# Guidelines for multiple imputations in repeated measurements with time-dependent covariates: a case study

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Missing data are one of the central problem that one encounter during the analysis of longitudinal data. If we fill in missing values with wrong data, we are adding bias.

# Imputations

- What is imputations?

**The process of replacing missing data with substituted values.**

- What is multiple imputations?

**Replace missing value with more than one imputed value, randomly drawn from a distribution of possible value.**

# Time- Dependent covariates

- Time – dependent covariates or time – varying covariates.
- What is time – varying covariates?
  - Variables whose values can change across time
- Example of time – varying covariates
  - C-reactive protein (CRP) and smoking status

# Classification Of Missing Data

MISSING DATA

- Missing completely at random (MCAR)
- Missing at random (MAR)
- Missing not at random (MNAR)

# MCAR

The missing data mechanism depends neither on observed nor on unobserved values.

# MAR

The missing data mechanism depends only on the observed values (and not on the unobserved values).

# MNAR

The missing data mechanism depends on the unobserved values (and perhaps also on observed values).

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ORIGINAL ARTICLE

# Guidelines for multiple imputations in repeated measurements with time-dependent covariates: a case study

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# Introduction

# Introduction

- Analysing longitudinal data over cross – sectional data is the possibility to describe individual profiles overtime.
- Characteristics of subject may vary over time.
- Problem ➔ missing data during longitudinal data analysis.

# Introduction

- This article provide : Research for practical guidelines to handle the most common missing repeated measurements data problems in observational studies.
- Key :
  - How to analyse longitudinal data if there are missing observation in the outcome only and / or if missing observation are extended to independent variables too.
  - Practicalities in producing imputations when there are many time – varying variables and repeated measurements.
  - Some common statistical package SPSS, SAS and R that are ready to use.

# Introduction

How to handle missing data in longitudinal study ?

Simulations study

Maastricht study on long-term dementia care environments (MLTD)

# Case Study

# Case Study

- Maastricht study on long-term dementia care environments (MLTD).
- This study investigated the effect of innovative dementia care environments (i.e. small scale, homelike) compared with traditional nursing homes (i.e. large scale) on residents' daily lives.
- Case study : **To compare the mood**

| The elderly living traditional large – scale wards (LSW) | VS | The elderly living innovative small – scale wards |
|---|---|---|

- N on this study is115

# Case Study

- Randomized observation schedule. Every participants observed for 1 minutes during 20 minutes period within 4.5 hours observation.
- Get break half hour in the each block.
- Each participants was observed on 7 days:
  - Two weekday mornings (07.00 – 11.00)
  - Two weekday afternoons (11.30 – 16.00)
  - Two weekday evenings (16.00 – 20.30)
  - One Saturday afternoon (16.00 – 20.30)
- Total = 12 (observation minutes per block in a day) x 7 (observations days) = 84 moment per participants.

# Case Study

- Mood and engagement in activity (activity) assessed by the Maastricht Electronic Daily Life Observation tool.
- 7 range of mood:
  - 1 = great sign of negative mood
  - 7 = very high positive mood
- The variable of activity measures :
  - Household activity
  - Musical activity

# Case Study

- What is missing in this data set?
  - **Outcome mood**
  - **Activity : 5 – 25 %**
  - **Observation across time (one dayparts) : 1 – 18%**

# Method

# Method

- Naïve Method :
  - Complete case analysis (CCA)
    - All missing values are deleted.
  - Available case analysis (AC)
    - Calculate observed values of the relevant variables(s).
  - Mean substitution (MS)
    - Missing value replace by arithmetic mean of that variables.

# Method

- Naïve method :
  - Missing indicator method (MIM)
    - Fill missing observation with fixed number and then add a dummy variable to the analysis model to indicate whether value of that variable was missing.
  - Last observation carried forward (LOCF)
    - Use the last observation to fill the next missing value.

# Method

- Multiple Imputations:
  - This method will replace missing value with more than one imputed value, randomly drawn from a distribution of possible value that determined using information from data.
  - Condition under MAR and MCAR.
  - Fully condition Specification (FCS) or chain equations is one popular method.
  - FCS will imputes missing data on a variable – by – variable.

# Statistical Analysis

Simulation Study

# Statistical Analysis

- Longitudinal design with three times point:
  - Correlated binary variables $X_1$, $X_2$, and $X_3$ were generated with equal marginal probabilities (i.e. $P(X_1 = 1) = P(X_2 = 1) = P(X_3 = 1) = 0.5$)
  - Also have equal correlation (i.e. $cor(X_1,X_2) = cor(X_1,X_3) = cor(X_2,X_3) = 0.5$)
  - Binary variables $X_1$, $X_2$ and $X_3$ generated using R package ‘bindata’.
  - Y generate using random intercept model.

$$Y_{it} = \beta_{0i} + \beta_1 X_{it} + \varepsilon_{it}$$

# Statistical Analysis

$$Y_{it} = \beta_{0i} + \beta_1 X_{it} + \varepsilon_{it}$$

- I = 1 … 115 (subject)
- t = 1, 2, 3 (time)
- $u_i$ = the random intercept (normal distribution with mean zero)
- $\varepsilon_{it}$ = the residual
- Note : the covariance structure implies that the outcome variable $Y_1$, $Y_2$, and $Y_3$ are correlated.

# Scenario 1

- Missing observation in the both outcome and independent variable under MCAR.
  - The outcome $Y_2$ or $Y_3$ (or both) were missing, constant probability 0.3.
  - Independent variable $X_2$ or $X_3$ (or both) were missing with same constant probability.
  - In total, 50% of the case was incomplete. The outcome and independent variables were never jointly.

# Analysis and Result

**Table 1.** Simulation results from five replications with a sample size of n = 115 and three repeated measurements

**Scenario 1: MCAR—x and y missing within total 50% incomplete.**

| | Statistics | | | | | |
|---|---|---|---|---|---|---|
| **Method** | $\hat{\beta}_0$ | $se(\hat{\beta}_0)$ | **95% CI coverage rate of** $\beta_0$ | $\hat{\beta}_1$ | $se(\hat{\beta}_1)$ | **95% CI coverage rate of** $\beta_1$ |
| REF | 2.01 | 0.095 | 0.95 | 0.50 | 0.101 | 0.95 |
| CCA | 2.01 | 0.136 | 0.95 | 0.50 | 0.145 | 0.95 |
| AC | 2.01 | 0.101 | 0.95 | 0.50 | 0.114 | 0.95 |
| MS | 2.05 | 0.091 | 0.90 | 0.42 | 0.104 | 0.88 |
| MIM | - | - | - | - | - | - |
| LOCF | 2.05 | 0.097 | 0.92 | 0.42 | 0.102 | 0.87 |
| MI | 2.03 | 0.101 | 0.95 | 0.45 | 0.117 | 0.93 |

Abbreviations: AC, available cases; CCA, complete case analysis; CI, confidence interval; LOCF, last observation carried forward; MI, multiple imputation; MIM, missing indicator method; MS, mean substitution; REF, reference.

# Scenario 2

- Missing observation in the outcome under MAR.
  - $Y_2$ or $Y_3$ (or both) were missing.
  - $Y_2$ was missing if $Y_1 \leq \bar{Y}_1$ ; $Y_3$ was missing if $Y_2 \leq \bar{Y}_2$.
  - The probability of missingness for $Y_2$ depends only on observed values of $Y_1$.
  - The probability of missingness for $Y_3$ depends only on observed values of $Y_2$.
  - Approximately 50% of the outcome variables was incomplete.

# Result Scenario 2

| Scenario 2: MAR—y missing with approximately 50% of the outcome variable incomplete | | | | | | |
|---|---|---|---|---|---|---|
| | Statistics | | | | | |
| Method | $\hat{\beta}_0$ | $se(\hat{\beta}_0)$ | 95% CI coverage rate of $\beta_0$ | $\hat{\beta}_1$ | $se(\hat{\beta}_1)$ | 95% CI coverage rate of $\beta_1$ |
| REF | 2.00 | 0.095 | 0.95 | 0.51 | 0.101 | 0.94 |
| CCA | 2.66 | 0.116 | 0.00 | 0.41 | 0.135 | 0.88 |
| AC | 2.00 | 0.100 | 0.96 | 0.50 | 0.112 | 0.94 |
| MS | 2.16 | 0.084 | 0.55 | 0.41 | 0.102 | 0.86 |
| MIM | - | - | - | - | - | - |
| LOCF | 2.00 | 0.096 | 0.95 | 0.40 | 0.096 | 0.82 |
| MI | 2.03 | 0.100 | 0.94 | 0.46 | 0.115 | 0.95 |

Abbreviations: AC, available cases; CCA, complete case analysis; CI, confidence interval; LOCF, last observation carried forward; MI, multiple imputation; MIM, missing indicator method; MS, mean substitution; REF, reference.

# Scenario 3

- Missing observations in the independent variable under MAR.
  - Independent variables $X_2$ and $X_3$ (Or both) were missing.
  - $X_2$ was missing if $Y_2$ was smaller than or equal to its first quartile.
  - $X_3$ was missing if $Y_3$ was smaller than or equal to its first quartile.
  - Approximately 40% of independent variables was incomplete.
  - Comparable MAR mechanism as in scenario 2.

# Result Scenario 3

| Scenario 3: MAR—approximately 40% of the independent variables was incomplete | | | | | | |
|---|---|---|---|---|---|---|
| | Statistics | | | | | |
| Method | $\hat{\beta}_0$ | $se(\hat{\beta}_0)$ | 95% CI coverage rate of $\beta_0$ | $\hat{\beta}_1$ | $se(\hat{\beta}_1)$ | 95% CI coverage rate of $\beta_1$ |
| REF | 2.00 | 0.095 | 0.95 | 0.50 | 0.102 | 0.96 |
| CCA | 2.53 | 0.097 | 0.00 | 0.38 | 0.112 | 0.80 |
| AC | 2.19 | 0.092 | 0.45 | 0.43 | 0.105 | 0.90 |
| MS | 2.07 | 0.101 | 0.92 | 0.35 | 0.109 | 0.72 |
| MIM | 1.16 | 0.123 | 0.00 | 0.42 | 0.097 | 0.85 |
| LOCF | 2.03 | 0.099 | 0.95 | 0.42 | 0.110 | 0.89 |
| MI | 2.04 | 0.102 | 0.94 | 0.43 | 0.128 | 0.93 |
| Scenario 4: MAR—approximately 50% of the dependent and independent variables was incomplete | | | | | | |

Abbreviations: AC, available cases; CCA, complete case analysis; CI, confidence interval; LOCF, last observation carried forward; MI, multiple imputation; MIM, missing indicator method; MS, mean substitution; REF, reference.

# Scenario 4

- Missing observation in the both outcome and independent variable under MAR.
  - Missing values $Y_2$ or $Y_3$ created as in scenario 2, or missing value on $X_2$ or $X_3$ where created as in scenario 3.
  - But not on the both
  - Independent variables are incomplete
  - Approximately 50% of cases were incomplete
  - Comparable MAR mechanism as in scenario 2 or scenario 3.

# Result Scenario 4

| Scenario 4: MAR—approximately 50% of the dependent and independent variables was incomplete | | | | | | |
|---|---|---|---|---|---|---|
| | Statistics | | | | | |
| Method | $\widehat{\beta}_0$ | $se(\widehat{\beta}_0)$ | 95% CI coverage rate of $\beta_0$ | $\widehat{\beta}_1$ | $se(\widehat{\beta}_1)$ | 95% CI coverage rate of $\beta_1$ |
| REF | 2.01 | 0.095 | 0.95 | 0.50 | 0.102 | 0.95 |
| CCA | 2.61 | 0.106 | 0.00 | 0.39 | 0.123 | 0.83 |
| AC | 2.10 | 0.097 | 0.81 | 0.46 | 0.110 | 0.94 |
| MS | 2.10 | 0.093 | 0.79 | 0.39 | 0.106 | 0.84 |
| MIM | - | - | - | - | - | - |
| LOCF | 2.02 | 0.097 | 0.93 | 0.41 | 0.104 | 0.84 |
| MI | 2.04 | 0.101 | 0.93 | 0.44 | 0.122 | 0.94 |

Abbreviations: AC, available cases; CCA, complete case analysis; CI, confidence interval; LOCF, last observation carried forward; MI, multiple imputation; MIM, missing indicator method; MS, mean substitution; REF, reference.

# Result from Scenario 1 - 4

- During 4 scenarios :
  - CCA can produce bias under MAR but can produce unbiased estimates under MCAR.
    - Scenario 1
  - AC analysis were unbiased when the outcome had missing observation. However will leaded biased estimated and lower coverage rare with missing data in the independent variables.
    - Scenario 2, 3 and 4 particularly $\beta_0$
  - Mean Substitutions produced biased estimates with lower coverage rates.
    - Bias in all scenarios

# Result from Scenario 1 - 4

- MIM only valid if missing data of the outcome conditional on the other independent variables. Also cannot handle missing observation in the outcome.
  - Bad performance in scenario 3
- LOCF leading biased estimates on all scenario.
  - Bad on the all situations
- MI provide best performance with negligible bias and acceptable coverage rates [~ 95%].
  - Work on the all scenario

# Statistical Analysis

Maastricht study on long-term dementia care environments (MLTD)

# Statistical Analysis for MLTD

- Compare the mood of participants in the large – scale wards and small – scale wards.
- Substantive model for analysis ➔ random intercept
  - Outcome variable : mood
  - Independent variables :
    - Large scale ward indicator (LSW = 1)
    - Activation indicator (activity = 1)
    - Part of the day (seven categories)
    - Repeated measurement of participants ( time tread as continuous)

# Statistical Analysis for MLTD

- Multiple Imputations:
  - Fully condition Specification (FCS) or chain equations.
  - Using R – Package MICE
  - Setting :
    - Number of imputation set to m = 20.
    - Data is formatted in wide format.
    - Applied "Just Another Variable"  and impute it separately.
    - The outcome is Mood10 ( mood multiple by a factor 10)

# Statistical Analysis for MLTD

- Tricks to work on the MLTD longitudinal study:
  - Data is formatted in wide format
  - Handle over parameterization
  - Apply “Just Another Variable” and impute it separately

# Statistical Analysis for MLTD

- Wide – format in MLTD :
  - Each person occupies only one record in the dataset, and observation made at different time points are coded as different column.
  - Because there 84 repeated measurements in MLTD:
    - Mood : 84
    - Activity : 84
    - Social Interaction : 84
    - Interaction where activity and social interaction are involved in the imputation model.
  - Total more than 300 time – varying covariates in wide formats.
  - N = 115 subjects

# Statistical Analysis for MLTD

- Handle over parameterization
  - This situation happen when the imputation include all variables as predictors for a particular variable cannot be fitted due to over parameterization.
  - In FCS ➔ for mood at time 1 need to imputed
    - Mood, activity, all interaction between activity and time
    - Use from time 2, 3 … at time 84

# Statistical Analysis for MLTD

- Applied "Just Another Variable" (JAV) and impute it separately:
  - The imputation of interaction term with missing value.
  - Example : Activity has missing observation and hence, its interaction with LSW has missing observations too.
  - In this study JAV → to imputed the interaction between Activity ( social interaction) and LSW

# Statistical Analysis for MLTD

- Why R – package MICE?
  - SPSS
  - SAS
  - R – package MICE

# Statistical Analysis for MLTD

SPSS

- Default FCS
- How interaction of categorical variables with missing values are handled?
- Not flexible enough to customize the variable’s role

# Statistical Analysis for MLTD

**SAS**

- FCS approach can optionally be used
- Control the role for each variable separately
- Interaction terms are passively imputed

# Statistical Analysis for MLTD

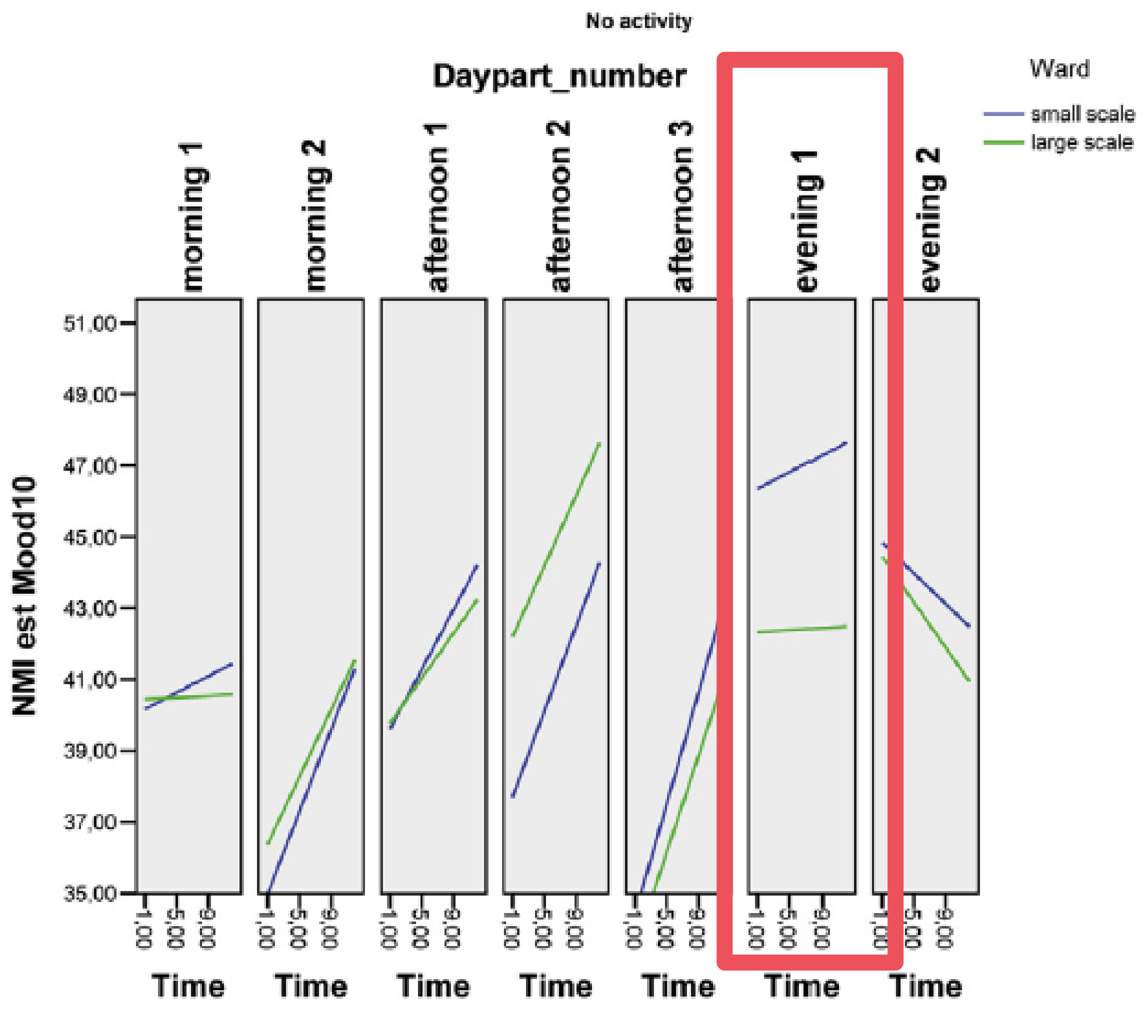
R - MICE

- FCS approach
- Customizable the role of variable
- JAV method can be use

**Table 2.** Relevant parameter estimates for Ward-effect with and without multiple imputation

| **Est LSW × effect** | **Substantive model** | |
|---|---|---|
| **Time, ward, activity, all first-order interactions as independent** | | |
| | **Complete case analysis (No multiple imputation)** | **MI, pooled estimates** |
| LSW | **−0.29 (0.46)** | **−0.11 (0.47)** |
| LSW × Daypart 1: Morning 1 | 0.67 (0.41) | 0.54 (0.43) |
| LSW × Daypart 2: Morning 2 | 0.89 (0.41) | 0.69 (0.45) |
| LSW × Daypart 3: Afternoon 1 | 0.19 (0.42) | 0.10 (0.46) |
| LSW × Daypart 4: Afternoon 2 | 1.12 (0.41) | 1.27 (0.44) |
| LSW × Daypart 5: Afternoon 3 | **−0.11 (0.41)** | **−0.02 (0.44)** |
| LSW × Daypart 6: Evening 1 | −0.60 (0.42) | −0.50 (0.44) |
| LSW × Daypart 7: Evening 2 | - | |
| LSW × time | −0.10 (0.03) | −0.09 (0.04) |
| LSW × Activity | **−0.09 (0.26)** | **−0.27 (0.32)** |

MI, multiple imputation.
Mood × 10 is the outcome.
Standard errors between brackets.



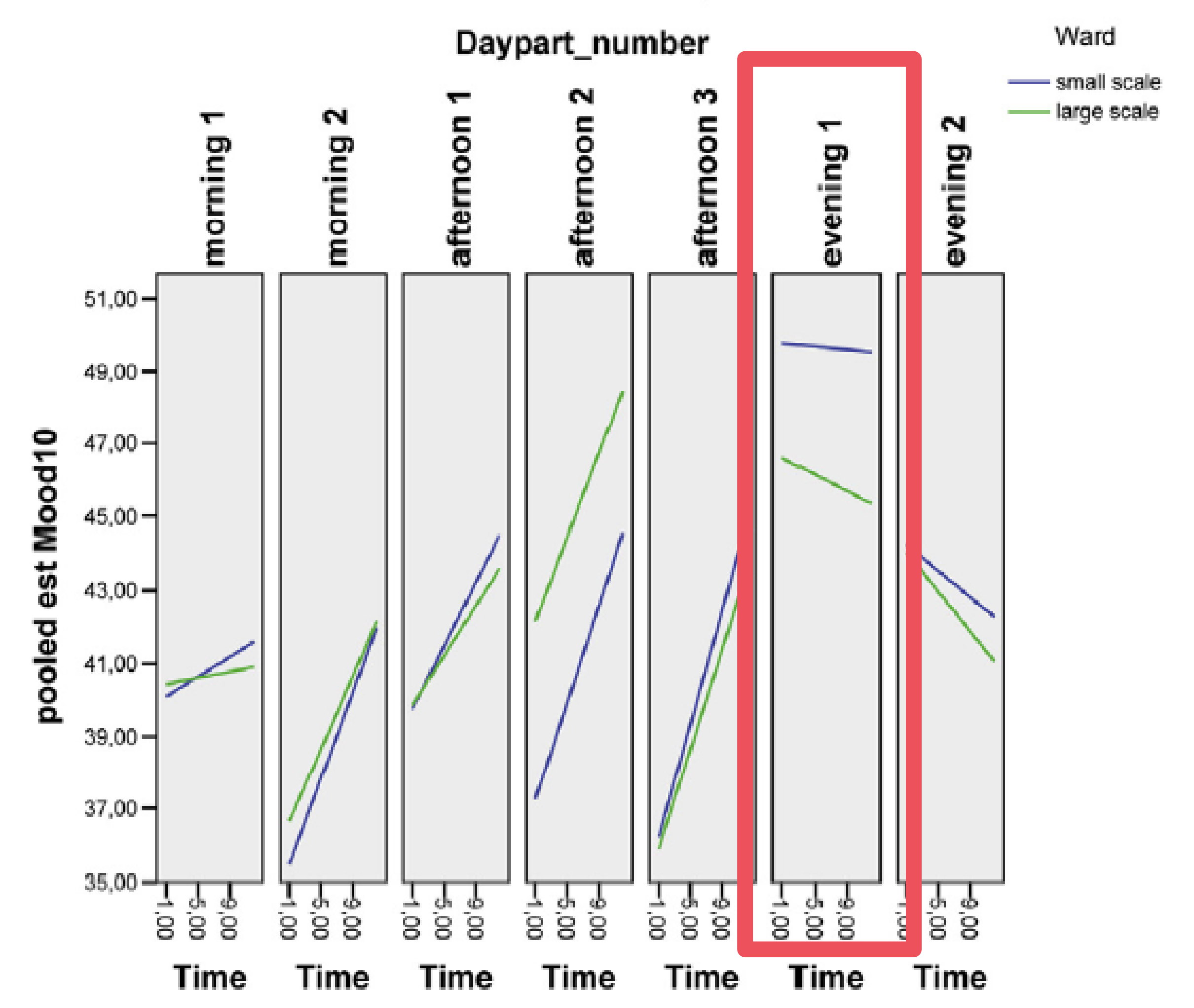




**Fig. 1.** Estimated difference between large- and small-scale wards and activity when not imputed and when imputed. NMI, no missing imputation.

# Discussion

# Key Finding

- Two situation require different approach :
  - When missing data on the outcome only (the independent variables are fully observed) ➔ use likelihood method and multiple imputation isn't important.
  - When missing data in the outcome and independent variables too ➔ multiple imputations
- Problem would be arise when there are more columns (variables per time points) than rows (subjects) ➔ wide format
- R – MICE is recommended application.

# Limitation

- Multilevel imputation has not been performed in this study. This study uses only standard FCS.
- Future study use multilevel imputations might be deal with the problem of higher level imputations.

# Thank you

Maria