Original Research Article

Title: The Missing Covariate Indicator Method is Nearly Valid Almost Always

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Abbreviations: HPFS, Health Professionals Follow-up Study; MAR, missing at random; MCAR, missing completely at random; MCIM, missing covariate indicator method; NHS, Nurses’ Health Study.

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Conflicts of Interest
The authors have no conflict of interest to disclose.

Source of Fund
This work was supported by grants of DPES025459 and K99CA215314 from the National Institutes of Health; by the 2017 AACR-AstraZeneca Fellowship in Immuno-oncology Research (Grant Number 17-40-12-SONG) from the American Association for Cancer Research; and by a Mentored Research Scholar Grant (MRSG-17-220-01 – NEC) in Applied and Clinical Research from the American Cancer Society. The authors assume full responsibility for analyses and interpretation of these data.

The data and computing code required to replicate the results reported in this work can be obtained by contacting the corresponding author directly.
Abstract

Background: Although the missing covariate indicator method (MCIM) has been shown to be biased under extreme conditions, the degree and determinants of bias have not been formally assessed.

Methods: We derived the formula for the relative bias in the MCIM and systematically investigated conditions under which bias arises.

Results: We found that the extent of bias is independent of both the disease rate and the exposure-outcome association, but is a function of 5 parameters: exposure and covariate prevalences, covariate missingness proportion, and associations of covariate with exposure and outcome. The MCIM was unbiased when the missing covariate is a risk factor for the outcome but not a confounder. The average median relative bias was zero across each of the parameters over a wide range of values considered. When missingness was no greater than 50%, less than 5% of the scenarios considered had relative bias greater than 10%. In several analyses of the Harvard cohort studies, the MCIM produced materially the same results as the multiple imputation method.

Conclusion: The MCIM is nearly valid almost always in settings typically encountered in epidemiology and its continued use is recommended, unless the covariate is missing in an extreme proportion or acts as a strong confounder.

Keywords: confounding, missing covariate indicator method, multiple imputation, relative bias.
INTRODUCTION

Missing data is a common problem encountered in many epidemiologic and clinical studies. It can occur in any of the variables in a study, including exposure, outcome, or covariates that may or may not be confounders of the exposure-outcome relationship.¹ In epidemiology, we typically treat missing data in potential confounders differently than missing data in the primary outcome and exposure variables for analysis. For example, missing data on outcomes can seriously compromise inferences from clinical trials, and robust prevention and treatment measures have been summarized.² In observational studies, participants without data on the primary exposure or outcome are typically excluded from the study. That is, not having data on the outcome of interest or the exposure under investigation is a primary exclusion criterion for most studies. If participants who are included in the study population are different in ways that lead to bias in the estimated measure of exposure-outcome association, selection bias results. In general, selection bias in the relative risk will result when the probability of being included in the study population depends jointly on exposure and outcome status, after properly controlling for confounders.³ Methods to deal with selection bias have been an active research area and will not be discussed any further here.⁴ In this study, we focus on missingness in covariates.

As the simplest approach, complete-case analysis is inefficient and can be biased, because subjects with complete data recorded for all covariates can be a small and biased subsample of the study subjects.⁵ Other more sophisticated modeling or imputation-based approaches have been developed during the past few decades, such as inverse probability weighting, multiple imputation, and maximum likelihood.⁶ Although these methods are theoretically appealing, their validity is dependent on correct specification of an additional model,⁷ invoking what are often empirically unverifiable assumptions that can pose even greater challenges for complex models.
in longitudinal settings.\textsuperscript{8} An additional practical limitation is their computational cost that may be prohibitive in large epidemiologic studies and even more so in this era of ‘big data’.

Another simple approach for missing covariates is the indicator method (MCIM), where a missing indicator is created and added to the model for each variable with missing data.\textsuperscript{9} The missing indicator takes the value 1 whenever the original variable is missing, and 0 otherwise. We then assign the value of 0 to the original covariate for all those originally missing on the covariate. Formally, let $M_i$ be the missing indicator for participant $i$ and $C_i$ be participant $i$’s value of the covariate that is sometimes missing. The new variables are $M_i$ and $(1 - M_i)C_i$. To apply the MCIM method to a stratified 2x2 table analysis, we stratify by both the missing indicator and the recoded original variable (with missing values replaced by 0) to estimate the relative risk, or, in a regression analysis, we control for both $M_i$ and $(1 - M_i)C_i$ in the model. Because all participants are included in the analysis, the missing indicator method is more efficient than the complete-case analysis. Although the missing indicator method has been shown to be biased under extreme conditions,\textsuperscript{10,11} the degree and determinants of bias have not been formally assessed. Therefore, in this study, we performed numerical calculations for the bias arising from the MCIM. To put our findings in the context of large cohort studies, we also compared the results from previously published studies that have used both the MCIM and the multiple imputation method.

METHODS
Numerical bias evaluation

Notation.

For illustrative purposes, we considered a binary exposure ($E$), outcome ($Y$), and covariate ($C$). For the covariate $C$ that is missing in some participants, the missing indicator method stratifies the data by three levels of the covariate: $C = 1, 0, \text{ and missing (Table 1)}$. For simplicity, we first assume that the missing covariate mechanism is completely at random (MCAR), that is, that the probability of missingness of the covariate is independent of any observed or unobserved data included in the primary outcome model. The stratified 2x2 tables for $C = 1$ and $0$ are unconfounded by the covariate $C$ and thus give valid estimates for the effect of exposure on outcome. The stratum with missing covariate is a crude table, collapsed over the two levels of the covariate. Therefore, it may yield a biased exposure estimate if $C$ is indeed a confounder. The convergent value of the final summary effect estimate of relative risk, $RR_e$, is then a weighted average of the convergent value of one biased estimate, $RR_{miss}$, along with the convergent value of two valid estimates, $RR_{C=1}$ and $RR_{C=0}$. Assuming homogeneity of relative risks across strata formed by levels of the covariate, $C$, $RR_{C=1}$ and $RR_{C=0}$ are equal, and denoted by $RR(E)$. It is usually the case that this assumption is valid $^{12}$.

Thus, $RR_e = [1 - Pr(C_{miss})] * RR(E) + Pr(C_{miss}) * RR_{miss}$, where $Pr(C_{miss})$ is the proportion of participants with the missing covariate. We derived an expression for $P_{bias}$ as a function of 5 underlying parameters (see Appendix 1): the prevalence of the exposure, $Pr(E)$, the prevalence of the covariate, $Pr(C)$, the proportion of missingness $Pr(C_{miss})$, the effect of the covariate on the outcome, $RR(C)$, and the association between the exposure and the covariate, $RR(E|C)$.
In many epidemiologic and clinical studies, the parameter of interest is the odds ratio. If the prevalence of the outcome, that is, $Pr(Y)$, is low, which is often the case, the odds ratio approximates the relative risk well. Then, formula (1) applies to the odds ratio as well.

In Appendix 2, we investigate under what circumstances the above formula applies when the missing covariate data mechanism is missing at random (MAR), that is, when the probability of missingness of the covariate depends only upon variables that are never missing in the data. We show that formula (1) is valid when missingness is independent of the outcome, $Y$, but applies even when covariate missingness depends on the exposure, $E$.

**Numerical Bias Evaluation of the MCIM.**

Based on the ranges typically encountered in epidemiologic studies, we assigned a range of values to each of the 5 determining parameters for $P_{bias} \%$ (Table 2). For example, we allowed the relative risk estimate for the effect of the covariate on the outcome to range from $1/5$ to $5$. We then calculated the $P_{bias} \%$ based on all 33,540 valid combinations of the values considered for each of the 5 parameters over the range. Because we were able to obtain a closed-form analytic expression for $P_{bias} \%$, the quantity of interest in this study, there is no need for simulations and this paper does not include any.

**The extent of covariate missingness in large observational cohort studies**
To examine the extent to which missingness occurs in some typical epidemiologic studies, we calculated the proportion of missing covariate data in two large cohort studies, the Nurses’ Health Study (NHS) I and II, using breast cancer risk factors as an example. The NHS I is a prospective cohort which began in 1976 when 121,700 female nurses aged 30-55 years completed a mailed health questionnaire. Similar questionnaires were returned in 1989 from the NHS II, comprised of 116,430 female nurses aged 25-42 years. Follow-up questionnaires were mailed biennially to members of the two cohorts to update lifestyle and medical information. Diet was assessed using a validated food frequency questionnaire every four years. We calculated the proportion of person-years for which the variables were missing among the total person-years. We considered a variety of reproductive and lifestyle breast cancer risk factors, including age at first birth, alcohol consumption, history of benign breast disease, family history breast cancer, age at menarche, age of menopause, physical activity, oral contraceptive use, postmenopausal hormone use, and body mass index.

**Comparison of the results produced by MCIM and multiple imputation**

Because investigators who use MCIM in their primary analyses are occasionally asked by reviewers to use multiple imputation for missing covariate data, at least as a sensitivity analysis, we performed a head-to-head comparison of the results produced by the two methods in the five published studies, among thousands using data from three cohort studies, the NHS I and II and the Health Professionals Follow-up Study (HPFS), where this was requested. The HPFS is an observational cohort that enrolled 51,529 male health professionals aged 40-75 years in 1986. Similar follow-up procedures have been used as in the NHS I and II.
RESULTS

When the covariate with missingness is a risk factor but not a confounder (or neither), the MCIM is unbiased

It is immediately evident from equation (1) that when \( RR(C) = 1 \) or \( RR(E|C) = 1 \), \( P_{bias} \% = 0 \). Often, risk factors for the outcome are adjusted for in the analysis when they are not confounders; in many models, doing so will improve the precision of the estimate of the parameter of interest, here, \( RR(E) \). Other times, to be conservative to strengthen the validity of a causal inference, investigators will adjust for known and suspected risk factors for the outcome even when they might not be confounders, in case they are. When this adjustment turns out to be unnecessary for validity purposes, as might often be the case, the MCIM method will be unbiased.

Almost no bias nearly always

Within each unique combination of the 5 parameters determining \( P_{bias} \% \), we calculated the median, 25th and 75th percentile of \( P_{bias} \% \), as well as the percentage of instances where \( P_{bias} \% \) was higher than 5% and 10% (Table 3). The median of \( P_{bias} \% \) was zero for each parameter value averaged over all the others, with the 25th and 75th percentiles below 0.5% in all but extreme cases, such as when the covariate missingness proportion exceeded 25%, or when the exposure or covariate was associated with a five-fold increase in risk of the outcome. Furthermore, \( P_{bias} \% \) exceeded 10% in only 1.1% of the parameter space explored. For example,
was greater than 10% in 4.8% of the scenarios considered when the covariate was missing in half of the study population, and was greater than 10% in 4.3% of the scenarios considered when the covariate was a strong confounder, with a relative risk for the outcome in relation to the confounder greater than 5. Even a $P_{bias}$% greater than 5%, as shown in the last column of Table 3, was a rare event in most scenarios considered here.

**Low missingness in large, well-established cohorts**

We explored the extent of missing covariate data in some well-established cohort studies, using the NHS I and II as an example. We calculated the proportion of missing data among common risk factors for breast cancer measured in these studies. As shown in Table 4, most risk factors were missing less than 5% of the person-time under follow-up and the extent of missingness rarely exceeded 10%.

**No difference between results from MCIM and multiple imputation**

Because MCIM has been considered a biased method, studies that use this method in their primary analysis are occasionally asked by journal reviewers to run additional analyses using more sophisticated methods for handling missing covariate data, such as multiple imputation. Therefore, to assess the extent to which the results are changed after switching from MCIM to multiple imputation, we compiled results from published studies in the three Harvard cohorts that have used both methods in the analysis. As shown in Table 5, multiple imputation yielded materially the same results as MCIM in all cases considered.
DISCUSSION

We derived an explicit expression for the bias associated with the use of MCIM. We were then able to show that when the covariate is not a confounder, MCIM is unbiased. We also conducted extensive numerical bias evaluations over a wide range of values typically encountered in epidemiologic settings for each parameter that determines the percent bias in MCIM. We found that the bias in MCIM was minimal in all but the most extreme cases. This result was further supported by empirical comparisons of results using the MCIM and multiple imputation in published studies.

Despite the ease of use, MCIM has generally been considered an unacceptably biased method for dealing with missing covariate data. This perception is largely based on two commonly cited studies published in 1990s. Vach and Belttner performed the first quantitative investigation of the bias due to MCIM and concluded that “an important result of our empiric investigation is that creating an additional category for the missing values always yields biased results”. However, this conclusion was drawn based on an assessment using extreme values for the parameters that determine the bias. For example, the authors used a relative risk of 0.36 for the outcome associated with covariate ($RR(C)$), and a relative risk of 9 for the relationship between the exposure and the covariate ($RR(E|C)$). Based on our numerical calculation, these values are indeed likely to produce biased results. However, these extreme values are rarely encountered in epidemiologic studies, and for them both to occur simultaneously in a single study setting is extremely unlikely.

Similarly, in the simulation study by Greenland and Finkle, the missing covariate proportion was set at 50%, indicating that half of the participants had missing data, and the resulting values for $RR(E)$ produced by the MCIM ranged from 1.43 to 1.58 when the true $RR(E)$ was 2. Again,
this relatively large bias is not surprising, given that, as shown in our Table 3, at

\( Pr(C_{\text{miss}}) = 0.50 \), about 9% of scenarios across the other parameters result in a \( P_{\text{bias}} \)% greater than 5%. Therefore, although it may first appear that our results are in conflict with the findings of these two previous studies, once the empirical values used in these investigations are considered, it is clear that while substantial bias can occur in rare, extreme cases, the bias is at most moderate in typical epidemiologic studies. This conclusion is consistent with the head-to-head comparisons of MCIM and multiple imputation in published studies from the Harvard cohorts 16-20.

While our derivation for the MCIM-related bias is based on the MCAR assumption, we also investigated under what circumstances the same formula (1) would apply when the missing covariate data mechanism is MAR. As demonstrated in Appendix 2, we found that the formula is valid in the case of MAR, as long as missingness of the covariate is independent of the outcome. This would typically be the case in cohort studies and in nested case-control studies, but may not be reasonable in population-based case-control studies. It should be noted that other methods, including the maximum likelihood and multiple imputation approaches, are also based on the MAR assumption. Finally, although for ease of communication we considered only one additional risk factor for the outcome as a possible determinant of the MAR mechanism, it is a simple extension that an arbitrary number of \( q \) additional covariates can be addressed by this work, simply by mapping them all into a single high or low risk indicator or through a propensity score.

In summary, through a comprehensive and systematic assessment using several approaches, we found no to minimal bias arising from the use of MCIM under a quite large range of circumstances that are typically encountered in epidemiologic studies. The continued use of
MCIM is recommended unless the covariate is missing in an extreme proportion or acts as a strong confounder, with a relative risk for the outcome in relation to the confounder greater than 5 or with a very strong association between the exposure and confounder, both of which rarely occur in practice.

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Table 1. 2×2 Tables for Analysis Using the Missing Covariate Indicator Method

|       | \( C = 1 \) | \( C = 0 \) | \( C = missing \) |
|-------|-------------|-------------|-------------------|
|       | \( E = 1 \) | \( E = 0 \) | \( E = 1 \) | \( E = 0 \) |
| \( Y = 1 \) | \( a_1 \) | \( b_1 \) | \( a_0 \) | \( b_0 \) | \( a_m \) | \( b_m \) |
| \( Y = 0 \) | \( c_1 \) | \( d_1 \) | \( c_0 \) | \( d_0 \) | \( c_m \) | \( d_m \) |
| Total | \( n_{11} \) | \( n_{10} \) | \( n_{01} \) | \( n_{00} \) | \( n_{m1} \) | \( n_{m0} \) |
Table 2. The Values of Each Parameter over which $P_{bias} \%$ was Numerically Evaluated

| Parameter | Value                  |
|-----------|------------------------|
| $Pr(C_{\text{miss}})$ | 0.005, 0.01, 0.05, 0.10, 0.25, 0.50 |
| $Pr(E)$   | 0.01, 0.05, 0.1, 0.25, 0.50, 0.75 |
| $Pr(C)$   | 0.01, 0.05, 0.1, 0.25, 0.50, 0.75 |
| $RR(C)$   | 1/5, 1/3, 1/2, 1/1.5, 1/1.25, 1/1.15, 1, 1.15, 1.25, 1.5, 2, 3, 5 |
| $RR(E|C)$ | 1/5, 1/3, 1/2, 1/1.5, 1/1.25, 1/1.15, 1, 1.15, 1.25, 1.5, 2, 3, 5 |
| Parameter value | Median | Percentile 25 | Percentile 75 | Percentage of $P_{bias}^\% > 10\%$ | Percentage of $P_{bias}^\% > 5\%$ |
|-----------------|-------|---------------|---------------|----------------------------------|----------------------------------|
| Overall         | 0     | -0.09         | 0.09          | 1.13                             | 2.61                             |
| Pr(E)           |       |               |               |                                  |                                  |
| 0.01            | 0     | -0.07         | 0.07          | 0.81                             | 2.07                             |
| 0.05            | 0     | -0.08         | 0.07          | 0.81                             | 2.07                             |
| 0.1             | 0     | -0.08         | 0.08          | 0.84                             | 2.15                             |
| 0.25            | 0     | -0.09         | 0.09          | 1.28                             | 2.73                             |
| 0.5             | 0     | -0.11         | 0.11          | 1.43                             | 3.15                             |
| 0.75            | 0     | -0.15         | 0.14          | 1.90                             | 3.99                             |
| Pr(C)           |       |               |               |                                  |                                  |
| 0.01            | 0     | -0.01         | 0.01          | 0                                | 0.07                             |
| 0.05            | 0     | -0.05         | 0.05          | 0.31                             | 0.87                             |
| 0.1             | 0     | -0.10         | 0.10          | 0.82                             | 1.87                             |
| 0.25            | 0     | -0.20         | 0.21          | 1.71                             | 3.88                             |
| 0.5             | 0     | -0.24         | 0.26          | 2.17                             | 4.99                             |
| 0.75            | 0     | -0.20         | 0.21          | 1.73                             | 3.90                             |
| Pr(C_{miss})    |       |               |               |                                  |                                  |
| 0.005           | 0     | -0.01         | 0.01          | 0                                | 0                                |
| 0.01            | 0     | -0.02         | 0.02          | 0                                | 0                                |
| 0.05            | 0     | -0.10         | 0.10          | 0.23                             | 0.23                             |
| 0.1             | 0     | -0.21         | 0.21          | 0.23                             | 1.29                             |
| 0.25            | 0     | -0.52         | 0.52          | 1.79                             | 4.74                             |
| 0.5             | 0     | -1.04         | 1.05          | 4.74                             | 9.37                             |
| RR(C)           |       |               |               |                                  |                                  |
| 1/5             | 0     | -0.24         | 0.28          | 3.02                             | 5.81                             |
| 1/3             | 0     | -0.18         | 0.22          | 2.09                             | 4.65                             |
| ½               | 0     | -0.13         | 0.16          | 1.01                             | 2.79                             |
| 1/1.5           | 0     | -0.08         | 0.09          | 0.19                             | 1.28                             |
| 1/1.25          | 0     | -0.05         | 0.05          | 0                                | 0.23                             |
| 1/1.15          | 0     | -0.03         | 0.03          | 0                                | 0.04                             |
| 1               | 0     | 0             | 0             | 0                                | 0                                |
| 1.15            | 0     | -0.04         | 0.03          | 0                                | 0.04                             |
| 1.25            | 0     | -0.06         | 0.05          | 0                                | 0.23                             |
| 1.5             | 0     | -0.11         | 0.10          | 0.19                             | 1.40                             |
| 2               | 0     | -0.21         | 0.19          | 1.16                             | 3.37                             |
| 3               | 0     | -0.34         | 0.32          | 2.64                             | 5.74                             |
| 5               | 0     | -0.54         | 0.51          | 4.34                             | 8.29                             |
| RR(E|C)           |       |               |               |                                  |                                  |
| 1/5             | 0     | -0.30         | 0.23          | 2.60                             | 5.13                             |
| 1/3             | 0     | -0.24         | 0.18          | 1.83                             | 4.12                             |
| ½               | 0     | -0.17         | 0.13          | 1.09                             | 2.75                             |
| 1/1.5           | 0     | -0.12         | 0.09          | 0.48                             | 1.65                             |
| 1/1.25          | 0     | -0.07         | 0.05          | 0.18                             | 0.64                             |
| 1/1.15          | 0     | -0.05         | 0.03          | 0.07                             | 0.28                             |
| 1               | 0     | 0             | 0             | 0                                | 0                                |
| 1.15            | 0     | -0.04         | 0.05          | 0.07                             | 0.36                             |
| 1.25            | 0     | -0.06         | 0.08          | 0.21                             | 0.82                             |
| 1.5             | 0     | -0.10         | 0.14          | 0.52                             | 2.12                             |
| 2               | 0     | -0.17         | 0.24          | 1.57                             | 4.05                             |
| 3               | 0     | -0.30         | 0.40          | 2.94                             | 6.32                             |
| 5               | 0     | -0.48         | 0.67          | 4.82                             | 8.97                             |
Table 4. Percentage of Missingness (%) in the Established Breast Cancer Risk Factors in the Nurses’ Health Study (NHS) I and II*

| Factor                        | NHS I (1976-2008) | NHS II (1989-2009) |
|-------------------------------|-------------------|--------------------|
| Age at 1st birth              | 2.22              | 0                  |
| Alcohol                       | 11.75             | 0.27               |
| History of benign breast disease | 0                | 0                  |
| Family history breast cancer  | 0                 | 0                  |
| Age at menarche               | 0.90              | 0.33               |
| Age of menopause menopause    | 9.37              | 6.57               |
| Physical Activity             | 8.78              | 0.07               |
| Oral contraceptive use        | 4.90              | 0.02               |
| Postmenopausal hormone use     | 1.05              | 0.05               |
| Body mass index               | 0.34              | 0.28               |

*Calculated as the proportion of person-years for which the variable had missing data among the total person-years.
| Publication Year (First Author) | Journal                  | Exposure of Interest                  | Outcome                             | Exposure Categories | Missing Covariate Indicator Method | Multiple Imputation |
|--------------------------------|--------------------------|---------------------------------------|-------------------------------------|---------------------|-----------------------------------|---------------------|
| 2010 (Fung T)                  | Ann Intern Med           | Low-carbohydrate diet score           | All-cause mortality                 | 5th vs. 1st decile  | 1.04 (0.96-1.12)                  | 1.06 (1.03-1.10)    |
| 2012 (Joosten MM)              | JAMA                     | Conventional cardiovascular risk factors | Peripheral artery disease          | Ever smoking        | 2.44 (1.98-3.00)                  | 2.43 (1.98-2.99)    |
|                                |                          |                                       |                                     | Hypertension         | 2.45 (2.01-2.98)                  | 2.47 (2.03-3.01)    |
|                                |                          |                                       |                                     | Cholesterolemia      | 1.42 (1.18-1.72)                  | 1.47 (1.22-1.77)    |
|                                |                          |                                       |                                     | Diabetes             | 2.45 (1.98-3.03)                  | 2.42 (1.96-2.90)    |
|                                |                          |                                       |                                     | Per 1 unit increment in score | 2.10 (1.92-2.30)                  | 2.12 (1.94-2.32)    |
| 2013 (Cahill LE)               | Circulation              | Breakfast eating                      | Coronary heart disease             | Skipping Breakfast  | 1.27 (1.06-1.53)                  | 1.29 (1.07-1.56)    |
|                                |                          |                                       |                                     | Late night eating    | 1.55 (1.05-2.29)                  | 1.53 (1.01-2.32)    |
|                                |                          |                                       |                                     | Eating frequency     |                                     |                     |
|                                |                          |                                       |                                     | 1-2 times/day        | 1.10 (0.91-1.31)                  | 1.17 (0.86-1.58)    |
|                                |                          |                                       |                                     | 3 times/day          | 1 (reference)                   | 1 (reference)       |
|                                |                          |                                       |                                     | 4-5 times/day        | 1.05 (0.94-1.18)                  | 1.05 (0.79-1.38)    |
|                                |                          |                                       |                                     | 6+ times/day         | 1.26 (0.90-1.77)                  | 1.21 (0.56-2.61)    |
| 2013 (Pan A)                   | JAMA Intern Med          | Change in red meat consumption        | Type II diabetes              | Decrease of >0.50    | 0.95 (0.84-1.07)                  | 0.98 (0.87-1.1)     |
|                                |                          |                                       |                                     | Decrease of 0.15-0.50 | 0.98 (0.89-1.08)                  | 0.99 (0.9-1.095)    |
|                                |                          |                                       |                                     | Change within ±0.14  | 1 (reference)                   | 1 (reference)       |
|                                |                          |                                       |                                     | Increase of 0.15-0.50 | 1.10 (0.99-1.21)                  | 1.09 (0.98-1.21)    |
|                                |                          |                                       |                                     | Increase of >0.50    | 1.22 (1.08-1.38)                  | 1.19 (1.06-1.35)    |
| 2016 (Mu F)                    | Circ Cardiovasc Qual Outcomes | Endometriosis                        | Coronary heart disease           | Endometriosis        | 1.62 (1.39-1.89)                  | 1.63 (1.38-1.92)    |
Appendix 1. Derivation of the percentage of bias

1. Parameter notations:

\( P_{bias} \% \): percentage of bias arising from missing covariate indicator method

\( \Pr(Y) \): cumulative incidence of outcome

\( \Pr(E) \): prevalence of exposure

\( \Pr(C) \): prevalence of covariate

\( \Pr(C_{miss}) \): proportion of missingness in covariate

\( RR(E) \): expected relative risk of outcome associated with exposure

\( RR_e \): estimated relative risk of outcome associated with exposure

\( RR_{miss} \): crude estimate of the relative risk of outcome associated with exposure in the stratum with missing covariate (see Table 1 in the main text)

\( RR(C) \): expected relative risk of outcome associated with covariate

\( RR(E|C) \): expected relative risk for the association between exposure and covariate

2. Derivation of \( P_{bias} \% \)

For this section, we assume that the missing covariate mechanism is missing completely at random (MCAR). The Appendix 2 demonstrates the sufficient conditions under which the same results would apply for missing at random (MAR).

The derivation is based on the complete data. Let \( N_C \) be the size of complete data, i.e., \( N_C = n_{00} + n_{01} + n_{10} + n_{11} \). Using the notation in Table 1,

\[
RR_{miss} = \left( \frac{a_1 + a_0}{a_1 + a_0 + c_1 + c_0} \right) \left( \frac{b_1 + b_0}{b_1 + b_0 + d_1 + d_0} \right) = \frac{(a_1 + a_0)(b_1 + b_0 + d_1 + d_0)}{(a_1 + a_0 + c_1 + c_0)(b_1 + b_0)}
\]

Given that \( \frac{E(b_1+b_0+d_1+d_0)}{E(a_1+a_0+c_1+c_0)} = \frac{1-\Pr(E)}{\Pr(E)} \), next we derive \( \frac{E(a_1+a_0)}{E(b_1+b_0)} \).

Based on Table 1, \( a_1 \) can be expressed as \( E(a_1) = \Pr(Y = 1|E = 1, C = 1)E(n_{11}) \).
Assume homogeneity of relative risks across the covariate \( C \), that is,

\[
RR(E) = \frac{\Pr (Y = 1|E = 1, C = 1)}{\Pr (Y = 1|E = 0, C = 1)} = \frac{\Pr (Y = 1|E = 1, C = 0)}{\Pr (Y = 1|E = 0, C = 0)}.
\]

Similarly,

\[
RR(C) = \frac{\Pr (Y = 1|E = 1, C = 1)}{\Pr (Y = 1|E = 1, C = 0)} = \frac{\Pr (Y = 1|E = 0, C = 1)}{\Pr (Y = 1|E = 0, C = 0)}.
\]

Based on Table 1, we have

\[
E(a_1) = \Pr(Y = 1|E = 1, C = 1)E(n_{11}) = \Pr(Y = 1|E = 1, C = 1) \Pr(C = 1|E = 1) \Pr(E = 1) N_C.
\]

Similarly,

\[
E(a_0) = \Pr(Y = 1|E = 1, C = 0) \Pr(C = 0|E = 1) \Pr(E = 1) N_C,
\]

\[
E(b_1) = \Pr(Y = 1|E = 0, C = 1) \Pr(C = 1|E = 0) \Pr(E = 0) N_C, \text{ and}
\]

\[
E(b_0) = \Pr(Y = 1|E = 0, C = 0) \Pr(C = 0|E = 0) \Pr(E = 0) N_C.
\]

By the law of total probability rule,

\[
\Pr(E = 1) = \Pr(E = 1|C = 1) \Pr(C) + \Pr(E = 1|C = 0) [1 - \Pr(C)]
\]

\[
= RR(E|C) \Pr(E = 1|C = 0) \Pr(C) + \Pr(E = 1|C = 0) [1 - \Pr(C)]
\]

\[
= \Pr(E = 1|C = 0) [RR(E|C) \Pr(C) + 1 - \Pr(C)]
\]

Therefore, \( \Pr(E = 1|C = 0) = \frac{\Pr(E)}{RR(E|C) \Pr(C) + 1 - \Pr(C)} \) and \( \Pr(E = 1|C = 1) = \frac{RR(E|C) \Pr(C)}{RR(E|C) \Pr(C) + 1 - \Pr(C)} \).

Then,

\[
\Pr(C = 1|E = 1) = \frac{\Pr(E = 1|C = 1) \Pr(C)}{\Pr(E)} = \frac{RR(E|C) \Pr(C)}{RR(E|C) \Pr(C) + 1 - \Pr(C)}.
\]  \hspace{1cm} (A1)

By the law of total probability rule again,

\[
\Pr(C = 1) = \Pr(C = 1|E = 1) \Pr(E) + \Pr(C = 1|E = 0) [1 - \Pr(E)].
\]

Then,
\[
Pr(C = 1|E = 0) = \frac{Pr(C) - Pr(C = 1|E = 1) Pr(E)}{1 - Pr(E)} \quad (A2)
\]

Therefore,
\[
E(a_1 + a_0) - E(b_1 + b_0) = \frac{Pr(Y = 1|E = 1, C = 1) Pr(C = 1|E = 1) + Pr(Y = 1|E = 1, C = 0) Pr(C = 0|E = 1)}{Pr(Y = 1|E = 0, C = 1) Pr(C = 1|E = 0) + Pr(Y = 1|E = 0, C = 0) Pr(C = 0|E = 0)} \times Pr(E) = \frac{RR(E) RR(C) Pr(C = 1|E = 1)}{RR(C) Pr(C = 1|E = 0) + 1 - Pr(C = 1|E = 0)}.
\]

Then, we have
\[
P_{bias} \% = \frac{RR_e - RR(E)}{RR(E)} \times 100 = \frac{[1 - Pr(C_{miss})]RR(E) + Pr(C_{miss}) RR_{miss} - RR(E)}{RR(E)} \times 100 = Pr(C_{miss}) \left(\frac{RR_{miss}}{RR(E)} - 1\right) \times 100.
\]

Then, we have,
\[
P_{bias} \% = Pr(C_{miss}) \left(\frac{[RR(C) - 1][Pr(C = 1|E = 1) - Pr(C = 1|E = 0)]}{RR(C) Pr(C = 1|E = 0) + 1 - Pr(C = 1|E = 0)}\right) \times 100. \quad (A3)
\]

Substituting (A1) and (A2) into (A3), after some simple algebras, we obtain,
\[
P_{bias} \% = \frac{Pr(C) [1 - Pr(C)] [RR(C) - 1][RR(E|C) - 1]}{[1 - Pr(E)][1 - Pr(C) + Pr(C) RR(C)RR(E|C)] - Pr (C)[1 - Pr (C)][RR(C) - 1][RR(E|C) - 1]} \times 100.
\]

Notice that the dependence of this expression on \(Pr(Y)\) and on \(RR(E)\) is eliminated.
3. Some special cases

1) When \( \Pr(C_{\text{miss}}) \to 0 \), then \( P_{\text{bias}} \% \to 0 \).
2) When \( \Pr(C) \to 0 \) or \( \Pr(C) \to 1 \), then \( P_{\text{bias}} \% \to 0 \).
3) When \( RR(C) = 1 \) (i.e., covariate has no effect on outcome), then \( P_{\text{bias}} \% = 0 \).
4) When \( RR(E|C) = 1 \) (i.e., covariate is not associated with exposure), then \( P_{\text{bias}} \% = 0 \).

For Cases 2, 3 and 4, the covariate is not a confounder of the exposure-outcome relationship, and hence there is no bias.

4. Restriction on the parameters

The values of each parameter considered in this paper are given in Table 2. However, some combinations of the values are invalid, in the sense that they produce probabilities outside the range of \([0,1]\). To see this, we calculated the following probabilities,

\[
\Pr(E = 1|C = 0) = \frac{\Pr(E)}{RR(E|C) \Pr(C) + 1 - \Pr(C)}, \quad \Pr(E = 1|C = 1) = \frac{RR(E|C) \Pr(E)}{RR(E|C) \Pr(C) + 1 - \Pr(C)},
\]

\[
\Pr(C = 1|E = 1) = \frac{RR(E|C) \Pr(C)}{RR(E|C) \Pr(C) + 1 - \Pr(C)}, \quad \text{and} \quad \Pr(C = 1|E = 0) = \frac{\Pr(C) - \Pr(C = 1|E = 1) \Pr(E)}{1 - \Pr(E)}.
\]

Note that \( \Pr(C = 1|E = 1) \) will always be between 0 and 1, but the others are not so restricted. We excluded from the numerical evaluation of \( P_{\text{bias}} \% \) the sets of parameter values that produced \( \Pr(C = 1|E = 0), \Pr(E = 1|C = 0) \) or \( \Pr(E = 1|C = 1) \) outside of 0 and 1. For example, when \( \Pr(C) = 0.5, \Pr(E) = 0.75, \) and \( RR(E|C) = 0.5 \), using the above formulae, we have

\[
\Pr(C = 1|E = 0) = 1.5, \Pr(E = 1|C = 0) = 1.25, \text{ and } \Pr(E = 1|C = 1) = 0.25.
\]

Thus, this combination of \( \Pr(C) = 0.5, \Pr(E) = 0.75, \) and \( RR(E|C) = 0.5 \) is not valid, and was excluded from the evaluation of \( P_{\text{bias}} \% \).

Appendix 2. Sufficient conditions for the results in Appendix 1 to apply when the missing mechanism is MAR
In Appendix 1, we assume that the covariate is missing completely at random (MCAR). Under MCAR, the RR estimated from the complete observations is the true RR, and the crude RR in the stratum with missing covariate is equal to the crude RR in the strata with complete observations.

In this appendix, we consider the case of missing at random (MAR), and investigate the condition for the results of Appendix 1 to apply.

Variables are defined as in the rest of this manuscript. Let $N$ be the total sample size of the study. Under MAR, the missingness of covariate $C$ may depend on $E$ and $Y$, but is independent of $C$. Let $f_{ye} = \Pr(\delta = 1|Y = y, E = e)$ be the probability of missing $C$, where $\delta = 1$ if the $C$ is missing and 0 otherwise. When $C = c$,

$$E(a_c) = N \Pr(C = c) \Pr(E = 1|C = c) \Pr(Y = 1|E = 1, C = c) f_{11}.$$ 

Similarly,

$$E(b_c) = N \Pr(C = c) \Pr(E = 0|C = c) \Pr(Y = 1|E = 0, C = c) f_{10},$$
$$E(c_c) = N \Pr(C = c) \Pr(E = 1|C = c) \Pr(Y = 0|E = 0, C = c) f_{01},$$
$$E(d_c) = N \Pr(C = c) \Pr(E = 0|C = c) \Pr(Y = 0|E = 0, C = c) f_{00}.$$ 

Assume again the RR is equal across the strata $C = 1$ and $C = 0$. In the stratum $C = c$, when the sample size approaches infinity, the observed RR

$$RR_c = \frac{a_c}{b_c} \frac{c_c}{d_c} \xrightarrow{p} \frac{\Pr(Y = 1|E = 1, C = c)}{\Pr(Y = 1|E = 0, C = c)} \times \frac{f_{11}}{f_{10}} \times \frac{\Pr(Y = 1|E = 0, C = c)}{\Pr(Y = 1|E = 1, C = c)} \times \frac{(f_{10} - f_{00}) + f_{00}}{(f_{11} - f_{01}) + f_{01}} \times \Pr(Y = 1|E = 0, C = c) (f_{10} - f_{00}) + f_{00}$$

So when $f_{10} = f_{00}$ and $f_{11} = f_{01}$, the observed RR converges to the true RR, $RR(E)$. In addition, the observed RR converges to the true RR when $f_{11} \times \frac{\Pr(Y = 1|E = 0, C = c)}{\Pr(Y = 1|E = 1, C = c)} (f_{10} - f_{00}) + f_{00} = 1$.

Thus, when $f_{10} = f_{00}$ and $f_{11} = f_{01}$, that is, when the probability of missingness of the covariate, $C$, is independent of the outcome, $Y$, but may depend on the exposure, $E$, the observed RR converges to the true RR.
We next investigate the conditions under which the crude RR in the missing stratum is equal to the crude RR in the complete data strata. In the missing stratum, we have

\[
E(a_m) = N[\Pr(C = 1)\Pr(E = 1|C = 1) \Pr(Y = 1|E = 1, C = 1) + \Pr(C = 0)\Pr(E = 1|C = 0) \Pr(Y = 1|E = 1, C = 0)](1 - f_{11}) \\
= E(a_1 + a_0) \times \frac{1 - f_{11}}{f_{11}}.
\]

Similarly,

\[
E(b_m) = E(b_1 + b_0) \times \frac{1 - f_{10}}{f_{10}} \\
E(c_m) = E(c_1 + c_0) \times \frac{1 - f_{01}}{f_{01}} \\
E(d_m) = E(d_1 + d_0) \times \frac{1 - f_{00}}{f_{00}}.
\]

The estimated crude RR in the missing stratum is \( \frac{a_m}{a_m + c_m} \), and the estimated crude RR in the complete observation strata is \( \frac{a_1 + a_0}{a_1 + a_0 + c_1 + c_0} \cdot \frac{b_1 + b_0}{b_1 + b_0 + d_1 + d_0} \).

When \( f_{10} = f_{00} \) and \( f_{11} = f_{01} \), we have

\[
\frac{E(a_m)}{E(a_m + c_m)} = \frac{E(b_m)}{E(b_m + d_m)} = \frac{E(a_1 + a_0)}{E(a_1 + a_0 + c_1 + c_0)} = \frac{E(b_1 + b_0)}{E(b_1 + b_0 + d_1 + d_0)}.
\]

Thus, under the conditions that \( f_{10} = f_{00} \) and \( f_{11} = f_{01} \), two crude RRs asymptotically coincide.

Again, the conditions \( f_{10} = f_{00} \) and \( f_{11} = f_{01} \) imply that the probability of missingness of the covariate, \( C \), is independent of the outcome, \( Y \), but may depend on the exposure, \( E \).