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MISCLASSIFICATION OF SMOKING HABITS AS A SOURCE OF BIAS IN THE STUDY OF ENVIRONMENTAL TOBACCO SMOKE AND LUNG CANCER

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SUMMARY

The relationship of environmental tobacco smoke to lung cancer risk in lifelong non-smokers is commonly studied using marriage to a smoker as the index of exposure. As smokers tend to marry smokers, relative risk estimates will be biased if some current or former smokers are misclassified as lifelong non-smokers. This paper shows how various factors affect the magnitude of the bias and describes a method for obtaining misclassification-adjusted relative risk estimates. Application of the method to U.S. and Asian data for women suggests misclassification is an important determinant of the slight excess risk observed in non-smokers married to smokers. Reasons why our conclusions differ from those of others are discussed, as are other difficulties in interpreting the association between spousal smoking and lung cancer risk.

1. INTRODUCTION

Error in the variables studied can bias the relationship of a risk factor to a disease. In 2×2 tables, random misclassification of exposure or disease biases relative risk (RR) estimate towards unity.[1–3] How the bias relates to the misclassification rate, and the disease and exposure frequency has been described.[4] Additional information on accuracy of exposure data can be used to obtain unbiased RR estimates.[5]

Random misclassification of exposure understates true associations, but random misclassification of confounding variables may not. How misclassification affects RR estimates adjusted for a single confounder with two levels has been studied.[6,7] With large ($\sim$ 30 per cent) errors in the confounder, adjustment has little effect. Even for smaller ($\sim$ 10 per cent) errors, about half the confounding effect remains after adjustment. Tzonou *et al.*[6] note that 'Generally, in the presence of strong risk factors which have potentially large confounding effects and which may have been imprecisely measured, the etiological significance of factors observed to be relatively weakly associated with disease must be treated with caution.

Since 1981, the possible association of lung cancer with environmental tobacco smoke (ETS) exposure has been extensively studied. Since this association, if it existed, would be much weaker than that with active smoking, and since it is hard to quantify precisely the many aspects of active smoking correlated with risk, ETS studies usually consider only lifelong non-smokers. The exposure index usually used, and that for which an association has been claimed,[7,8] is marriage to a smoker, there being far more data for females than males. Some 10 years ago[9] one of us (PNL) pointed out that, as smokers tend to marry smokers, misclassification of some current or former

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smokers as lifelong non-smokers would bias the spousal smoking RR. Since then many attempts have been made to quantify the bias,[7,8,10-12] with conflicting conclusions about its importance.

This paper reviews the issue of bias from smoking misclassification in ETS/lung cancer studies. Section 2 considers misclassification in a 2×2 table assuming no true ETS effect, and describes the relationship of the observed spousal smoking/lung cancer association to various factors and assumptions. It is shown that misclassification of smokers as non-smokers causes much greater bias than misclassification, either of non-smokers as smokers or of spousal smoking. Restricting attention to misclassification of smoking subjects, Section 3 considers the possibility of a true ETS effect, acting multiplicatively or additively with active smoking. It also reveals errors in published methodologies for bias adjustment.[7,10] Section 4 allows for different misclassification rates for different types of smokers, and shows how to estimate bias based on observed rather than true underlying data. Weaknesses in the methods of the U.S. Environmental Protection Agency (EPA)[8] are demonstrated, and an alternative methodology described. Using this, and the complex set of misclassification rates used by EPA,[8] the estimated biases are shown to be virtually the same as those estimated using a single misclassification rate, of ever smokers as never smokers. After considering plausible values of the between-spouse smoking concordance rate and of the ever-smoker/never-smoker misclassification rate, the simplified methodology is then, in Section 5, applied to U.S. data. In Section 6 the methodology is applied to data from Asian studies, accounting for possible higher misclassification rates. Section 7 discusses other issues affecting interpretation of the ETS/lung cancer relationship, and in Section 8 the main findings are reviewed and discussed.

2. MISCLASSIFICATION IN A 2×2 TABLE; NO TRUE EFFECT OF ETS EXPOSURE

2.1. The simplest situation

Consider N married individuals of which a proportion s smokes. Let the proportion whose spouse smokes be m_1 for non-smokers and m_2 for smokers. Assume $m_2 > m_1$. Let the lung cancer risk for a given period be y for non-smokers and Ry for smokers, and be independent of spouse smoking. Assume a random proportion p (> 0) of smokers are misclassified as non-smokers. Expected numbers of subjects before ('true data') and after ('observed data') misclassification are then:

Group	Smoking habits		True data		Observed data	
	Subject	Spouse	Population	Cases	Population	Cases
1	Non-smoker	Non-smoker	$a = N(1-s)(1-m_1)$	$A = ya$	$a^* = a + pc$	$A^* = y(a + pRc)$
2	Non-smoker	Smoker	$b = N(1-s)m_1$	$B = yb$	$b^* = b + pd$	$B^* = y(b + pRd)$
3	Non-smoker	All	$u = N(1-s)$	$U = yu$	$u^* = u + pv$	$U^* = y(u + pRv)$
4	Smoker	Non-smoker	$c = Ns(1-m_2)$	$C = yRc$	$c^* = (1-p)c$	
5	Smoker	Smoker	$d = Nsm_2$	$D = yRd$	$d^* = (1-p)d$	
6	Smoker	All	$v = Ns$	$V = yRv$	$v^* = (1-p)v$	$V^* = y(1-p)Rv$

Asterisks indicate observed rather than true data. Upper and lower case letters indicate cases and the population, respectively. The bias calculations do not depend on the scaling factors N and y. The mathematics below deals only with expected values, and not sampling distributions.

2.2. Effect of misclassification on the concordance ratio

The association of husbands' and wives' smoking habits is often measured by the concordance ratio $k = ad/bc = m_2(1 - m_1)/m_1(1 - m_2)$. Since $m_2 > m_1$, $k > 1$. The observed concordance ratio $k^* = a^*d^*/b^*c^*$ satisfies the conditions $1 < k^* < k$.

2.3. Effect of misclassification on the active smoking risk

The observed active smoking RR, obtained by dividing risks in groups 6 and 3 (ignoring spousal smoking) is $R^* = R(u + pv)/(u + pRv)$. It satisfies $1 < R^* < R$. The ratio of observed to true excess risks $(R^* - 1)/(R - 1)$ equals $(1 - s)/(1 - s + pRs)$ and declines as the misclassification rate, proportion of smokers and true risk increase.

2.4. Effect of misclassification on the spousal smoking risk

The observed spousal smoking RR, obtained by dividing risks in groups 2 and 1 (in non-smokers), is $E^* = (a + pc)(b + pRd)/(b + pd)(a + pRc)$ and satisfies $E^* > 1$. Thus misclassification creates an apparent risk from spousal smoking when no true effect exists. We refer to this as the 'misclassification bias'.

2.5. Maximum misclassification bias and rate

E^* can be expressed in terms of the observed population by:

$$E^* = [(b^* + d^*(R - 1)p/(1 - p))a^*]/[(a^* + c^*(R - 1)p/(1 - p))b^*].$$

E^* is a maximum when R is infinite. E^* then equals k^*, so the bias cannot exceed the observed concordance ratio. When R is infinite, $R^* = (u + pv)/pv = u^*(1 - p)/v^*p$, and $p = u^*/(u^* + R^*v^*)$, which is thus the maximum misclassification consistent with the observed active smoking data.

2.6. Factors affecting the magnitude of the misclassification bias

Defining $Q = c^*(R - 1)p/a^*(1 - p)$, $E^* = (1 + k^*Q)/(1 + Q)$. E^* increases monotonically with k^* and Q. Given an observed distribution of smoking habits (a^*, c^* and k^*) E^* thus increases strongly with the misclassification rate (being, for small p, approximately proportional to p) and with the active smoking RR (being proportional to $(R - 1)$). This formulation also suggests E^* increases with the concordance ratio and with the proportion of smokers. Defining $z = m_2/m_1 > 1$, E^* can be expressed as the cross-product ratio of four ratios of observed to true data:

Cases: Spouse smoker	$h_1 = (b + pRd)/b = 1 + pRsz/(1 - s) = 1 + \delta_1$
Cases: Spouse non-smoker	$h_2 = 1 + pRs(1 - m_1z)/(1 - s)(1 - m_1) = 1 + \delta_2$
Population: Spouse smoker	$h_3 = 1 + psz/(1 - s) = 1 + \delta_3$
Population: Spouse non-smoker	$h_4 = 1 + ps(1 - m_1z)/(1 - s)(1 - m_1) = 1 + \delta_4$

For small p, δ_i are small, so E^* can be estimated approximately by

$$E^* = \frac{(1 + \delta_1)(1 + \delta_4)}{(1 + \delta_2)(1 + \delta_3)} \simeq 1 + \delta_1 + \delta_4 - \delta_2 - \delta_3 = 1 + \frac{p(R - 1)s(z - 1)}{(1 - s)(1 - m_1)}.$$

Table I. Variation in misclassification bias according to variation in p, $R-1$, s, m_1 and k

Misclassification rate (p)	Excess smoking risk ($R-1$)	Proportion of subjects smoking (s)	Proportion of spouses who smoke (m_1)								
			0·1			0·3			0·5		
			Concordance ratio (k)								
			2·0	3·0	4·0	2·0	3·0	4·0	2·0	3·0	4·0
0·01	4	0·2	1·009	1·016	1·023	1·008	1·012	1·016	1·007	1·010	1·012
		0·4	1·023	1·043	1·059	1·020	1·032	1·041	1·017	1·026	1·031
		0·6	1·050	1·091	1·125	1·043	1·070	1·088	1·037	1·057	1·068
	9	0·2	1·020	1·037	1·051	1·017	1·028	1·035	1·015	1·022	1·027
		0·4	1·051	1·093	1·129	1·043	1·071	1·090	1·038	1·057	1·069
		0·6	1·105	1·193	1·267	1·091	1·150	1·192	1·080	1·123	1·149
	19	0·2	1·041	1·076	1·105	1·035	1·057	1·073	1·031	1·046	1·056
		0·4	1·101	1·187	1·260	1·087	1·144	1·184	1·077	1·118	1·143
		0·6	1·198	1·366	1·511	1·174	1·292	1·377	1·155	1·242	1·298
0·02	4	0·2	1·018	1·032	1·045	1·015	1·024	1·031	1·013	1·020	1·024
		0·4	1·045	1·081	1·112	1·038	1·062	1·079	1·033	1·051	1·061
		0·6	1·091	1·165	1·227	1·079	1·130	1·165	1·070	1·107	1·130
	9	0·2	1·039	1·071	1·098	1·033	1·054	1·069	1·029	1·044	1·053
		0·4	1·095	1·174	1·241	1·082	1·135	1·172	1·072	1·110	1·134
		0·6	1·183	1·335	1·463	1·161	1·269	1·346	1·144	1·225	1·276
	19	0·2	1·078	1·144	1·200	1·067	1·111	1·141	1·059	1·090	1·109
		0·4	1·181	1·334	1·466	1·158	1·265	1·341	1·141	1·219	1·269
		0·6	1·318	1·589	1·824	1·287	1·491	1·643	1·261	1·420	1·526
0·05	4	0·2	1·042	1·077	1·106	1·036	1·059	1·074	1·031	1·048	1·057
		0·4	1·099	1·180	1·247	1·086	1·142	1·181	1·077	1·117	1·142
		0·6	1·179	1·321	1·437	1·161	1·266	1·342	1·145	1·227	1·280
	9	0·2	1·090	1·165	1·228	1·077	1·127	1·162	1·068	1·104	1·126
		0·4	1·197	1·361	1·500	1·175	1·292	1·377	1·157	1·245	1·302
		0·6	1·321	1·583	1·803	1·295	1·504	1·660	1·273	1·441	1·556
	19	0·2	1·172	1·318	1·443	1·150	1·251	1·323	1·133	1·207	1·254
		0·4	1·338	1·626	1·876	1·306	1·526	1·692	1·280	1·452	1·570
		0·6	1·482	1·889	2·241	1·456	1·806	2·086	1·432	1·732	1·954

The bias increases with the misclassification rate, the smoking excess risk, the proportion of smokers and the concordance ratio (here parameterized indirectly by z) and decreases with the proportion of spouses who smoke. Table I shows how E^* actually (not approximately varies with these parameters. The same relationships apply.

2.7. Case/control rather than prospective study

E^* can be calculated by dividing an estimate (h_1/h_2) based on case data by an estimate (h_3/h_4) based on population data. If the controls are representative of the population, and if misclassification is independent of case-control status, the above procedures can also be applied to case-control study data. Note misclassification of cases produces upward bias, while misclassification of controls produces downward bias. For small p, the upward bias $= h_1/h_2 \simeq 1 + Rg$ and the downward bias $= h_3/h_4 \simeq 1 + g$, where $g = ps(z-1)/(1-s)(1-m_1)$.

2.8. Risk of disease associated with misclassification

In Section 2.1 misclassification of smoking was assumed random, with the same risk in misclassified and correctly classified smokers. This may well be untrue in practice. Misclassified

smokers may have smoked less and/or longer ago, suggesting a *lower* risk than smokers who report their smoking. On the other hand, misclassification may be common in subjects who have ignored doctor's advice to give up smoking following a visit relating to symptoms rendering them at *higher* than average risk.

If correctly classified smokers have w times the risk of misclassified smokers, and R' and R'' are their risks, relative to true non-smokers, we can solve $R' = wR''$ and $(1 - p)R' + pR'' = R$ to give $R'' = R/(p + (1 - p)w)$ and $R' = wR/(p + (1 - p)w)$. The observed active smoking RR is then given by $R^* = R'(u + pv)/(u + pR''v)$. R^* is usually $< R$, but this need not be so, for example, if p is small and u is much larger than v, $R^* \simeq R'$ which is $> R$ if $w > 1$.

The observed spousal smoking RR is given by the same formulae as in Sections 2.4–2.6 with R replaced by R''. Assuming the risk of misclassified smokers exceeds that of non-smokers, positive misclassification bias will occur.

2.9. Misclassification associated with spousal smoking habits

The random misclassification assumption also means that rates are independent of spousal smoking. This may also be untrue, with people married to a non-smoker less willing to admit smoking.

If the misclassification rate is p_1 when the spouse smokes and p_2 when the spouse does not, $E' = (a + p_2c)(b + p_1Rd)/(b + p_1d)(a + p_2Rc)$. It is clear p_1 causes positive bias and p_2 negative bias. Given p_1, E' declines with increasing p_2, the overall bias ceasing to be positive ($E' = 1$) if $p_2/p_1 = k$. If $p_2 > kp_1$, negative bias will occur.

2.10. Misclassification of non-smokers as smokers

So far it has been assumed no non-smokers are misclassified as smokers. Now if q is the proportion of misclassified non-smokers, we have:

Group	Smoking habits		Observed data	
	Subject	Spouse	Population	Cases
1	Non-smoker	Non-smoker	$a^{**} = (1 - q)a + pc$	$y((1 - q)a + pRc)$
2	Non-smoker	Smoker	$b^{**} = (1 - q)b + pd$	$y((1 - q)b + pRd)$
3	Non-smoker	All	$u^{**} = (1 - q)u + pv$	$y((1 - q)u + pRv)$
4	Smoker	Non-smoker	$c^{**} = qa + (1 - p)c$	
5	Smoker	Smoker	$d^{**} = qb + (1 - p)d$	
6	Smoker	All	$v^{**} = qu + (1 - p)v$	$y(qu + (1 - p)Rv)$

If $p + q < 1$, as should always be true in practice, the observed concordance ratio $k^{**} = a^{**}d^{**}/b^{**}c^{**}$ satisfies $1 < k^{**} < k^* < k$.

The observed active smoking RR is given by

$$R^{**} = (qu + (1 - p)Rv)((1 - q)u + pv)/(qu + (1 - p)v)((1 - q)u + pRv).$$

If $p + q < 1$, R^{**} satisfies $1 < R^{**} < R^* < R$.

The observed spousal smoking RR is given by

$$E^{**} = ((1 - q)a + pc)((1 - q)b + pRd)/((1 - q)b + pd)((1 - q)a + pRc).$$

Writing $p^{**} = p/(1 - q)$ it is clear the formula for E^{**} is identical to that in Section 2.4, with p^{**} replacing p. Thus, for example, a 5 per cent misclassification rate of smokers as non-smokers causes the same bias as a 5·26 per cent rate in both directions. Misclassification of smokers is clearly a much more important cause of bias than is the reverse misclassification, which has no effect on its own and only slightly reduces the spurious RR estimate otherwise. Because of this, and as false claiming of smoking is probably quite rare, most attempts to quantify the bias have ignored this reverse misclassification.

2.11. Misclassification of spousal smoking

So far it has been assumed subjects but not spouses are misclassified. If r is the proportion of smoking spouses misclassified we have:

Group	Smoking habits		Observed data	
	Subject	Spouse	Population	Cases
1	Non-smoker	Non-smoker	$a^{***} = (a + pc) + r(b + pd)$	$y((a + pRc) + r(b + pRd))$
2	Non-smoker	Smoker	$b^{***} = (1 - r)(b + pd)$	$y(1 - r)(b + pRd)$
3	Non-smoker	All	$u^{***} = u + pv$	$y(u + pRv)$
4	Smoker	Non-smoker	$c^{***} = (1 - p)(c + rd)$	
5	Smoker	Smoker	$d^{***} = (1 - p)(1 - r)d$	
6	Smoker	All	$v^{***} = (1 - p)v$	$y(1 - p)Rv$

The observed concordance ratio $k^{***} = a^{***}d^{***}/b^{***}c^{***}$ is a more severely biased estimate of k, satisfying $1 < k^{***} < k^{*} < k$.

Misclassification of spousal smoking does not affect the observed active smoking risk, so $R^{***} = R^{*}$.

The observed spousal smoking RR is given by

$$E^{***} = (a + pc + r(b + pd))(b + pRd)/(a + pRc + r(b + pRd))(b + pd).$$

If $p = 0$, $E^{***} = 1$, so that misclassification of spousal smoking causes no apparent effect of spousal smoking when no true risk exists. Assuming $p > 0$, E^{***} satisfies $1 < E^{***} < E^{*}$. For small p, $(E^{***} - 1)/(E^{*} - 1)$ approximately equals $a^{*}/(a^{*} + rb^{*})$. For small r this is close to 1, implying that ignoring misclassification of spousal smoking only leads to slight overestimation of the spousal smoking RR, which arises mainly from misclassification of smoking by the subject.

The above calculations assume misclassification of subject and spousal smoking are independent. If they are positively correlated, which might occur, if, say, both were reported by the same respondent, E would be reduced. If all smokers who deny their smoking also deny their spouse's, the observed spousal smoking RR will be < 1.

2.12. Summary

The results above show that misclassification of a subject's smoking habits leads to underestimation of the strength of the active smoking/lung cancer relationship and of the concordance between husbands' and wives' smoking habits, consistent with the general thesis that random misclassification leads to underestimation of the strength of positive associations.

By contrast, providing there is positive concordance between spouses' smoking habits, random misclassification of some subjects who smoke as non-smokers leads to an apparent relationship of spousal smoking to risk in non-smokers when no true relationship exists. The size of the

misclassification bias depends on the misclassification rate, the excess active smoking risk, the proportion of smokers, the concordance ratio, and the proportion of spouses who smoke. It is little affected by misclassification of non-smokers as smokers, or of smoking by spouses, which will be ignored hereafter. More crucial to the size of the bias are the possibilities that misclassification rates may depend on risk of disease or on spousal smoking habits. If smokers with a relatively low risk of lung cancer or who are married to non-smokers tend to be more likely to deny smoking, the bias will be less than indicated by the formula in Section 2.4.

3. MISCLASSIFICATION IN A 2×2 TABLE: TRUE EFFECT OF ETS EXPOSURE

3.1. Multiplicative and additive model

Let the risk be y for non-smokers married to non-smokers, with RRs in groups 1, 2, 4 and 5 in the ratios 1:E:R:RE and 1:E:R:E + R − 1 for the multiplicative model and for the additive model. Expected numbers of subjects after misclassification are then:

Group	Smoking habits		Population	Observed data	
	Subject	Spouse		Cases (multiplicative)	Cases (additive)
1	Non-smoker	Non-smoker	$a^* = a + pc$	$y(a + pRc)$	$y(a + pRc)$
2	Non-smoker	Smoker	$b^* = b + pd$	$yE(b + pRd)$	$y(Eb + p(E + R - 1)d)$
3	Non-smoker	All	$u^* = u + pv$		By summation
4	Smoker	Non-smoker	$c^* = (1 - p)c$	$yR(1 - p)c$	$yR(1 - p)c$
5	Smoker	Smoker	$d^* = (1 - p)d$	$yRE(1 - p)d$	$y(E + R - 1)(1 - p)d$
6	Smoker	All	$v^* = (1 - p)v$		By summation

The changed assumptions, which only affect risks, do not change the effect of misclassification on the concordance ratio (see Section 2.2).

3.2. Effect of misclassification on the active smoking relative risk

For the multiplicative model, the observed active smoking RR is given by

$$R_M^* = R(c + Ed)(u + pv)/v((a + pRc) + E(b + pRd)).$$

This is biased even without misclassification ($p = 0$) due to failure to adjust for spousal smoking. When adjustment for spousal smoking is made, the active smoking RR will be biased downwards by misclassification. For example, within subjects with non-smoking spouses, the observed active smoking RR will be given by the expression $R(a + pc)/(a + pRc)$, which is $< R$.

For the additive model, the observed active smoking RR is given by

$$R_A^* = (Rc + (E + R - 1)d)(u + pv)/v((a + pRc) + Eb + p(E + R - 1)d).$$

The ratio of risks in smokers to non-smokers, among those married to a smoker is equal to $(E + R - 1)/E$. As this is $< R$, the active smoking RR will be biased downwards even when there is no misclassification and when adjustment is made for spousal smoking.

3.3. Effect of misclassification on the spousal smoking relative risk

For the multiplicative model, the observed spousal smoking RR is given by

$$E_M^* = E(a + pc)(b + pRd)/(b + pd)(a + pRc) = EE^*.$$

Thus any circumstances causing a given bias in the simple model described in Section 2 will multiply a true risk associated with spousal smoking by the same factor.

For the additive model, the observed spousal smoking RR is given by

$$E_A^* = (a + pc)(Eb + p(E + R - 1)d)/(b + pd)(a + pRc).$$

This satisfies $E_A^* < E_M^*$. Given p, E_A^* increases with increasing E, starting at the value E^* when $E = 1$. The increase in E_A^* is less steep than that in E, so that $E_A^* = E$ when $E = a^*d/b^*c$, which is approximately equal to the concordance ratio k. For higher values of E, E_A^* will *underestimate* E, though this is unlikely in practice since estimates of concordance ratio usually substantially exceed estimates of spousal smoking relative risk.

3.4. Estimates of Wald and of the US National Research Council

In 1986, Wald *et al.*[10] and the US National Research Council[7] used an additive model to correct spousal smoking RR estimates for bias. The methodology used was similar to that described here. However, it was applied using observed data to estimate s, m_1 and R, ignoring the fact that these data would themselves be subject to misclassification. This resulted in understatement of the bias. Thus, Wald *et al.*,[10] using estimates of $s = 0{\cdot}50$, $p = 0{\cdot}07$, $m_1 = 0{\cdot}59$, $m_2 = 0{\cdot}81$, $R = 2$ and $E = 1{\cdot}3$ calculated the observed spousal smoking RR should be 1·3454, that is, an upward bias by 3·5 per cent. In fact, after accounting for misclassification, appropriate estimates of s, m_1 and R are 0·5376, 0·5721 and 2·3079. The observed spousal smoking RR can then be estimated as 1·3725, that is, an upward bias by 5·6 per cent, almost 60 per cent more than Wald *et al.*[10] calculated.

4. MISCLASSIFICATION IN A $2 \times N$ TABLE

4.1. The Wells–Stewart method

In their report, the EPA[8] described and used the method of Wells and Stewart to correct individual study RR estimates for smoking misclassification. The method has two notable features. First, rather than simply classify subjects as smokers or non-smokers, four groups are considered: regular; occasional; former smokers, and lifelong non-smokers. The association with spousal smoking (which remains classified in two groups) is studied in observed lifelong non-smokers, which contain true lifelong non-smokers together with misclassified regular, occasional and former smokers, the misclassification rate varying by smoking group. Second, the method is based on observed data. While in Sections 2 and 3 above, emphasis is on describing how observed RRs depend on the misclassification rate, given *true* underlying values of parameters such as s, m_1, m_2, k, E and R, the Wells–Stewart method aims at estimating the true value of E, given assumed misclassification rates, and *observed* values of the parameters, including the spousal smoking RR.

Elsewhere, Lee[13] discusses the Wells–Stewart method in detail. He points out the method depends on many inadequately explained and justified assumptions and imprecisely known parameters, and refers to errors in the method. Thus: (i) it was assumed, totally implausibly, that the spousal smoking RR multiplies the former smoking RR, but not the current smoking RR; (ii) the multiplicative model was applied to observed RRs when logically it would only apply (were it appropriate) to true RRs, that is, RRs before misclassification; (iii) the estimated RR for current (versus never) smoking was applied to current regular smoking, but current smokers include both regular and occasional smokers; (iv) in estimating the observed smoking habit distribution of the cases, the frequency of all former smokers (long-term and short term) has been multiplied by a risk factor derived for long-term smokers only; and (v) the actual method of

estimating corrected numbers of never smokers, given the observed distribution of cases and controls by self and spouse's smoking habits and the assumed misclassification rates, is mathematically erroneous.

In the following we describe an alternative procedure which is simpler, exact and involves fewer assumptions. As with the EPA method, it estimates E based on observed data, and allows various categories of smokers to be misclassified (though it can also be applied to the simple smoker/non-smoker case).

4.2. Adjusting the spousal smoking relative risk using observed data – assumptions and notation

Let subjects who smoke be categorized into n increasing levels ($i = 1, \ldots, n$). The notation previously used is extended by a subscript for smoking level. The true distribution of smoking in controls is then:

Spouse	Subject				
	Never	Level 1	⋯	Level i	⋯ Level n
Non-smoker	a	c_1		c_i	c_n
Smoker	b	d_1		d_i	d_n
Total	u	v_1		v_i	v_n

with asterisks used for the observed distribution.

For a multiplicative model, the true RRs are:

Spouse	Subject				
	Never	Level 1	⋯	Level i	⋯ Level n
Non-smoker	1	R_1		R_i	R_n
Smoker	E	R_1E		R_iE	R_nE

The true distribution for cases (ignoring scaling factors) is given by multiplying corresponding elements in the two tables. Upper case letters indicate the result, for example, $D_i = d_iR_iE$ for a multiplicative model. For an additive model, R_iE is replaced by $R_i + E - 1$.

Let p_{ij} be the probability a smoker at level i is misclassified at a lower level j. The relationship between true and observed distributions (for controls or cases, for spouse non-smoker or smoker) can be written down easily, for example, with $n = 2$ and considering cases married to a smoker:

$$\begin{aligned} B^* &= B + P_{10}D_1 + p_{20}D_2 \\ D_1^* &= (1 - p_{10})D_1 + p_{21}D_2 \\ D_2^* &= (1 - p_{20} - p_{21})D_2. \end{aligned}$$

These formulae can be inverted to estimate true from observed data.

Following the EPA, it is assumed there is no misclassification of never smokers as smokers or of spousal smoking and that misclassification of smoking by the subject is independent of spousal smoking and of disease status.

4.3. The estimation procedure – Step 1: obtaining observed and true smoking habit distributions for controls

The case-control study for which the RR is to be adjusted provides estimates of observed number of never smokers by spousal smoking, a^* and b^*, which can be summed to give u^*.

Data on the total number of subjects who smoke, $t^* = \Sigma v_i^*$, can be obtained directly in some studies, or indirectly from an estimate of smoking frequency in the population, s^*, by $t^* = s^*u^*/(1 - s^*)$. t^* can then be multiplied by estimates of the relative frequency of smoking in the n categories to give v_i^*.

Given a_i^*, b_i^* and v_i^*, and estimates of the concordance ratio for each smoking level, k_i^*, c_i^* and d_i^* can then be estimated by solving $c_i^* + d_i^* = v_i^*$ and $k_i^* = a^*d_i^*/b^*c_i^*$.

This gives the whole of the table for observed controls from which, as described in Section 4.2, the table for true controls can then be estimated.

4.4. The estimation procedure – Step 2: obtaining smoking habit distributions for cases regardless of spouse smoking

The study for which the RR is to be adjusted provides estimates of observed numbers of never smokers by spousal smoking, A^* and B^*, which can be summed to give U^*. Given estimates of the observed smoking RR in the various categories, R_i^*, estimates of V_i^* can then be obtained by $R_i^* = V_i^*u^*/v_i^*U^*$.

Alternatively, if the total number of smokers in the cases, $T^* = \Sigma V_i^*$, is known and estimates of the excess risks of smoking in the various categories, X_i^*, relative to category $n(X_n^* = 1)$, are available, estimates of V_i^* can be obtained from $2n$ equations: $R_i^* = V_i^*u^*/v_i^*U^*$ $(i = 1, \ldots, n)$, $R_i^* = 1 + X_i^*(R_n^* - 1)$ $(i = 1, \ldots, n - 1)$, and $T^* = \Sigma V_i^*$.

The relationships of Section 4.2 are then used to give U and V_i, the total number of true cases subdivided by subject's smoking.

4.5. The estimation procedure – Step 3: estimating the true spousal smoking relative risk

Assume a starting value of $E = \hat{E}$, perhaps the observed value of the spousal smoking RR $\hat{E} = B^*a^*/A^*b^*$ or a value somewhat less. Solve $\hat{E} = Ba/Ab$ and $U = A + B$ to give $A = aU/(a + b\hat{E})$ and $B = U - A$.

For the multiplicative model $R_i = C_ia/Ac_i$, $R_i = D_ib/Bd_i$ and $C_i + D_i = V_i$. Solving gives $C_i = Abc_iV_i/(Bad_i + Abc_i)$ and hence D_i and R_i.

For the additive model, the second equation is replaced by $(R_i + \hat{E} - 1)/\hat{E} = D_ib/Bd_i$, and solving gives

$$C_i = Ac_i(bV_i\hat{E} - Bd_i(\hat{E} - 1))/(Bad_i + Abc_i\hat{E})$$

and hence D_i and R_i.

The whole table for true cases has now been obtained, and using the relationships in Section 4.2, the complete table for observed cases can then be estimated. If the estimate of B^* exceeds the actual study value assume a lower value of $\hat{E}$; if it is less try a higher value.

The whole procedure is then repeated iteratively until the estimate of B^* equals that observed. This gives the value of E adjusted for smoking habit misclassification.

The relationships of Section 4.2 then allow completion of the table of observed case data and hence of observed RRs. 95 per cent confidence limits of E and $\hat{E}$ can be estimated in the normal way from the true and observed 2×2 tables (a, b, A, B and a^*, b^*, A^*, B^*).

4.6. Example

As in the EPA report,[8] data from Correa *et al.*[14] study are used to illustrate the method. The data observed are as follows:

Smoking habits Subject		Observed number of subjects Controls	Cases
Non-smoker	Non-smoker	$a^* = 72$	$A^* = 8$
Non-smoker	Smoker	$b^* = 61$	$B^* = 14$
Smoker	All	$t^* = 119$	$T^* = 244$

Associated with these data are estimates of 52·8 per cent for the observed proportion of subjects who had never smoked and of 2·066 and 12·396 for the observed spousal and active smoking RRs.

Following to a considerable extent the EPA report,[8] we assume:

1. Three levels of smoking by the subject: former ($i = 1$), occasional ($i = 2$), and regular ($i = 3$).
2. Former smokers are 35·5 per cent of ever smokers ($v_1^* = 0{\cdot}355t^*$).
3. 90 per cent of current smokers are regular smokers ($v_3^* = 0{\cdot}9\ (v_2^* + v_3^*)$).
4. The concordance ratio for ever/never smokers is 2·8 ($a^*\Sigma d^* = 2{\cdot}8b^*\Sigma c^*$).
5. The concordance ratio for former/never smokers is 2·2 ($k_1^* = 2{\cdot}2$).
6. The concordance ratios for occasional/never and regular/never smokers are the same ($k_2^* = k_3^*$).
7. The observed excess risks for former and occasional smokers are, respectively, 9 per cent and 20 per cent of those for regular smokers.
8. There is a multiplicative model between the true risks.
9. The true to observed misclassification probabilities (p_{ij}) are

True	Observed (j) Regular (3)	Occasional (2)	Former (1)	Never (0)
Regular (3)	—	0·0000	0·0107	0·0107
Occasional (2)		—	0·0910	0·1770
Former (1)			—	0·1081
Never (0)				—

Assumption 8 is the main difference from the EPA assumptions. Their multiplicative model applied to observed rather than true smokers, and did not apply to current smokers.

Following Section 4.3 (with minor adaptation as the concordance ratios are not given level by level) the data, together with assumptions 1 to 6, lead to the following table of observed control data:

Spouse	Subject			
	Never	Former	Occasional	Regular
Non-smoker	72	14·751	2·054	18·484
Smoker	61	27·494	5·622	50·596
Total	133	42·245	7·676	69·080

This is essentially identical to Table B-13 of the EPA report.[8]

The misclassification probability matrix can now be applied to convert these to true control data:

Spouse	Subject			
	Never	Former	Occasional	Regular
Non-smoker	69·569	16·026	2·806	18·888
Smoker	55·907	29·423	7·680	51·702
Total	125·476	45·449	10·486	70·590

Using assumption 7, and the procedures in Section 4.4, we estimate the following table of data and risks, ignoring spousal smoking:

	Subject				
	Never	Former	Occasional	Regular	Ever
Observed data					
Cases	22	18·449	5·897	219·655	244
Relative risk	1.00	2·640	4·645	19·223	12·396
True data					
Cases	16·316	17·170	8·056	224·458	249·684
Relative risk	1·00	2·905	5·908	24·453	15·176

Finally, the iterative procedures of Section 4.5, in conjunction with the multiplicative model assumption, lead to:

Multiplicative model	Subject			
	Never	Former	Occasional	Regular
Observed data – spouse non-smoker				
Cases	8	4·255	1·039	38·702
Relative risk	1·00	2·596	4·553	18.845
Observed data – spouse smoker				
Cases	14	14·194	4·858	180·953
Relative risk	2·066	4·646	7·777	32·188
True data – spouse non-smoker				
Cases	6·877	4·151	1·419	39·548
Relative risk	1·00	2·621	5·118	21·182
True data – spouse smoker				
Cases	9·440	13·018	6·637	184·910
Relative risk	1·708	4·476	8·742	36·181

The misclassification corrected spousal smoking RR is thus 1·708, so that misclassification has caused upward bias by a factor 2·066/1·708 = 1·209. An additive model would lead, as shown below, to a corrected RR of 1·900, a bias of 1·087. The latter is closer to the EPA bias estimate of 1·10 (corrected RR = 1·89), presumably as the RRs in the current smoking groups are less dependent on spousal smoking, so being more consistent with their assumptions.

Additive model	Subject			
	Never	Former	Occasional	Regular
Observed data – spouse non-smoker				
Cases	8	5·438	1·452	57·643
Relative risk	1·00	3·318	6·364	28·067
Observed data – spouse smoker				
Cases	14	13·011	4·445	162·012
Relative risk	2·066	4·259	7·116	28·819
True data – spouse non-smoker				
Cases	6·458	5·188	1·984	58·903
Relative risk	1·00	3·487	7·618	33·596
True data – spouse smoker				
Cases	9·859	11·982	6·072	165·555
Relative risk	1·900	4·387	8·517	34·496

4.7. Simplification of the model

In the example above, the upward bias depends on assumed values of six misclassification probabilities. To simplify further work, the relationship of the bias to these probabilities was investigated further.

First, it was clear the values of the misclassification probabilities from regular or occasional to former smokers had little effect on the bias. Setting these to zero changed the bias only from 1·2093 to 1·2167 (multiplicative model) or from 1·0873 to 1·0871 (additive).

Second, it was also clear misclassification of regular smokers as never smokers contributed most to the bias. With other misclassification rates set to zero and using a multiplicative model, the biases resulting from misclassification of regular, occasional or former smokers only were, respectively, 1·1021, 1·0416 and 1·0427. These represent excess biases that are, respectively, 47, 19 and 20 per cent compared with the bias, 1·2167, associated with all three misclassification probabilities combined. These excess biases are in the ratio 1 : 0·407 : 0·418, quite close to that predicted 1 : 0·368 : 0·378 by assuming bias is proportional to the product of misclassification rate, observed excess risk, observed concordance ratio and observed frequency of the smoking category in the controls, an approximate formula suggested by Section 2. For the additive model, the biases resulting from misclassification of regular, occasional and former smokers only were, respectively, 1·0480, 1·0190 and 1·0040. These represent excess biases that are respectively 55, 22 and 5 per cent compared with the combined bias of 1·0871.

Thirdly, for both multiplicative and additive models the bias from the full analysis described in Section 4.6 was quite close to that arising from a simpler model with only one smoking level, in which 1·75 per cent of ever smokers were misclassified as never smokers, with the concordance ratio set as 3·0. Thus, for a multiplicative model, this simpler model gave a bias of 1·1850 compared with 1·2093 for the full model. For the additive model, the simpler model gave 1·0806 and the full model 1·0873.

These general conclusions were confirmed using data from other studies. Table II summarizes results for the Correa study[14] and for four other large U.S. studies.[15–18] These show misclassification to former smokers is unimportant, misclassification of regular smokers as never smokers accounts for about half of the total bias and that the assumptions used are similar in effect to using the simpler model with a misclassification rate of 1·75 per cent and a concordance ratio of 3·0. The biases for the multiplicative and additive models are similar where the observed spousal

Table II. Biases from five studies in U.S. females under various assumptions

	Study				
	Correa[14]	Brownson[15]	Fontham[16]	Garfinkel[17]	Stockwell[18]
Observed spousal risk	2·066	0·972	1·263	1·233	1·600
Multiplicative model					
1. Bias from full model	1·209	1·117	1·099	1·045	1·089
2. Bias ignoring misclassification to former smokers	1·217	1·120	1·102	1·046	1·092
3. Bias from misclassification of regular smokers only	1·102	1·059	1·050	1·0235	1·046
% of excess bias (3 of 2)	47·1	48·7	48·9	50·9	49·5
4. Bias from 'simpler' model	1·185	1·102	1·088	1·040	1·080
Additive model					
1. Bias from 'full' model	1·087	1·132	1·088	1·039	1·060
2. Bias ignoring misclassification to former smokers	1·087	1·137	1·090	1·040	1·061
3. Bias from misclassification of regular smokers only	1·048	1·062	1·044	1·021	1·032
% of excess bias (3 of 2)	55·1	45·6	48·6	51·5	55·2
4. Bias from 'simpler' model	1·081	1·114	1·077	1·035	1·055

RR is near unity (Brownson, Fontham, Garfinkel). For larger spousal risks (Stockwell, Correa) the bias from the multiplicative model is larger.

5. APPLICATION OF THE METHODOLOGY TO DATA FOR U.S. FEMALES

5.1. Introduction

The simplified methodology of Section 4 is now applied to available data for U.S. females. Studies conducted in the U.S. and in Asia (considered in Section 6) are the main contributors to the evidence, and data for females are much more extensive than for males. The U.S. data are described in Section 5.2, followed by discussion, in Sections 5.3 and 5.4, of appropriate ranges of concordance ratios and misclassification rates to use. The methodology is applied in Section 5.5, and the results compared with those of others in Section 5.6.

5.2. U.S. epidemiological data on lung cancer and spousal smoking in females

Table III summarizes relevant data from 13 U.S. studies.[14–26] (Data from one study[27] are ignored, being based on only nine lung cancer cases, and only one in ever smokers whose risk, unusually, was *less* than in never smokers.) Points to note about the studies are:

(i) Only one study[21] was prospective. For this study, 'number of controls' are number of subjects at the start of the study.
(ii) Most studies concerned all histological types of lung cancer but three[14, 19, 26] considered specific types only.
(iii) The index of exposure varied. Ten studies concerned spousal smoking but varied as to whether smoking of products other than cigarettes was considered, and when smoking occurred. Three studies[19, 20, 25] concerned at home exposure, not specifically from the spouse. For one study[19] the index related only to heavier exposure.

Table III. Data from 13 studies of lung cancer and spousal smoking in U.S. females

Study	Year reference	Number of controls				Number of cases				Histological type	Index of exposure	% exposed	Spousal risk (95% limits)		% smoked	Active risk
		Never smoked			Ever smoked	Never smoked			Ever smoked				Crude	Adjusted		
		Spousal smoking														
		No	Yes	Total	Total	No	Yes	Total	Total							
Brownson *et al.*	1987[19]	40	7	47	19	15	4	19	33	Adenocarcinoma	Presence of person smoking 4 + hours/day	12·8	1·52 (0·39–5·96)	1·68 (0·39–6·90)	28·8	4·30
Brownson *et al.*	1992[15]	568	598	1166	—	213	218	431	—	All types	Spouse smoked	51·3	0·97 (0·78–1·21)	1·00 (0·80–1·20)	[43·0]	[8·0]
Buffler *et al.*	1984[20]	32	164	196	279	8	33	41	412	All types	Household member smoked regularly	83·7	0·80 (0·34–1·90)	—	58·7	7·06
Correa *et al.*	1983[14]	72	61	133	119	8	14	22	244	All except bronchoalveolar	Spouse ever smoked cigarettes	45·9	2·07 (0·81–5·25)	—	47·2	12·40
Fontham *et al.*	1994[16]	487	766	1253	—	218	433	651	—	All types	Spouse ever smoked tobacco	61·1	1·26 (1·04–1·54)	1·29 (1·04–1·60)	[43·0]	[8·0]
Garfinkel	1981[21]	81859	94880	176739	—	65	88	153	—	All types	Spouse currently smoked cigarettes	53·7	1·17 (0·85–1·61)	1·18 (0·90–1·54)	22·0	3·58
Garfinkel *et al.*	1985[17]	148	254	402	—	43	91	134	—	All types	Spouse ever smoked	63·2	1·23 (0·81–1·87)	—	[34·0]	[6·0]
Humble *et al.*	1987[22]	71	91	162	111	5	15	20	223	All types	Spouse ever smoked	56·2	2·34 (0·81–6·75)	2·20 (0·80–6·60)	40·7	16·28
Janerich *et al.*	1990[23]	58	86	144	—	68	76	144	—	All types	Spouse smoked cigarettes while living with the subject	59·7	0·75 (0·47–1·20)	—	[42·0]	[8·0]
Kabat and Wynder	1984[24]	10	15	25	—	11	13	24	—	All types	Spouse ever smoked	60·0	0·79 (0·25–2·45)	—	42·0	5·90
Kabat	1990[25]	45	97	142	—	18	35	53	—	All types	Exposed in adulthood at home	68·3	0·90 (0·46–1·76)	—	[42·0]	[8·0]
Stockwell *et al.*	1992[18]	36	55	91	—	18	44	62	—	All types	Spouse smoked	60·4	1·60 (0·80–3·20)	1·60 (0·80–3·00)	[42·0]	[8·0]
Wu *et al.*	1985[26]	22	33	55	87	9	19	28	120	Adenocarcinoma	Spouse smoked	60·0	1·41 (0·54–3·67)	1·20 (0·50–3·30)	61·3	2·71

(iv) The crude spousal RR corresponds to the 2×2 table of unexposed and exposed never smoking controls and cases. For the prospective study,[21] the RR and numbers of controls are in fact age standardized, crude data not being presented.

(v) Adjusted spousal RRs are as reported, with the potential confounding variables considered varying by study.

(vi) Some studies[14,19,20,22,26] gave direct data on numbers of ever smoking cases and controls, from which estimates of proportions of ever smokers and of active smoking RRs could be calculated directly. For other studies, estimates were either taken from other publications or, shown in square brackets, calculated from other studies conducted at a similar time.

The data in Table III are as used by EPA[8] except: (a) three additional studies[15,18,25] have been included; (b) the Fontham *et al.* study data are updated from a recent report;[16] (c) for the Garfinkel case-control study[21] data were used for 'spouse ever smoked' rather than 'spouse smoked at home', the former index being more consistent with that used in other studies; (d) numbers for the Janerich *et al.* study,[23] given for the sexes combined by EPA, have been estimated separately for females;[12] and (e) ever smoking RRs have been used for the Wu *et al.* study[26] whereas EPA gave current smoking risks.

Ignoring misclassification, the data show some evidence of a positive association for spousal smoking. Fixed-effects meta-analysis[28] gives an RR estimate of 1·13 (95 per cent CI 1·01–1·27) for the unadjusted data and 1·13 (95 per cent CI 1·01–1·26) for the covariate-adjusted data. As adjustment for covariates had little effect, as the misclassification adjustment procedures are not designed to deal with data subdivided by covariates, and as the source papers rarely if ever present such subdivided data anyway, misclassification adjustment will (in Sections 5.5 and 6) be applied to the data unadjusted for covariates.

5.3. Concordance ratios

EPA[8] assumed that, for the 2×2 table subject: never/ever smoker; spouse: never/ever smoker, the concordance (cross-product) ratio is 2·8, and that, for the 2×2 table subject; never/ex-smoker; spouse: never/ever smoker, is 2·2. A value of 3·2 for the concordance ratio subject: never/current smoker; spouse: never/ever smoker, was also provided, but not used in the adjustment procedure, as this would lead to over definition.

As support for these estimates, EPA cited four references,[29–32] but gave no detailed data. In fact, the first reference[29] gives no relevant data at all, the second[30] only gives data relevant to a different concordance ratio, while the third[31] only gives data relevant to the first of the three concordance ratios (giving a value of 1·74 for women and 2·49 for men). Only the fourth reference[32] gives a joint breakdown of smoking habits of subjects and spouses by never/ex/current status and even that was estimated indirectly, and suggests concordance ratios of 2·4, 1·9 and 2·8 rather than 2·8, 2·2 and 3·2.

EPA also assumed that for current smokers the association with spousal smoking was the same for occasional and regular smokers. In fact, the only study cited[32] actually showed that the more the subject smoked the more likely the subject was to be married to a smoker.

The concordance ratio estimates of EPA are not solidly based. Elsewhere[12] Lee summarizes data from 17 studies. Four provide estimates of the subject: never/ever smoker; Spouse: never/ever smoker concordance ratio. For females the estimates were 1·74, 2·67, 2·19 and 2·65. For males, the estimates (whose expected values are the same due to symmetry) were 2·49, 1·95, 2·32 and 3·10. The mean of these values is 2·39. The remaining studies provided 16 independent estimates of the subject: non-current/current smoker; spouse: non-current/current smoker

concordance ratio which ranged from 2·56 to 6·04, with a mean of 3·98. Based on the 3 × 3 table of Lee,[32] the non-current/current concordance ratio should be about 1·36 times higher than the never/ever concordance ratio. If so, the mean of 3·98 for the former ratio implies a value of 2·93 for the latter ratio, rather higher than the mean of 2·39 for the four studies providing direct data. This look at the data suggests an appropriate value of the never/ever concordance ratio is almost definitely in the range 2 to 4, probably below 3 and probably nearer 3 than 2. However, we should bear in mind there is highly significant variation between estimates for different studies. Concordance may depend, among other things, on national characteristics, the exact questions asked and the circumstances of interview. Limited evidence[12] suggests no clear relationship with age, however.

5.4. Misclassification rates

Evidence on the extent of misclassification has been discussed by Lee[11,12,33] and Wells.[8,34,35] There are two main sources of data, studies in which biochemical markers of smoke uptake are used to validate statements about current smoking, and studies in which statements made on different occasions about smoking are checked for consistency. It is useful to summarize the evidence from these studies, so highlighting difficulties in obtaining reliable rate estimates for use in adjustment procedures.

As increases in carbon monoxide and thiocyanate commonly occur from sources other than smoking, both Lee and Wells have restricted attention to studies using cotinine, a major metabolite of nicotine, as a biochemical marker of uptake. Although there are some dietary sources of nicotine, these cannot produce cotinine levels typical even of a light smoker.[36] Cotinine levels of current smokers are about two orders of magnitude higher than those of ETS exposed non-smokers. Although there may be slight overlap between levels in very light smokers and very heavily ETS-exposed non-smokers, it seems generally accepted that a cut-off of 10 per cent of the level of average smokers can be used to distinguish true smokers. A 30 per cent cut-off is often used to distinguish regular smokers. Reviewing evidence from cotinine studies, virtually all conducted in the U.S., U.K. or other Western populations, some points emerge.

First, misclassified smokers (that is, self-reported non-smokers above the cut-off) have lower cotinine levels than self-reported smokers; occasional smokers more often deny smoking than regular smokers (but see Section 6).

Second, with similar cut-offs there is wide variation in the proportion of non-smokers found to be smokers. Studies in which smokers are advised to give up smoking often report very high proportions of 15–40 per cent. Even ignoring such studies, as Lee and Wells have done, there is still marked heterogeneity, proportions ranging from under 1 per cent to over 6 per cent.[12] Clearly, study circumstances affect misclassification rates, and, as the cotinine and ETS/lung cancer studies may not be comparable, there is uncertainty in extrapolating results from one study type to another. Wells[8] suggests misclassification rates from 'general population studies' may be much higher than those from 'epidemiological studies', but this runs counter to the conclusions of Velicer *et al.*[37] that the less the likelihood of intervention the greater the accuracy of self-report. In any case the distinction between such study types is unclear.

Many cotinine studies only record current smoking habits, and some studies only report data for self-reported non-smokers. Misclassification adjustment requires knowledge, not of the proportion of non-smokers found to be current smokers, but of the proportion of current smokers reporting they are *lifelong* non-smokers. Wells[8] estimates 1·07 per cent of true regular smokers and 17·7 per cent of true occasional smokers are misclassified as never smokers. Elsewhere[33] Lee presents data from more studies showing, in total, 68 per cent higher rates of misclassification of current smoking.

Various studies have compared smoking as reported by subjects on two occasions, some years apart. In a large study in Scotland, for example, cited by Lee,[12] 10·1 per cent of ex-smokers and 2·5 per cent of current smokers at initial interview later claimed never to have smoked. Such studies may underestimate misclassification, as smokers may deny smoking on both occasions. Data from six other studies were summarized by Wells,[8] from which similar estimates of 11·7 per cent for ex-smokers and 3·9 per cent for current smokers were calculated. The individual study estimates varied considerably, however, for ex-smokers ranging from 0·0 per cent to 26·8 per cent. Compared with subjects who consistently report being ex-smokers, subjects reporting past smoking on only one occasion tend to report having given up longer ago and to have smoked less when they were smoking.[32] Because of this, Wells, in the EPA report,[8] assumed that inconsistent ex-smokers could be assigned the excess risk of long-term ex-smokes, estimated as 9 per cent of that of current smokers. As some recent ex-smokers deny smoking this estimate may be somewhat too low.

The misclassification estimates of Wells[8] are similar in effect to assuming about 1·75 per cent of average ever smokers are misclassified as never smokers. Based on higher misclassification rates found in a more extensive data review, Lee[33] estimated 2·5 per cent would be more appropriate. Taking into account other points (multiple report studies may miss subjects denying on each occasion; some recent ex-smokers may deny smoking), the figure would be slightly higher than this. However, there are considerable uncertainties. An appropriate figure is probably in the range 2–3 per cent but could, not implausibly, be anywhere in the range 1–4 per cent.

Strictly, bias calculations should allow for a smoker being more ready to deny his habit if married to a non-smoker. The limited data on this[12] do not suggest this is a major issue. Full investigation would require a study with cotinine measured for both husband *and* wife.

There is no evidence whether, given actual smoking habits, subjects who deny smoking are more or less at risk of *lung cancer* than those who admit it. In a Danish prospective study (Gyntelberg, personal communication), five deaths occurred from *ischaemic heart disease* among men who had reported not smoking but with cotinine levels consistent with current smoking. This compared with 0·8 expected for men of similar age reporting smoking ($p < 0·001$).

5.5. Effect of misclassification adjustment on spousal risk estimates

Table IV presents meta-analysis RRs for the U.S. data assuming: (i) various levels of misclassification; (ii) various concordance ratios; and (iii) either a multiplicative or an additive model. The combined RR risk estimate decreases with increasing misclassification, and (for a non-zero misclassification) with increasing concordance. For low misclassification rates, estimates from the multiplicative and additive models are very similar, but for higher misclassification rates, the additive model gives slightly lower RR estimates. Even with an estimated misclassification rate as low as 0·5 per cent, the RR estimate becomes non-significant. For a rate of 1·75 per cent and a concordance ratio of 3·0, shown above to give results comparable to EPA's more complex assumptions, the unadjusted RR of 1·13 reduces to 1·05. Assuming a 2·5 per cent misclassification rate, as noted to be reasonable, the association essentially disappears, with RR 1·01 (95 per cent CI 0·90–1·14) for a concordance of 3·0. While there is uncertainty about the true misclassification rate and concordance ratio, these analyses are consistent with the slight excess lung cancer risk observed in relation to smoking by the husband, being due not to ETS exposure, but to an artefact arising from misclassification of some smokers as non-smokers.

Table IV. Lung cancer risk associated with spousal smoking (95 per cent CI) after adjustment for misclassification of smoking habits – based on meta-analysis of data from 13 studies in U.S. females (see Table III)

Misclassification rate (%)	Multiplicative model			Additive model		
	Concordance ratio					
	2·0	3·0	4·0	2·0	3·0	4·0
0	1·13 (1·01–1·27)	1·13 (1·01–1·27)	1·13 (1·01–1·27)	1·13 (1·01–1·27)	1·13 (1·01–1·27)	1·13 (1·01–1·27)
0·5	1·11 (0·99–1·25)	1·11 (0·99–1·24)	1·10 (0·98–1·24)	1·11 (0·99–1·25)	1·11 (0·99–1·24)	1·10 (0·98–1·24)
1·0	1·10 (0·98–1·23)	1·08 (0·96–1·22)	1·07 (0·96–1·21)	1·10 (0·98–1·24)	1·08 (0·96–1·22)	1·08 (0·96–1·21)
1·5	1·08 (0·96–1·22)	1·06 (0·94–1·19)	1·05 (0·93–1·18)	1·08 (0·96–1·22)	1·06 (0·94–1·19)	1·05 (0·93–1·18)
1·75	1·07 (0·95–1·21)	1·05 (0·93–1·18)	1·03 (0·92–1·16)	1·08 (0·96–1·21)	1·05 (0·93–1·18)	1·03 (0·92–1·16)
2·0	1·06 (0·94–1·20)	1·03 (0·92–1·17)	1·02 (0·90–1·15)	1·07 (0·95–1·20)	1·04 (0·92–1·17)	1·02 (0·90–1·15)
2·5	1·05 (0·93–1·18)	1·01 (0·90–1·14)	0·99 (0·88–1·12)	1·05 (0·93–1·18)	1·01 (0·89–1·14)	0·99 (0·87–1·11)
3·0	1·03 (0·91–1·16)	0·99 (0·87–1·11)	0·96 (0·85–1·08)	1·03 (0·91–1·17)	0·98 (0·84–1·16)	0·95 (0·84–1·08)
4·0	1·00 (0·88–1·13)	0·94 (0·83–1·06)	0·90 (0·80–1·02)	0·99 (0·87–1·12)	0·92 (0·81–1·04)	0·88 (0·78–1·00)

5.6. Difference from conclusions reached by others

In 1986 the NRC[7] summarized data from 13 studies, five in the U.S.A. They estimated an overall adjusted RR of 1·34 (95 per cent CI 1·18–1·53). After misclassification adjustment the RR was estimated to be about 1·25, and at least 1·15. Although (see Section 3.4) the methodology used was incorrect, the conclusions were similar to those derived from Table IV. Thus the NRC suggested a bias of 1·34/1·25 = 1·07 and at most 1·34/1·15 = 1·17. Applied to the unadjusted U.S. estimate of 1·13 for the updated data, these biases would give adjusted figures of 1·06 and 0·97. The NRC conclusion that misclassification bias could not explain the association was not due to inadequate adjustment but to the much higher RR they started with. In this context, it is notable that there has been a striking tendency for more recent studies to report lower RRs. Thus, while the 22 worldwide studies reporting findings up to 1988 provided a covariate-adjusted meta-analysis RR estimate of 1·35 (95 per cent CI 1·20–1·52) for spousal smoking, the 15 studies reported later provide a RR estimate of only 1·01 (95 per cent CI 0·91–1·11).

The analysis of Wald *et al.*[10] also conducted in 1986, was similar to that of the NRC, being based on the same 13 studies. However, as they assumed an exceptionally low misclassification rate, a lower bias estimate of only 1·35/1·30 = 1·04 was calculated.

The recent EPA report[8] considered data from 11 U.S. studies, with an RR estimate of 1·22 (95 per cent CI 1·04–1·44) reducing to 1·19 (95 per cent CI 1·01–1·38) after adjustment. Assuming a 1·75 per cent misclassification rate, and a concordance ratio of 3·0, our analysis reduces an RR of 1·13 (95 per cent CI 1·01–1·27) to 1·05 (95 per cent CI 0·93–1·18). There are three main reasons why our misclassification adjusted RR is much lower than that of EPA, and non-significant: (i) our analysis includes three studies not considered by EPA,[15,18,25] one[15] a large study. Overall

the three studies show no association with spousal smoking (RR = 1·01; 95 per cent CI 0·82–1·23); (ii) the individual study data we used give slightly lower RRs (see Section 5.2). Thus our estimate for the same 11 studies EPA used is 1·20 (95 per cent CI 1·05–1·38) rather than 1·22; (iii) the actual bias estimated by EPA, of 1·03, is substantially lower than we estimate, 1·08, using apparently similar assumptions. The most notable difference is for the largest study,[16] where we estimate 1·08 and the EPA only 1·01. This study was unusual as urine samples were used to determine cotinine levels. As no self-reported lifelong non-smoking women with lung cancer were found to have cotinine levels consistent with regular smoking, the EPA assumed a misclassification rate of zero for regular smoking for this study. This assumption is wholly unjustified. Urine samples were taken in hospital after diagnosis. Since many smokers give up smoking at time of diagnosis of lung cancer, it is unusual for smoking to be permitted in hospitals, and cotinine has a relatively short half life of about a day, one cannot infer that none of those cases who were regularly smoking around the time of diagnosis reported being lifelong never smokers.

6. EFFECT OF MISCLASSIFICATION IN ASIAN FEMALES

Of 37 studies of ETS and lung cancer worldwide, 16 have been conducted in Japan, China or Hong Kong.[38] Based on 1918 lung cancer cases in females, an overall RR estimate, unadjusted for covariates or misclassification, is a marginally significant 1·16 (95 per cent CI 1·03–1·31). For these data, misclassification adjustment at about the level suggested by EPA[8] (that is, using an ever/never smoker misclassification rate of 1·75 per cent, a concordance ratio of 3·0, and an additive model) has very little effect, reducing the RR only by 0·01 to 1·15 (95 per cent CI 1·02–1·30). This trivial adjustment, as EPA[8] also reported, is due to the few Asian women who smoke and the lower RR when they do. However, this assumes misclassification rates in Asian and Western populations are similar, as the evidence on misclassification comes almost exclusively from Western populations. Great doubt has been cast on this assumption by a recent study[39] of 400 married Japanese women, in which as many as 20·8 per cent of current smokers (as determined by cotinine) reported being never smokers. The misclassified smokers had very similar cotinine levels to smokers who admitted smoking. While the circumstances of interview (door-to-door interviews) and age range (20–55) differed from the ETS/lung-cancer studies, the findings fit in with a long-held suspicion that misclassification rates may be much higher in Japanese than U.S. women, smoking by women being socially unacceptable in Japan. A concordance ratio of 3·0 and a 20 per cent misclassification rate applied to the overall Asian data would totally eliminate the association (RR = 0·99, 95 per cent CI = 0·87–1·12), while even a 10 per cent rate would render it non-significant (RR = 1·09, 95 per cent CI 0·97–1·23). The Japanese study actually suggested rather a higher concordance than seen in Western studies, further emphasizing the importance of bias due to misclassification.

7. OTHER ISSUES AFFECTING INTERPRETATION OF DATA ON ETS AND LUNG CANCER

7.1. Other sources of bias

Misclassification of smoking is not the only source of bias relevant to the relationship of spousal smoking to lung cancer. Others include:

(i) *Inaccuracy of exposure.* Misclassification of spousal exposure will (see Section 2.10) underestimate any true risk. Also, as some non-smokers married to non-smokers are exposed to ETS, the RR for non-smokers married to smokers, as traditionally calculated,

will underestimate their risk relative to a truly non-exposed population. Layard[40] reviews the difficulties in adjusting for background risk.

(ii) *Inaccuracy of diagnosis.* Without autopsy, a false-positive clinical diagnosis of lung cancer is common.[41] In many of the Asian and European studies a high proportion of cases were diagnosed without histological confirmation.

(iii) *Recall bias.* Almost all the ETS/lung cancer studies are case-control, in which recall of smoking, ETS, and other exposures may be affected by disease presence.

(iv) *Confounding.* For many lifestyle risk factors for many diseases, prevalence is not only increased in smokers, but is also somewhat increased in ETS-exposed never smokers. A recent study[42] concluded that 'confounding by multiple risk factors may be an important issue in passive smoking studies'.

(v) *Publication bias.* Spousal smoking RR estimates tend to be lower for studies with large numbers of cases.[12,43] Based on the latest data, this difference is significant ($p = 0{\cdot}01$) with (covariate-adjusted) RRs of 1·07 (95 per cent CI 0·97–1·17), 1·35 (95 per cent CI 1·14–1·59) and 1·42 (95 per cent CI 1·07–1·90) for studies with, respectively, more than 100, 50–100, and less than 50 cases. This is consistent with publication bias. A technique for carrying out a meta-analysis whilst adjusting for publication bias has been proposed.[44]

(vi) *Study quality.* Elsewhere[43] Lee defined a study as having a serious weakness if any of seven criteria were present. 16 studies can be classified 'inferior' using these criteria including 9 out of 10 of the studies with the highest RRs. The overall RR (adjusted for covariates) for the 'inferior' studies is 1·29 (95 per cent CI 1·15–1·45), significantly ($p < 0{\cdot}01$) greater than that for the 21 'superior' studies, which, at 1·03 (95 per cent CI 0·93–1·14), show no significant association with spousal smoking.

7.2. Evidence from other indices of ETS exposure

Early ETS/lung cancer studies presented data only for husband's smoking, and published meta-analyses have tended to concentrate on this index. This includes the EPA report,[8] which considered these results at length but did not give even basic results for any other index, although considerable evidence has accumulated for workplace and childhood ETS exposure. Based on 15 individual sex-specific RR estimates from 12 studies, a combined RR estimate (adjusted for covariates) for workplace exposure is 1·00 (95 per cent CI 0·91–1·08). Based on 15 estimates from 14 studies, the RR estimate for childhood exposure is 0·96 (95 per cent CI 0·87–1·06). This compares with 1·14 (95 per cent CI 1·06–1·23), based on 37 studies, for husband's smoking. Concentration on the index showing an association, at the expense of others which do not, is a major form of publication bias. Two alternative extreme views of the conflict between the spousal and the workplace/childhood results are possible. One is that spousal smoking is much more susceptible than the other indices to misclassification, and perhaps also confounding, bias as concordance is much stronger for spouses than for co-workers or for parents and their children. The other is that working with a smoker and having a parent smoke in childhood are both very poor markers of actual exposure, spousal smoking finding an association as it is the only adequate marker. This second explanation seems weak. Working with a smoker is clearly correlated with increased ETS exposure (though probably less so than is marriage to a smoker), and, if ETS exposure really increased risk, an association with lung cancer incidence would be expected.

7.3. Dose–response relationships

Our methodology compares risk in non-smokers according to whether or not the husband smoked, regardless of how much he smoked. The EPA report[8] stressed the existence of

a dose–response relationship, with RR estimates generally highest in the women whose husbands smoked the most. In interpreting this finding it should be noted that studies reporting relatively high RRs for spousal smoking are much more likely to present data by amount smoked than those that do not. Thus, for the 19 studies which presented dose–response data, the overall spousal smoking RR (adjusted for covariates) was 1·36 (95 per cent CI 1·23–1·51), highly significantly ($p < 0·001$) greater than the RR of 0·93 (95 per cent CI 0·83–1·04) for the 18 studies which did not. This form of publication bias means RR estimates for non-smoking women married to heavily smoking husbands are strongly biased upward. It may also be that, given a choice of indices of ETS exposure, an author may only present detailed findings for the index showing the clearest trend. Other biases may affect the dose–response relationship. Thus, as concordance increases with amount smoked, smoking misclassification will also contribute to the observed dose response.

7.4. Histological type

The association of lung cancer with active smoking is much greater for squamous carcinoma than for adenocarcinoma. If ETS is seen, crudely, as a smaller dose of active smoking, it might be expected, had it any effect at all, to be more strongly associated with risk of squamous carcinoma. Findings for those ETS/lung cancer studies reporting results separately by histological type do not fit in with this expectation. While for some studies the results do seem more consistent with a relationship with squamous carcinoma, there are an equal number where the relationship seems more with adenocarcinoma, as well as some studies with similar, or a lack of, relationship with either.[43]

7.5. Plausibility

Active smoking is strongly associated with risk of lung cancer and ETS and mainstream smoke contain many chemicals in common, albeit in different relative concentrations.[8] It can be argued (especially by adherents of the 'no-threshold' hypothesis) that an association of ETS with lung cancer is to be expected. However, the amount of particulate matter ('tar') retained by passive smokers is thousands of times lower than that retained by active smokers. If, as many believe, 'tar' retention is relevant to lung carcinogenesis, and the dose–response relationship is approximately linear, the observed spousal smoking RR (about 1·15–1·20) would be much higher than expected on dosimetric grounds (about 1·01–1·02). Based on this argument, most of the observed association could be due to bias.

8. DISCUSSION

Misclassification of smoking habits leads to underestimation of the association of lung cancer with active smoking. Given positive concordance between smoking habits of spouses, however, random misclassification of some smokers as non-smokers will result in overestimation of the association of lung cancer with ETS in studies of non-smokers where marriage to a smoker is the index of exposure. Sections 2 and 3 show how this bias depends on various factors. It tends to increase with an increasing misclassification rate of smokers as non-smokers, concordance, proportion of subjects who smoke, and proportion of spouses who smoke. Misclassification of non-smoking subjects as smokers or of smoking by spouses has little effect on the bias, and the mathematics is simplified by ignoring these possibilities. Bias estimates can be materially affected if misclassification of smoking is not random. Section 4 accounts for one important form of non-randomness, arising as current regular smokers are less likely to deny smoking than are

occasional or long-term ex-smokers. However, various other mechanisms may cause non-randomness. If, for example, smokers tend to be much more likely to deny smoking if their spouse does not smoke, the bias will be reduced and may even be reversed. If, on the other hand, smokers who are ill and at more risk of developing lung cancer are also more likely to deny smoking, the bias may be increased. Without hard data indicating the existence or importance of these forms of non-randonness, we make no attempt to account for them. However, there is need for further research here, for example, a study where smoking by husbands and wives is both assessed and *separately* validated using cotinine assays.

Section 4 considers the possibility that misclassification may vary by type of smoker, and improves the correction method used by EPA, which has numerous errors. Given known misclassification rates and concordance ratios, and various other assumptions, the methodology allows estimation of true numbers of cases and controls in the various smoking categories from the observed data, and hence of the misclassification-adjusted RR associated with marriage to a smoker. RR estimates for individual studies can then be meta-analysed. This method is problematic due to the large number of misclassification rates and concordance ratios assumed, with data sparse or non-existent for many of them. Luckily matters are simplified by noting (see Section 4.7) that for many studies the bias implied by the assumed values of the misclassification rates and concordance ratios is virtually identical to that implied by a simpler model with only two smoking categories (never, ever), a single misclassification rate of 1·75 and a single concordance ratio of 3·0.

In Section 5 this simpler model is applied to data for U.S. females. With the misclassification rate of 1·75 and concordance ratio of 3·0, a marginally significant unadjusted meta-analysis RR of 1·13 drops to a non-significant 1·05. In fact the misclassification rate could well be higher than 1·75 per cent, further reducing the RR estimate. Though there is some doubt as to the appropriate rate, misclassification can certainly explain most of the observed association of spousal smoking with lung cancer.

As fewer Asian women smoke, and have lower active smoking RRs when they do, a given misclassification rate will cause far less bias in Asian than U.S. studies. However, evidence (which needs replicating) from Japan suggests misclassification rates may be much higher in Asian women. If so, misclassification may cause marked bias there. Until results of the IARC multicentre study are published, European data are rather sparse and are not considered here.

Misclassification is only one reason to be wary of accepting the association of lung cancer risk with spousal smoking as indicative of a true effect of ETS. As discussed in Section 7, there are other sources of bias (such as confounding). There is also evidence of a lack of association with workplace or childhood ETS exposure. The very low particulate matter retention of passive smokers also suggests the association with spousal smoking may be mainly an artefact.

Our paper emphasizes the difficulties of interpreting weak associations in epidemiology, and the need to quantify the various sources of bias before coming to a firm conclusion. Though there are difficulties in quantifying the exact effects of smoking habit misclassification, our analyses show its likely importance and cast doubt on simple interpretation of the association between lung cancer and spousal smoking as indicative of a cause and effect relationship.

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