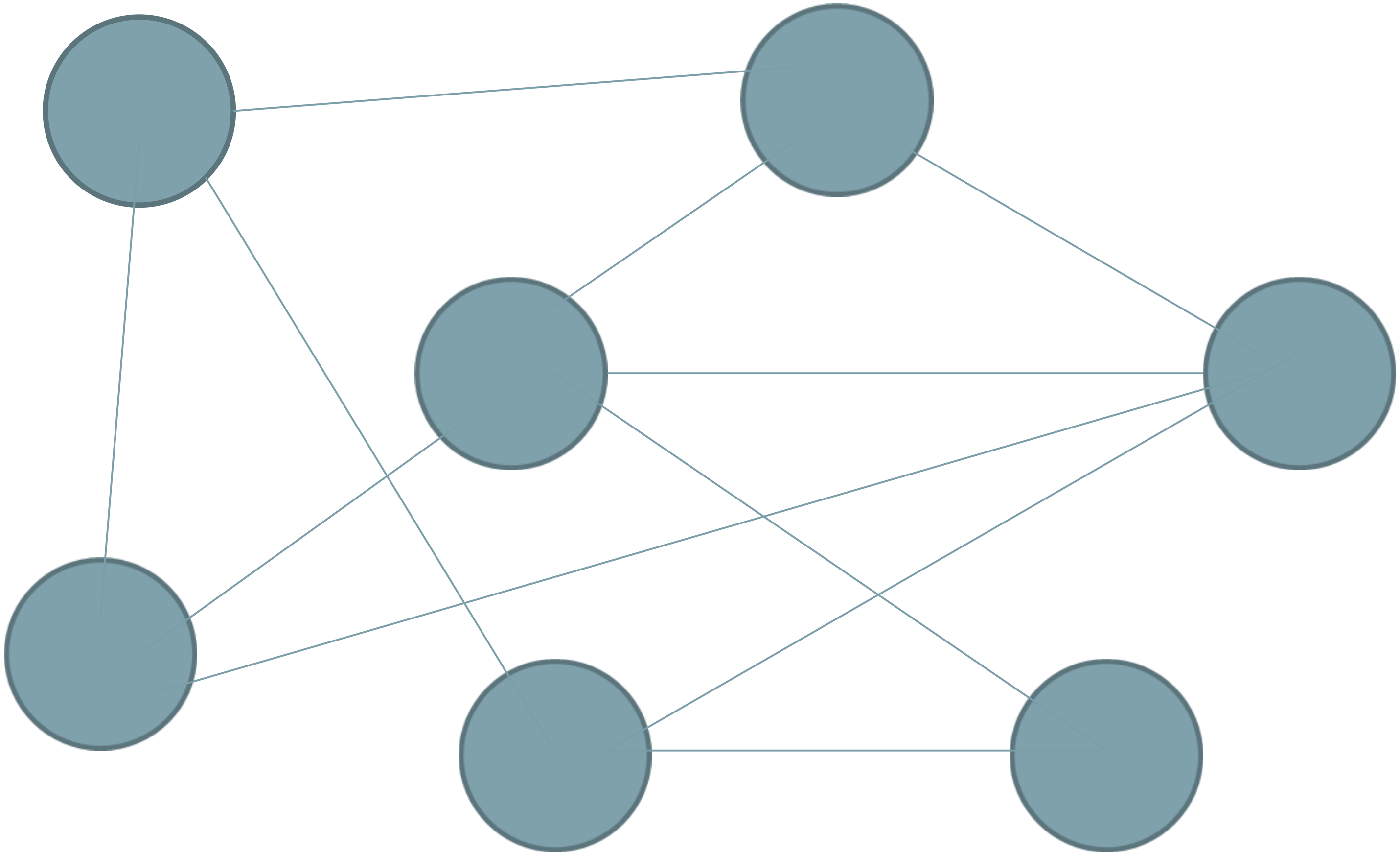
Julia Hippisley-Cox, professor of clinical epidemiology and general practice,[1] Carol Coupland, senior lecturer in medical statistics,[1] Yana Vinogradova, research fellow in medical statistics,[1] John Robson, senior lecturer in general practice,[2] Margaret May, research fellow in medical statistics,[3] Peter Brindle research and development strategy lead[4]

First Qrisk model

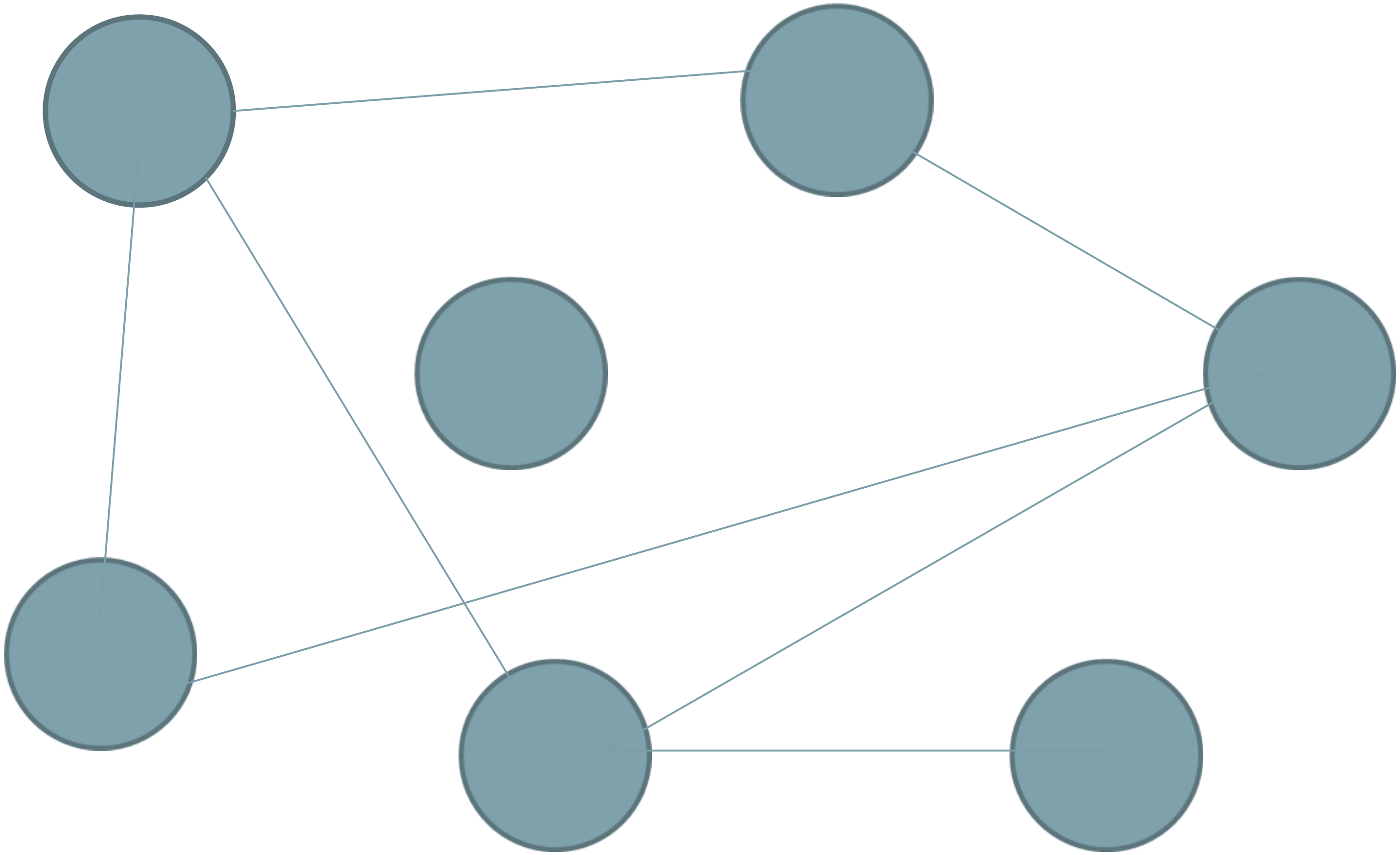
- Cox model for prediction of cardiovascular events in 1.3m UK patients aged 35–74 from GP data
- Found no association between Total/HDL cholesterol and CVD outcome (1.001 (95% CI 0.999 to 1.002))

- Outcome was **not** properly included in the imputation model.
  - Included time to event, but not the variable indicating an event
- MI of ratios can be tricky (see Morris et al)

Clear idea of your analysis model



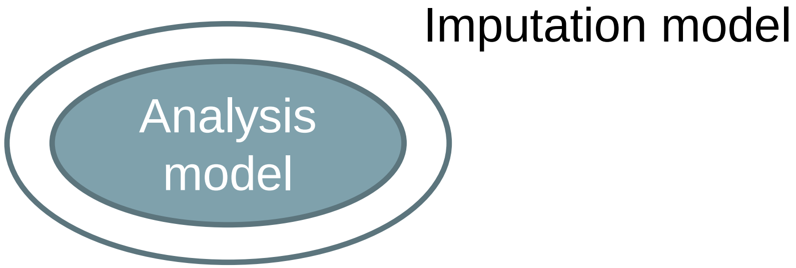
Clear idea of your analysis model



How to select the variables for MI

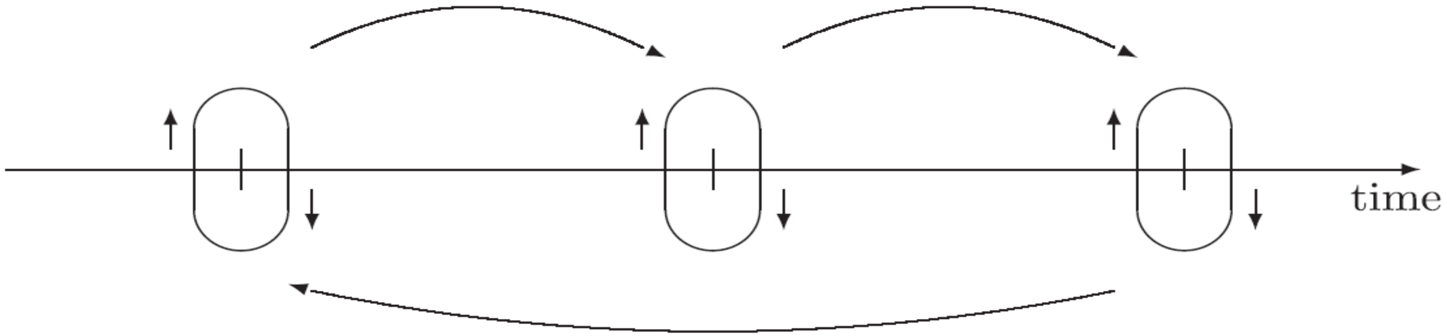
- <u>All</u> variables that will go into analysis model

- Add <u>extra</u> variables (not in analysis model)
  - Auxiliary variables
  - Increase the likelihood that data are MAR
  - Improve precision and decrease potential bias



Longitudinal multiple imputation – Twofold FCS algorithm

- Impute data at a given time block
- Use information available +/- one time block
- Move on to next time block
- Repeat procedure x times



Nevalainen J, Kenward MG, Virtanen SM. Stat Med 2009; 28(29):3657-3669.

Two-fold FCS algorithm implemented in Stata

The Stata Journal (2014)
14, Number 2, pp. 418–431

Application of multiple imputation using the two-fold fully conditional specification algorithm in longitudinal clinical data

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Abstract. Electronic health records of longitudinal clinical data are a valuable resource for health care research. One obstacle of using databases of health records in epidemiological analyses is that general practitioners mainly record data if they are clinically relevant. We can use existing methods to handle missing data,

UCL

Research Article

Statistics in Medicine

Received 5 May 2013, Accepted 3 April 2014 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6184

Evaluation of two-fold fully conditional specification multiple imputation for longitudinal electronic health record data

Catherine A. Welch,[a] Irene Petersen,[a*†] Jonathan W. Bartlett,[b] Ian R. White,[c] Louise Marston,[a] Richard W. Morris,[a] Irwin Nazareth,[a] Kate Walters[a] and James Carpenter[b,d]

Before we finish we will go back to our example

Risk of cardiovascular diseases in 42,213 people with mental illnesses

	Complete case	After MI
	N=3,736	N= 42,313
	Hazard ratio (95% CI)	
Age, years (per unit increase)	1.05 (1.04 to 1.06)	1.06 (1.06 to 1.06)
Sex: Females v males	1.19 (0.86 to 1.66)	0.74 (0.68 to 0.81)
SBP, mmHg (per unit increase)	1.94 (1.33 to 2.82)	1.87 (1.67 to 2.09)
Diabetes: Yes v no	1.19 (0.82 to 1.71)	1.60 (1.38 to 1.86)
Smoking: Never	1	1
Ex	1.77 (1.23 to 2.53)	1.36 (1.24 to 1.50)
Current	1.56 (1.07 to 2.28)	1.55 (1.40 to 1.71)

Literature

- Petersen et al. **Health indicator recording in UK primary care electronic health records: key implications for handling missing data.** *Clinical Epidemiology 2019*
- Pedersen et al. **Missing data and multiple imputation in clinical epidemiological research.** *Clinical Epidemiology 2017*
- White, I. Royston, P. Wood, A. **Multiple imputation using chained equations: Issues and guidance for practice**. *Statistics in Medicine* 2010
- Sterne *et al.* **Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls** *BMJ* 2009; 338:b2393
- Marston, L. *et al.* **Issues in multiple imputation of missing data for large general practice clinical databases**. *Pharmacoepidemiol Drug Saf.* 2010 Jun;19(6):618-26
- Morris TP, White IR, Royston P, Seaman SR, Wood AM. **Multiple imputation for an incomplete covariate that is a ratio**. Stat Med. 2014 Jan 15;33(1):88–104.

Books

- Van Buuren **Flexible Imputation of Missing Data** 2012
- Carpenter and Kenward **Multiple Imputation and its Application** 2013