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Miscellaneous

Periodontal treatment among mothers with mild to moderate periodontal disease and preterm birth: reanalysis of OPT trial data accounting for selective survival

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Abstract

Background: The Obstetrics and Periodontal Therapy (OPT) study, a randomized controlled trial, reported no effect of periodontal treatment on preterm birth. Even though there were more spontaneous abortions or stillbirths in the control group, sensitivity analyses using conventional approaches did not change the results. The development of newer epidemiological methods to assess bias caused by the truncated outcome, and the availability of OPT study data in the public domain, allowed us to reanalyse these data.
Methods: We used the survivor average causal effect (SACE), also known as the principal strata effect, to correct potential bias resulting from unequal survival of fetuses in the treatment and control arms of the OPT study.
Results: The risks of preterm and spontaneous abortions or stillbirths were respectively 49/413 (11.86%) and 5/413 (1.21%) in the periodontal treatment group, and 52/410 (12.68%) and 14/410 (3.33%) respectively in the control group. The risk differences (%) comparing periodontal treatment and control groups were -0.82%: 95% confidence interval (CI) -5.30% to 3.67% for preterm birth, and -2.12%: 95% CI -4.14% to -0.11% for spontaneous abortions or stillbirths before correction. Risk differences for preterm birth comparing periodontal treatment and control groups increased in magnitude, reached statistical significance and showed a beneficial effect of periodontal treatment after correction for bias using SACE.
Conclusions: Periodontal treatment provided to mothers with mild to moderate periodontal disease before 21 weeks of gestation may prevent preterm births.

Key words: Periodontal disease, periodontal treatment, preterm birth, selective survival, survivor average causal effect, principal strata effect

Key Messages

- Survivor bias in randomized controlled trials can occur when the outcome is preterm birth, and fetal losses are unequal in the intervention and control arms.
- The survivor average causal effect (SACE) method corrects for survivor bias.
- Applying the SACE method to the OPT trial changes the interpretation of the initial results, suggesting that periodontal treatment among pregnant women with periodontal disease may have a beneficial effect on preterm birth.

Introduction

Periodontal treatment had no effect on preterm birth in the Obstetrics and Periodontal Therapy (OPT) randomized controlled trial.[1] During follow-up there were fewer spontaneous abortions or stillbirths in the treatment group compared with the control group (5/413 versus 14/410, respectively) which could cause bias (Figure 1).[1] Mothers who had spontaneous abortions or stillbirths had more risk factors for preterm births because these conditions share common causes.[2] As the control group had more spontaneous abortions or stillbirths, mothers remaining in that group at the end of follow-up had fewer preterm birth risk factors than those remaining in the treatment group, even if the two groups were equivalent at baseline though randomization. Thus, survival bias would offset any potential beneficial effect of periodontal treatment on preterm birth, which multivariable adjustment or competing risks analysis would not correct.[3–5]

Chiba and VanderWeele recently proposed a method to address this issue, in which the effect of treatment on the outcome is compared in the subpopulation that would have survived either arm.[3] This has been called the survivor average causal effect (SACE) or principal strata effect, and relies on the causal inference or potential outcomes approach.[3,4,6] In the application of this method to the OPT study data, we would compare the potential incidence of preterm birth under treatment and control interventions among survivors of both treatment and control arms (counterfactual comparison). It is important to conduct this analysis, because it could change interpretation of the OPT study results, with significant implications for clinical practice.

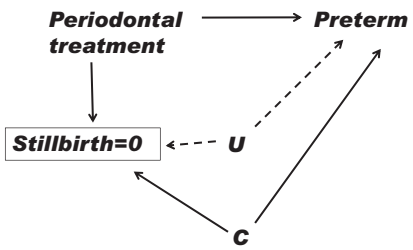

Figure 1. Directed acyclic graph describing bias caused by fetal loss in intention-to-treat analysis, Obstetrics and Periodontal Therapy (OPT) study. C describes measured risk factors of preterm and stillbirth. U describes unmeasured risk factors of preterm and stillbirth. There are backdoor paths from preterm to periodontal treatment through C and U, because stillbirth is a collider and the intention-to-treat analysis is estimated conditional on stillbirth. The backdoor path through U remains open even after control of measured confounders.

The objective of this analysis was to assess the degree to which bias caused by unequal survival of fetuses in the treatment and control arms in the OPT study affected its results, by applying the SACE method.

Methods

We used data from the OPT study placed in the public domain for this reanalysis.[7] The OPT study was a randomized controlled trial evaluating the effect of periodontal treatment, consisting of scaling and root planing, on pregnancy outcomes. The study was approved by the relevant institutional review boards and was registered (ClinicalTrials.gov number, NCT00066131).[1]

Study population

Details are provided elsewhere.[1] Briefly, participants were recruited from Hennepin County Medical Center (MN), the University of Kentucky, the University of Mississippi Medical Center and Harlem Hospital (NY). Participants at enrolment were at least 16 years of age and at less than 16 weeks and 6 days of gestation, with at least 20 natural teeth and periodontal disease.[1] Participants were excluded if they were pregnant with multiple fetuses, in need of antibiotic prophylaxis for periodontal procedures, had a medical condition precluding elective dental treatment, had extensive tooth decay or were at risk of extensive tooth loss.[1]

Study intervention

Eligible participants were randomized to treatment ($n = 413$) and control ($n = 410$) groups. Treatment group

participants received up to four visits for periodontal scaling and root planing and oral hygiene instruction before 21 weeks of gestation. Control group participants received up to four visits consisting of dental examination during the course of the study, followed by periodontal scaling and root planing after delivery.

Outcome

The primary outcome of interest was preterm birth (delivered before 37 weeks of gestation), which occurred in 49 women in the treatment group and 52 in the control group. There were five spontaneous abortions or stillbirths in the treatment group and 14 in the control group. The intention-to-treat hazard ratio for preterm birth comparing the treatment versus control groups was 0.93: 95% confidence interval (CI) 0.63 to 1.37.

Statistical analysis

We compared the characteristics of mothers who had spontaneous abortions or stillbirths and those who did not, and also by treatment groups at baseline and end of follow-up, using t-tests to compare continuous data and exact tests for categorical data.

Estimation of SACE

We used the method described by Chiba and VanderWeele to estimate SACE.[3] A denotes treatment status, with $A = 1$ indicating that the mother received periodontal treatment and $A = 0$ otherwise; S indicates survival of fetus, with $S = 1$ indicating that there was a live birth and $S = 0$ otherwise. The observed outcome, preterm birth, is represented by Y.

The counterfactual variable S_1 describes whether or not a mother would have had a live birth if she received periodontal treatment; $S_1 = 1$ indicates that such a mother would have had a live birth if she received periodontal treatment, and $S_1 = 0$ otherwise. Similarly, S_0 describes whether or not a mother would have had a live birth if she did not receive treatment; $S_0 = 1$ indicates that such a mother would have had a live birth if she did not receive periodontal treatment, and $S_0 = 0$ otherwise. However, S_1 is only observed for mothers who actually received periodontal treatment ($A = 1$), and S_0 only for mothers who did not receive treatment ($A = 0$).

Similarly Y_1 describes whether a preterm birth would have occurred in mothers receiving periodontal treatment, and Y_0 if a preterm birth would have occurred in mothers not receiving periodontal treatment, irrespective of the treatment that they actually received.[3] However, as these are counterfactual variables, outcomes in the OPT data were only observed for mothers who actually received treatment or were untreated. We did not know whether or not a mother in the periodontal treatment group would give birth to a preterm baby if, contrary to the fact, she did not receive treatment. Likewise, we did not know if a mother in the control group would give birth to a preterm baby if, contrary to the fact, she received treatment.

The effect of periodontal treatment on preterm delivery was estimated by comparing risks of preterm birth between periodontal treatment and control groups, among mothers who had live births, denoted by the expression: $E[Y|A = 1, S = 1] - E\{Y|A = 0,\ S = 1\}$;[3] this is biased because it is conditional on the descendent of treatment, in this case fetal loss, which is unequal in the treatment and control groups (Figure 1).[8] SACE would estimate the unbiased effect of periodontal treatment on preterm birth by comparing counterfactual risks of preterm if mothers received treatment versus if they did not and had live births in both scenarios. This is expressed by: $SACE = E[Y_1 - Y_0|S_1 = S_0 = 1]$.[3] However, because this expression contains counterfactual entities, it cannot be directly estimated from the data. Chiba and VanderWeele showed that SACE could be estimated from the data by the following expression: $SACE = E[Y|A = 1, S = 1] - E[Y|A = 0, S = 1] - \propto$, under two assumptions described later.[3] The first part of this expression is the risk difference estimated from the data, and $\propto$ is a sensitivity parameter approximated by the investigator based on biological plausibility. In this case, $\propto$ would be the expected counterfactual risk difference of preterm birth comparing mothers randomized to the treatment group having live births versus those in the control group having live births if, contrary to the fact, all mothers received periodontal treatment ($\propto = E[Y_1|A = 1, S = 1] - E[Y_1|A = 0, S = 1]$). To estimate SACE using the expressions above, the following two assumptions need to hold.

Assumption 1: This is the assumption of monotonicity, under which $S_0 \leq S_1$ for all individuals, which means that periodontal treatment has either a beneficial effect or no effect on the survival of all the fetuses. The effect of periodontal treatment on stillbirths in the OPT study was risk difference -2.12%: 95% CI -4–14% to -0.11%, and in a meta-analysis of clinical trials odds ratio 0.79: 95% CI 0.55 to 1.22.[1,9] This is likely satisfied because periodontal treatment has been shown to have either a beneficial effect or no effect on spontaneous abortions orstillbirths, and periodontal treatment was not related to adverse outcomes in the OPT study.[1]

Assumption 2: Under this assumption, $E[Y_1|A = 1, S = 1] - E[Y_1|A = 0, S = 1] \geq 0$. This means that the value of the sensitivity parameter would be greater than or equal to zero ($\propto \geq 0$).[3] In this case, we expect the SACE

estimates of the risk differences to be less than or equal to those obtained from intention-to-treat analyses of the OPT data. At the end of follow-up, the control group had more low-risk fetuses than the treatment group because more high-risk fetuses were lost through spontaneous abortions or stillbirths.[1] By contrast, more high-risk fetuses remained in the treatment group at the end of follow-up because more fetuses survived spontaneous abortions or stillbirths.[1]

To get biologically plausible results, we derived a range of $\propto$-values based on published reports of preterm birth risk factors from a large sample of US women, in which odds ratio estimates for various risk factors ranged from 0.9 to 3.2.[10] We further assumed that the risk of preterm birth was 12%, close to that observed in the OPT study, and that it was the same in the treatment and control groups. For example, if we assume that the risk of preterm birth was approximately 12% in the control group (as observed in the OPT study), and the relative risk of preterm delivery after loss of exchangeability to be 1.2, the estimated risk of preterm birth in the treatment group would be 1.2*12% = 14.4%, and $\propto$= 14.4 – 12.0 = 2.4, and so on. Potential confounders in the treatment and control groups were similar at baseline due to randomization, making them exchangeable. However, as the study progressed, more stillbirths in the control group caused the distribution of confounders in the two groups to change, causing loss of exchangeability. The mothers remaining in the treatment group were, on average, at higher risk of preterm birth compared with those remaining in the control group.

We calculated the risk difference and its 95% CI for preterm births and spontaneous abortions and stillbirths, comparing periodontal treatment and control groups from the publicly available OPT data. We estimated SACE by assigning $\propto$-values ranging from -2.5 to 6.0 by increments of 0.5 to the point estimates and 95% confidence limits of risk difference. We repeated the SACE analyses for live births.

To get a point estimate of SACE, we used the two-stage regression-based method to estimate the odds ratio, and bootstrapping to get its 95% CI for live births, as proposed by Tchetgen Tchetgen *et al*.[11] For comparison we also calculated odds ratios for intention-to-treat, multivariable adjusted, and inverse probability weighting[5] analyses for live births.

Results

A total of 823 participants were randomly assigned to either the periodontal treatment (n = 413) or the control group (n = 410). Risk factors of preterm birth were similar in the periodontal treatment and control groups after randomization. There were 49 preterm births and five spontaneous abortions or stillbirths in the periodontal treatment group, and 52 preterm births and 14 spontaneous abortions or stillbirths in the control group. Mothers with spontaneous abortions or stillbirths had more previous poor birth outcomes, and diabetes or hypertension, than those having live births; they were also more likely to be Black and had higher body mass index (Table 1). At the end of follow-up, of the 11 spontaneous abortions or stillbirths among mothers with previous poor pregnancy outcomes, two were in the treatment and nine in the control group (Table 2). Of the 14 spontaneous abortions or stillbirths among Black mothers, five were in the treatment and nine in the control group (Table 2). The treatment group had approximately twice as many mothers with diabetes or hypertension than the control group (Table 2).

The risks of preterm and spontaneous abortion or still birth were respectively 49/413 (11.86%) and 5/413 (1.21%) in the treatment group, and 52/410 (12.68%) and 14/410 (3.33%) in the control group. The intention-to-treat risk differences (%) comparing treatment and control groups were -0.82%: 95% CI -5.30% to 3.67% for preterm birth, and -2.12%: 95% CI -4.14% to -0.11% for spontaneous abortion or stillbirth (Table 3). This analysis was repeated for live births.

SACE estimates for all preterm births are described in Figure 2A and for live births in Figure 2B. The point estimates of SACE were smaller with increasing values of the sensitivity parameter $\propto$, and reached statistical significance when $\propto$ = 4 and the upper bound of the estimate was less than 0 (Figure 2; Supplementary Table 1, available as Supplementary data at *IJE* online). A comparison of different approaches to estimate the effect of periodontal treatment on preterm birth among live births is described in Table 4. The SACE point estimate of the effect of periodontal treatment on preterm birth was protective, even though the CI included 1.

Discussion

Reanalysis of publicly available OPT study data, using newly developed epidemiological methods accounting for truncated preterm birth assessment due to spontaneous abortions or stillbirths, suggests that nonsurgical periodontal treatment before 21 weeks of gestation may have a beneficial effect on birth outcomes in mothers with early to moderate periodontal disease.

This finding is contrary to the conclusion of the OPT study, which was that periodontal treatment did not affect preterm birth.[1] The effect estimates in the OPT study were likely biased because spontaneous abortions and stillbirths

Table 1. Characteristics of mothers having spontaneous abortions or stillbirths and live births

Characteristic	Spontaneous abortion or stillbirth ($n = 19$)	Live birth ($n = 804$)	*P*-value
Group, no. (%)[d]			
Treatment	5 (26.3)	408 (50.8)	0.04
Control	14 (73.7)	396 (49.3)	
Age, years[a]	25.63 (5.19)	25.99 (5.58)	0.78
Baseline Pocket Depth Average, mm[a]	2.76 (0.43)	2.87 (0.56)	0.4
Fraction of sites with PD ≥4 mm[a]	22.45 (13.29)	25.73 (16.35)	0.39
Clinic, no. (%)			
KY	4 (21.1)	207 (25.8)	0.16
MN	2 (10.5)	245 (30.5)	
MS	7 (36.8)	185 (23.0)	
NY	6 (31.6)	167 (20.8)	
Previous pregnancies, no. (%)	15 (78.9)	596 (74.1)	0.64
Previous poor birth outcome[b], no. (%)	11 (57.9)	322 (40.1)	0.12
Race, no. (%)[d]			
Black	14 (73.7)	352 (44.0)	0.01
Non-Black	5 (26.3)	449 (56.1)	
Body mass index[a,c,d]	32.28 (10.08)	27.56 (7.01)	0.005
Tobacco and/or alcohol use. no. (%)	1 (5.3)	98 (12.2)	0.36
Diabetes and/or hypertension, no. (%)	2 (10.5)	44 (5.5)	0.34

PD = Pocket Depth.
[a]Values are means (SD).
[b]Poor birth outcomes include: previous preterm birth, stillbirth, spontaneous abortion and induced abortion.
[c]Body-mass index is the weight in kilograms divided by the square of the height in metres.
[d]$P < 0.05$.

occurred more frequently in the control than in the treatment group, and mothers having spontaneous abortions or stillbirths had more risk factors for preterm birth than those having live births (Table 1). Mothers with a history of previous preterm birth[12] or spontaneous abortion or stillbirth[13] are at higher risk of subsequent preterm birth. Of the 11 mothers with a history of past adverse pregnancy outcomes, who had fetal losses during follow-up in the OPT study, two were in the treatment and nine in the control group. Similarly, of the 14 Black mothers in the OPT study who had fetal losses, five were in the treatment and 11 in the control group. There were approximately twice as many mothers with hypertension or diabetes in the treatment than in the control group. Black race, past adverse birth outcome and hypertension or diabetes in the mother are associated with increased risk of preterm birth.[10,12–16] Though the two arms of the trial may have been exchangeable[17] at the start of the study due to randomization, they were not so by the end of follow-up.

If periodontal treatment had a favourable effect on spontaneous abortions and stillbirths, it could lead to loss of exchangeability during follow-up because spontaneous abortions or stillbirths would be prevented in the treatment but not the control group. Scaling and root planing reduced the risk of spontaneous abortions or stillbirths in the OPT study, risk difference -2.12%: 95% CI -4.14% to -0.11%. In a meta-analysis of clinical trials, the summary effect estimate of periodontal treatment on spontaneous abortions or stillbirths (a secondary outcome) was consistent with a beneficial effect of treatment [odds ratio (OR) = 0.79: 95% CI 0.51 to 1.22].[9] *Fusobacterium nucleatum*, that is found in subgingival plaque and is associated with periodontal disease[18] and its progression,[19] was isolated from the amniotic sac and the tissues of a fetus that was stillborn at term, in a pregnancy that was proceeding normally until the mother had an upper respiratory tract infection.[20] The *F. nucleatum*, matching the organism found in the fetus, was isolated from subgingival plaque of the mother but not from her vagina or rectum, suggesting that *F. nucleatum* originating from periodontal infection in the mother caused the stillbirth.[20] Other case reports linking *F. nucleatum* with stillbirth have subsequently been published,[21,22] and stillbirth has been induced in pregnant mice after infecting them with *F. nucleatum*.[23] Mothers in the periodontal treatment group had lower risk of spontaneous abortion or stillbirth compared with those in the control group in the OPT study, risk

Table 2. Characteristics of the treatment and control groups

Characteristic	Total study population at baseline			Study population after fetal losses		
	Treatment ($n=413$)	Control ($n=410$)	*P*-value	Treatment ($n=408$)	Control ($n=396$)	*P*-value
Age, years[a]	26.1 (5.6)	25.9 (5.5)	0.56	26.1 (5.6)	25.9 (5.5)	0.59
Baseline Pocket Depth average, mm[a]	2.9 (0.6)	2.8 (0.5)	0.13	2.9 (0.6)	2.8 (0.5)	0.13
Fraction of sites with PD ≥4 mm[a]	26.5 (16.6)	24.8 (15.9)	0.13	26.6 (16.7)	24.9 (16.0)	0.13
Clinic, no. (%)						
KY	106 (25.7)	105 (25.6)		106 (26.0)	101 (25.5)	
MN	124 (30.0)	123 (30.0)		123 (30.2)	122 (30.8)	
MS	96 (23.2)	96 (23.4)		94 (23.0)	91 (23.0)	
NY	87 (21.1)	86 (21.0)	0.99	85 (20.8)	82 (20.7)	0.99
Previous pregnancies, no. (%)	306 (74.1)	305 (74.4)	0.92	304 (74.5)	292 (73.7)	0.80
Previous poor birth outcome[b], no. (%)	163 (39.5)	170 (41.5)	0.54	161 (39.5)	161 (40.7)	0.73
Race, no. (%)						
Black	187 (45.6)	179 (43.7)		182 (44.9)	170 (42.9)	
Non-Black	223 (54.4)	231 (56.3)	0.57	223 (55.1)	226 (57.1)	0.57
Body mass index[a,c]	27.9 (7.4)	27.5 (6.9)	0.41	27.7 (7.2)	27.4 (6.8)	0.47
Tobacco and/or alcohol use, no. (%)	52 (12.6)	47 (11.5)	0.62	51 (12.5)	47 (11.9)	0.78
Diabetes and/or hypertension, no. (%)[d]	30 (7.3)	16 (3.9)	0.04	29 (7.1)	15 (3.8)	0.04

PD = Pocket Depth.
[a]Values are means (SD).
[b]Poor birth outcomes include: previous preterm birth, stillbirth, spontaneous abortion and induced abortion.
[c]Body mass index is the weight in kilograms divided by the square of the height in metres.
[d]$P<0.05$.

Table 3. Risk of preterm and spontaneous abortions/or stillbirths in periodontal treatment and control groups and the risk difference in intention–to-treat analysis

	Preterm nirths, *n*	*n*	Risk %	Risk difference: 95% CI
Periodontal treatment	49	413	11.86%	−0.82% to -5.30%, 3.67%
Control	52	410	12.68%	–
	Spontaneous abortions or stillbirths, *n*			
Periodontal treatment	5	413	1.21%	−2.12% to -4.14%, -0.11%
Control	14	410	3.33%	

difference -2.12%: 95% CI -4.14% to -0.11%. Also in the OPT study, scaling and root planing were effective in controlling periodontal disease[1] and reducing numbers of periodontal organisms in subgingival plaque, including *F. nucleatum*.[24] Moreover, previous case-control[25] and prospective studies[26,27] support the relation between periodontal disease and spontaneous abortion. It is plausible, therefore, that periodontal treatment prevented spontaneous abortion or stillbirth induced by periodontal disease in the OPT study, but its effect on preterm birth was masked by loss of exchangeability.

When treatment affects survival in a randomized controlled trial, intention to treat and competing risk analyses are biased because effect estimates are calculated conditional on a post-treatment factor, namely survival.[3,4] Inverse probability weighting, a causal inference-based method, is used to correct for bias resulting from loss to follow-up.[5] That method assumes that participant characteristics measured at baseline accurately predict loss to follow-up. Because known risk factors explain just 19% of the variance of stillbirth incidence,[16] inverse probability weighting would likely not correct for potential bias in this case because it would not account for unmeasured confounding (Figure 1). Other potential sources of bias in randomized controlled trials include random confounding[28] and imperfect adherence.[29] The use of stratified block randomization minimized the chances of random confounding. In the OPT study, 77% of the participants attended at least five out of six visits, and 96% of those in the intervention group received periodontal treatment,[1] minimizing the

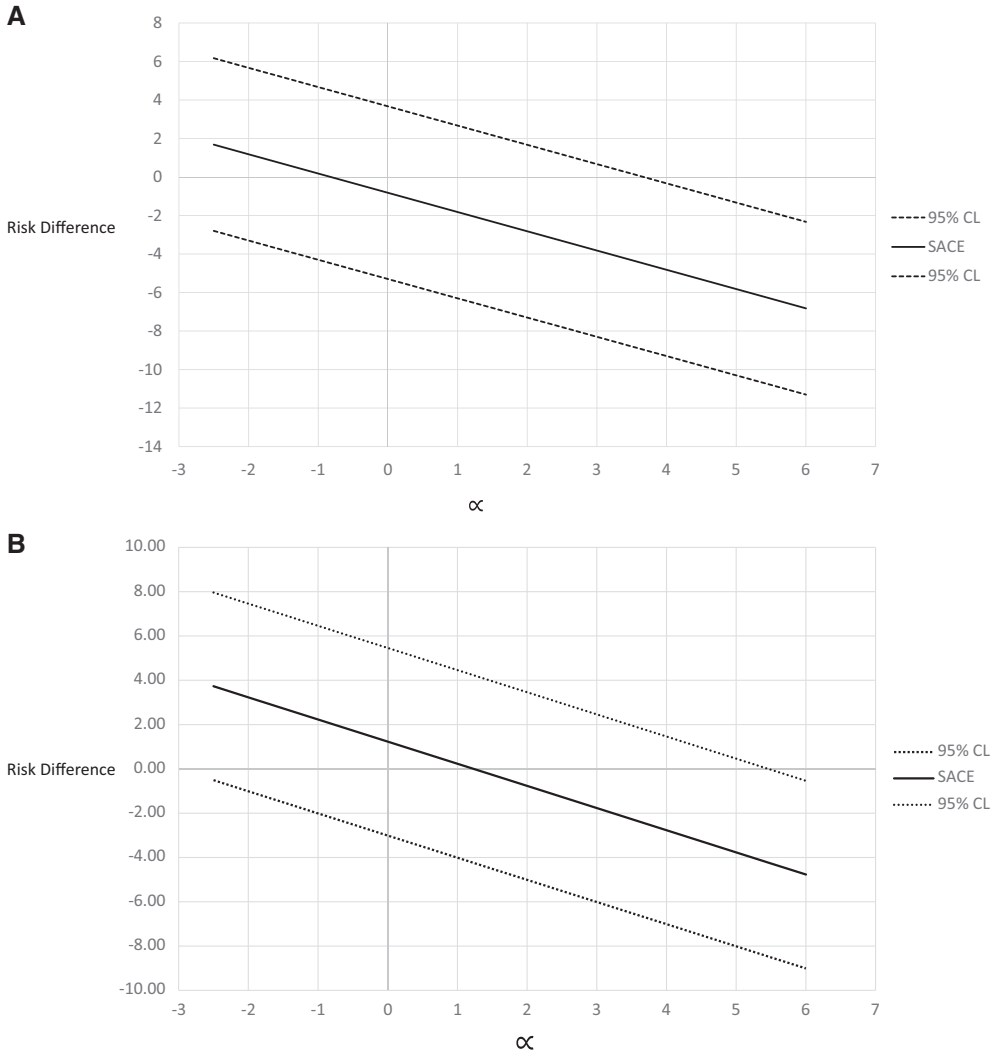

Figure 2. Survivor average causal effect (SACE) estimates and 95% confidence intervals of the effect of periodontal treatment on preterm birth, estimated from publicly available data of the Obstetrics and Periodontal Therapy study. (A) All preterm. (B) Live preterm. Mothers with live births in the treatment group were at higher risk of delivering preterm babies than those in the control group over the course of the study, and therefore had a higher expected risk of preterm than those in the treatment group. If both these groups of mothers were to receive periodontal treatment, the treatment group would have more preterm births than the control group because of the risk profiles of those groups. A measure of the excess risk of the treatment group is captured by the sensitivity parameter $\propto$. Formally, $\propto$ is the expected counterfactual risk difference of preterm birth comparing mothers randomized to the treatment group having live births versus those in the control group having live births if, contrary to the fact, all mothers received periodontal treatment ($\propto = E[Y_1|A=1, S=1] - E[Y_1|A=0, S=1]$). The upper bound of the confidence interval for the risk difference is below 0 when $\propto$ is approximately 4 in A.

chances of imperfect adherence from affecting the results. The principal strata approach or SACE is unbiased because effects are evaluated within strata of counterfactual or potential variables, which are not affected by treatment. However, estimating effects of counterfactual variables from observed data has been challenging.[4,6] Chiba and VanderWeele developed a simple method to estimate SACE, which is based on counterfactual variables, but can be obtained using observed data.[3] A limitation of this approach is that the analyst assigns values to the sensitivity parameter, $\propto$, that is needed to estimate SACE. We used conservative estimates of $\propto$, approximated from published studies, resulting in corrected effect estimates that were within the range of those reported in previous clinical trials.[9] Another limitation is that this method gives a range of corrected values and not a single point estimate and confidence interval. Bias correction, which is being encouraged,[30] typically gives a range of values which is more likely to contain the truth than point estimates obtained from hypothesis testing.[31] Moreover, the point estimate of SACE obtained from the two-stage regression described by Tchetgen Tchetgen *et al.*,[11] also suggested a protective

Table 4. Results of different approaches to estimate the effect of periodontal treatment on live preterm births

	Odds ratio: 95% CI
Intention-to-treat[a]	1.14: 0.72 to 1.81
Multivariable adjusted[b]	1.08: 0.67 to 1.73
Inverse probability weighting[c]	1.04: 0.66 to 1.65
SACE[d]	0.94: 0.48 to 1.82

[a]No adjustment (control group reference in all models).

[b]Adjusted for clinic, race, diabetes or hypertension, tobacco or alcohol intake, previous poor birth outcome in conventional multivariable model.

[c]Inverse probability weighting accounting for all variables in multivariable model and censoring.

[d]SACE using two-stage regression models with 95% confidence intervals obtained by bootstrapping.

effect of periodontal treatment on preterm birth. The convergence of SACE results obtained from two different approaches increases confidence in the results.

Access to publicly available data allowed us to reanalyse the OPT data, applying emerging epidemiological methods to correct for potential bias caused by selective survival. Our findings, together with recent reports clarifying the mechanisms through which periodontal infection can affect pregnancy outcomes, warrants reassessment of the conclusions of the OPT study. Non-surgical periodontal treatment consisting of scaling and root planing, provided to mothers with mild to moderate periodontal disease before 21 weeks of gestation, may prevent preterm births.

Supplementary Data

Supplementary data are available at *IJE* online.

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References

1. Michalowicz BS, Hodges JS, DiAngelis AJ *et al*. Treatment of periodontal disease and the risk of preterm birth. *N Engl J Med* 2006;**355**:1885–94.
2. Flenady V, Koopmans L, Middleton P *et al*. Major risk factors for stillbirth in high-income countries: a systematic review and meta-analysis. *Lancet* 2011;**377**:1331–40.
3. Chiba Y, VanderWeele TJ. A simple method for principal strata effects when the outcome has been truncated due to death. *Am J Epidemiol* 2011;**173**:745–51.
4. Frangakis CE, Rubin DB. Principal stratification in causal inference. *Biometrics* 2002;**58**:21–29.
5. Hernan MA, Hernandez-Diaz S, Robins JM. A structural approach to selection bias. *Epidemiology* 2004;**15**:615–25.
6. Hayden D, Pauler DK, Schoenfeld D. An estimator for treatment comparisons among survivors in randomized trials. *Biometrics* 2005;**61**:305–10.
7. Hodges JS. Public-use data from the Obstetrics and Periodontal Therapy (OPT) Study, a randomized trial of periodontal therapy to prevent pre-term birth. Division of Biostatistics, University of Minnesota, 2013.
8. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology* 1999;**10**:37–48.
9. Polyzos NP, Polyzos IP, Zavos A *et al*. Obstetric outcomes after treatment of periodontal disease during pregnancy: systematic review and meta-analysis. *BMJ* 2010;**341**:c7017.
10. Johnson TS, Rottier KJ, Luellwitz A, Kirby RS. Maternal prepregnancy body mass index and delivery of a preterm infant in Missouri 1998-2000. *Public Health Nurs* 2009;**26**:3–13.
11. Tchetgen Tchetgen EJ, Phiri K, Shapiro R. A simple regression-based approach to account for survival bias in birth outcomes research. *Epidemiology* 2015;**26**:473–80.
12. Kazemier BM, Buijs PE, Mignini L, Limpens J, de Groot CJ, Mol BW. Impact of obstetric history on the risk of spontaneous preterm birth in singleton and multiple pregnancies: a systematic review. *BJOG* 2014;**121**:1197–208; discussion 209.
13. Swingle HM, Colaizy TT, Zimmerman MB, Morriss FH Jr. Abortion and the risk of subsequent preterm birth: a systematic review with meta-analyses. *J Reprod Med* 2009;**54**:95–108.
14. Romero R, Dey SK, Fisher SJ. Preterm labor: one syndrome, many causes. *Science* 2014;**345**:760–65.
15. Salihu HM, Lynch O, Alio AP, Liu J. Obesity subtypes and risk of spontaneous versus medically indicated preterm births in singletons and twins. *Am J Epidemiol* 2008;**168**:13–20.
16. Stillbirth Collaborative Research Network Writing Group. Association between stillbirth and risk factors known at pregnancy confirmation. *JAMA* 2011;**306**:2469–79.
17. Greenland S, Robins JM. Identifiability, exchangeability and confounding revisited. *Epidemiol Perspect Innov* 2009;**6**:4.
18. Socransky SS, Haffajee AD. Periodontal microbial ecology. *Periodontol 2000* 2005;**38**:135–87.
19. Yang NY, Zhang Q, Li JL, Yang SH, Shi Q. Progression of periodontal inflammation in adolescents is associated with increased number of Porphyromonas gingivalis, Prevotella intermedia, Tannerella forsythensis, and Fusobacterium nucleatum. *Int J Paediatr Dent* 2014;**24**:226–33.
20. Han YW, Fardini Y, Chen C *et al*. Term stillbirth caused by oral Fusobacterium nucleatum. *Obstet Gynecol* 2010;**115**:442–45.
21. Bohrer JC, Kamemoto LE, Almeida PG, Ogasawara KK. Acute chorioamnionitis at term caused by the oral pathogen Fusobacterium nucleatum. *Hawaii J Med Public Health* 2012;**71**:280–81.
22. Gauthier S, Tetu A, Himaya E *et al*. The origin of Fusobacterium nucleatum involved in intra-amniotic infection and preterm birth. *J Matern Fetal Neonatal Med* 2011;**24**:1329–32.
23. Han YW, Redline RW, Li M, Yin L, Hill GB, McCormick TS. Fusobacterium nucleatum induces premature and term stillbirths in pregnant mice: implication of oral bacteria in preterm birth. *Infect Immun* 2004;**72**:2272–79.

24. Novak MJ, Novak KF, Hodges JS *et al*. Periodontal bacterial profiles in pregnant women: response to treatment and associations with birth outcomes in the obstetrics and periodontal therapy (OPT) study. *J Periodontol* 2008;**79**:1870–79.
25. Pitiphat W, Chanomethaporn A, Wara-Aswapati N *et al*. Relationship between periodontitis and spontaneous abortion: a case-control study. *J Dent Res* 2015;**94**(Spec Iss A):2026.
26. Farrell S, Ide M, Wilson RF. The relationship between maternal periodontitis, adverse pregnancy outcome and miscarriage in never smokers. *J Clin Periodontol* 2006;**33**:115–20.
27. Moore S, Ide M, Coward PY *et al*. A prospective study to investigate the relationship between periodontal disease and adverse pregnancy outcome. *Br Dent J* 2004;**197**:251–58.
28. Greenland S, Mansournia MA. Limitations of individual causal models, causal graphs, and ignorability assumptions, as illustrated by random confounding and design unfaithfulness. *Eur J Epidemiol* 2015;**30**:1101–10.
29. Mansournia MA, Higgins JP, Sterne JA, Hernan MA. Biases in randomized trials: a conversation between trialists and epidemiologists. *Epidemiology* 2017;**28**:54–59.
30. Lash TL, Fox MP, MacLehose RF, Maldonado G, McCandless LC, Greenland S. Good practices for quantitative bias analysis. *Int J Epidemiol* 2014;**43**:1969–85.
31. Lash TL. The harm done to reproducibility by the culture of null hypothesis significance testing. *Am J Epidemiol* 2017;**186**:627–35.