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Prior spontaneous and induced pregnancy loss and secondary infertility: type-specific associations in a matched case-control study

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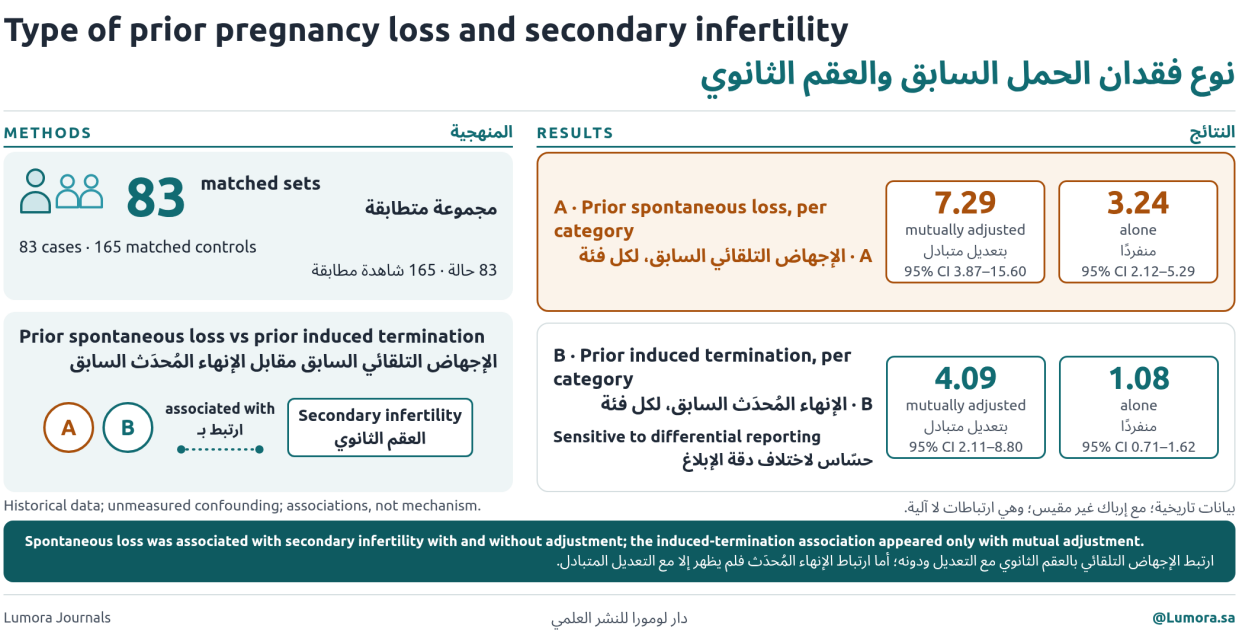
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Graphical abstract



Graphical abstract: Spontaneous loss was associated with secondary infertility with and without adjustment; the induced-termination association appeared only with mutual adjustment. Designed by the Lumora Journals production team using hand-coded HTML/SVG rendered in Google Chrome.

Abstract

Background: Reports of secondary infertility present induced terminations and spontaneous losses side by side without testing whether they are associated with the outcome to the same degree. We asked whether the association is specific to the type of loss.

Methods: We reanalysed a matched case-control study of secondary infertility, each case matched individually to controls on age, parity and education. Conditional logistic regression entered both exposures as ordered scores; a likelihood-ratio test compared it with the model constraining their coefficients to be equal. Reporting error and unmeasured confounding were quantified by reclassification and E-values.

Results: 83 cases and 165 controls formed 83 matched sets, of which 59 and 62 carried information. Mutually adjusted odds ratios per category increase were 4.09 (95% CI 2.11–8.80) for induced terminations and 7.29 (95% CI 3.87–15.60) for spontaneous losses, and were not equal ($p = 0.022$). Fitted alone, terminations showed no association (1.08 (95% CI 0.71–1.62)). With random as well as systematic error included, the bias-corrected interval for any induced termination included 1 once controls were assumed to report terminations less completely than cases; with complete reporting among cases, from a completeness of 0.88 among controls (a reporting differential of 0.12).

Conclusions: Spontaneous loss was associated with secondary infertility with and without adjustment, whereas the association with induced termination appeared only with spontaneous losses held constant at fixed parity and was sensitive to modest differential reporting; the two are not interchangeable summaries of pregnancy-loss history.

Keywords: case-control studies; pregnancy loss; abortion, spontaneous; infertility, female; conditional logistic regression; misclassification bias; matched analysis

1. Introduction

After a pregnancy loss, a woman usually asks whether it will be harder to conceive again. Most women who have lost a pregnancy go on to deliver, but a minority do not, and contemporary series do not resolve whether the prospect depends on how the previous pregnancy ended [1]. A loss that reflects impaired conception or implantation would predict later difficulty however the pregnancy ended, whereas a loss followed by instrumentation of the uterus belongs to a different and potentially modifiable pathway; the two accounts can be separated only in data that record both types of loss on the same women.

Earlier reports did not make that comparison formally. The study that established the association found that women investigated for secondary infertility more often reported induced termination than matched controls, but it predates methods for individually matched data and gave neither mutually adjusted estimates nor a comparison between types of loss [2]. A later case-control study in the same setting reported terminations and miscarriages in parallel, with tobacco smoking [3], and a study of tubal infertility examined terminations alone [4].

Induced termination is also reported incompletely. When self-administered questionnaire responses were linked to medical records, 19% of women with a recorded termination under-reported their terminations [5]; a national household survey recovered between 45% and 59% of the terminations expected, depending on the interview method [6], and later survey methods have not resolved the shortfall [7]. If women investigated for infertility report more fully than other women, an association will appear where none exists; how large that asymmetry would have to be can be quantified with established methods [8].

We therefore reanalysed the matched case-control data on secondary infertility to estimate the association of each type of prior loss within matched sets, each adjusted for the other; to test whether the two associations differ, against the alternative that only the number of losses matters; and to state how much differential reporting, and how strong an unmeasured common cause, would be needed to set the associations aside. These data are a widely used teaching dataset whose standard documentation fits the same conditional model, so the contribution is not a new estimate but the formal test of equal effects, the reporting of the matched sets that carry information, and a quantitative bias analysis. The claim is one of association in the population that produced these data, and nothing stronger.

2. Materials and Methods

The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology recommendations for case-control studies [9].

2.1. Study Design and Data Source

This is a reanalysis of an individually matched case-control study of secondary infertility conducted in obstetric and gynaecological services in Athens, Greece, and first reported in 1976 [2]. The de-identified participant records have been distributed for several decades with the standard statistical software environment used in epidemiology and were obtained from a public archive of that collection. The release is the dataset infert of the R datasets package, a widely used teaching dataset whose standard documentation fits the same conditional logistic model with both exposure scores. The copy originally analysed was retrieved on 3 September 2026; the copy used for the present analysis (SHA256 digest 38c7332f1ba72d1b5e68ae634ce4ba0fa32a8e667437276075a8077df42e56d8) reproduces every reported estimate with the code in Supplementary Material S1.

The source population comprised women of reproductive age with at least one previous pregnancy who attended those services during the study period. Sampling was on the outcome: women with secondary infertility were the cases and controls were drawn from women attending the same services who had not been so investigated and who would have become cases had secondary infertility been recognised. The sampling design and the two bias analyses are summarised in Figure S1.

2.2. Participants

Cases were women investigated for secondary infertility, defined as failure to achieve a further pregnancy after at least one previous pregnancy, as in the source study [2]; the release does not record any duration criterion or the recruitment dates. Each case was matched individually to controls on age in completed years, parity and level of education, with the matched-set identifier carried in the release. Participants were eligible for the present analysis if they belonged to a matched set containing exactly one case and at least one control and had complete exposure and matching information. The eligibility flow is shown in Figure 1. The source study enrolled 100 cases and found two matched controls for 83 of them [2]; the release contains these 83 cases and 165 controls, one matched set (set 74) having a single control. The documentation of the release states that one case with two prior spontaneous and two prior induced losses was omitted before distribution. The counts are consistent with the omitted record belonging to the set that now has a single control, but neither the documentation nor the release confirms this; no woman in the release reports two or more losses of both types, and whether other such women existed in the source data cannot be determined from the release.

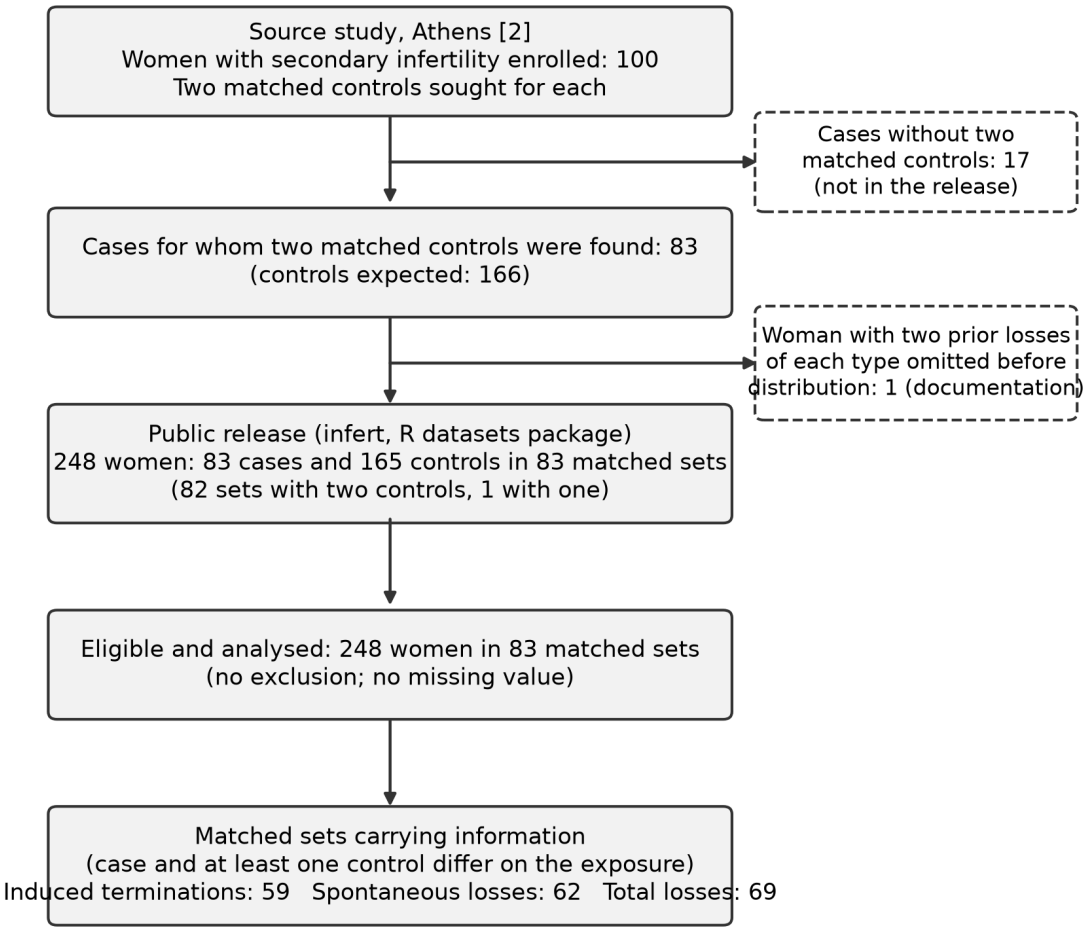


Figure 1. Assembly of the analysed matched sets from the published release of the source case-control study, with the number of sets that carry information for each exposure.

Counts are participants remaining after each step. A matched set carries information for an exposure only when the case and at least one of her controls report different numbers of losses of that type; sets in which everyone reports the same number contribute nothing to the estimate.

The documentation describes the age variable as the age of the case, so its constancy within matched sets follows from how the release was constructed and does not by itself confirm the matching; parity and level of education also take a single value within every matched set. Because these three variables are constant within sets, their own associations with secondary infertility are not estimable from the matched analysis, and no such association is reported here.

2.3. Variables

The two exposures were the number of prior induced terminations and the number of prior spontaneous losses, each recorded at interview in three categories: none, one, and two or more. Exposure was ascertained after the outcome had become apparent, which is the design's principal vulnerability and is addressed quantitatively in Section 2.5.

Three codings were used: an ordered score taking the values 0, 1 and 2; an indicator set with no prior loss of that type as the reference; and a binary contrast of any against no prior loss of that type. A fourth variable, the total number of prior losses of either type, was formed as the sum of the two type-specific counts; the model containing it is the primary model with the two coefficients constrained to be equal, so it expresses the hypothesis that only the number of losses matters and not their type. Category boundaries were those of the source release.

2.4. Statistical Analysis

The primary analysis was conditional logistic regression stratified by matched set, with the two ordered exposure scores entered simultaneously. Conditional estimation was chosen because matching was individual; analysing individually matched data without regard to the matched structure biases estimates towards the null when the matching factors are related to exposure, and conditional estimation is also less dependent on the correct modelling of the matching strata than the unconditional alternative [10–13]. Odds ratios are reported with profile-likelihood confidence intervals, which were preferred to Wald intervals because the number of informative matched sets is small and the likelihood is appreciably asymmetric; the interval for the ratio of the two odds ratios is also a profile-likelihood interval.

The primary test was a likelihood-ratio test with one degree of freedom comparing the type-specific model with the constrained cumulative-burden model. Because the two exposures are entered in one model, their coefficient estimates are correlated, and the difference between them is estimated more precisely than the two separate intervals suggest; the comparison was therefore made by a test of the constraint rather than by inspecting the two intervals. Secondary analyses were the cumulative-burden model, the unconstrained categorical model, whose comparison with the ordered-score model is a test of departure from a constant gradient, the binary model, and a product term between the two exposure scores. Each exposure was also fitted alone, so that estimates unadjusted for the other type of loss are available alongside the mutually adjusted ones. No subgroup analysis was undertaken. No analysis variable had a missing value in the release.

Six sensitivity analyses were run. The first replaced the conditional model with unconditional logistic regression in which age, parity and level of education were entered as covariates. The second and third reduced the matching ratio to one control per set, once by a fixed rule (the first control listed for each set in the release) and once by 500 random draws summarised by the median and the central 95 per cent of the draws. The fourth excluded the matched set containing a single control. The fifth omitted each matched set in turn. The sixth is described in Section 2.5. Resampling used the random-number seed 20261101, and the draws can be regenerated with the code in Supplementary Material S1.

Diagnostics were the number of cases and controls in every exposure category, the number of matched sets discordant on each exposure, verification of the matching, convergence of the conditional maximisation, and the correlation between the exposure coefficients. Analyses were performed in Python 3.11 with statsmodels 0.15 and in R 4.3 with the survival package 3.5; the conditional likelihood was additionally maximised by a purpose-written Newton-Raphson routine that uses no modelling library, and every reported estimate was recomputed in the other two implementations. Figures 1, 4, 5, S1, S3 and S5 were drawn in Python with matplotlib.

2.5. Quantitative Bias Analysis

Two threats were quantified rather than described. For incomplete reporting, specificity of report was fixed at one, on the reasoning that a woman does not report a termination that did not occur, and reporting completeness was varied from 0.40 to 1.00 in steps of 0.05 separately among cases and among controls, giving 169 combinations. The lower bound covers the lowest completeness documented in the validation studies: about 90% of women with a recorded termination reported at least one when questionnaire responses were linked to medical records, although 19% failed to report one or more [5], and between 45% and 59% of terminations were reported in a national survey, with about 40% in its lowest-income group [6]; the review of newer survey methods gives no numerical completeness [7]. The survey figures refer to the number of terminations, whereas the correction applies to any against no termination, so they overstate the incompleteness that matters for this binary exposure. At each combination, a woman who reported no termination was reclassified as exposed with the probability implied by her group's reporting completeness and by her modelled probability of true exposure given case status, prior spontaneous loss, age, parity and level of education; the binary conditional model was then refitted. Two thousand reclassifications were run at each combination, with the random-number seed 20261101. Each combination is summarised by the median corrected estimate and by a total-error interval, which adds to each corrected log odds ratio a normal deviate scaled by its standard error before the central 95 per cent is taken, so that random as well as systematic error is reflected [8]; the central 95 per cent of the corrected estimates alone, which reflects systematic error only, is also reported. For each case completeness, the highest control completeness at which the total-error interval included 1 was recorded; with complete reporting among cases, this value was located to 0.01. The conditioning set matters: an imputation model narrower than the analysis model attenuates the corrected estimate, and the procedure used here was checked on simulated matched sets with a known association and a known reporting completeness, where it recovers the generating value while the uncorrected estimate is attenuated.

The analysis was confined to induced termination because that is the exposure for which the completeness of self-report has been measured directly against records [5,6] and because it is the more sensitive of the two to disclose; spontaneous loss is also self-reported and may be reported incompletely, but no comparable validation exists from which a grid could be constructed, so no corrected estimate is offered for it. For unmeasured confounding, E-values were computed for the primary estimates and for the confidence limits nearest the null [14]. Because secondary infertility is not a rare outcome in the population that produced these data, the odds ratio was first converted to the risk-ratio scale by the square-root approximation; the value obtained by treating the odds ratio directly as a risk ratio is also reported so that the numbers can be compared with those in the literature, where the rare-outcome convention is usual.

2.6. Reporting and Ethics

The study analyses publicly available, fully de-identified data that were published several decades ago and contain no identifiers. The approval and consent arrangements of the source study are not documented in the distributed release, and no claim is made about them. The analysis was not prospectively registered.

3. Results

The source study enrolled 100 women with secondary infertility and found two matched controls for 83 of them [2]; the release contains these 83 cases. All 248 women in the release met the eligibility criteria, so no participant was excluded (Figure 1). They formed 83 matched sets containing 83 cases and 165 controls,

of which 82 sets contained two controls and 1 contained one. Participants were aged between 21 and 44 years, with a mean of 31.5 years, and the median parity was 2.0.

3.1. Participants and Exposure Distribution

Characteristics of cases and controls are given in Table 1.

Table 1. Characteristics of the women with secondary infertility and of their matched controls.

Characteristic	Overall (n = 248)	Cases (n = 83)	Controls (n = 165)
Age, years, mean (SD)	31.5 (5.3)	31.5 (5.3)	31.5 (5.3)
Parity (previous live births), mean (SD)	2.1 (1.3)	2.1 (1.3)	2.1 (1.2)
Level of education, n (%)			
0–5 years	12 (4.8)	4 (4.8)	8 (4.8)
6–11 years	120 (48.4)	40 (48.2)	80 (48.5)
12 years or more	116 (46.8)	39 (47.0)	77 (46.7)
Prior induced terminations, n (%)			
0	143 (57.7)	47 (56.6)	96 (58.2)
1	68 (27.4)	23 (27.7)	45 (27.3)
2 or more	37 (14.9)	13 (15.7)	24 (14.5)
Prior spontaneous losses, n (%)			
0	141 (56.9)	28 (33.7)	113 (68.5)
1	71 (28.6)	31 (37.3)	40 (24.2)
2 or more	36 (14.5)	24 (28.9)	12 (7.3)
Total prior losses, n (%)			
0	67 (27.0)	7 (8.4)	60 (36.4)
1	92 (37.1)	34 (41.0)	58 (35.2)
2	74 (29.8)	32 (38.6)	42 (25.5)
3	15 (6.0)	10 (12.0)	5 (3.0)
Members of the matched set, n (%)			
2	2 (0.8)	1 (1.2)	1 (0.6)
3	246 (99.2)	82 (98.8)	164 (99.4)

Values are means (standard deviations) for continuous variables and numbers (percentages) for categorical variables. Age, parity and level of education were matching factors and are identical within every matched set, so the small differences between the columns arise only from the differing numbers of cases and controls. No value was missing for any variable.

Numbers in every exposure category are given in Table 2 and are shown against the corresponding odds ratios in Figure 2. The smallest category contained 12 women, so every reported odds ratio is identified and no category was collapsed. The distribution of the total number of losses is shown in Figure S2.

Table 2. Numbers of cases and controls in each exposure category, with the corresponding odds ratios.

Exposure category	Cases, n (%)	Controls, n (%)	Odds ratio (95% CI)
Induced termination: none	47 (56.6)	96 (58.2)	1 (reference)
Induced termination: one	23 (27.7)	45 (27.3)	4.00 (95% CI 1.67–10.47)
Induced termination: two or more	13 (15.7)	24 (14.5)	16.77 (95% CI 4.30–79.46)
Spontaneous loss: none	28 (33.7)	113 (68.5)	1 (reference)
Spontaneous loss: one	31 (37.3)	40 (24.2)	7.72 (95% CI 3.34–20.04)
Spontaneous loss: two or more	24 (28.9)	12 (7.3)	51.16 (95% CI 13.91–244.60)

Percentages are within case status. Odds ratios come from a single conditional logistic model stratified by matched set that contains indicator terms for both exposures, so each is adjusted for the other. CI, confidence interval.

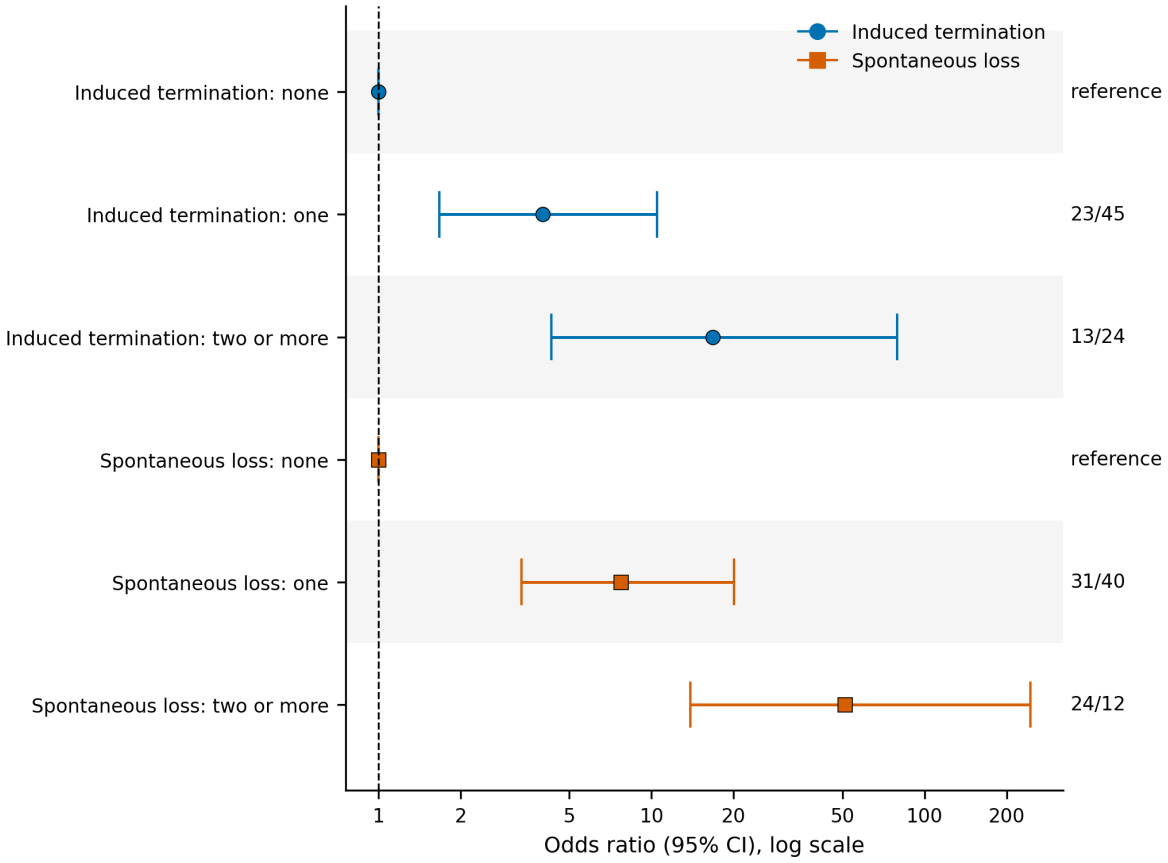


Figure 2. Odds ratios for secondary infertility by number of prior losses of each type, from a single conditional logistic model containing indicator terms for both exposures.

Estimates come from one model stratified by matched set, so each exposure is adjusted for the other and age, parity and level of education are controlled by the matching. Intervals are profile-likelihood intervals.

The annotation beside each row gives the number of cases and the number of controls in that category. CI, confidence interval.

The information available to a matched analysis is carried by sets in which the case and at least one of her controls report different numbers of losses. There were 59 such sets for prior induced terminations, 62 for prior spontaneous losses and 69 for the total count; the remaining sets contribute nothing to the estimates, and the precision reported below reflects those numbers rather than the number of women.

3.2. Type-Specific Associations

In the primary model the odds of secondary infertility rose by a factor of 4.09 (95% CI 2.11–8.80) per one-category increase in prior induced terminations and by 7.29 (95% CI 3.87–15.60) per one-category increase in prior spontaneous losses, each adjusted for the other and estimated within matched sets (Table 3). The conditional maximisation converged in 6 iterations. Fitted alone, without adjustment for the other type of loss, prior induced terminations carried an odds ratio of 1.08 (95% CI 0.71–1.62) and prior spontaneous losses 3.24 (95% CI 2.12–5.29), so the association with induced terminations was apparent only when prior spontaneous losses were held constant. The two exposure scores were negatively correlated within matched sets (correlation -0.50), and no woman in the release reported two or more losses of both types.

Table 3. Odds ratios for secondary infertility under the primary and the alternative exposure specifications.

Specification	Contrast	Odds ratio (95% CI)
One exposure at a time	Per one-category increase in induced terminations	1.08 (95% CI 0.71–1.62)
One exposure at a time	Per one-category increase in spontaneous losses	3.24 (95% CI 2.12–5.29)
Type-specific ordered scores (primary)	Per one-category increase in induced terminations	4.09 (95% CI 2.11–8.80)
Type-specific ordered scores (primary)	Per one-category increase in spontaneous losses	7.29 (95% CI 3.87–15.60)
Type-specific ordered scores (primary)	Ratio of the two odds ratios (spontaneous to induced)	1.78 (95% CI 1.08–3.06)
Cumulative burden (constrained)	Per additional prior loss of either type	5.90 (95% CI 3.26–12.06)
Binary	Any against no prior induced termination	2.98 (95% CI 1.38–6.90)
Binary	Any against no prior spontaneous loss	8.45 (95% CI 4.01–19.89)

All models are conditional logistic regressions stratified by matched set. The first two rows contain one exposure at a time and are therefore unadjusted for the other type of loss; every later row is mutually adjusted. The cumulative-burden model is the primary model constrained so that the two exposures share one coefficient; the likelihood-ratio test between them appears in the text. All intervals are profile-likelihood intervals. The binary rows use a different exposure scale and are not comparable with the ordered-score rows. CI, confidence interval.

The two coefficients were not equal. The likelihood-ratio test of the constraint gave a chi-square statistic of 5.22 on one degree of freedom (p = 0.022), and the odds ratio for spontaneous loss was 1.78 (95% CI 1.08–3.06) times that for induced termination. The two coefficient estimates were strongly positively correlated (correlation 0.729), which is why their separate intervals overlap while the test of their difference

does not support equality. Constraining the two to be equal, that is, counting losses without regard to type, gave 5.90 (95% CI 3.26–12.06) per additional loss.

3.3. Shape of the Gradient

Odds ratios from the unconstrained categorical model are given by category in Table 2 and Figure 2. The intervals for the highest categories are wide, and the ordering of the two exposures at the top of the range is not established by them.

The categorical model did not fit better than the ordered-score model (chi-square 0.05 on two degrees of freedom, p = 0.97), so a single coefficient per exposure describes the gradient adequately over the observed range; the two are compared directly in Figure 3. A product term between the two exposure scores gave no evidence that the association with one type depends on the number of the other (chi-square 0.06, p = 0.81). On the binary scale, any prior induced termination carried an odds ratio of 2.98 (95% CI 1.38–6.90) and any prior spontaneous loss 8.45 (95% CI 4.01–19.89).

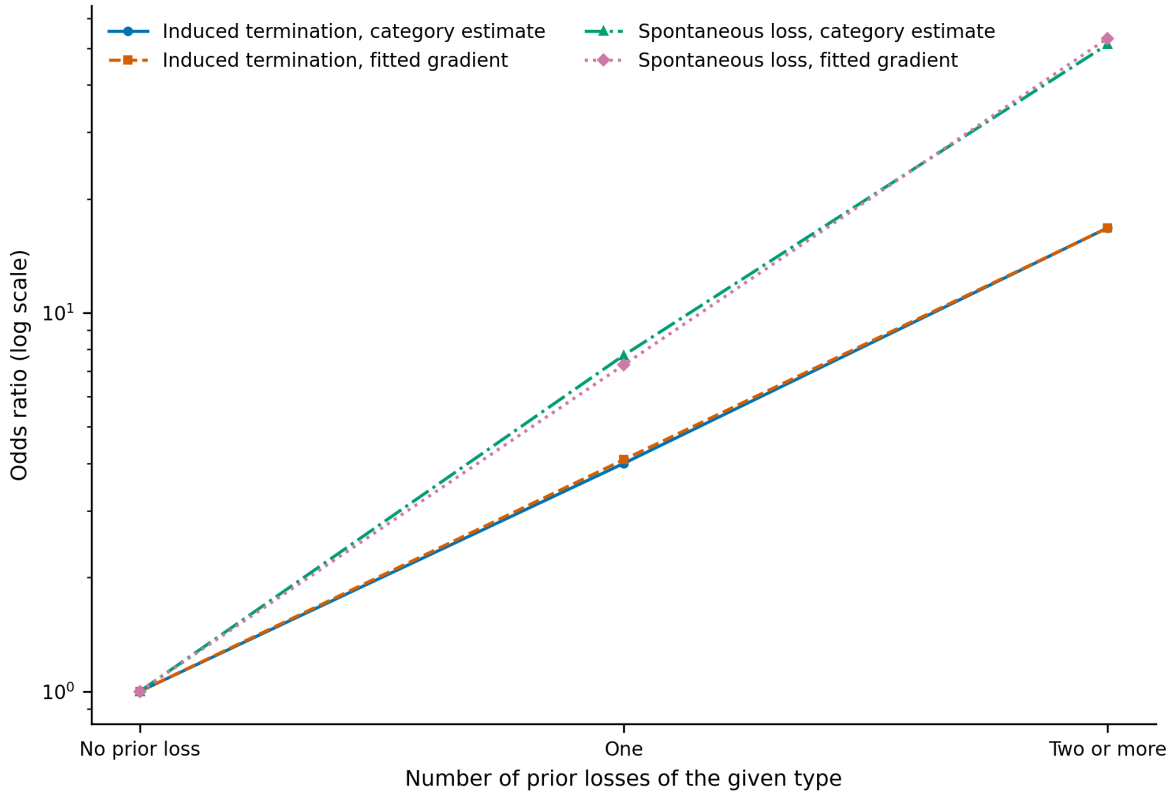


Figure 3. Category-specific odds ratios compared with the gradient implied by the ordered-score model, for each type of prior loss.

Markers are the unconstrained category estimates; the lines are the odds ratios implied by the model that assigns one coefficient per exposure and multiplies it by the category score. The two are compared by a likelihood-ratio test with two degrees of freedom. Confidence intervals are omitted here so that the two curves can be compared; they are given in the preceding figure, in Table 2 and in the results text.

3.4. Sensitivity to Specification and to the Control Sample

Estimates under the alternative specifications are shown in Figure 4 and Table 4. Abandoning the matched structure and entering the matching factors as covariates gave 3.63 (95% CI 2.01–6.55) for induced terminations and 7.74 (95% CI 4.21–14.21) for spontaneous losses, so that the estimate for induced terminations moved towards the null and that for spontaneous losses away from it. Retaining the first control listed in each set gave 3.16 (95% CI 1.61–7.00) and 6.55 (95% CI 3.17–16.50), and across 500

random one-control subsamples the median estimates were 3.98 and 6.34, with the middle 95 per cent of the draws spanning 2.79–6.62 and 4.55–10.48; this spread describes the dependence on which control is retained and is not a confidence interval (Figure S3). Excluding the set with a single control left the estimates at 4.09 (95% CI 2.11–8.80) and 7.29 (95% CI 3.87–15.60).

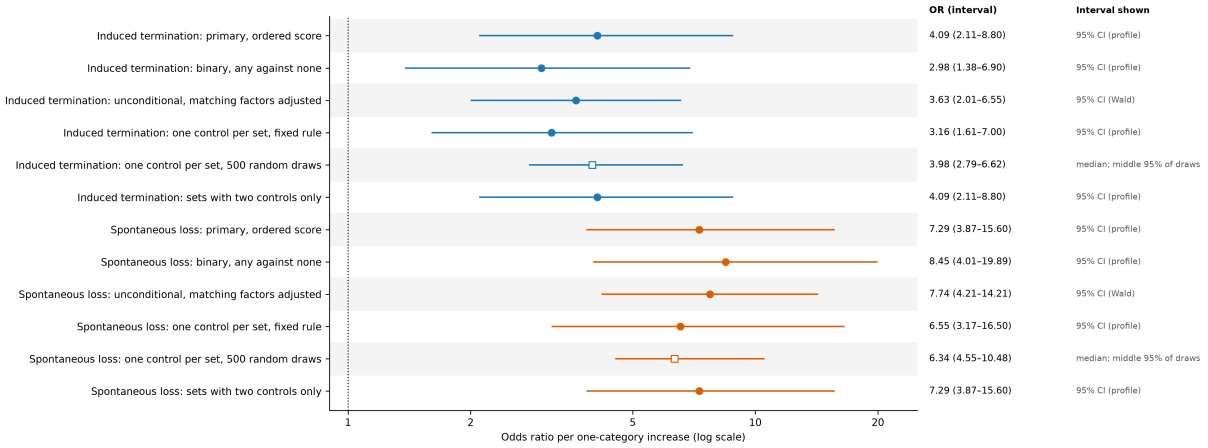


Figure 4. Odds ratios for each exposure under the primary specification and under the alternative specifications and control samples.

The binary row contrasts any against no loss of the given type and is therefore on a different exposure scale from the ordered-score rows. The unconditional row abandons the matched structure and enters age, parity and level of education as covariates. The subsample rows retain one control per set. Intervals are profile-likelihood intervals except for the unconditional row, which uses a Wald interval, and the repeated-subsample row, whose interval is the range of the middle 95 per cent of the draws and is not a confidence interval. CI, confidence interval.

Table 4. Sensitivity analyses and quantitative bias analyses.

Analysis	Specification	Result
Unconditional, matching factors adjusted	Induced terminations	3.63 (95% CI 2.01–6.55)
Unconditional, matching factors adjusted	Spontaneous losses	7.74 (95% CI 4.21–14.21)
One control per set, first listed control	Induced terminations	3.16 (95% CI 1.61–7.00)
One control per set, first listed control	Spontaneous losses	6.55 (95% CI 3.17–16.50)
One control per set, median of 500 draws (middle 95% of draws)	Induced terminations	3.98 (2.79–6.62)
One control per set, median of 500 draws (middle 95% of draws)	Spontaneous losses	6.34 (4.55–10.48)
Sets with two controls only	Induced terminations	4.09 (95% CI 2.11–8.80)
Sets with two controls only	Spontaneous losses	7.29 (95% CI 3.87–15.60)
Reporting completeness 0.80 in both groups	Any prior induced termination	3.88 (total-error interval 1.51–11.16)
Reporting completeness 1.00 in cases and 0.80 in controls	Any prior induced termination	1.80 (total-error interval 0.77–3.81)

Analysis	Specification	Result
Reporting completeness 1.00 in cases and 0.70 in controls	Any prior induced termination	1.38 (total-error interval 0.65–3.12)
Reporting completeness 1.00 in cases and 0.60 in controls	Any prior induced termination	1.01 (total-error interval 0.44–2.38)
Reporting completeness 1.00 in cases and 0.88 in controls (total-error interval first includes 1)	Any prior induced termination	2.16 (total-error interval 0.98–4.67)
Unmeasured confounding	E-value for induced terminations (estimate; lower limit)	3.46; 2.26
Unmeasured confounding	E-value for spontaneous losses (estimate; lower limit)	4.84; 3.35
Leave-one-set-out	Largest change in the odds ratio (induced; spontaneous)	1.06; 2.16

Reporting-completeness rows give the median odds ratio for any prior induced termination after record-level reclassification of women reporting no termination, with specificity fixed at one and 2,000 simulations per scenario, and the total-error interval, which includes random as well as systematic error; the full grid, with the intervals reflecting systematic error only, is given in Table S1. E-values give the strength of association, on the risk-ratio scale, that an unmeasured common cause would need with both the exposure and the outcome to account for the estimate; they are computed on the square-root approximation appropriate to an outcome that is not rare. CI, confidence interval.

No single matched set determined the result. Across the leave-one-set-out refits the odds ratio for induced terminations ranged from 3.82 to 5.15, a largest single change of 1.06, and that for spontaneous losses from 7.06 to 9.44 (Figure S4).

3.5. Reporting Error and Unmeasured Confounding

At interview, 43.4 per cent of cases and 41.8 per cent of controls reported at least one prior induced termination, so the association is carried entirely by comparisons within matched sets and not by the overall difference between the two groups. The corrected odds ratios across the grid of reporting completeness are shown in Figure 5. When both groups were assumed to report equally incompletely, at eight terminations in ten, the corrected odds ratio was 3.88 (total-error interval 1.51–11.16), that is, further from the null than the uncorrected estimate.

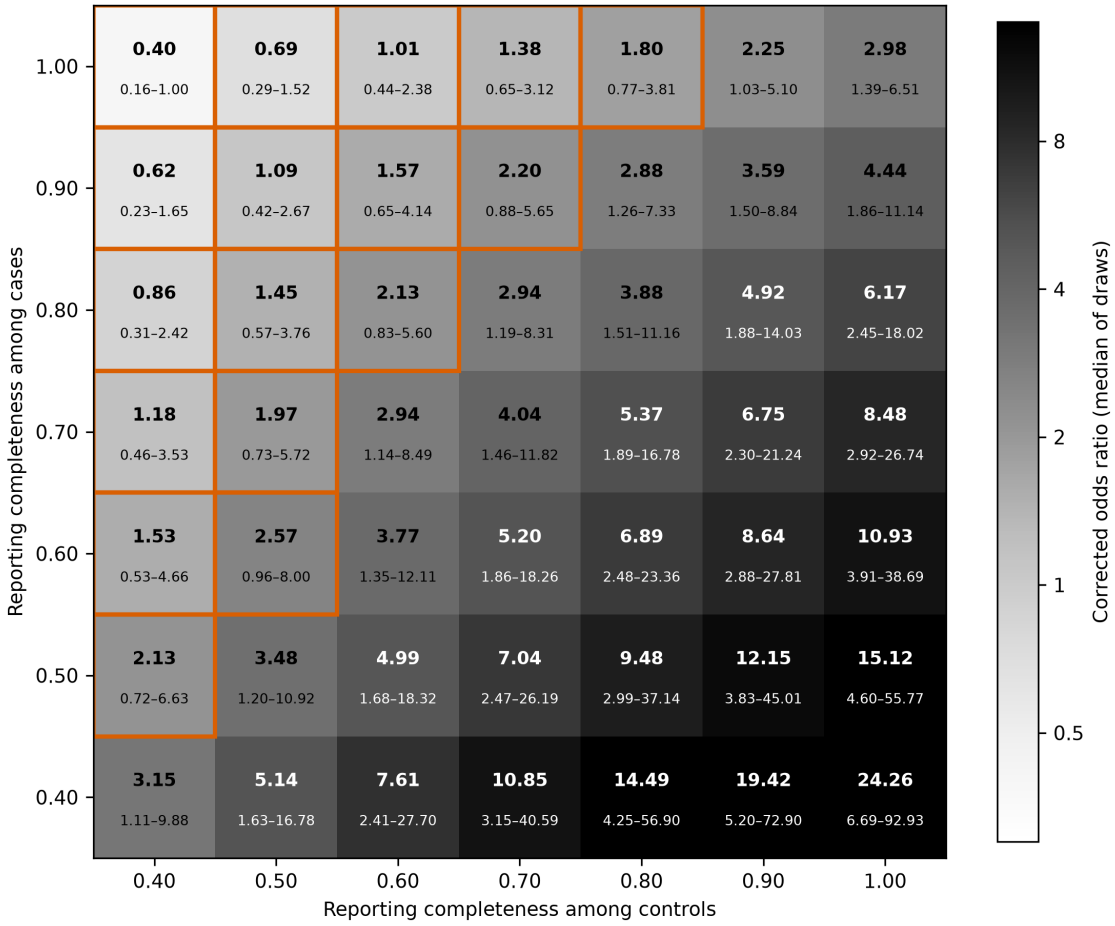


Figure 5. Odds ratio for any prior induced termination after correcting for incomplete reporting, across combinations of reporting completeness among cases and among controls.

Each cell gives the median of 2,000 record-level reclassifications and, below it, the total-error interval, which includes random as well as systematic error. A woman who reported no termination is reassigned as exposed with the probability implied by the reporting completeness of her group and by her modelled probability of exposure given case status, prior spontaneous loss and the matching factors; specificity is fixed at one. Outlined cells are those in which the total-error interval includes 1. The grid is shown in steps of 0.10; the full grid in steps of 0.05 is given in Table S1. The top right cell, complete reporting in both groups, is the uncorrected estimate. Along the diagonal, where both groups report equally completely, the corrected estimate rises from 2.98 to 4.04 as completeness falls to 0.70 and then declines to 3.15 at 0.40. This is not simulation noise. The implied probability of true exposure, the modelled probability divided by the completeness, exceeds one for a growing number of women as completeness falls and is then truncated at one, so those women are reclassified as exposed with certainty whatever their case status, which offsets the correction away from the null.

The association weakened only when controls were assumed to report less completely than cases. With cases assumed to report every termination, the corrected odds ratio was 1.80 (total-error interval 0.77–3.81) when controls reported eight in ten, 1.38 (0.65–3.12) at seven in ten and 1.01 (0.44–2.38) at six in ten; the corresponding intervals reflecting systematic error only were 1.41–2.22, 1.05–1.79 and 0.73–1.36. With cases complete, the total-error interval first included 1 when the completeness among controls fell to 0.88; across the grid it included 1 once controls were assumed to report between 0.05 and 0.20 less completely than cases, the margin being smaller at lower completeness (Table S1). The total-error interval

included 1 in 58 of the 169 combinations, and the corrected estimate itself was 1 or below in 12, all with case completeness of 0.80 or more and control completeness of 0.55 or less.

An unmeasured common cause of exposure and outcome would need associations of at least 3.46 with both, on the risk-ratio scale, to account for the association with induced terminations, and at least 2.26 to move the confidence limit nearest the null to no association. The corresponding values for spontaneous losses were 4.84 and 3.35. Under the rare-outcome convention usual in the literature the corresponding values for the two exposures would be 7.65 for induced terminations and 14.05 for spontaneous losses.

4. Discussion

Both kinds of prior pregnancy loss were associated with secondary infertility, but not to the same degree: the odds ratio per category of prior spontaneous loss was close to twice that per category of prior induced termination, and a model that counts losses without regard to type was rejected. A single coefficient per exposure described the gradient well, with no evidence of a threshold within the observed range and no evidence that the association with one type depends on the number of losses of the other. A summary that adds terminations and miscarriages together therefore discards information that the data contain [2–4].

This difference is what a marker interpretation of spontaneous loss would predict: a spontaneous loss may signal an impairment of conception or implantation, whereas an induced termination is a decision rather than a symptom, and its association with later infertility is more plausibly mediated by events that follow it. The data cannot establish this, because they contain no information on infection, procedure or gynaecological history; an equally consistent reading is that women in whom conception has always been difficult were less likely to seek a termination and more likely to lose the pregnancies they achieved.

Fitted alone, prior induced terminations showed no association with secondary infertility; the association appears only when prior spontaneous losses are held constant. The two exposures are negatively correlated within matched sets, as a fixed parity implies, and adjustment for a strongly associated exposure that is negatively correlated with a weakly associated one moves the weaker estimate away from the null. The release sharpens this correlation: no woman reports two or more losses of both types, and the documentation states that one woman with that combination was omitted before distribution. The adjusted estimate for terminations is therefore the association at fixed parity and a fixed number of spontaneous losses, conditional on that structure; it is not a robust summary of what a history of termination alone conveys and should not be quoted as one. The association with spontaneous loss is present with and without adjustment.

Only 59 of the 83 matched sets distinguish the case from her controls on prior induced termination, and 62 on prior spontaneous loss; the confidence intervals reflect those sets and not the number of women, so the estimates do not have the precision of an equal number of independent observations.

Incomplete reporting of induced termination is the threat this design cannot avoid, and the one we could quantify. Reporting that is equally incomplete in both groups does not manufacture the association; correcting for it moves the estimate away from the null. Once random error is included, however, the association is sensitive to modest differential reporting: with cases reporting every termination, the total-error interval included no association when controls reported 0.88 of their terminations or fewer. Validation studies describe larger shortfalls in general populations [5,6], although not how completeness differs between clinical groups, so differential reporting of this size cannot be excluded.

Unmeasured confounding is less easily dismissed. Pelvic infection, smoking, contraceptive history and partner factors are not recorded, and the later study in the same setting reported smoking to be associated with secondary infertility [3]. The E-values indicate that an unmeasured common cause would need associations of 3.46 with both the exposure and the outcome to account for the association with terminations; this is larger than the association reported for smoking in that study [3] but not beyond the range that a strong marker of underlying gynaecological disease might show.

Matching on parity raises a further problem. Parity is partly a consequence of the woman's underlying fertility and partly a consequence of her losses (Figure S5), and conditioning on it can bias the estimates in either direction; the direction here is not known. The unconditional analysis also adjusts for parity and cannot resolve this; in it the estimate for induced terminations moved towards the null (3.63 against 4.09) and that for spontaneous losses away from it (7.74 against 7.29) [10,11,13]. We therefore make no claim that the estimates are conservative in this respect, and the association with induced termination is presented as conditional on fixed parity and a fixed number of spontaneous losses.

Other limitations follow from the source of the data. The study was conducted in one city in the mid-1970s, and termination technique, infection prophylaxis and the investigation of infertility have changed since, so the size of the associations should not be transported to contemporary practice. Cases were prevalent rather than incident, so survival in the investigated state is mixed with its occurrence. The source study enrolled 100 cases but found two matched controls for only 83 [2]; the other 17 are not in the release, and if the availability of controls was related to reproductive history the analysed cases may not represent all those enrolled. The top exposure category is open-ended, so an estimate per category increment is not an estimate per event. Control sampling was cumulative and the sampling fraction is unknown, so the odds ratios approximate rate ratios only under assumptions the data cannot check and cannot be translated into absolute risks. Reporting completeness was probed only for induced termination; differential incomplete reporting of spontaneous loss in the same direction would act on the larger association. Secondary infertility was defined as in the source study, without independent adjudication.

For practice, the findings suggest only that the type of prior loss may carry information that a simple count does not, which would need confirmation in contemporary data before it could inform the assessment of women presenting with difficulty conceiving. For research, reports of matched case-control studies should state how many sets carry information, compare related exposures by testing the constraint rather than by inspecting intervals, and convert the standard recall caveat into a number.

5. Conclusions

Prior spontaneous losses and prior induced terminations were associated with secondary infertility to different degrees in this matched case-control study, and a count of losses without regard to type was not compatible with the data. The association with spontaneous loss was present whether or not terminations were taken into account, whereas that with induced termination emerged only when spontaneous losses were held constant at fixed parity, is conditional on that structure, and is compatible with modest differential reporting of terminations once random error is included. The findings are associations in a historical population, not evidence about mechanism. Matched case-control reports should state the information their matched sets carry, test the comparisons they invite, present each exposure with and without mutual adjustment, and put a number, with an interval that includes random error, on the recall problem they acknowledge.

Declarations

Supplementary Materials: The following supporting information is available: Figure S1, study schematic; Figure S2, distribution of the total number of prior pregnancy losses among cases and controls; Figure S3, distribution of the odds ratios across 500 random one-control subsamples; Figure S4, odds ratios from the primary model when each matched set in turn is omitted; Figure S5, the assumed causal structure; Table S1, corrected odds ratios with total-error and systematic-error intervals across the full grid of reporting completeness; Sections S1–S4, extended methods, descriptions of the supplementary figures and data materials; Supplementary Material S1, analysis code, data digest and outputs.

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Institutional Review Board Statement: As a secondary analysis of publicly available data, the study was exempt from ethics review. The data are fully de-identified and contain no direct or indirect identifiers. The approval and consent arrangements of the source study conducted in 1976 are not documented in the distributed release, and no claim is made about them.

Informed Consent Statement: The analysis used publicly available de-identified data collected in an earlier study; no participant could be identified and no new contact with participants took place.

Data Availability Statement: The participant records analysed here are publicly available: they are published as the dataset named infert in the datasets package of the R statistical environment, and a comma-separated copy is redistributed by the Rdatasets archive at https://raw.githubusercontent.com/vincentarelbundock/Rdatasets/master/csv/datasets/infert.csv.

Code Availability Statement: The analysis code (Python), with the digest of the data file and all outputs, is provided as Supplementary Material S1.

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Conflicts of Interest: The authors declare no conflicts of interest.

Author contributions: [Pending: CRediT author contributions and confirmation that all authors approved the final version — to be supplied by the authors]

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Abbreviations and symbols

CI, confidence interval.

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