Figure 1 demonstrates that the effect of maternal smoking during pregnancy on offspring birthweight is considerably greater than that of paternal smoking during pregnancy, and mutual adjustment (to take account of associative mating by smoking) attenuates the paternal effect to zero. This is in line with the considerable body of evidence that maternal smoking has a causal effect on offspring birthweight. There has been enthusiasm for the proposition that fetal exposure to maternal smoking leads to increased obesity in offspring. Although maternal smoking during pregnancy does indeed demonstrate the expected association, the strength of association with paternal smoking during pregnancy is similar before and after mutual adjustment (Fig. 2). This casts doubt on the causal nature of the association between intrauterine exposure to maternal smoking and offspring adiposity.

As Lipsitch and colleagues argue, the use of negative controls could be usefully expanded in epidemiology. If associations are found with such controls, this does not invalidate the observation under interrogation but does encourage further intensive scrutiny of potential biases and confounding that may underlie what is seen.

**The authors respond:**

We thank George Davey Smith for his thoughtful comments on our paper and for drawing attention to his previous use of a negative control exposure. We agree with his interpretation that the lack of association of paternal smoking during pregnancy (negative control exposure B as shown in Fig. 3 in our original paper, and reproduced here in simplified form as the Figure) with birth weight strengthens the causal interpretation of an observed association of maternal smoking (A) with low birth weight (Y). Comparing Figure 1a and b of Davey Smith, paternal smoking has a univariate association with low birth weight, but this association disappears in a model including maternal smoking. This example emphasizes why the negative control exposure (B) should be evaluated in a model including the exposure of interest (A). The negative control is used to see whether there is evidence for a causal arrow from unobserved confounders (U) to the outcome (Y). Even if no U→Y arrow exists, B will be associated with Y under the alternative hypothesis (A→Y) through the path B→U→A→Y. Conditioning on (A) by including it in the model will close this path.

This example also nicely illustrates the subject-matter knowledge needed to interpret negative controls. A potential problem with paternal smoking as a negative control for maternal smoking is that paternal smoking causes maternal passive smoking; therefore, paternal smoking might be associated with the outcome causally. Observing an association of paternal smoking with birth weight would thus not invalidate in utero effects interpretation of the maternal-smoking-birth weight association in this study. Nonetheless, the lack of an association with paternal smoking in the birth weight case is reassuring.

The later-life BMI outcome in offspring discussed by Davey Smith is possibly more complicated. Postnatal outcomes could be associated with in utero and postnatal exposures. The finding of an association with paternal smoking during pregnancy (B) after adjustment for in utero exposure to maternal smoking during pregnancy (A) could reflect any combination of three nonmutually exclusive possibilities: (i) uncontrolled confounding of the A→Y association; (ii) an additional causal link B→Y via in utero exposure to passive smoke; or (iii) that some or all of the association A-Y and B-Y is due to effects of postnatal exposure to smoke from either parent. That is, the observed association between parental smoking during pregnancy and adiposity may reflect a causal relationship between postnatal parental smoking and adiposity, combined with a tendency of parents who smoke during pregnancy to continue smoking after the baby is born.

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**REFERENCES**

Leisure Time Activities and Lung Cancer

To the Editor:

Occupation is one of the most important nonsmoking-related risk factors for lung cancer. Some leisure-time activities or hobbies (eg, painting, woodworking, model-making, furniture-varnishing) involve the use of several agents that, in the occupational setting, are established carcinogens. Hobbyists sometimes spend considerable time in these leisure activities, often with little or no protection against these carcinogenic agents, leading to levels of exposure that can be as high as those in high-risk occupations.

A hospital-based case-control study of lung cancer was conducted in Galicia, North-west Spain between 2004 and 2007. The study included 442 cases with primary confirmed bronchopulmonary cancer and 548 controls (persons having trivial surgery unrelated to tobacco consumption).

We retrieved information about aspects of lifestyle, focusing on smoking, occupational history, lifetime participation in leisure activities that potentially involve exposure to carcinogens and use of certain types of substances. The activities considered were model-building, painting/artwork, furniture-refinishing, and wood-working or home carpentry. Subjects were classified as exposed if they had performed any of these hobbies and also reported exposure to wood dust, paints, lacquers, stains, organic solvents, or glues.

A multivariate logistic regression analysis was performed, in which the dependent variable was the case or control status and the independent variable was having performed any high-risk leisure-time activity. As adjustment variables, we considered sex, age (continuous), smoking (classified as never-smokers, former-smokers, and current smokers), and having worked in occupations carrying a risk of lung cancer.

Fifteen cases were exposed to high-risk leisure time activities, as were 9 controls. ORs for lung cancer according to self-reported exposures during leisure time are shown in the Table. The crude risk of lung cancer associated with high-risk hobbies was elevated, with an OR of 2.3 (95% confidence interval = 1.0–5.5) compared with those not engaged in those activities. When the results were adjusted for risky occupations and tobacco consumption, the OR was further elevated (2.82 [1.1–7.3]).

There is scant information on this topic, with one publication that reported a risk of lung cancer more than 5-fold higher for those engaged in risky leisure activities. Other papers on the effect of these activities on other cancers provide conflicting results.

The association between these leisure activities and lung cancer could be explained by the continued exposure to suspected or proven carcinogens such as wood dust, paints, lacquers, stains, organic solvents, and glues used in those hobbies. Although the leisure levels of exposure are usually minimal compared with occupational exposures, subjects exposed during leisure time are often unaware of (or not adequately informed about) the toxic nature of many products, and thus take fewer precautions. Hobbyists may work for many hours using materials in closed or poorly ventilated settings, and at a short distance from the source of exposure.

Our findings are consistent with occupational data suggesting elevated lung cancer risk for employment as a painter, carpenter, and employment in the wood or rubber industry—occupations that have profiles of exposure similar to the studied activities. Among the hobbyists we analyzed, the risk associated with leisure exposure seemed to surpass that found for these occupations.

<table>
<thead>
<tr>
<th>Tobacco</th>
<th>Cases No.</th>
<th>Controls No.</th>
<th>Adjusted OR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never-smokers</td>
<td>57</td>
<td>229</td>
<td>1.00</td>
</tr>
<tr>
<td>Ex-smokers</td>
<td>234</td>
<td>227</td>
<td>10 (6.2–16)</td>
</tr>
<tr>
<td>Current smokers</td>
<td>151</td>
<td>92</td>
<td>19 (11–32)</td>
</tr>
</tbody>
</table>

Carcinogenic exposures during leisure time

No: 427 cases, 539 controls

Yes: 15 cases, 9 controls

*Adjusted for age, sex, and high-risk occupations.

References