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Maternal smoking and twinning

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In order to investigate a possible association between maternal smoking during pregnancy and twinning, information on 1 096 330 single births and 12 342 twin births in 1983–95 was obtained from the Swedish Medical Birth Registry (MBR). All odds ratios (OR) were estimated after stratification for year of birth and maternal age, parity, and educational level. Smoking women, compared with non-smoking women, were at increased risk of having dizygotic (DZ) twins, but the risk increase was only evident among multiparas. A strong association between previous involuntary childlessness and dizygotic (DZ) twinning (especially in primiparas) was found. The strongest association between maternal smoking and DZ twinning was found among multiparas without any history of involuntary childlessness (OR: 1.35, 95%CI:1.22–1.49), whereas among women who had experienced involuntary childlessness, the opposite was seen (OR: 0.82, 95%CI:0.66–1.00, no difference between parity strata). Weinberg's differential method was used to estimate the number of monozygotic (MZ) twins, and a method of estimating stratified ORs among mothers of MZ twins was presented. No association was found between MZ twinning and maternal smoking (OR: 0.96, 95%CI:0.86–1.07), and no confounding by parity or previous involuntary childlessness was indicated. Several non-causal explanations to the positive association between DZ twinning and maternal smoking among multiparas were discussed, but homogeneity over strata indicated that maternal smoking may be a true risk factor for double ovulation.

Keywords: twins, twinning rate, registry, fecundity, infertility, parity

Introduction

Dizygotic (DZ) twinning has frequently been used as a measure of human fertility.[1] As maternal smoking during pregnancy is known to have several adverse effects on human reproduction, the reports by Yerushalmy,[2] Olsen et al,[3] and Parazzini et al[4] of a positive association between DZ twinning and maternal smoking were rather unexpected. No significant association has been reported between monozygotic (MZ) twinning and maternal smoking.

If maternal smoking is a true risk factor for twinning, it would be of great public interest since twin pregnancies generally are associated with increased obstetric hazards.[5]

The question of a putative association between DZ and MZ twinning and maternal smoking during pregnancy needs to be investigated further.

Material and methods

The present study is based on all singleton and twin births of Swedish women in 1983–95. Information was obtained from the Swedish Medical Birth Registry (MBR), containing medical information on nearly all deliveries in Sweden (coverage about 99%). Nearly all pregnant women receive free antenatal care. At the first visit (usually during weeks 10–12), each woman is interviewed by a midwife and, among other things, the smoking habit of the woman (none, < 10 cigarettes per day, or ⩾ 10 cigarettes per day), number of years of involuntary childlessness, and the presence or not of infertility treatment (only from 1994 and onwards) is stated. Standardised record forms are used at all antenatal clinics, all delivery units, and at all pediatric examinations of newborn infants. Copies of these forms are sent to the National Board of Health where they are computerised.

In order to collect information on maternal educational level, the Medical Birth Registry (MBR) was linked with the Registry of Education kept by Statistics Sweden. The latter registry contains information on the educational level of each woman (including nine years of compulsory education) and the educational level at 1 January 1996 was extrapolated from it. Thus, the educational level used in this study to estimate socio-economic status does not necessarily refer to the actual educational level of each woman at the time she is giving birth. This makes it possible to estimate socio-economic status for young women too.

All odds ratios (OR) in this report were calculated using Mantel-Haenszel's technique. Stratification was made for year of birth, maternal age (5-year classes), parity (previous births +1, 1–4+), and educational level (< 10 years, 10–12 years, 13–14 years, and ⩾ 15 years); 95% confidence intervals (CI) were estimated using Miettinens method.[6]

Information on zygosity is lacking in the MBR. To represent mothers of DZ twins, all mothers of unlike-sexed pairs were chosen, whereas the number of MZ pairs was estimated by subtracting the number of unlike-sexed pairs

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from the number of like-sexed pairs.[7] Details of the procedure to estimate adjusted OR for smoking among mothers of MZ twins are shown in Appendix 1.

The percentage of women reporting involuntary childlessness among those with stated procedures against infertility was calculated (information obtainable only for women giving birth in 1994–95). This percentage is used as an estimate of the reporting completeness of involuntary childlessness in the registry.

Based on this rate estimate, the number of women with previous involuntary childlessness for whom no information about this condition was available, was estimated. The 'true' number of women with or without earlier involuntary childlessness was then estimated by applying this rate estimate to the observed numbers. Appendix B shows the procedure used to estimate stratified OR among the estimated number of women with or without involuntary childlessness.

When comparing two stratified odds ratios, two-tailed z-tests were carried out, using the same variance as used to estimate the 95% CI. Tests of homogeneity of the odds ratios across strata were based on weighted sums of the squared deviations of the stratum specific log-odds ratios from their weighted means.

Results

Table 1 shows the number of mothers of twins or singletons on which the study is based. As mentioned in the Material and Methods section, information on zygosity is lacking in the MBR, which is why the number of monozygotic (MZ) twins was estimated instead from the number of like-sexed and unlike-sexed twins. Table 2 shows the adjusted ORs for maternal smoking among mothers of all twins, dizygotic (DZ), or MZ twins (estimated), respectively, vs mothers of singletons. As shown in Table 1, smoking women, compared with non-smoking women, are at increased risk of having DZ, but not MZ, twins. The risk increase for DZ twinning is, however, only evident among multiparous women (P for homogeneity over parity strata = 0.0014). No heterogeneity in the association between DZ twinning and maternal smoking over other strata was detected (P for homogeneity over year of birth strata, maternal age strata, and educational level strata was 0.16, 0.26, and 0.46, respectively). The difference between the ORs for any smoking among mothers of MZ twins and mothers of DZ twins is statistically significant (all parities: P = 0.003, parity 2+: P < 0.00001). No significant dose-response effect was shown, neither among mothers of DZ nor among mothers of MZ twins.

The heterogeneity of the association between DZ twinning and maternal smoking over parity strata gave reason to investigate a putative association between hypo- or hyperfertility and twinning. After stratification for year of birth, maternal age and education, the ORs (with 95% CI) for previous involuntary childlessness (> 1 year) among mothers of twins compared with mothers of singletons were 3.32 (2.97–3.70) and 1.58 (1.34–1.86) among primiparas and multiparas, respectively. Between MZ twinning and involuntary childlessness, no association was indicated.

Over the period studied, the DZ twinning rate has consistently increased from about 0.4% in 1983 to about 0.9% in 1995. Figure 1 shows the age-adjusted ORs for DZ twinning among deliveries taking place in one period as specified vs all other periods. The most dramatic increase of the DZ twinning-rate over the studied period is the group of primiparas with previous involuntary childlessness; but among women without any reported history of involuntary

Table 1 Mothers of twins or singletons, respectively, according to smoking habits, Sweden 1973–95

	Mothers of:		
	like-sexed twins	unlike-sexed twins	singletons
Smoking <10 cigs/day	1352	616	173 629
Smoking >=10 cigs/day	814	390	105 617
Non-smoking	6371	2799	817 084

Table 2 ORs for smoking with 95% CI according to zygosity and parity, stratified for year, maternal age, parity, and educational level, Sweden 1983–95

	All parities	Parity 1	Parity 2+
All twins			
any smoking	1.08 (1.04–1.13)	0.97 (0.91–1.04)	1.17 (1.10–1.23)
<10 cigs/day	1.08 (1.03–1.13)	0.99 (0.92–1.07)	1.15 (1.07–1.23)
>=10 cigs/day	1.08 (1.02–1.15)	0.94 (0.85–1.04)	1.19 (1.10–1.28)
Dizygotic twins (unlike-sexed)			
any smoking	1.17 (1.04–1.13)	0.99 (0.87–1.12)	1.30 (1.18–1.43)
<10 cigs/day	1.15 (1.05–1.26)	1.00 (0.86–1.16)	1.27 (1.13–1.42)
>=10 cigs/day	1.20 (1.07–1.34)	0.99 (0.82–1.20)	1.34 (1.17–1.53)
Monozygotic twins (estimated)			
any smoking	0.96 (0.86–1.07)	0.95 (0.86–1.05)	0.96 (0.87–1.05)
<10 cigs/day	0.98 (0.87–1.11)	0.99 (0.88–1.11)	0.97 (0.86–1.08)
>=10 cigs/day	0.92 (0.78–1.08)	0.87 (0.74–1.03)	0.95 (0.83–1.09)

childlessness, an increase of the DZ twinning rate over time is also seen. Among 3827 women with available information of procedures against involuntary childlessness, 2435 (63.6%) had reported previous involuntary childlessness. When attempts to adjust for the under-reporting of involuntary childlessness (as specified in the Material and Methods section and Appendix 2), the association between year of birth and DZ twinning among women without any information of previous involuntary childlessness diminished but remained significant: the OR for DZ twinning among women without previous involuntary childlessness giving birth in 1993–95 compared with women without previous involuntary childlessness giving birth in 1983–92 was 1.23 (1.13–1.34) (no significant difference between parity strata).

The OR for smoking (after stratification for year of birth, maternal age and parity) among women undergoing fertility treatment compared with all other women was 0.84 (95% CI:0.72–0.98).

The adjusted ORs (and 95% CI) for involuntary childlessness (> 1 year) among smoking mothers of singletons vs non-smoking mothers of singletons were 1.08 (1.06–1.11), and 1.29 (1.25–1.32) among primiparas and multiparas, respectively. Among primiparas, heterogeneity over year of birth-strata was shown: the association between maternal smoking and involuntary childlessness among primiparas decreased considerably over the period studied, and in 1995 the OR for involuntary childlessness (> 1 year) among primiparous smoking mothers of singletons compared with primiparous non-smoking mothers of singletons was 0.89 (0.79–0.99) (P for time trend = 0.00006).

The data set was divided into two groups: presence or absence of previous involuntary childlessness, and the association between dizygotic twinning and maternal smoking within the groups was estimated separately (Figure 2). Figure 2 shows an association between maternal smoking and DZ twinning (especially in multiparas) among women

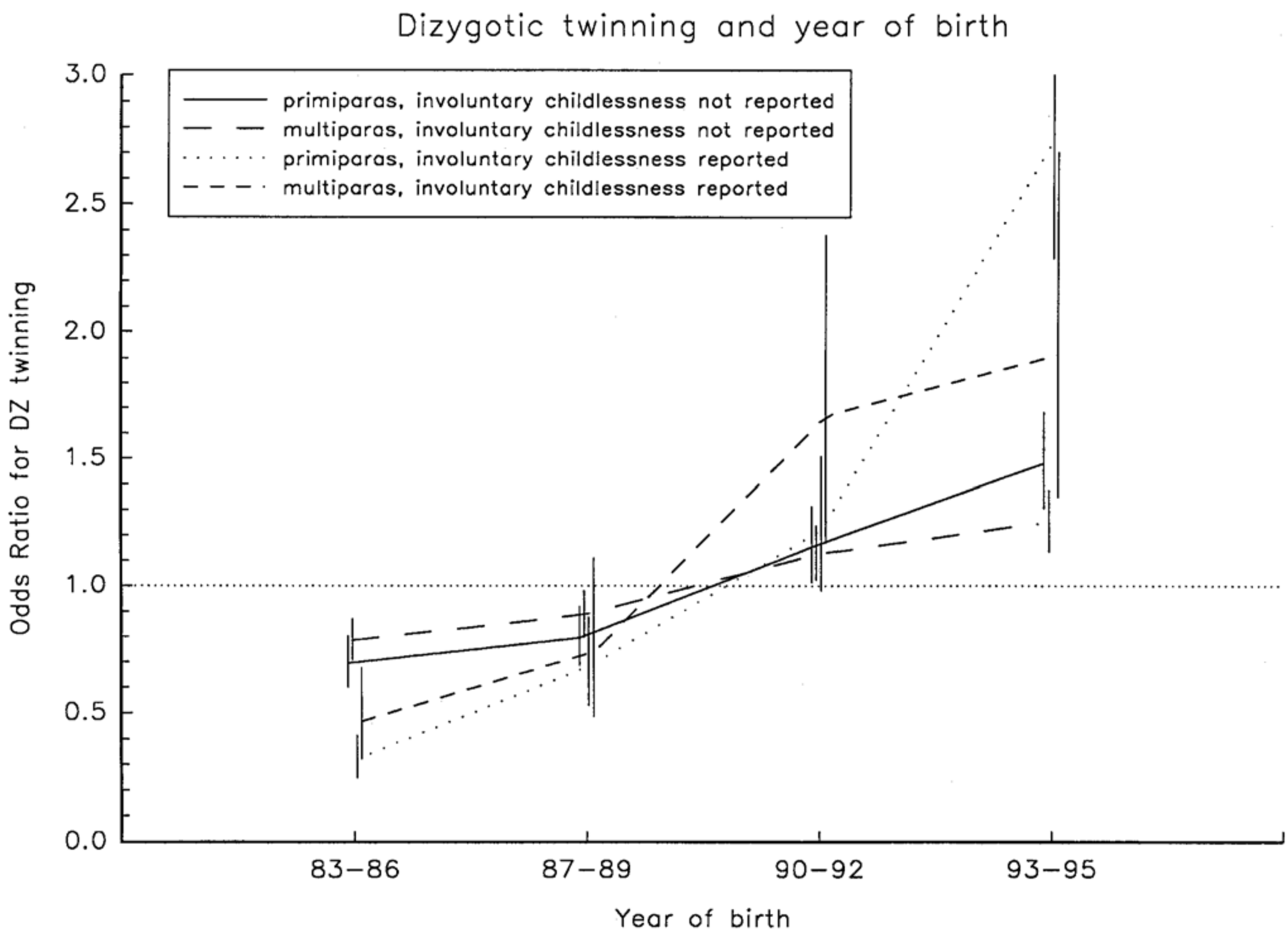

Figure 1 OR (with 95% CI as vertical bars) for DZ twinning among deliveries taking place in one period as specified vs all other periods, according to history of involuntary childlessness and parity, stratified for maternal age, smoking, and educational level.

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without any history of involuntary childlessness, whereas among women who have experienced involuntary childlessness, decreased smoking rates could be seen.

Discussion

The results of the present study support earlier findings of a positive association between DZ twinning and maternal smoking, but only among multiparous women, a finding which has not been described before. The heterogeneity over parity strata, and the finding of different directions of the association between maternal smoking and DZ twinning (depending on the presence or absence of previous involuntary childlessness), suggest caution in the interpretation of the results.

Smoking is believed to have a negative effect on fecundity,[8,9] a knowledge which in itself is likely to confound any investigation of the association between involuntary childlessness and maternal smoking because women with severe fertility problems probably may be more likely than other women to give up smoking in order to maximise their chances of becoming pregnant. This could be the explanation to the finding in the present study of an association between involuntary childlessness and maternal smoking only at the beginning of the study period, whereas at the end of the study period (when the negative effect of maternal smoking on reproduction was more well-known), a negative association was found instead.

The doubling of the Swedish DZ twinning rate during the study period agrees with the rise seen in other developed countries, and is believed to be due to increasing use of ovulation-inducing agents and in vitro fertilisation.[1,10] The strong association between the year of birth and DZ twinning among women with previous involuntary childlessness which was found in the present study supports this theory but another unknown cause of the increasing DZ twinning rate could not be ruled out. In the present study, increasing DZ twinning rates over time could also be seen among women without previous involuntary childlessness even after attempts to adjust for under-reporting of involuntary childlessness. However, it is quite possible that the rate of under-reporting was underestimated, and that no other important cause of the increasing DZ twinning rate than hormonal treatments exists. This problem illustrates a serious

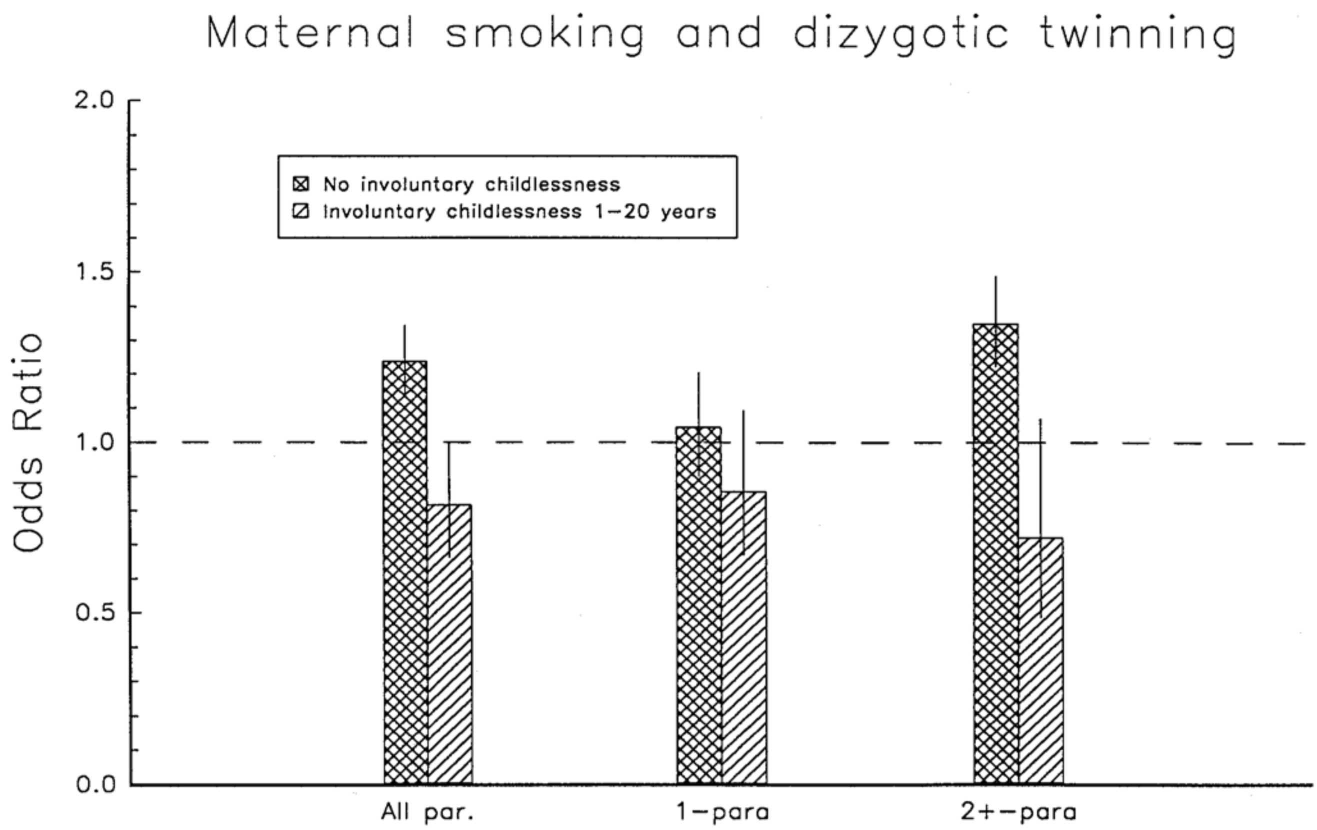

Figure 2 OR (with 95% CI as vertical bars) for maternal smoking among mothers of dizygotic twins vs mothers of singletons, according to history of involuntary childlessness and parity, stratified for year of birth, maternal age, and educational level, Sweden 1983–95.

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shortcoming of this study (and other large population based studies): the impossibility of checking each twin pregnancy in order to decide whether it was spontaneous or not.

Women who undergo fertility treatment are, as shown in the present study, less likely to smoke than other women and are more likely to give birth to DZ twins. The negative association which was found in the present study between maternal smoking and DZ twinning among women with a history of involuntary childlessness is thus expected.

The results could be important to bear in mind while evaluating other studies concerning maternal smoking and other conditions where different reproductive histories in case and control mothers are suspected.

It has been speculated that the association between maternal smoking and DZ twinning found in previous studies might be causal or due to confounding. In a retrospective study, Olsen et al[3] found an association between heavy smoking and DZ twinning and argued that 'a change in the hormonal balance between estrogen, follicle-stimulating and luteinizing hormones might increase the probability of double ovulation'. Parazzini et al[4] who (in a retrospective study based on 133 case mothers) found a non-significant association between maternal smoking and DZ twinning, were on the other hand cautious in interpreting their data and did not believe in a biological mechanism behind the association between maternal smoking and DZ twinning. In a review article, James[11] offered a non-causal hypothesis in which the association between DZ twinning and maternal smoking is believed to be due to the hormonal characteristics of women who are destined to become smokers.

In the present study, the estimated reporting rate of involuntary childlessness was only 64%. Thus, among DZ twin mothers without any reported involuntary childlessness, especially the group of primiparas, there may be hidden a significant proportion of women who have conceived after hormonal treatment. The OR estimated among multiparas could thus be a better estimate of the association between maternal smoking and DZ twinning.

Among pregnant Swedish women, the use of tobacco is closely related to social class: well educated women smoke significantly less than women with poor education.[12] In the present study, no association between educational level and DZ twinning (indicating different hormonal characteristics in well educated women and women with a short education time) was found (data not shown). If hormonal characteristics were a major determinant for smoking, the association between maternal smoking and DZ twinning would have shown heterogeneity over educational strata. In the present study, the association between maternal smoking and DZ twinning was independent of educational level.

Another non-causal explanation of the association between maternal smoking and DZ twinning among multiparas could be based on the fact that mothers of DZ twins belong to a group of highly fertile women with a comparatively high proportion of unplanned pregnancies.[13] As many women give up smoking while planning a pregnancy, mothers of DZ twins could be more likely to smoke.

However, the size, homogeneity over time and educational strata, statistical significance, and concordance of published studies on the association between DZ twinning and maternal smoking, suggest caution before ruling out maternal smoking as a true risk factor for double ovulation.

A 'protective' effect of maternal smoking has been found by some investigators for two types of birth defects: Down syndrome (DS)[14–18] (in one study only among primiparas[19]) and neural tube defects (NTD) (most non-significant,[20] one significant[21]). If maternal smoking increases early loss of 'susceptible' embryos (eg DS or NTD), smoking should lower the twinning rate because the twinning rate is believed to be increased among spontaneous abortions.[22,23] However, to use twinning rate in order to evaluate the early loss theory is complicated, partly due to the putative association between maternal smoking and double ovulation, and partly due to the magnitude of confounding by parity, year of birth, and previous involuntary childlessness when studying the association between maternal smoking and DZ twinning. For MZ twins, no confounding by parity or previous involuntary childlessness has been observed and no significant effect of smoking is found, a finding which is in accordance with the report by Olsen et al.[3] The weak, non-significant negative association between maternal smoking and MZ twinning found in this paper does not support the early loss theory, but cannot reject it either.

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Appendix 1

Procedures for estimation of stratified OR among mothers of MZ twins

Table 3 Denotations of the observed and estimated counts for stratum i

	Exposed	Unexposed
Unlike-sex pairs	a_i^1	b_i^1
Like-sex pairs	a_i^2	b_i^2
MZ twins (estimated)	$a_i = a_i^1 - a_i^2$	$b_i = b_i^1 - b_i^2$
Singletons	c_i	d_i

Following the Mantel-Haenszel procedure, the common OR was then estimated:

$$OR\ (\Sigma\, a_i d_i/n_i / \Sigma\, b_i c_i/n_i)\quad n_i = a_i + b_i + c_i + d_i$$

The Mantel-Haenszels statistic (χ^2 with 1 df) for testing difference between groups is obtained by summation over all strata of each upper left-hand cell frequency (a_i) (exposed cases) with its expected value $E(a_i)$ under the hypothesis of no difference between groups, divided by summation of the variance (based on a hypergeometric distribution) of each a_i.

$$(\Sigma[a_i - E(a_i)]^2/\Sigma\, V(a_i)$$

When the cases were defined as MZ twins, the variance of each a_i [$V(a_i)$] was estimated by:

$$V(a_i) = V(a_i^1 - a_i^2) = V(a_i^1) + V(a_i^2)$$

95% CI was then estimated using Miettinen's method.[6]

Appendix 2

Procedures for estimation of stratified OR among mothers with or without information on previous involuntary childlessness, adjusting for a reporting rate c_1.

Table 4 Denotations of the observed and estimated counts for exposed cases in stratum i

Involuntary childlessness	Exposed cases
Yes, observed number	a_i^1
No, observed number	a_i^2
Yes, estimated number	$a_i^{1*} = a_i^1 + c * a_i^1$
No, estimated number	$a_i^{2*} = a_i^2 - c * a_i^1$

$c = 1/c_1 - 1$

The variances of the estimated counts of exposed cases within each stratum were estimated by:

$$V(a_i^{1*}) = V(a_i^1) + c^2 * V(a_i^1)$$

$$V(a_i^{2*}) = V(a_i^2) + c^2 * V(a_i^1)$$

The ORs and CIs were then calculated as specified in Appendix 1.

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