eRegQual analysis

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# Introduction

This document presents the methods used to analyze the adverse pregnancy and process outcome data for the eRegQual trial and presents the results.

# Methods

Because outcome data were missing for about a third of participants (see results), we used Little's tests (Little 1988) of the null hypotheses that missing values of the constituent outcomes were jointly missing completely at random (MCAR) and covariate-dependent missing (CDM). We then used multiple imputation via chained equations (van Buuren 2007) to create and analyze 5 multiply-imputed datasets. We imputed each of the constituent outcomes using the auxiliary variables age, BMI, years of education, average monthly household income (transformed to the log scale due to the skewed distribution of income), and variables that indicated whether a laboratory or ultrasound were available at the clinics; the variables included in the analysis described below were also included. We were not able to include auxiliary variables that indicated previous pregnancy with pre-eclampsia or previous history of GDM due to collinearity. We evaluated the convergence of the imputation algorithm by inspecting trace plots and evaluated imputed data by inspecting kernel density and bar plots comparing the distributions of imputed and complete case data.

For each imputed data set, we computed the composite outcome from the imputed constituent outcome data. An adverse pregnancy outcome was defined to have occurred if at least one of the constituent outcomes occurred, and not to have occurred if none of the constituent outcomes occurred. For each imputed data set and outcome, we estimated a risk ratio to compare treatment to control and used generalized estimating equations (GEE; binomial errors and log link) to account for the cluster-randomized design. We combined estimates for each outcome using Rubin's rules (Rubin 2004). For comparison, we also performed a complete case analysis under the MCAR assumption. We estimated the intraclass correlation coefficient (ICC) using the complete cases.

We used logistic regression to estimate the relative odds of each of the process outcomes under the treatment versus control conditions. For outcomes measured at multiple time points, we modelled clustering within each pregnancy using random-effects, and computed cluster-robust standard errors to account for the cluster-randomized design. For outcomes measured at only one time point within each pregnancy, we accounted for the cluster-randomized design using random effects. For each of the process outcomes, we plotted marginal predictive probabilities of attendance or successful screening and management with respect to cluster size, laboratory availability, age, and parity. No data were missing for the process outcome analyses.

We adjusted for the stratification variable (CHMP 2015) and the variables used to constrain randomization (Li 2017) as fixed effects in all analyses, using individual- rather than cluster-level measurements where possible. We followed the intention-to-treat principle for all analyses: participants were analyzed in the arms to which they were randomized and — with the exception of the complete case analyses for the adverse pregnancy analysis — all participants were included in the analyses. We computed 95% confidence intervals and used the significance criterion P<0.05 throughout. Statistical analyses were performed using Stata 16 (StataCorp LLC, College Station, Texas, USA). The statistician was not involved in data collection and was blinded to treatment allocation during analysis. Protocol deviations are documented in Appendix 1.

# Results

## Adverse pregnancy outcomes

Outcome data were missing for between 11.8% and 35.5% of the constituent outcomes, and 33.8% of the composite outcome. We were unable to reject the MCAR and CDM hypotheses (P=0.15 and P=0.64, respectively). Distributions of the original and the first five imputed data sets are shown in Appendix 2. Table 1 shows the result of the adverse pregnancy outcome analysis. The risk ratio was estimated to be 1.02 (95% CI 0.93 to 1.11, P = 0.71). This compares to the complete case risk ratio of 0.99 (95% CI 0.91 to 1.08, P = 0.85). Tables 2–6 show results for the constituent outcomes. The ICC was estimated to be close to zero and no greater than 0.007 (upper bound of 95% CI).

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| --- | --- | --- | --- | --- | --- | --- |
| Table 1. Adverse pregnancy outcome (multiply-imputed result) | | | | | | |
| y | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.02 | 0.04 | 0.37 | 0.71 | 0.93 | 1.11 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.10 | 0.09 | 1.25 | 0.21 | 0.94 | 1.29 |
| 9d5ed6 | 0.94 | 0.09 | -0.64 | 0.52 | 0.77 | 1.14 |
| e1e1d3 | 1.09 | 0.09 | 1.07 | 0.28 | 0.93 | 1.27 |
| ff4457 | 1.15 | 0.09 | 1.83 | 0.07 | 0.99 | 1.34 |
|  |  |  |  |  |  |  |
| \_cons | 0.23 | 0.02 | -21.19 | 0.00 | 0.20 | 0.27 |

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| Table 2. Anemia at birth (multiply-imputed result) | | | | | | |
| y1 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.17 | 0.26 | 0.71 | 0.48 | 0.75 | 1.82 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.39 | 0.57 | 0.80 | 0.42 | 0.62 | 3.12 |
| 9d5ed6 | 1.85 | 0.94 | 1.22 | 0.23 | 0.68 | 5.05 |
| e1e1d3 | 2.10 | 0.85 | 1.82 | 0.07 | 0.94 | 4.68 |
| ff4457 | 1.91 | 0.74 | 1.69 | 0.09 | 0.90 | 4.07 |
|  |  |  |  |  |  |  |
| \_cons | 0.01 | 0.00 | -11.99 | 0.00 | 0.00 | 0.02 |

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| Table 3. Severe hypertension at birth (multiply-imputed result) | | | | | | |
| y2 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.56 | 0.68 | 1.03 | 0.32 | 0.60 | 4.04 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.01 | 1.08 | 0.01 | 0.99 | 0.09 | 11.88 |
| 9d5ed6 | 0.57 | 0.80 | -0.40 | 0.69 | 0.03 | 11.43 |
| e1e1d3 | 1.39 | 1.03 | 0.45 | 0.66 | 0.32 | 6.10 |
| ff4457 | 3.52 | 2.56 | 1.73 | 0.10 | 0.78 | 15.91 |
|  |  |  |  |  |  |  |
| \_cons | 0.00 | 0.00 | -7.61 | 0.00 | 0.00 | 0.02 |

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| Table 4. SGA undetected at birth (multiply-imputed result) | | | | | | |
| y3 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.02 | 0.11 | 0.21 | 0.84 | 0.82 | 1.27 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 0.87 | 0.15 | -0.81 | 0.42 | 0.61 | 1.23 |
| 9d5ed6 | 0.67 | 0.17 | -1.56 | 0.12 | 0.40 | 1.11 |
| e1e1d3 | 0.92 | 0.16 | -0.51 | 0.61 | 0.65 | 1.29 |
| ff4457 | 0.94 | 0.16 | -0.34 | 0.74 | 0.68 | 1.32 |
|  |  |  |  |  |  |  |
| \_cons | 0.09 | 0.01 | -16.21 | 0.00 | 0.06 | 0.12 |

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| Table 5. Malpresentation undetected at birth (multiply-imputed result) | | | | | | |
| y4 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 1.14 | 0.17 | 0.84 | 0.40 | 0.84 | 1.53 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.19 | 0.36 | 0.58 | 0.56 | 0.66 | 2.15 |
| 9d5ed6 | 0.76 | 0.37 | -0.55 | 0.58 | 0.29 | 2.03 |
| e1e1d3 | 1.85 | 0.56 | 2.04 | 0.05 | 1.01 | 3.37 |
| ff4457 | 1.49 | 0.44 | 1.35 | 0.18 | 0.83 | 2.68 |
|  |  |  |  |  |  |  |
| \_cons | 0.02 | 0.01 | -14.38 | 0.00 | 0.01 | 0.04 |

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| Table 6. Large for gestational age (multiply-imputed result) | | | | | | |
| y5 | Risk Ratio | Std. Err. | t | P>|t| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| D | 0.94 | 0.07 | -0.85 | 0.40 | 0.82 | 1.08 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.18 | 0.13 | 1.42 | 0.16 | 0.94 | 1.47 |
| 9d5ed6 | 1.12 | 0.16 | 0.76 | 0.44 | 0.84 | 1.48 |
| e1e1d3 | 1.00 | 0.12 | -0.01 | 0.99 | 0.79 | 1.26 |
| ff4457 | 1.14 | 0.13 | 1.15 | 0.25 | 0.91 | 1.42 |
|  |  |  |  |  |  |  |
| \_cons | 0.12 | 0.01 | -20.41 | 0.00 | 0.10 | 0.15 |

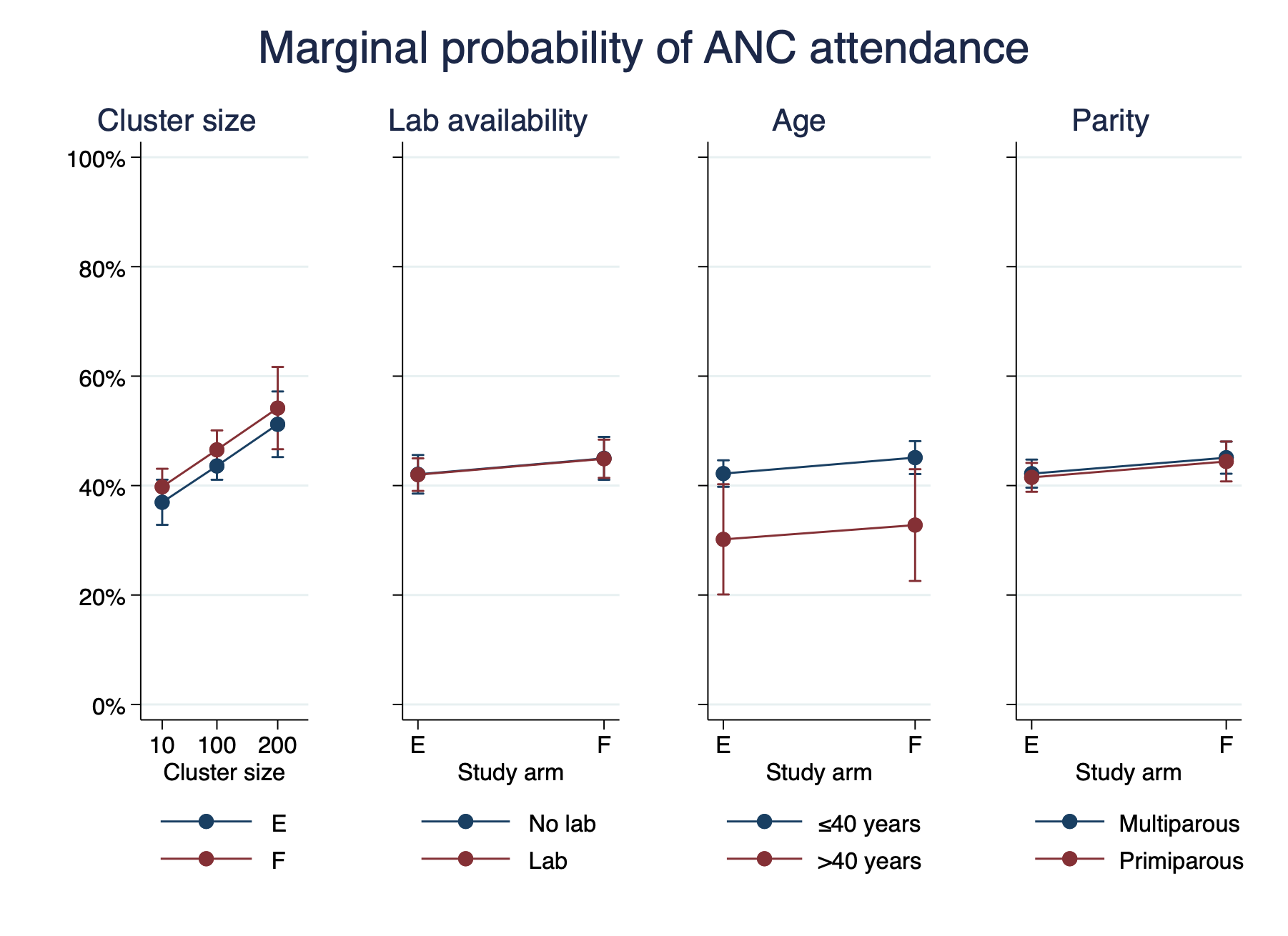
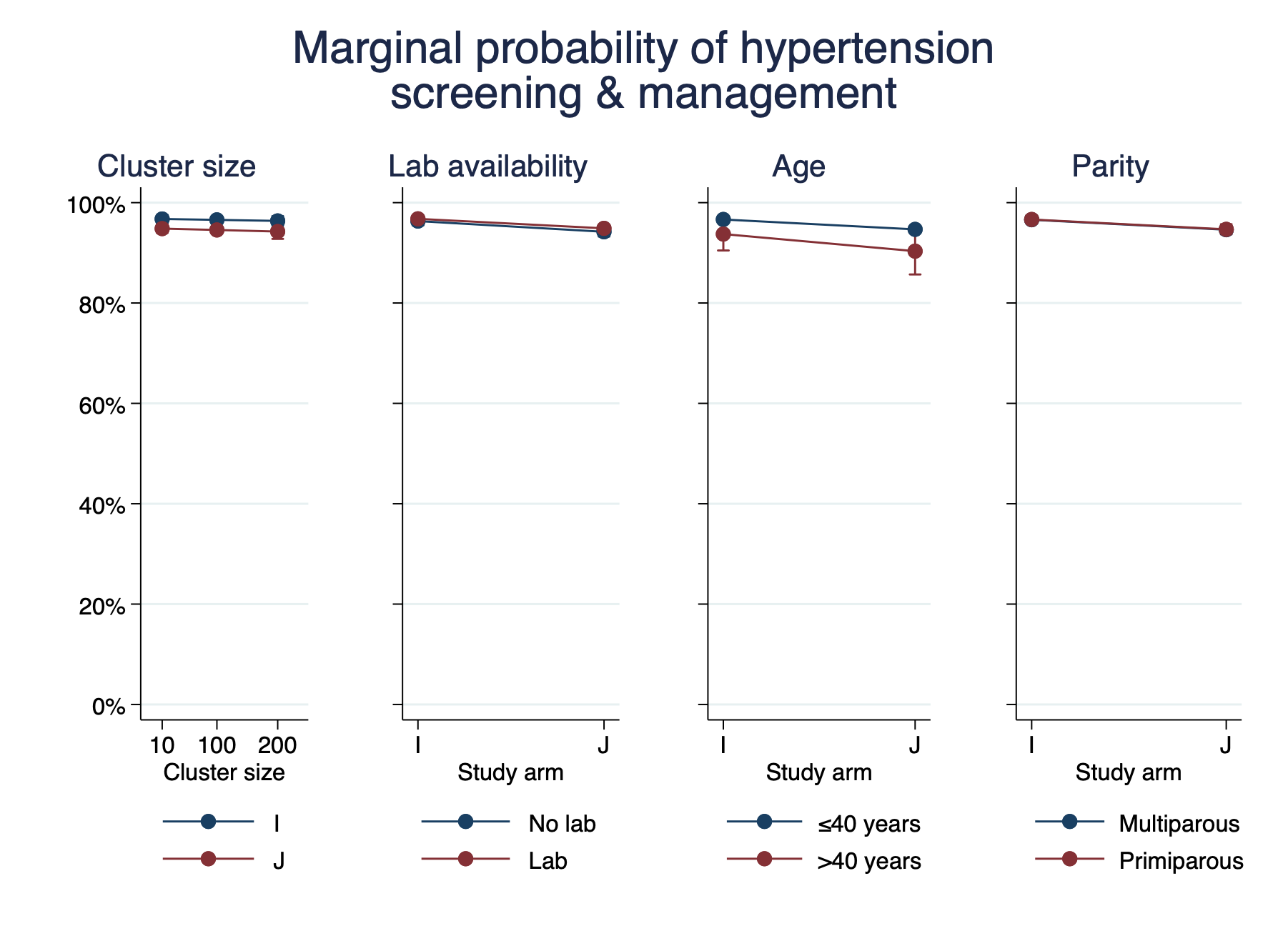
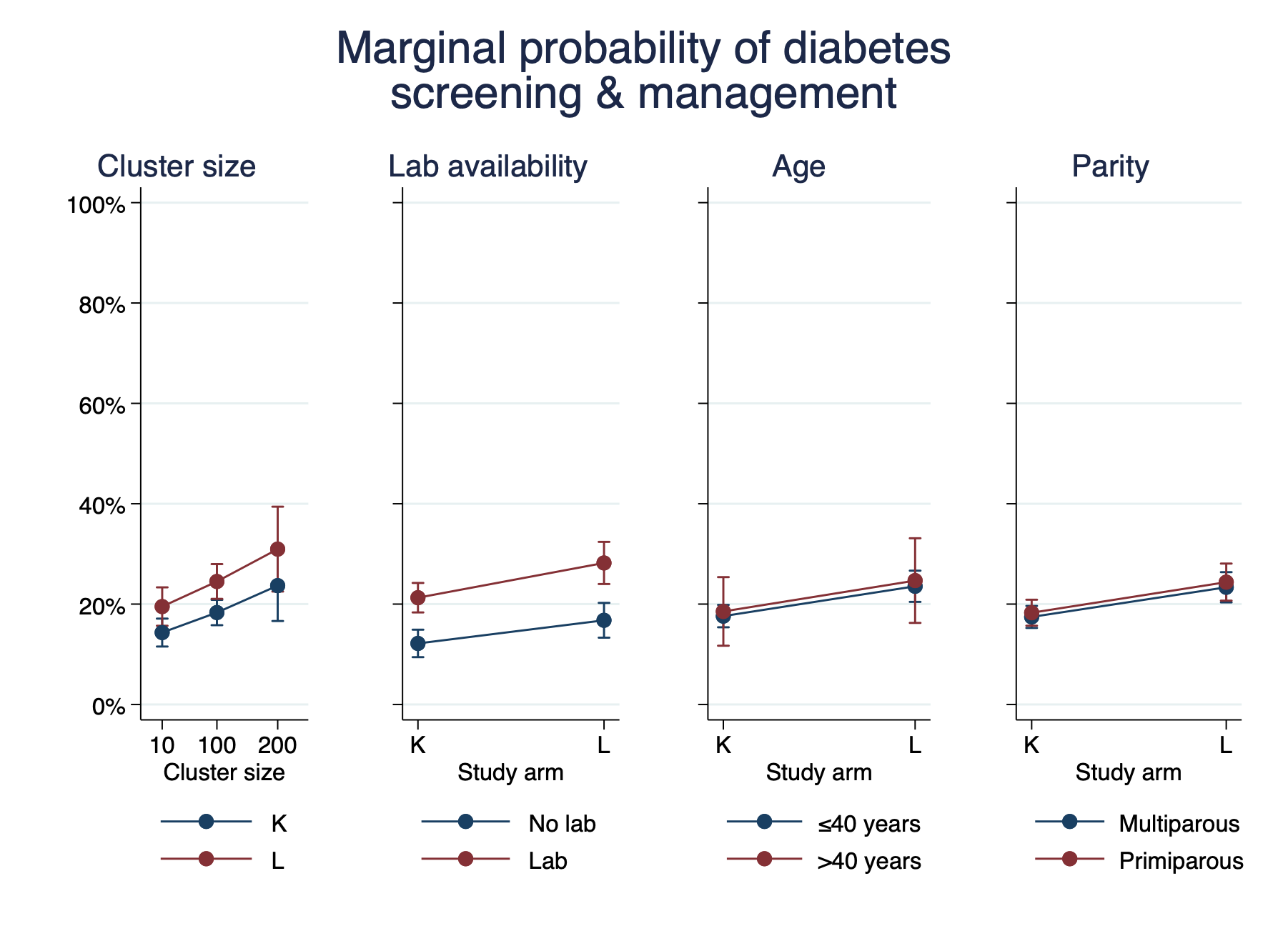
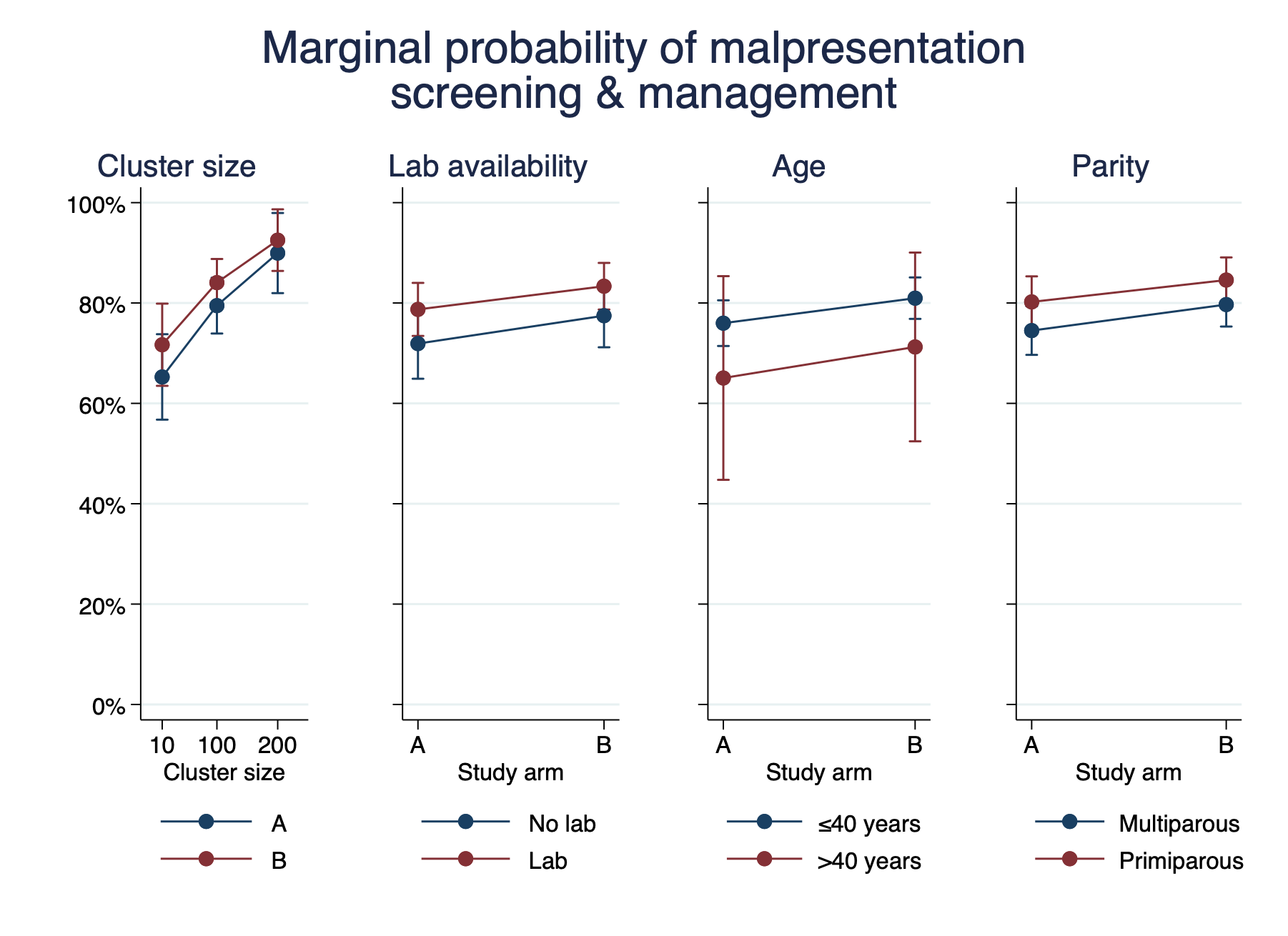
## Process outcomes

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| Table 7. Successful attendance | | | | | | |
|  | Odds Ratio | Robust |  |  |  |  |
| y |  | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| F | 1.18 | 0.13 | 1.46 | 0.15 | 0.95 | 1.47 |

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| Table 8. Successful hypertension | | | | | | |
|  | Odds Ratio | Robust |  |  |  |  |
| y |  | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| J | 0.60 | 0.07 | -4.24 | 0.00 | 0.48 | 0.76 |

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| --- | --- | --- | --- | --- | --- | --- |
| Table 9. Successful diabetes | | | | | | |
|  | Odds Ratio | Robust |  |  |  |  |
| y |  | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| L | 1.46 | 0.18 | 3.13 | 0.00 | 1.15 | 1.85 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Table 10. Successful malpresentation | | | | | | |
| y | Odds Ratio | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| B | 1.42 | 0.31 | 1.61 | 0.11 | 0.93 | 2.18 |

The following figures show marginal predictive probabilities for each process outcome.  
  
  


# References

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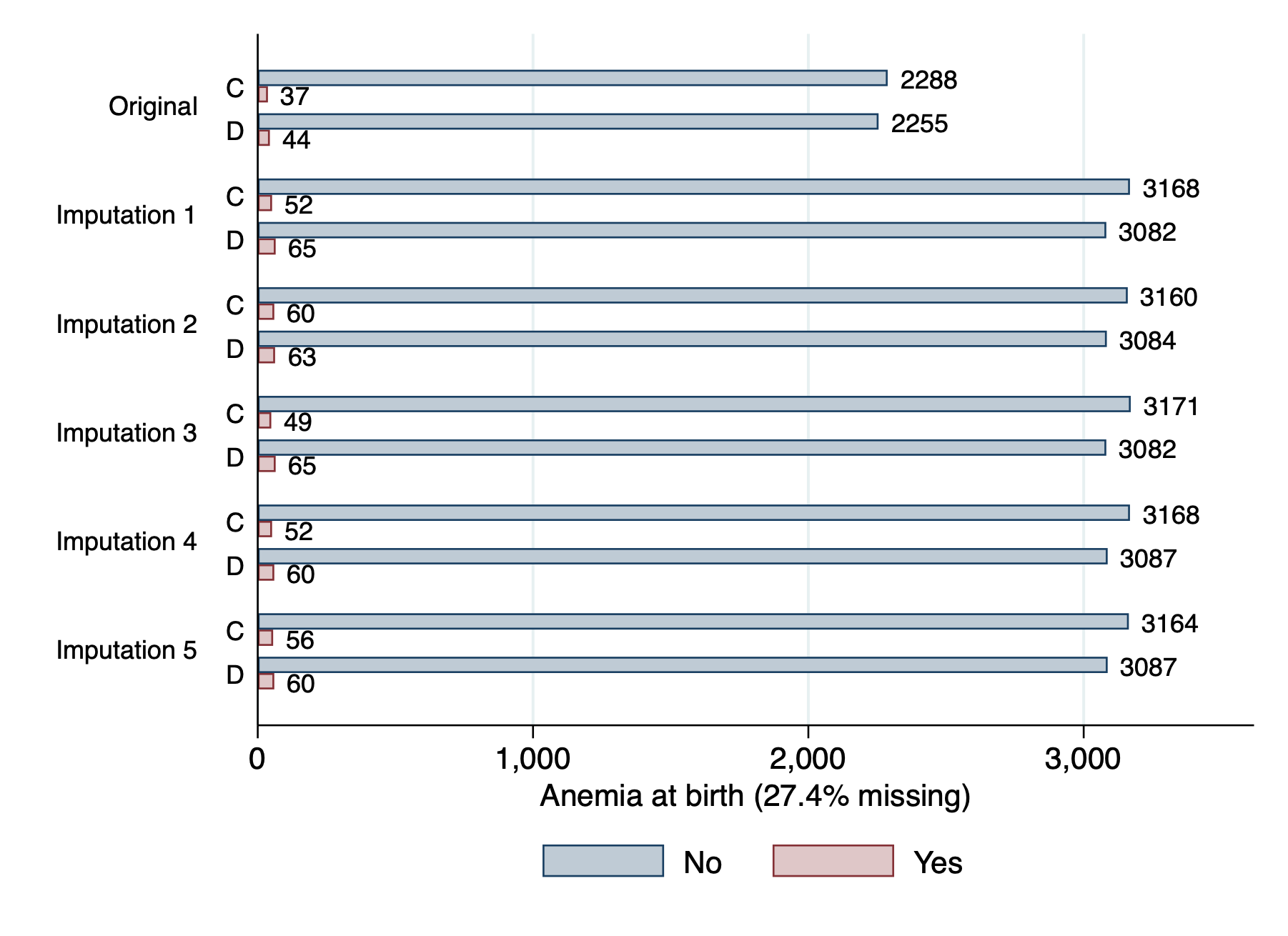
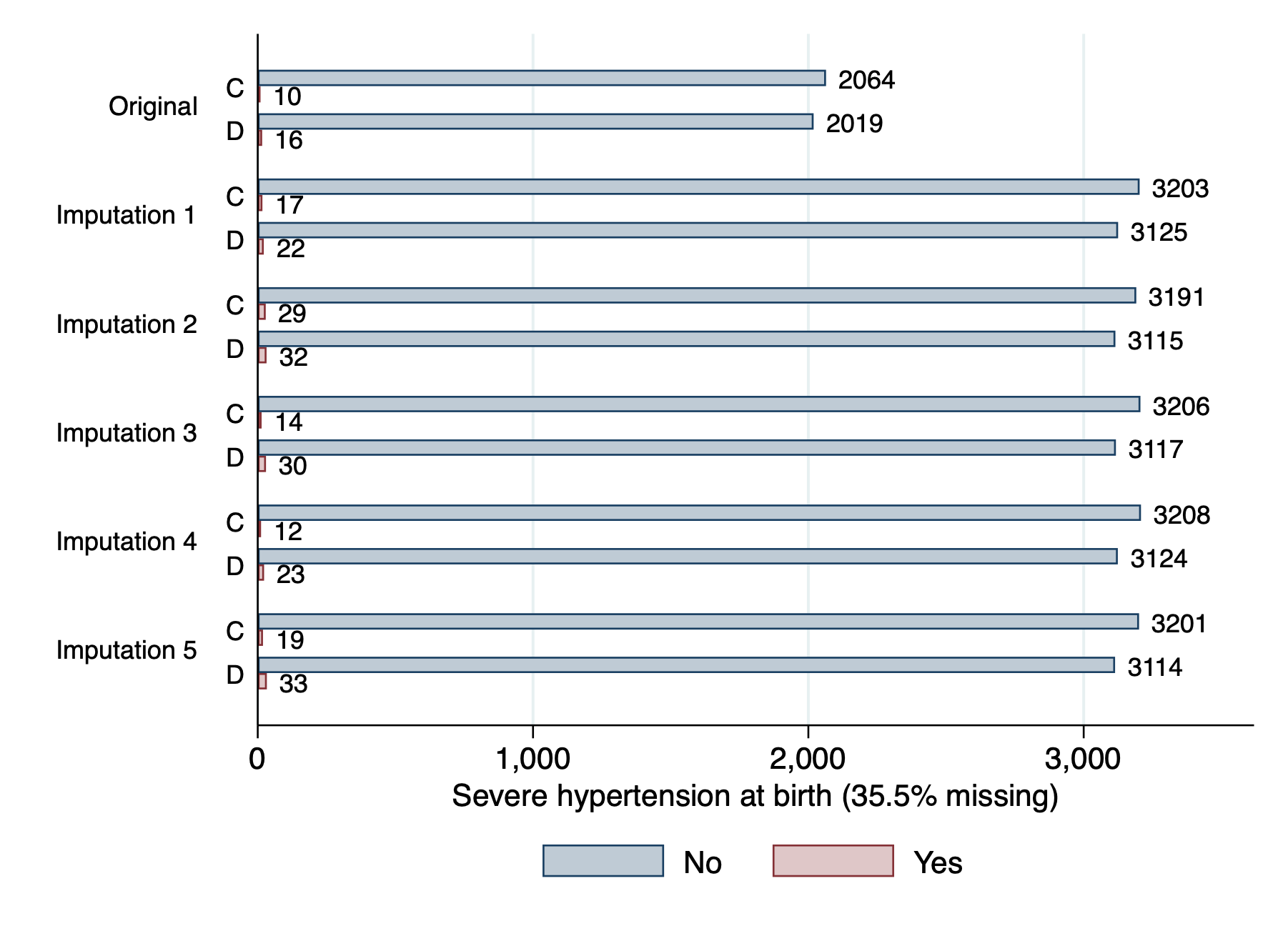
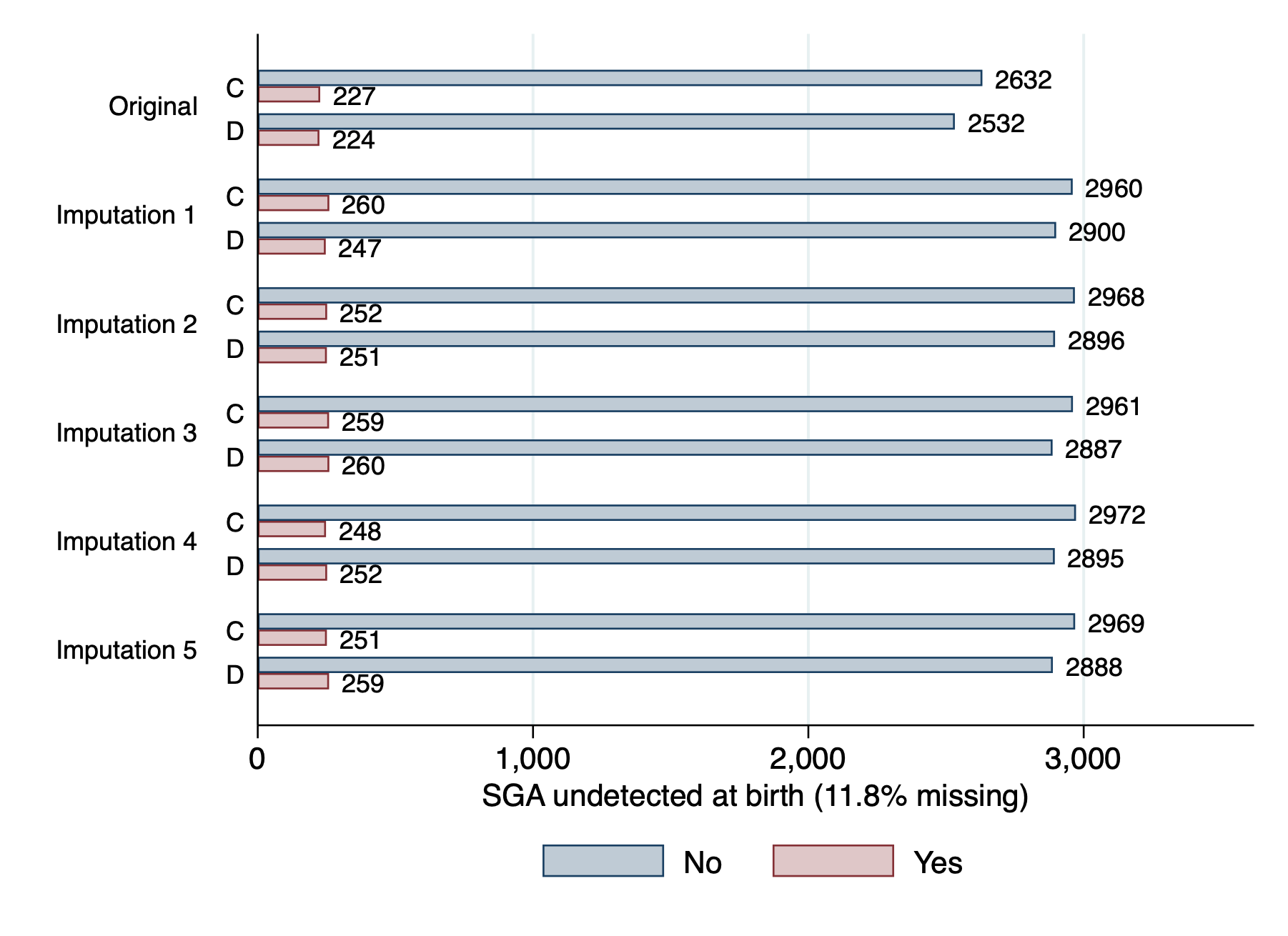
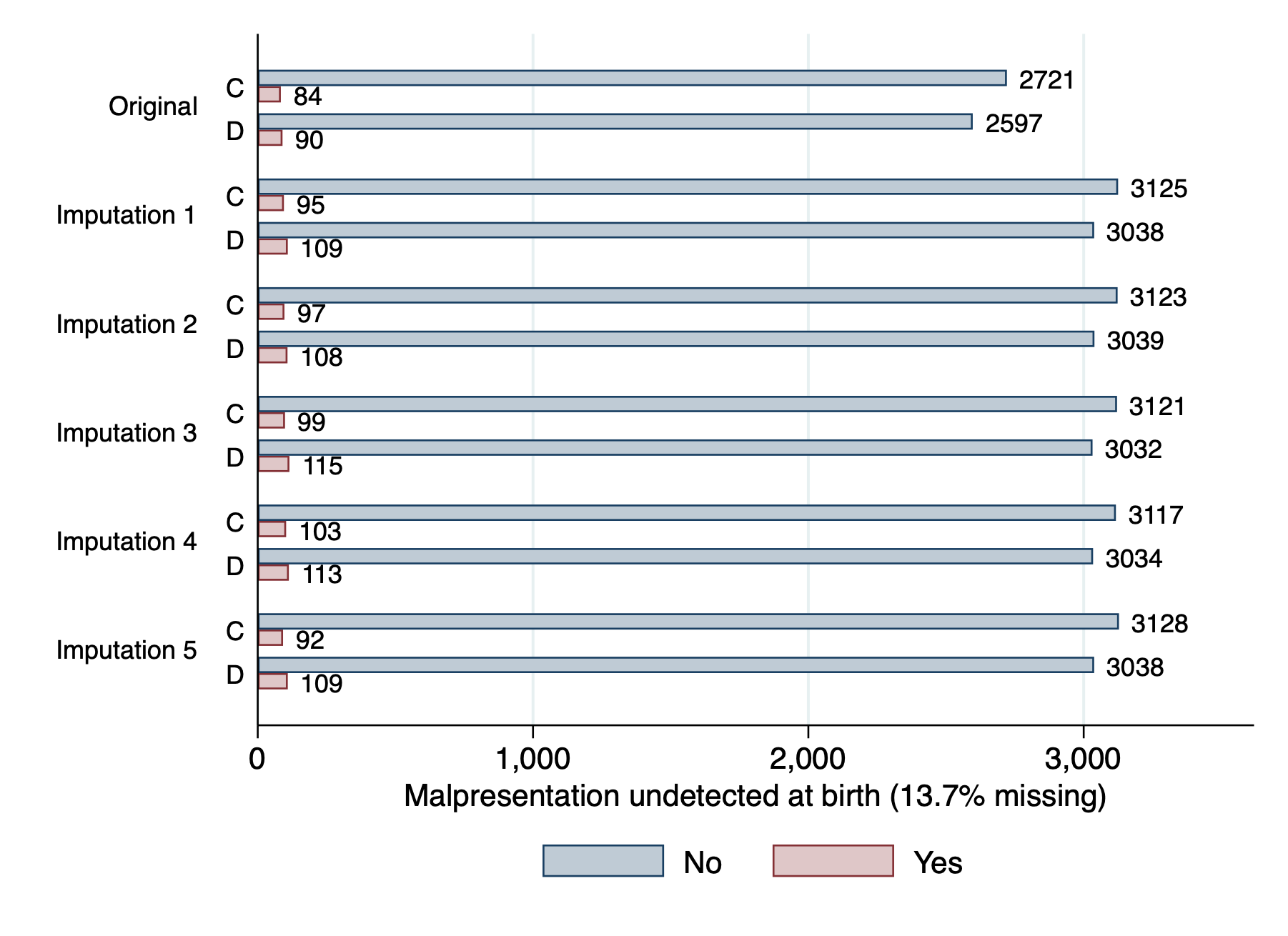
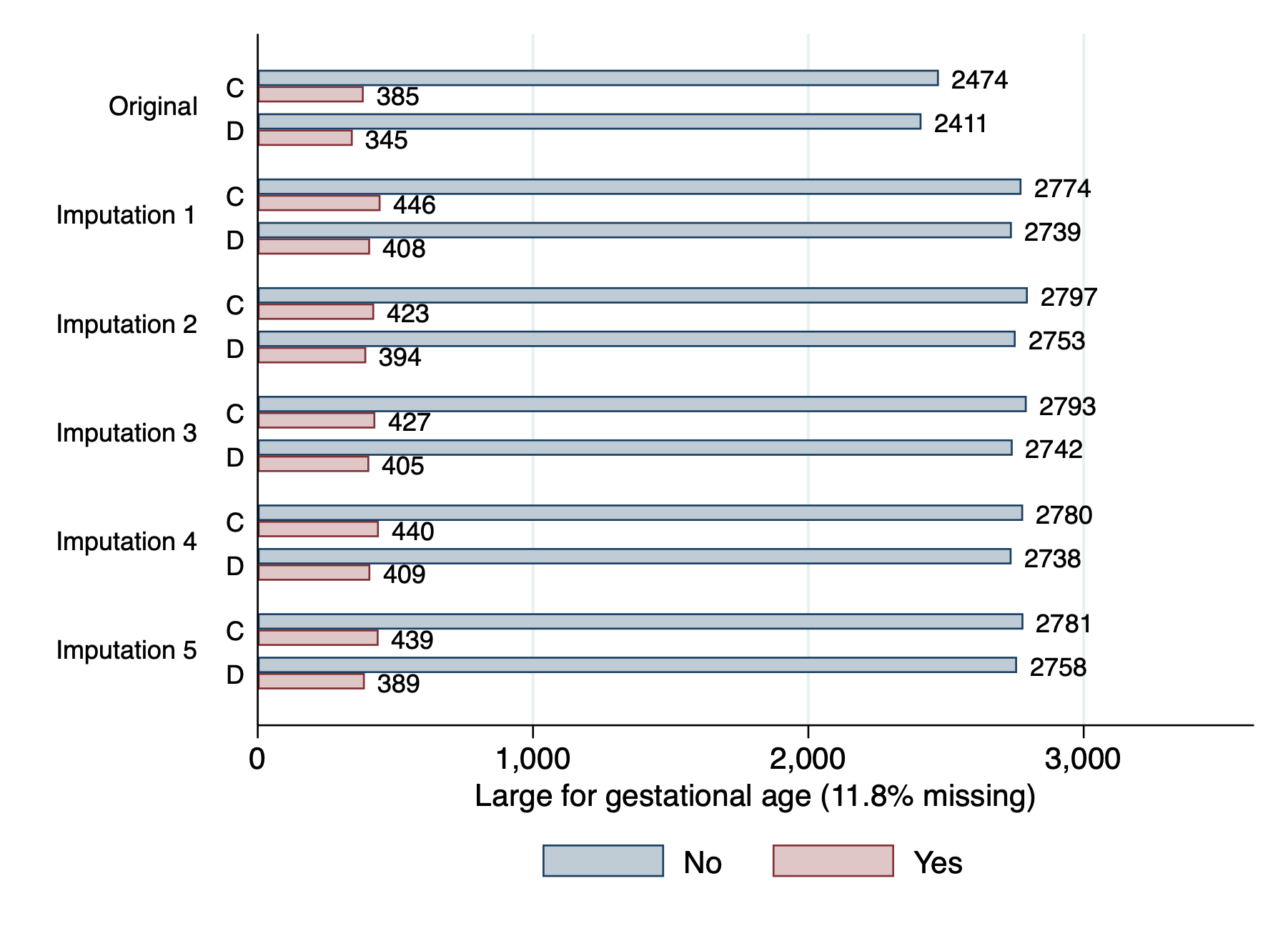
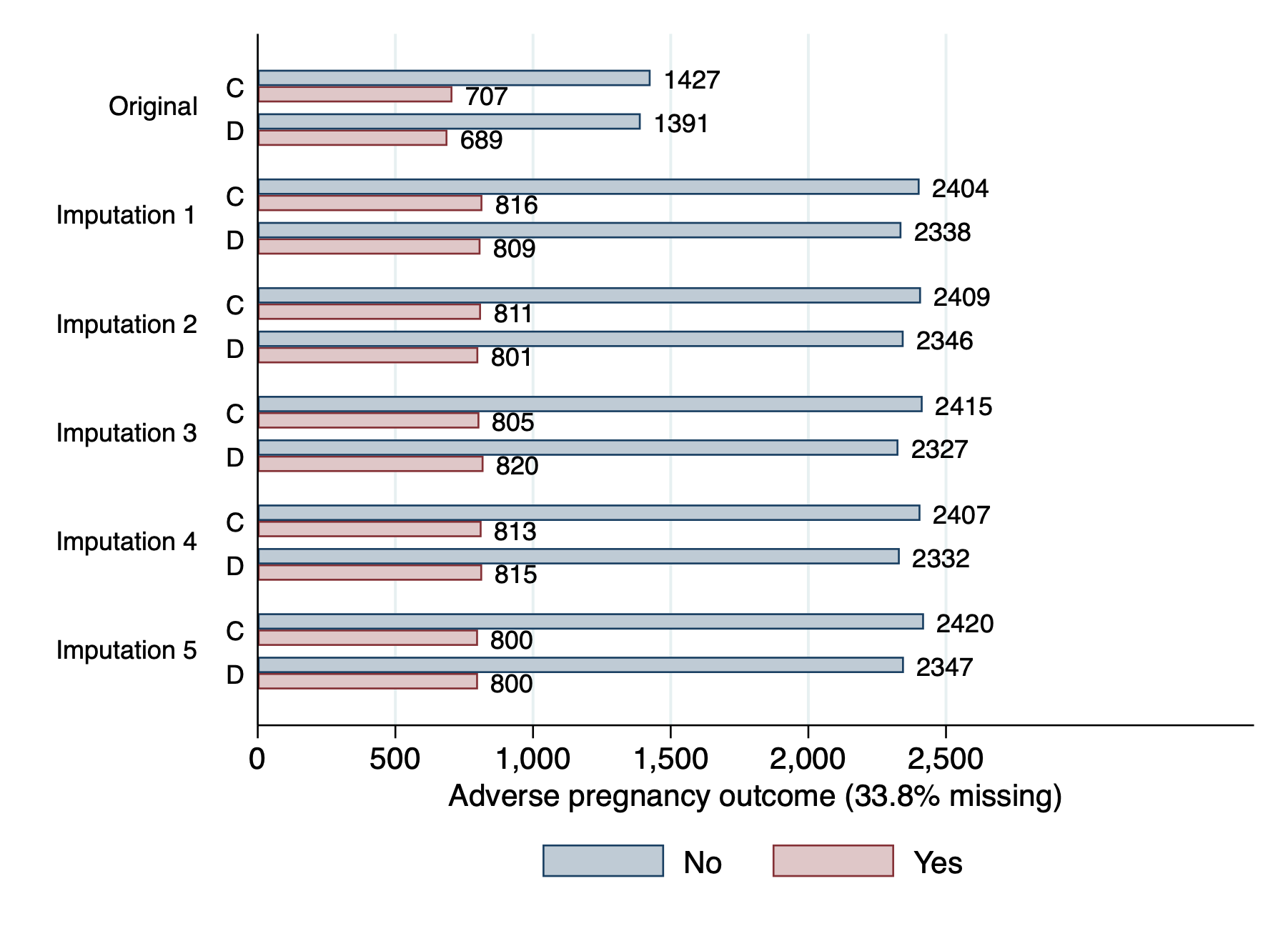
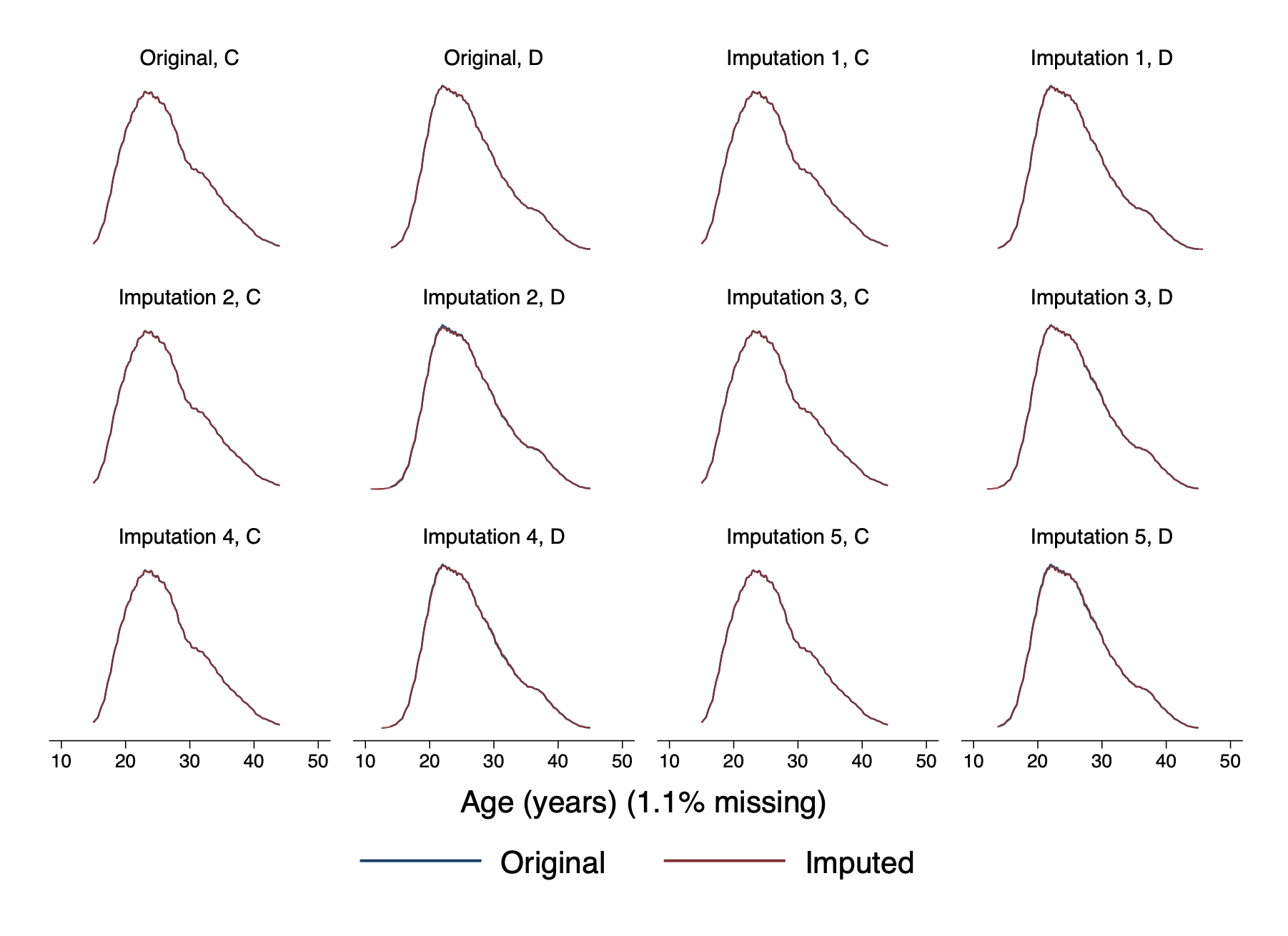
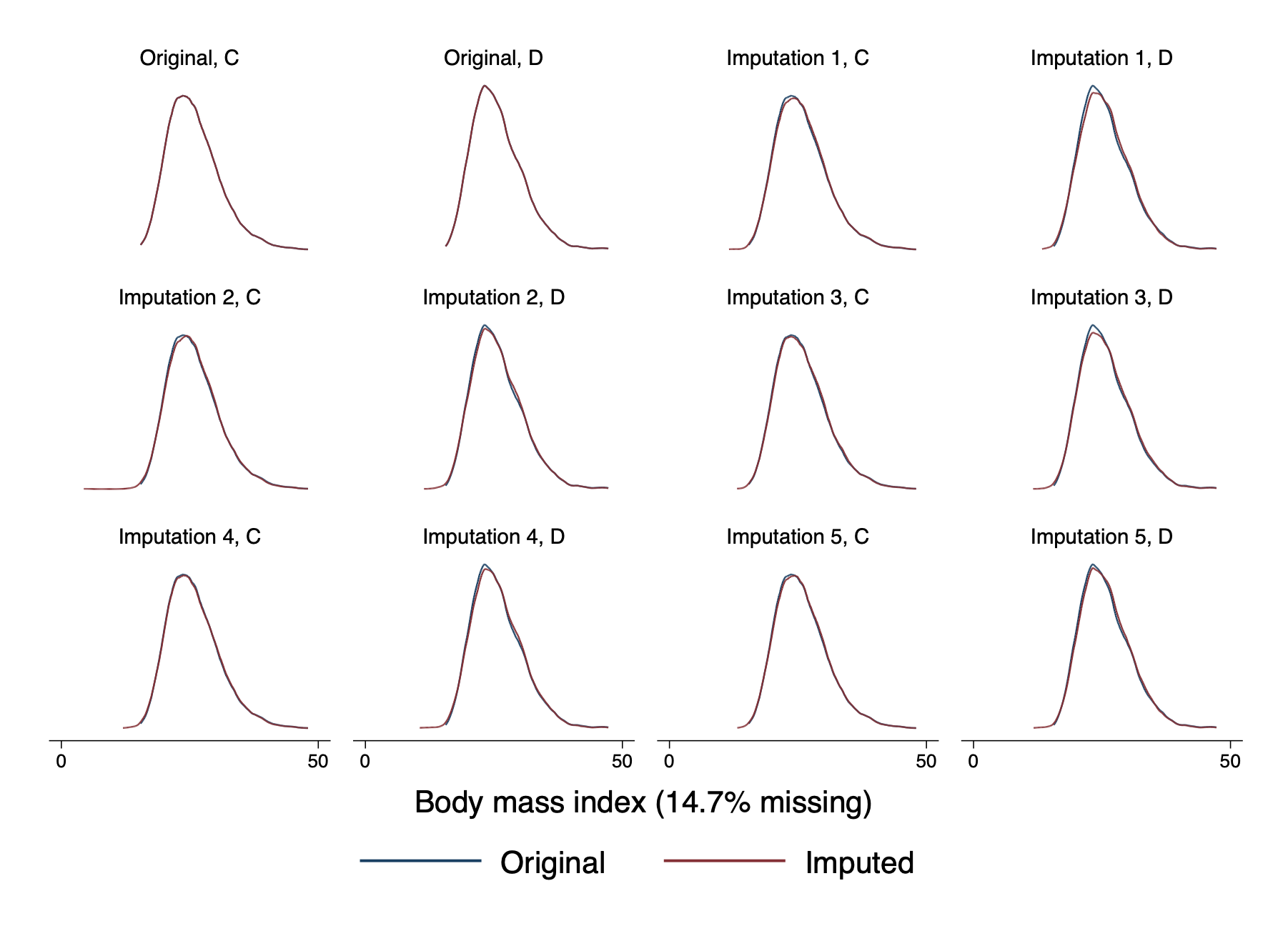
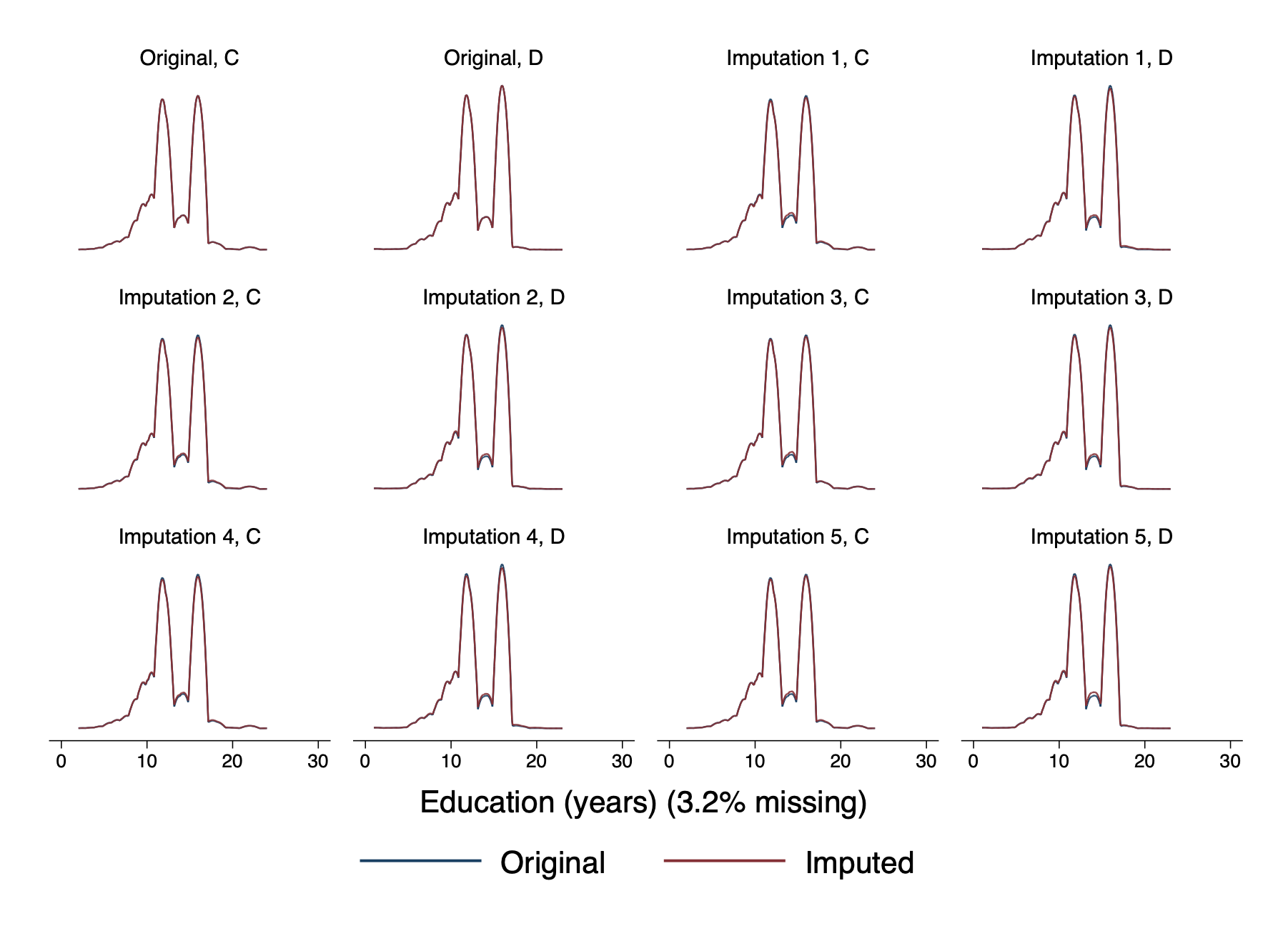
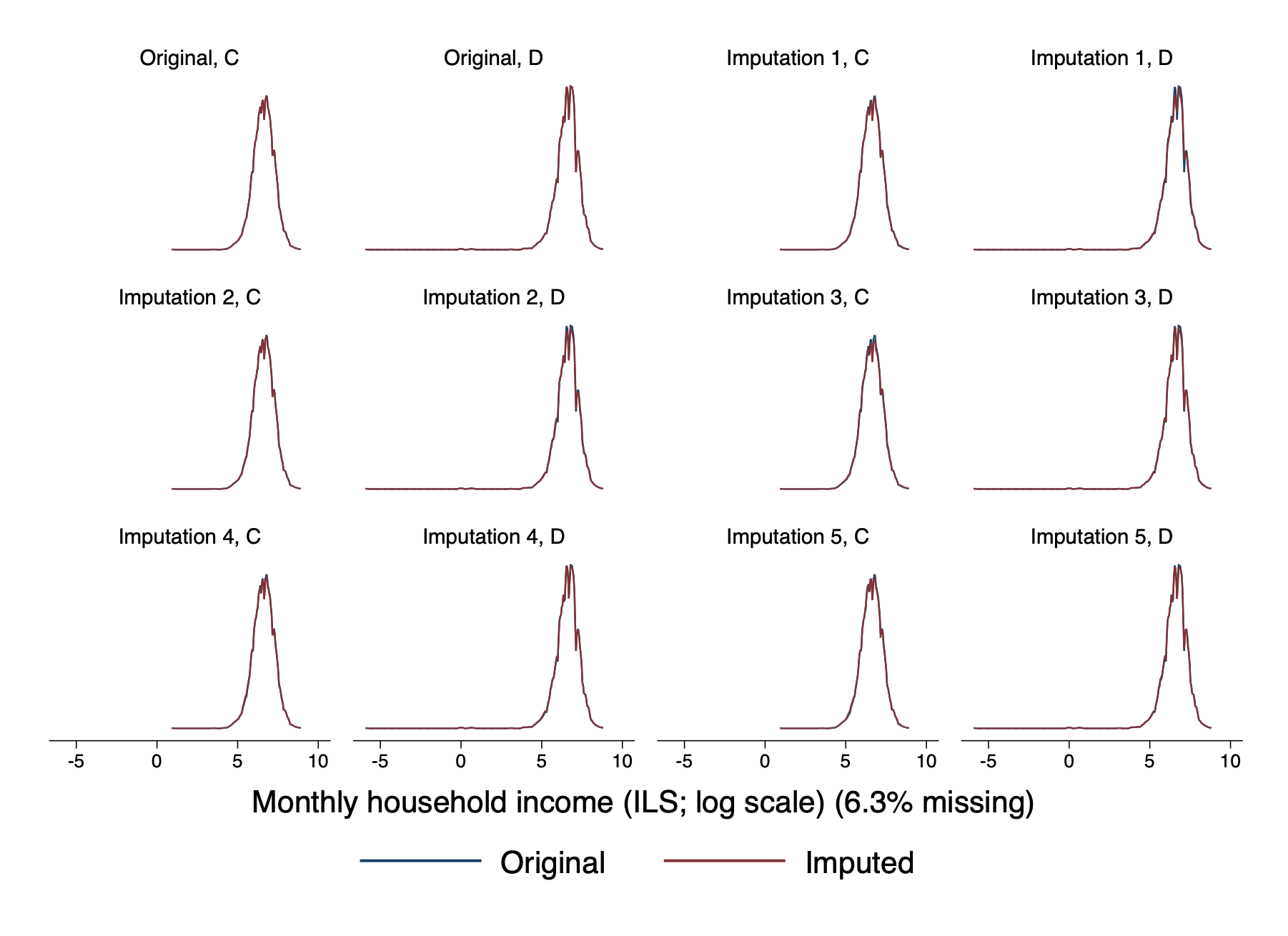
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# Appendix 1 — Protocol Deviations

We planned to use generalized estimating equations (GEEs) to account for the cluster-randomized design but used random-effect logistic regression because it was necessary to analyze the process outcome data in which outcomes are clustered within pregnancy (over time) and within clinic. Stata's XTGEE command can compute robust standard errors that account for clustering within pregnancy, but not additionally at the clinic level. We chose to use a common model for all analyses, rather than use GEEs for some outcomes and logistic regressions for others. We planned to report risk ratios, but report odds ratios as provided by logistic regression. We did not plan to adjust for the stratification variable or the variables used as constraints in the randomization, but have done so based on guidance from the European Medicines Agency and research that was not available when the protocol was being developed. We planned to visually explore differences in process outcomes between clusters using spider graphs but judged that plots of marginal predictive probabilities show the required information more clearly and provide confidence intervals.

# Appendix 2 — Imputation

The following figures show the distributions of the original and a selection of the imputed data.  
  
  
  
  
  
  
  
  


# Appendix 3 — Full Process Outcome Results

The following tables show the full regression results for the process outcomes.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Table 11. Successful attendance | | | | | | |
|  | Odds Ratio | Robust |  |  |  |  |
| y |  | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| F | 1.18 | 0.13 | 1.46 | 0.15 | 0.95 | 1.47 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 0.59 | 0.11 | -2.93 | 0.00 | 0.41 | 0.84 |
| 9d5ed6 | 1.38 | 0.26 | 1.72 | 0.09 | 0.96 | 1.98 |
| e1e1d3 | 1.19 | 0.20 | 1.04 | 0.30 | 0.86 | 1.67 |
| ff4457 | 1.75 | 0.30 | 3.24 | 0.00 | 1.25 | 2.47 |
|  |  |  |  |  |  |  |
| cluster\_size | 1.52 | 0.20 | 3.19 | 0.00 | 1.18 | 1.98 |
|  |  |  |  |  |  |  |
| lab\_available |  |  |  |  |  |  |
| Lab | 1.00 | 0.12 | -0.03 | 0.97 | 0.78 | 1.27 |
|  |  |  |  |  |  |  |
| age\_over\_40 |  |  |  |  |  |  |
| >40 years | 0.49 | 0.16 | -2.21 | 0.03 | 0.26 | 0.92 |
|  |  |  |  |  |  |  |
| primiparous |  |  |  |  |  |  |
| Primiparous | 0.96 | 0.06 | -0.64 | 0.53 | 0.85 | 1.08 |
| \_cons | 0.43 | 0.08 | -4.31 | 0.00 | 0.29 | 0.63 |
| /lnsig2u | 0.61 | 0.08 |  |  | 0.45 | 0.76 |
| sigma\_u | 1.35 | 0.05 |  |  | 1.25 | 1.46 |
| rho | 0.36 | 0.02 |  |  | 0.32 | 0.39 |

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| Table 12. Successful hypertension | | | | | | |
|  | Odds Ratio | Robust |  |  |  |  |
| y |  | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| J | 0.60 | 0.07 | -4.24 | 0.00 | 0.48 | 0.76 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.16 | 0.24 | 0.73 | 0.46 | 0.78 | 1.74 |
| 9d5ed6 | 1.51 | 0.27 | 2.34 | 0.02 | 1.07 | 2.13 |
| e1e1d3 | 1.21 | 0.22 | 1.01 | 0.31 | 0.84 | 1.74 |
| ff4457 | 1.74 | 0.31 | 3.11 | 0.00 | 1.23 | 2.47 |
|  |  |  |  |  |  |  |
| cluster\_size | 0.94 | 0.10 | -0.58 | 0.56 | 0.76 | 1.16 |
|  |  |  |  |  |  |  |
| lab\_available |  |  |  |  |  |  |
| Lab | 1.15 | 0.15 | 1.11 | 0.27 | 0.90 | 1.47 |
|  |  |  |  |  |  |  |
| age\_over\_40 |  |  |  |  |  |  |
| >40 years | 0.50 | 0.15 | -2.34 | 0.02 | 0.28 | 0.89 |
|  |  |  |  |  |  |  |
| primiparous |  |  |  |  |  |  |
| Primiparous | 1.02 | 0.11 | 0.16 | 0.87 | 0.83 | 1.25 |
| \_cons | 30.86 | 7.28 | 14.54 | 0.00 | 19.44 | 48.99 |
| /lnsig2u | -0.17 | 0.26 |  |  | -0.68 | 0.34 |
| sigma\_u | 0.92 | 0.12 |  |  | 0.71 | 1.19 |
| rho | 0.20 | 0.04 |  |  | 0.13 | 0.30 |

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| Table 13. Successful diabetes | | | | | | |
|  | Odds Ratio | Robust |  |  |  |  |
| y |  | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| L | 1.46 | 0.18 | 3.13 | 0.00 | 1.15 | 1.85 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 0.68 | 0.13 | -2.10 | 0.04 | 0.47 | 0.97 |
| 9d5ed6 | 0.57 | 0.13 | -2.42 | 0.02 | 0.36 | 0.90 |
| e1e1d3 | 0.49 | 0.10 | -3.37 | 0.00 | 0.33 | 0.74 |
| ff4457 | 0.72 | 0.11 | -2.10 | 0.04 | 0.53 | 0.98 |
|  |  |  |  |  |  |  |
| cluster\_size | 1.40 | 0.20 | 2.28 | 0.02 | 1.05 | 1.86 |
|  |  |  |  |  |  |  |
| lab\_available |  |  |  |  |  |  |
| Lab | 1.97 | 0.29 | 4.54 | 0.00 | 1.47 | 2.63 |
|  |  |  |  |  |  |  |
| age\_over\_40 |  |  |  |  |  |  |
| >40 years | 1.07 | 0.25 | 0.27 | 0.79 | 0.67 | 1.70 |
|  |  |  |  |  |  |  |
| primiparous |  |  |  |  |  |  |
| Primiparous | 1.06 | 0.05 | 1.20 | 0.23 | 0.96 | 1.17 |
| \_cons | 0.15 | 0.03 | -10.31 | 0.00 | 0.11 | 0.22 |
| /lnsig2u | -14.34 | . |  |  | . | . |
| sigma\_u | 0.00 | . |  |  | . | . |
| rho | 0.00 | . |  |  | . | . |

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| --- | --- | --- | --- | --- | --- | --- |
| Table 14. Successful malpresentation | | | | | | |
| y | Odds Ratio | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| arm |  |  |  |  |  |  |
| B | 1.42 | 0.31 | 1.61 | 0.11 | 0.93 | 2.18 |
|  |  |  |  |  |  |  |
| strat\_var |  |  |  |  |  |  |
| 8d9c30 | 1.45 | 0.56 | 0.95 | 0.34 | 0.68 | 3.09 |
| 9d5ed6 | 3.60 | 1.85 | 2.49 | 0.01 | 1.31 | 9.88 |
| e1e1d3 | 1.28 | 0.46 | 0.70 | 0.49 | 0.64 | 2.57 |
| ff4457 | 1.79 | 0.66 | 1.59 | 0.11 | 0.87 | 3.67 |
|  |  |  |  |  |  |  |
| cluster\_size | 2.55 | 0.85 | 2.81 | 0.01 | 1.33 | 4.92 |
|  |  |  |  |  |  |  |
| lab\_available |  |  |  |  |  |  |
| Lab | 1.55 | 0.40 | 1.70 | 0.09 | 0.94 | 2.57 |
|  |  |  |  |  |  |  |
| age\_over\_40 |  |  |  |  |  |  |
| >40 years | 0.52 | 0.29 | -1.17 | 0.24 | 0.18 | 1.55 |
|  |  |  |  |  |  |  |
| primiparous |  |  |  |  |  |  |
| Primiparous | 1.48 | 0.23 | 2.56 | 0.01 | 1.10 | 1.99 |
| \_cons | 0.86 | 0.33 | -0.40 | 0.69 | 0.41 | 1.82 |
| /lnsig2u | -0.28 | 0.24 |  |  | -0.75 | 0.19 |
| sigma\_u | 0.87 | 0.10 |  |  | 0.69 | 1.10 |
| rho | 0.19 | 0.04 |  |  | 0.13 | 0.27 |