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

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). We masked the treatment allocation from the statistician during analysis.

# Results

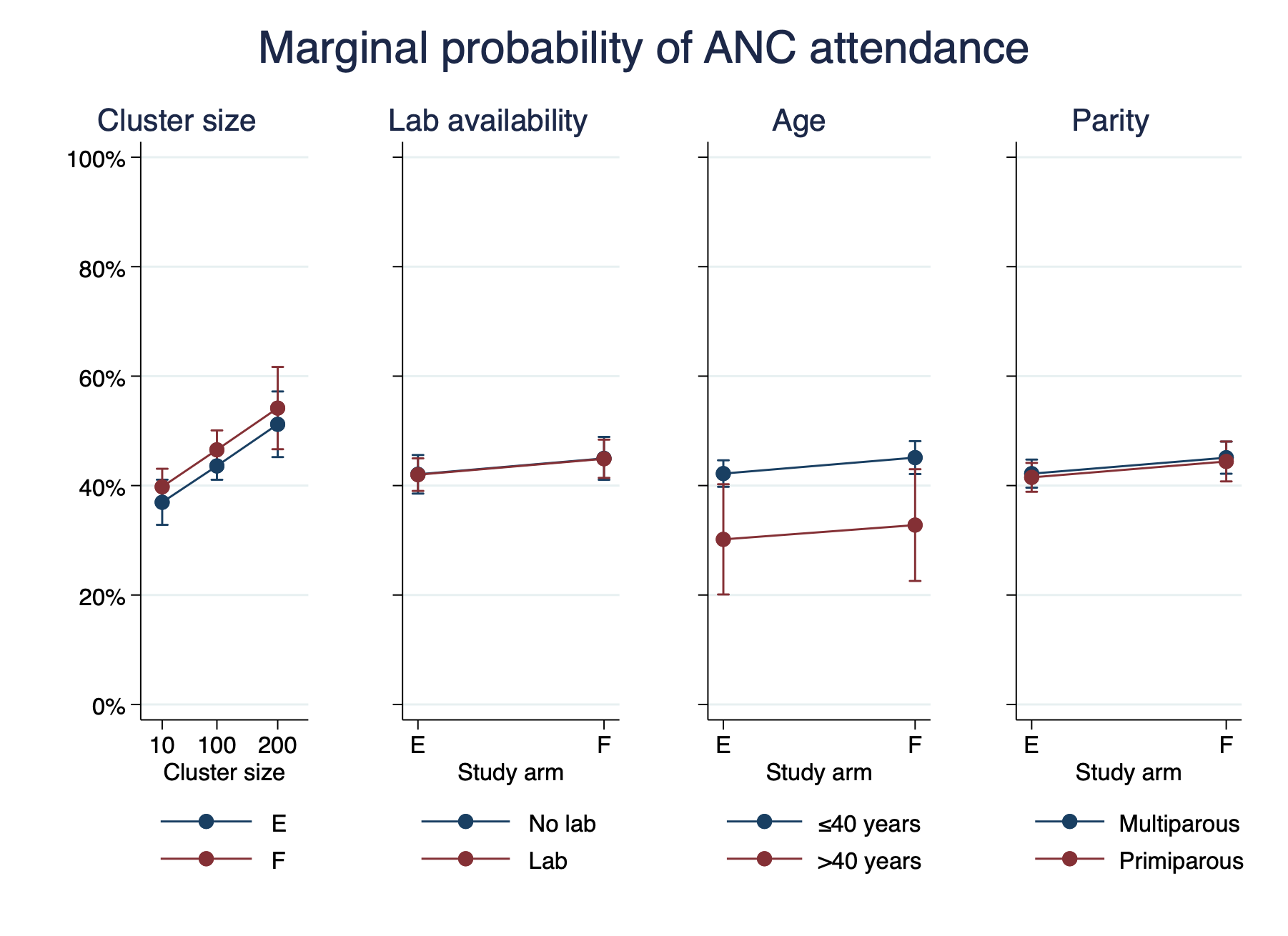
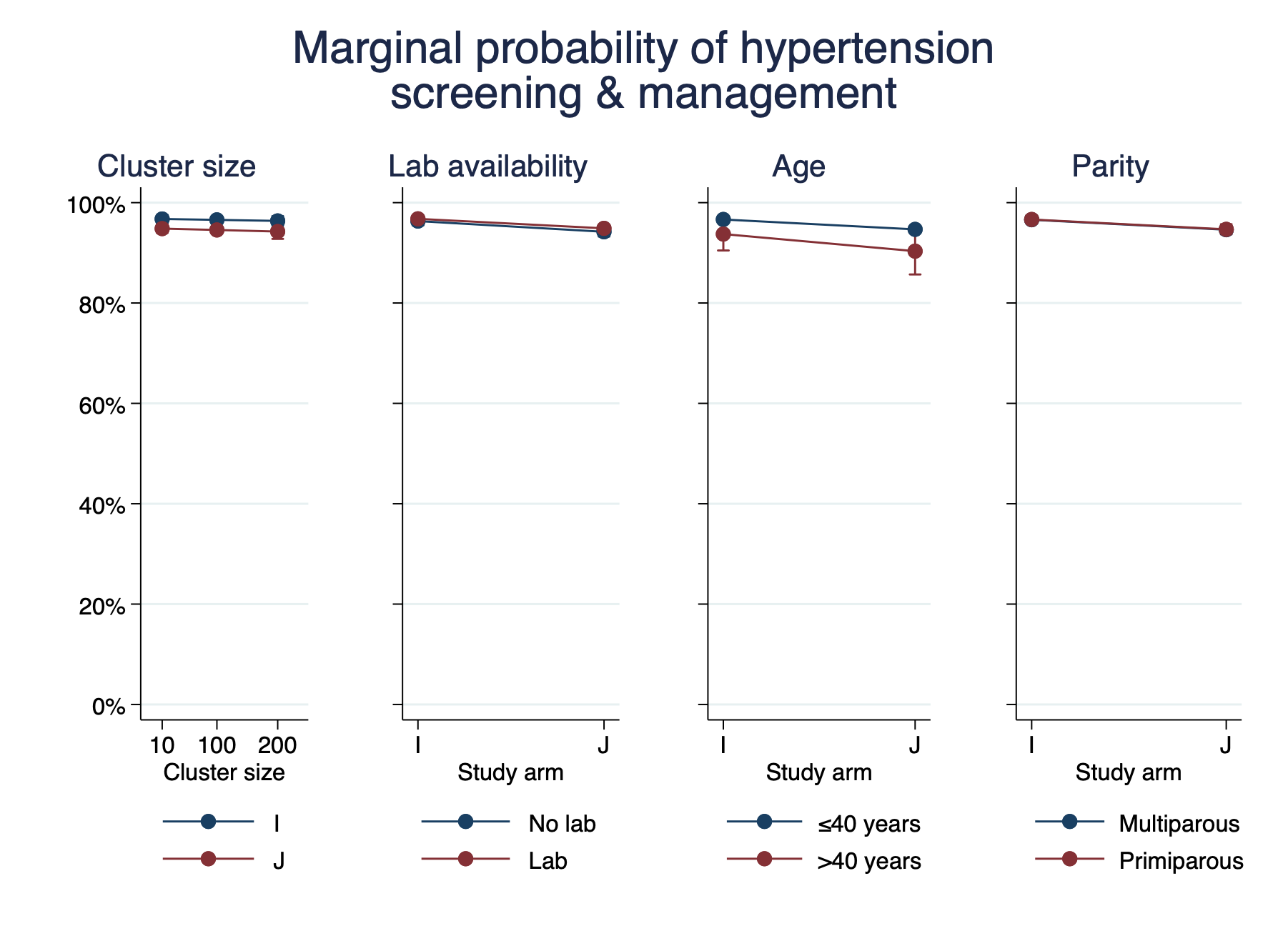
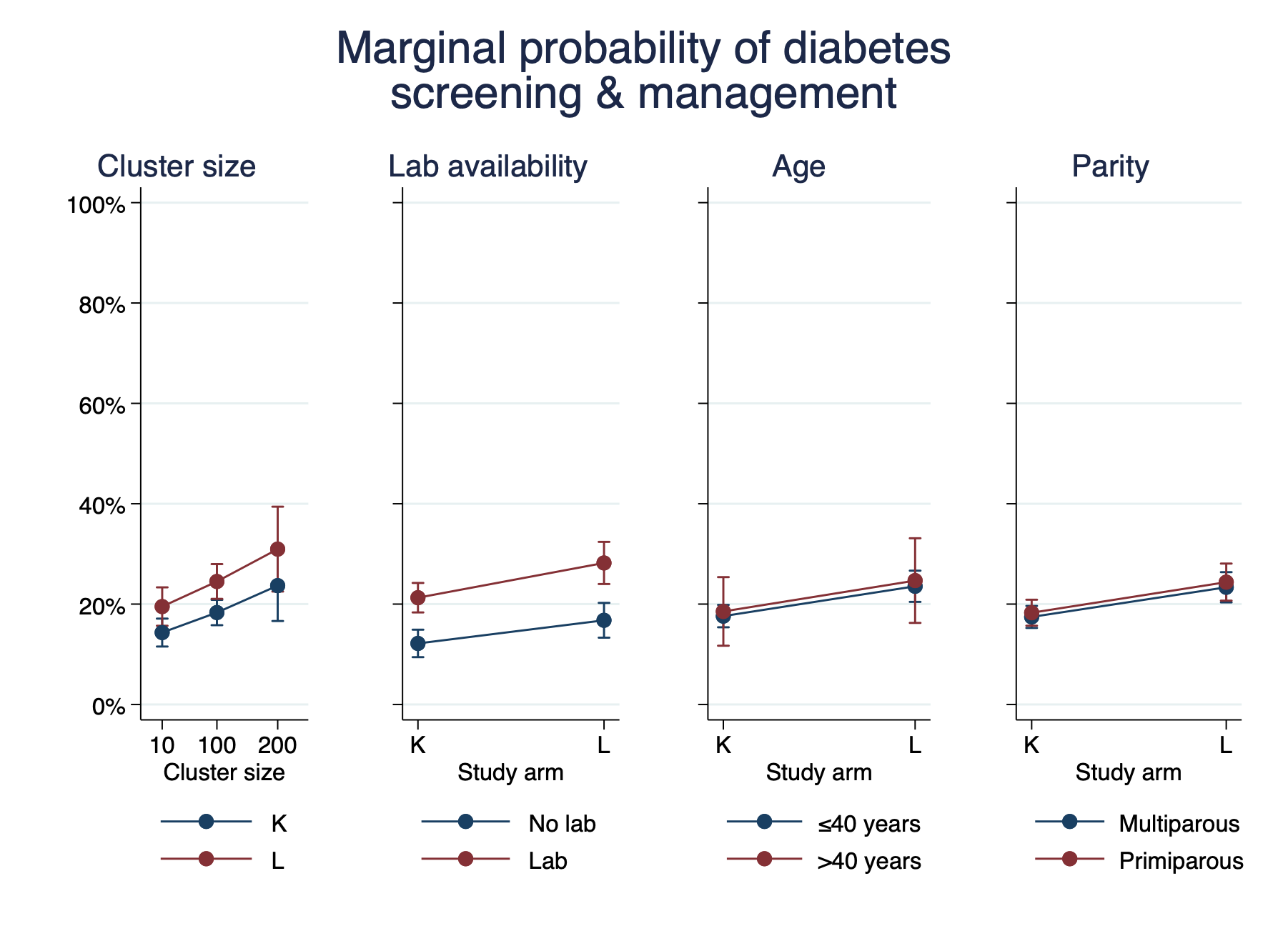
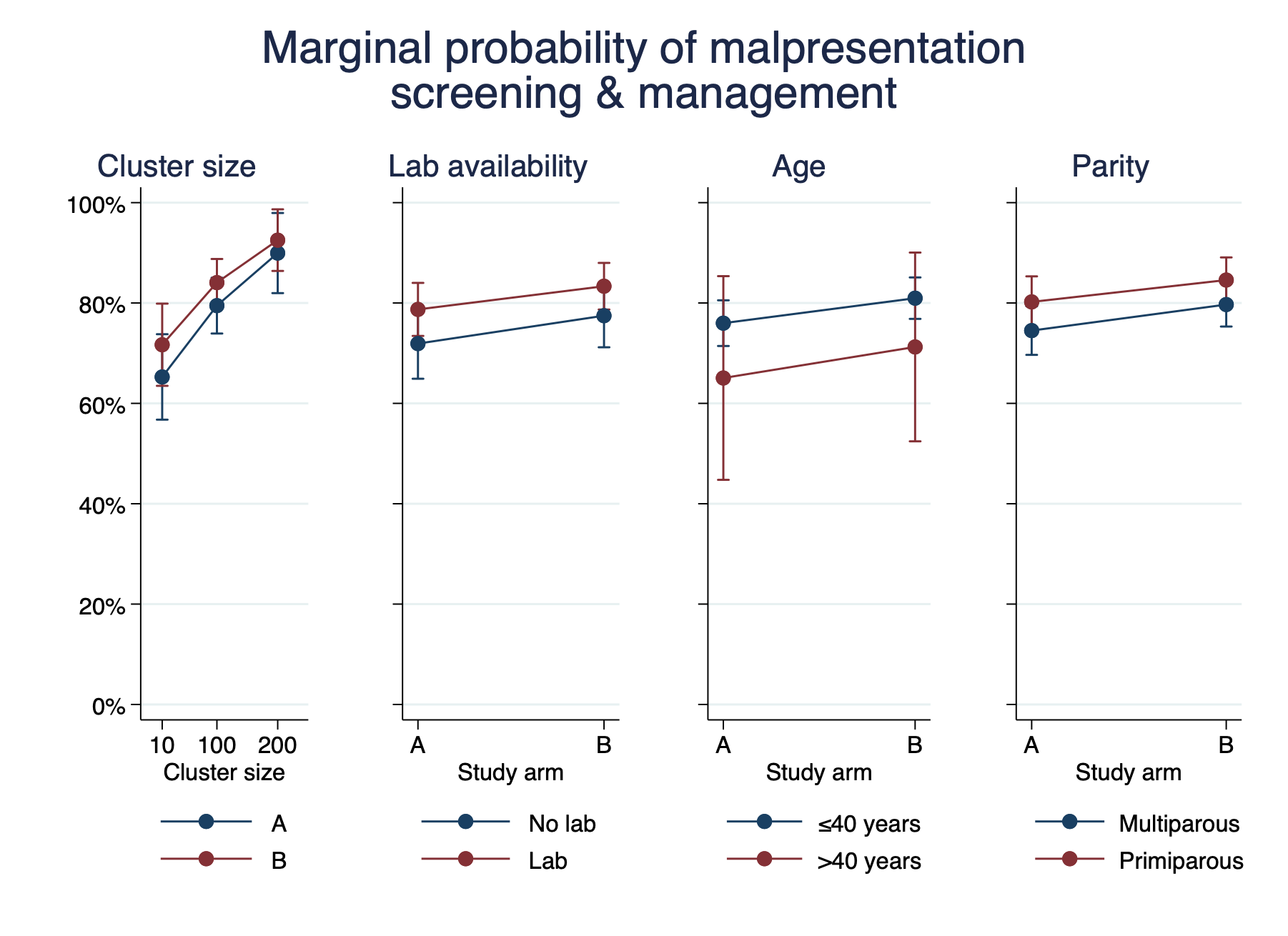
## Process outcomes

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| --- | --- | --- | --- | --- | --- | --- |
| Table 1. 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 |

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Table 2. 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 3. 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 |

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| --- | --- | --- | --- | --- | --- | --- |
| Table 4. 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

Committee for Medicinal Products for Human Use (CHMP) (2015). Guideline on adjustment for baseline covariates in clinical trials. London: European Medicines Agency.

van Buuren, S. (2007). Multiple imputation of discrete and continuous data by fully conditional specification. Statistical methods in medical research, 16(3), 219-242.

Li, F., Turner, E. L., Heagerty, P. J., Murray, D. M., Vollmer, W. M., & DeLong, E. R. (2017). An evaluation of constrained randomization for the design and analysis of group‐randomized trials with binary outcomes. Statistics in medicine, 36(24), 3791-3806.

Little, R. J. (1988). A test of missing completely at random for multivariate data with missing values. Journal of the American statistical Association, 83(404), 1198-1202.

Rubin, D. B. (2004). Multiple imputation for nonresponse in surveys (Vol. 81). John Wiley & Sons.

# 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 3 — Full Process Outcome Results

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

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| Table 5. 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 6. 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 7. 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 8. 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 |