Environmental tobacco smoke and cardiometabolic risk in young children: results from a survey in south-west Germany

Gabriele Nagel1*, Frank J. Arnold4, Manfred Wilhelm2, Bernhard Link3, Iris Zoellner3, and Wolfgang Koenig4

1Institute of Epidemiology, Ulm University, Helmholtzstr.22, 89081 Ulm, Germany; 2Institute of Informatics (Medical Documentation and Statistics), Ulm University of Applied Sciences, Ulm, Germany; 3Baden-Württemberg State Health Office, Stuttgart, Germany; and 4Department of Internal Medicine II—Cardiology, Ulm University Medical Center, Ulm, Germany

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Aims
We explored the association between exposure to environmental tobacco smoke (ETS) and various cardiometabolic biomarkers in 10-year-old children.

Methods and results
A population-based cross-sectional study was carried out. Data on ETS exposure and potential confounders were collected by parental questionnaire. Adiponectin, leptin, markers of inflammation, apolipoproteins (apo) A1 and B, and lipoprotein-associated phospholipase A2 (Lp-PLA2) were measured. Linear and logistic regression models were applied using the 90th percentile as a cut-off point except for adiponectin and apoAI (10th percentile). In linear models, ETS exposure was significantly associated with increasing plasma concentrations of leptin, C-reactive protein, fibrinogen, interleukin (IL)-6, and Lp-PLA2. When compared with none, ETS exposure of more than 10 cigarettes per day was associated with elevated concentrations of leptin (OR 6.40; 95% CI, 2.67–15.39), C-reactive protein (OR 3.17; 95% CI, 1.31–7.68), Lp-PLA2 (OR 2.97 95% CI, 1.32–6.68), low adiponectin (OR 2.69; 95% CI, 1.10–6.57), and low apoAI (OR 4.48; 95% CI, 2.16–10.85). Increasing dose of ETS exposure was related to an increasing number of abnormal cardiometabolic markers.

Conclusion
Among children, ETS exposure was associated with a low-grade inflammatory response and altered markers of lipid metabolism, which may initiate atherosclerosis in early life. However, longitudinal studies are necessary to determine the potential causal relevance of these associations.

Keywords
Leptin • Adiponectin • Apolipoproteins • Inflammation • Environmental tobacco smoke • Children

Introduction
Exposure to environmental tobacco smoke (ETS) increases the risk of coronary heart disease (CHD) and mortality in adults. Observational studies in adults provide evidence for an association between ETS and endothelial dysfunction, platelet aggregation, acceleration of lipid peroxidation, and an increase in systemically measurable inflammatory markers. Recent evidence also suggests that exposure to ETS carries adverse health effects in children. ETS exposure was associated with impaired endothelial function an established precursor of CHD among 11-year-old children in a prospective study in Finland and higher levels of fibrinogen but not of C-reactive protein in 10- to 11-year-old children and in never smoking adults. In adults, markers of low-grade inflammation such as interleukin (IL)-6 and, in particular, C-reactive protein are considered as risk factors for the metabolic syndrome and cardiovascular disease (CVD). In addition, markers of the lipid metabolism including apolipoprotein AI (apoAI), apolipoprotein B (apoB), and lipoprotein-associated phospholipase A2 (Lp-PLA2) have been shown to predict CVD. Leptin correlates with body mass index (BMI) by regulating food intake and basal metabolism, and is linked to CHD. Adiponectin
is inversely related to BMI and plays a role in the regulation of insulin sensitivity and fatty acid metabolism. To date, little is known about the relationship between exposure to ETS and biomarkers of cardiometabolic risk in children. The purpose of this study therefore was (i) to explore the association between ETS and plasma concentrations of cardiometabolic markers and (ii) to cluster abnormal levels of cardiometabolic biomarkers according to ETS in a representative large group of 10-year-old children.

Methods
Study population
A cross-sectional study on body weight was undertaken within the framework of a health surveillance program in children. The investigation was coordinated by the Baden-Württemberg State Health Office and approved by the local Ethics Committee. In the state of Baden-Württemberg, six schools were randomly selected, from which 934 children were invited to participate in the study. After written informed consent had been obtained from the parents 536 (47% boys, 53% girls) fourth grade schoolchildren were recruited (October 2004 to March 2005). Data from 450 children (84%) with a complete set of anthropometric and laboratory parameters were available for analysis (47% boys, 34% with high and 7% with low parental education). Information on ETS exposure (yes, no) was available in 439 children. Data of 383 of them with information on the dose of ETS (cigarettes/day) formed the basis of the present analyses (46% boys, 27% with low and 34% with high parental education).

Laboratory methods
Among 450 children non-fasting EDTA blood was drawn. After centrifugation, samples were aliquoted and stored at −80 °C until analysis. All laboratory analyses were performed in a single laboratory at the Department of Internal Medicine II-Cardiology, Ulm University Medical Centre.

Leptin (ng/mL), adiponectin (µg/mL), and IL-6 (pg/mL) were measured by ELISA (R&D Systems, Wiesbaden, Germany) in EDTA plasma samples. The lower detection limits were ~0.057 ng/mL for leptin, 0.246 ng/mL for adiponectin, and 0.039 pg/mL for IL-6. Inter-assay coefficients of variation (CV) were 3.9% for leptin, 5.8% for adiponectin, and 7.7% for IL-6. Lipoprotein-associated phospholipase A2 (ng/mL) was also determined by ELISA (PLAC test, diaDexus, South San Francisco, USA). Detection limit was 1.3 µg/L and the inter-assay CV was 5.8%. C-reactive protein (mg/L), fibrinogen (g/L), and apoA1 (g/L) and apoB (g/L) were measured by immunonephelometry on a BN II analyser (Dade Behring, Marburg, Germany). Detection limits were 0.16 mg/L for C-reactive protein and 0.15 g/L for fibrinogen. The inter-assay CVs were 4.7% for C-reactive protein, and 1.1% for Fibrinogen. The inter-assay CV for apoA1 was 6.7% and the corresponding CV for apoB was 4.6%.

For most of the analyzed biomarkers, no accepted external cut-off point was available to define increased concentrations in children. Therefore, we used values above the 90th percentile of the biomarker distribution in our population, except for apoA1 and adiponectin, for which the 10th percentile were biologically plausible cut-off points. Sex-specific increased concentrations were calculated separately for boys and girls: C-reactive protein (≥ 1.65 mg/L for boys and ≥ 1.99 mg/L for girls), IL-6 (≥ 0.28 pg/mL for boys and ≥ 0.28 pg/mL for girls), fibrinogen (≥ 2.82 g/L for boys and ≥ 2.92 g/L for girls), apoB (≥ 0.88 g/L for boys and ≥ 0.88 g/L for girls), leptin (≥ 13.89 ng/mL for boys and ≥ 20.16 ng/mL for girls), and Lp-PLA2 (≥ 193 ng/mL for boys and ≥ 0.192 ng/mL for girls). For adiponectin (≤ 4.63 µg/mL for boys and ≤ 5.17 µg/mL for girls) and apoAI (≤ 1.29 g/L for boys and ≤ 1.27 g/L for girls), elevated levels were defined as values below the 10th percentile.

Exposure
Parental questionnaires were used to collect data on environmental and lifestyle factors. The question “Is a smoker living in your child’s home?” (yes, no) was applied to determine exposure to ETS. And the question “How many cigarettes are in average per day smoked in your home?” in order to collect information on the dose (none, 1–10 cigarettes per day, > 10 cigarettes per day). Smoking during the child’s first year (yes, no) was assessed with the question: ‘Did the child’s mother smoke during the child’s first year of life?’.

Covariates
The following variables were considered as potential confounders in the analyses: time of breastfeeding (none, 1–6 months, > 6 months), birth weight (< 2500 g, ≥ 2500 g), and educational attainment, which summarizes the highest achieved level of paternal or maternal school education and which was classified in primary school or less (low), secondary school (middle), and grammar school (high).

During a physical examination, height and weight was measured in a standardized manner. Body mass index was calculated as weight (kg)/height² (m).

Statistical analysis
Descriptive analyses were carried out separately for each gender and exposure levels to ETS. P-values were calculated using χ² test or Fisher’s exact test for categorical data and Kruskal–Wallis test for continuous data in order to test differences among ETS levels. Median and interquartile range (IQR, 25th to 75th percentile) were computed for each biomarker using the same subgroups.

Except for C-reactive protein, apoAI, and Lp-PLA2, no major sex differences were seen, therefore, boys and girls were pooled for application of regression models. Linear regression models for continuous response variables (log-transformed if not normally distributed) as well as logistic regression models for binary response variables were applied using the non-passive smokers as reference. We determined three adjustments for the linear and logistic regression models during the model-building process in order to calculate β-coefficients and odds ratios and 95% confidence intervals (CIs) for biomarker concentrations (continuous) and abnormal biomarker levels (binary). Model 1 was adjusted only for age (continuous); in Model 2, adjustment for age and maternal smoking during child’s first year of life (yes/no) was performed, and Model 3 was additionally adjusted for BMI. Since sex-specific cut-off points for the biomarkers were applied, no further adjustment for sex was performed. In addition, clustering of elevated levels by number of cigarettes smoked was determined using all biomarkers. For all statistical analyses, P-values < 0.05 from two-sided tests were considered to be statistically significant. All analyses were performed with the statistical software package SAS release 9.1 (SAS Institute, Cary, NC, USA).

Results
In 127 (33.2%) of 383 children, exposure to ETS has been reported. In both boys and girls, ETS exposure was significantly
associated with the duration of breastfeeding, parental education, German nationality, and maternal smoking during the first year of life (Table 1). Children’s age was only associated with ETS exposure in boys, whereas BMI was only associated with ETS exposure in girls. In our data, no relationship between birth weight and ETS exposure was seen.

Table 2 shows the distribution of cardiometabolic markers by ETS exposure and sex. In boys, exposure to increasing levels of ETS was associated with differences in C-reactive protein, IL-6, and leptin. In girls, significant differences between levels of ETS exposure were observed for IL-6, leptin, apoAI, and Lp-PLA2 concentrations.

Table 3 shows the β-coefficients and 95% CI of the cardiometabolic markers according to ETS exposure levels. In the adjusted model (Model 2), ETS exposure to more than 10 cigarettes per day was positively associated with increased leptin, C-reactive protein, IL-6, Lp-PLA2, and a trend was seen for increased fibrinogen concentrations. Between plasma adiponectin, apoAI, and apoB concentrations and ETS exposure, no statistically significant association was observed. With increasing dose of cigarette smoke (1–10 and >10 cigarettes per day), the associations became stronger, indicating a dose-dependent relationship between ETS exposure and cardiometabolic markers. No substantial changes in the associations between ETS exposure and cardiometabolic markers were found after additional adjustment of Model 1 for breastfeeding, German nationality, parental education, or playing outdoor (data not shown).

As expected, further adjustment for BMI attenuated the relationships (Model 3). Only the association with Lp-PLA2 concentrations remained statistically significant.

The results for the 90th percentile or 10th percentile, respectively, of cardiometabolic marker as outcome variable are presented in Table 4. When compared with no exposure, exposure to more than 10 cigarettes of ETS per day was associated with elevated plasma concentrations of leptin, C-reactive protein, and Lp-PLA2. Environmental tobacco smoke exposure was also associated with low plasma concentrations of adiponectin and apoAI. Further adjustment for BMI (Model 3) again attenuated the relationships, except for Lp-PLA2.

Figure 1 shows the clustering of abnormal cardiometabolic marker concentrations by exposure level to ETS. With increasing exposure to ETS, the number of abnormal cardiometabolic markers increased: among children exposed to 1–10 cigarettes per day ~50% revealed at least one abnormal marker, and among children exposed to 10 or more cigarettes per day ~70% had at least one abnormal marker.

Discussion
There is growing evidence of an association between ETS exposure and obesity in childhood. To date, studies including biomarkers to elucidate such relationship are scarce. The present study provides information on the association between ETS exposure and biochemical markers of metabolism and CVD in children. Both linear and logistic regression models revealed associations between exposure to ETS and cardiometabolic markers including elevated plasma leptin, C-reactive protein, fibrinogen, Lp-PLA2, and low apoAI concentrations. Dose-dependent relationships were apparent between ETS exposure and cardiometabolic markers. Our observations indicate a link between exposure to ETS and unfavourable concentrations of cardiometabolic biomarkers in 10-year-old children, which may contribute to CVD risk in later life.

Our findings are consistent with previous research showing associations between cigarette smoking and increased prevalence of an inflammatory response, insulin resistance, and dyslipidaemia in adults. Among children, exposure to ETS was related to increased C-reactive protein concentrations, endothelial dysfunction, and the metabolic syndrome. In agreement with these results, we observed a clustering of cardiometabolic markers according to ETS exposure level.

Adipokines
Our observation that ETS exposure is associated with elevated leptin levels is in line with research on childhood obesity. Research in adults revealed inconsistent results. However, it is well established that among adults smoking results in a loss of body weight and changes in body composition. In contrast, our study in children revealed a statistically significant association in the opposite direction, which, however, was attenuated after further adjustment for BMI. Consistent with our observation of an association between ETS exposure and low adiponectin concentrations, lower adiponectin levels were found in adult Japanese smokers compared with never smokers. Thus, low adiponectin concentrations may link smoking with adiposity and insulin resistance.

Markers of inflammation
In line with the literature on active and passive smoking in adults and on ETS exposure in children, we found associations between ETS exposure and higher levels of circulating inflammatory markers in the linear models. In the dichotomized models, only high C-reactive protein concentrations remained significantly associated with ETS exposure, whereas for fibrinogen and IL-6 positive trends were observed. C-reactive protein concentrations were positively associated with IL-6, fibrinogen, and leptin levels. Constituents of ETS may cause a systemic inflammatory response through activation of immune cells, which subsequently may result in vascular damage.

Lipid metabolism
In adults, cigarette smoking is associated with lower HDL and elevated LDL concentrations indicating a more atherogenic lipid profile. Our observation of an association between ETS exposure and low apoAI concentrations is consistent with these findings. Exposure to ETS induces oxidative stress, converting LDL to oxidized LDL (oxLDL). Lipoprotein-associated phospholipase A2 is involved in the generation of inflammatory mediators from oxLDL. The association between exposure to ETS and high Lp-PLA2 concentrations in the logistic regression model are consistent with this mechanism and further supported by findings in 3-month-old children.
<table>
<thead>
<tr>
<th></th>
<th>Environmental tobacco smoke</th>
<th>Boys</th>
<th>Girls</th>
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<tr>
<td></td>
<td></td>
<td>Non-exposed</td>
<td>1–10 Cig/day</td>
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<td></td>
<td></td>
<td>(n) 538</td>
<td>383</td>
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<tr>
<td>n</td>
<td></td>
<td>116 (65.9%)</td>
<td>33 (18.8%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td>Mean (SD) 9.5 (0.6)</td>
<td>9.8 (0.7)</td>
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<tr>
<td>BMI (kg/m²)</td>
<td></td>
<td>Mean (SD) 17.4 (2.7)</td>
<td>17.9 (3.1)</td>
</tr>
<tr>
<td>German nationality</td>
<td></td>
<td>No 12 (11.3%)</td>
<td>12 (46.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Yes 94 (88.7%)</td>
<td>14 (53.9%)</td>
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<tr>
<td>Breast feeding time</td>
<td></td>
<td>None 15 (13.6%)</td>
<td>5 (17.2%)</td>
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<tr>
<td></td>
<td></td>
<td>≤6 months 47 (42.7%)</td>
<td>20 (69.0%)</td>
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<tr>
<td></td>
<td></td>
<td>&gt;6 months 48 (43.6%)</td>
<td>4 (13.8%)</td>
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<tr>
<td>Birth weight</td>
<td></td>
<td>&lt;2500 g 13 (11.5%)</td>
<td>5 (16.1%)</td>
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<td></td>
<td></td>
<td>≥2500 g 100 (88.5%)</td>
<td>26 (83.9%)</td>
</tr>
<tr>
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<td></td>
<td>Low 20 (18.7%)</td>
<td>12 (46.2%)</td>
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<tr>
<td></td>
<td></td>
<td>Medium 40 (37.4%)</td>
<td>11 (42.3%)</td>
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<tr>
<td></td>
<td></td>
<td>High 47 (43.9%)</td>
<td>3 (11.5%)</td>
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<tr>
<td>Maternal smoking in first year of life</td>
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<td>No 104 (89.7%)</td>
<td>26 (78.8%)</td>
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<td></td>
<td></td>
<td>Yes 12 (10.3%)</td>
<td>7 (21.2%)</td>
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</table>
Table 2  Median (interquartile range) of cardiovascular biomarkers by environmental tobacco smoke exposure and gender (n = 383)

| Boys | Non-exposed | 1–10 Cig/day | >10 Cig/day | P-value | Girls | Non-exposed | 1–10 Cig/day | >10 Cig/day | P-value |
|------|-------------|--------------|-------------|---------|------|-------------|--------------|-------------|---------|--------|
| n    | 116         | 33           | 27          |         | 140  | 41           | 26           |             |         |        |
| Adiponectin (µg/mL) | 9.25 (4.73) | 10.50 (7.69) | 7.87 (9.20) | 0.496  | 9.06 (5.57) | 9.80 (5.80) | 8.73 (4.49) | 0.513  |        |
| Leptin (ng/mL) | 2.26 (3.84) | 3.60 (5.55) | 5.18 (12.48)| 0.031  | 3.93 (6.74) | 5.67 (13.27)| 12.53 (14.13) | <0.001 |        |
| Lipoproteins | | | | | | | | | |
| ApoA (g/L) | 1.50 (0.24) | 1.47 (0.20) | 1.48 (0.28) | 0.575 | 1.51 (0.23) | 1.43 (0.24) | 1.40 (0.32) | 0.025 |        |
| ApoB (g/L) | 0.67 (0.19) | 0.64 (0.15) | 0.63 (0.16) | 0.377 | 0.69 (0.19) | 0.66 (0.20) | 0.68 (0.18) | 0.962 |        |
| Lp-PLA2 (ng/mL) | 148 (48) | 140 (44) | 156 (53) | 0.247 | 145 (43) | 145 (30) | 173 (47) | <0.001 |        |
| Inflammatory markers | | | | | | | | | |
| C-reactive protein (mg/L) | 0.20 (0.40) | 0.20 (0.56) | 0.62 (1.46) | 0.025 | 0.26 (0.63) | 0.32 (0.82) | 0.74 (1.15) | 0.150 |        |
| Fibrinogen (g/L) | 2.09 (0.55) | 2.28 (0.76) | 2.41 (0.74) | 0.100 | 2.18 (0.57) | 2.16 (0.64) | 2.36 (0.74) | 0.409 |        |
| IL-6 (pg/mL) | 0.79 (0.85) | 0.88 (1.25) | 1.20 (0.92) | 0.041 | 0.92 (1.12) | 0.84 (0.63) | 1.94 (1.59) | 0.039 |        |

Biological plausibility

In our study, further adjustment for duration of breastfeeding attenuated the relationships between ETS exposure and elevated plasma leptin levels. By exclusion of children with low birth weight (<2500 g) in the logistic regression models, the strength of the associations was attenuated, but except for Lp-PLA2, associations remained statistically significant. After further adjustment for smoking, the association pattern between ETS and cardiometabolic markers did not change substantially.

Various mechanisms have been suggested to link smoking to body weight and body fat distribution. Recent results in a mouse model have shown a decrease of the HDL/LDL ratio. The association between ETS exposure and cardiometabolic biomarkers did not change substantially.
Table 3  β-Coefficient estimates and 95% confidence interval of concentrations of adipokines, lipoproteins, and inflammatory markers by environmental tobacco smoke exposure

<table>
<thead>
<tr>
<th>Environmental tobacco smoke</th>
<th>Model 1</th>
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<th>Model 2</th>
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<th>Model 3</th>
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<td>1–10 Cig/day</td>
<td>&gt;10 Cig/day</td>
<td>Non-exposed</td>
<td>1–10 Cig/day</td>
<td>&gt;10 Cig/day</td>
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<td>1–10 Cig/day</td>
<td>&gt;10 Cig/day</td>
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<td>n</td>
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<td>74</td>
<td>53</td>
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<tr>
<td>Adipokines</td>
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<tr>
<td>Adiponectin*</td>
<td>β-Coefficient</td>
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<td>-0.19</td>
<td>1.00</td>
<td>-0.88</td>
<td>-0.44</td>
<td>1.09</td>
<td>0.11</td>
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<tr>
<td>95% CI</td>
<td>-0.07 to 2.07</td>
<td>-1.42 to 1.04</td>
<td>-0.21 to 1.96</td>
<td>-1.71 to 0.84</td>
<td>0.01–2.16</td>
<td>-1.19 to 1.40</td>
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<td>Leptin*</td>
<td>β-Coefficient</td>
<td>0.46</td>
<td>0.72</td>
<td>0.44</td>
<td>0.67</td>
<td>1.19</td>
<td>0.38</td>
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<tr>
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<td>0.16–0.77</td>
<td>0.37–1.07</td>
<td>0.13–0.75</td>
<td>0.31–1.04</td>
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<td>Lipoproteins</td>
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<tr>
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<td>-0.09 to 0.01</td>
<td>-0.14 to 0.02</td>
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<tr>
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<td>-0.04 to 0.04</td>
<td>-0.06 to 0.03</td>
<td>-0.05 to 0.03</td>
<td>-0.08 to 0.01</td>
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<tr>
<td>Lp-PLA₂</td>
<td>β-Coefficient</td>
<td>-3.55</td>
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<tr>
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<td>-12.67 to 4.22</td>
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<tr>
<td>C-reactive protein*</td>
<td>β-Coefficient</td>
<td>0.16</td>
<td>0.61</td>
<td>0.16</td>
<td>0.61</td>
<td>0.13</td>
<td>0.56</td>
<td>0.01</td>
<td>0.24</td>
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<tr>
<td>95% CI</td>
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<td>0.27–0.95</td>
<td>-0.17 to 0.43</td>
<td>0.21–0.91</td>
<td>-0.27 to 0.29</td>
<td>-0.09 to 0.58</td>
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<tr>
<td>Fibrinogen*</td>
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<td>0.17</td>
<td>0.05</td>
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</tr>
<tr>
<td>95% CI</td>
<td>-0.08 to 0.19</td>
<td>0.01–0.32</td>
<td>-0.09 to 0.19</td>
<td>0.00–0.33</td>
<td>-0.12 to 0.15</td>
<td>-0.09 to 0.23</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>IL-6*</td>
<td>β-Coefficient</td>
<td>0.02</td>
<td>0.55</td>
<td>0.01</td>
<td>0.52</td>
<td>0.02</td>
<td>0.04</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>-0.36 to 0.40</td>
<td>0.11–0.99</td>
<td>-0.38 to 0.39</td>
<td>0.07–0.98</td>
<td>-0.43 to 0.35</td>
<td>-0.06 to 0.87</td>
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</tr>
</tbody>
</table>

Model 1: adjusted for age; Model 2: adjusted for age and maternal smoking in child’s first year of life; Model 3: additional adjustment for BMI (continuous).

*Abnormal concentrations are defined as ≥90th percentile (leptin, C-reactive protein, fibrinogen, IL-6, apoB, Lp-PLA₂) or ≤10th percentile (adiponectin, apoA1).
Table 4  Odds ratio and 95% confidence interval of abnormal<sup>a</sup> concentrations of adipokines, lipoproteins, and inflammatory markers by environmental tobacco smoke exposure

<table>
<thead>
<tr>
<th>Environmental tobacco smoke</th>
<th>Model 1 Non-exposed</th>
<th>1–10 Cig/day</th>
<th>&gt;10 Cig/day</th>
<th>Model 2 Non-exposed</th>
<th>1–10 Cig/day</th>
<th>&gt;10 Cig/day</th>
<th>Model 3 Non-exposed</th>
<th>1–10 Cig/day</th>
<th>&gt;10 Cig/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>256</td>
<td>74</td>
<td>53</td>
<td>256</td>
<td>74</td>
<td>53</td>
<td>256</td>
<td>74</td>
<td>53</td>
</tr>
<tr>
<td>Adipokines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adiponectin: &lt;10%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.33</td>
<td>1.97</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.55</td>
<td>2.69</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.41</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.59–3.04</td>
<td>0.84–4.59</td>
<td>0.67–3.58</td>
<td>1.10–6.57</td>
<td>0.60–3.29</td>
<td>0.78–5.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leptin: &gt;90%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>2.86</td>
<td>6.34</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>2.87</td>
<td>6.40</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>2.82</td>
</tr>
<tr>
<td>95% CI</td>
<td>1.20–6.77</td>
<td>2.76–14.59</td>
<td>1.20–6.86</td>
<td>2.67–15.39</td>
<td>0.82–9.64</td>
<td>1.11–12.16</td>
<td></td>
<td></td>
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<tr>
<td>Lipoproteins</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ApoA1: &lt;10%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>0.74</td>
<td>4.14</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>0.80</td>
<td>4.84</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>0.74</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.27–2.03</td>
<td>1.95–8.81</td>
<td>0.29–2.22</td>
<td>2.16–10.85</td>
<td>0.27–2.07</td>
<td>1.73–9.32</td>
<td></td>
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<tr>
<td>ApoB: &gt;90%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.50</td>
<td>1.19</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.46</td>
<td>1.15</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.27</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.66–3.42</td>
<td>0.43–3.34</td>
<td>0.63–3.40</td>
<td>0.39–3.34</td>
<td>0.54–3.03</td>
<td>0.27–2.51</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lp-PLA&lt;sub&gt;2&lt;/sub&gt;: &gt;90%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>0.48</td>
<td>2.67</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>0.50</td>
<td>2.97</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>0.49</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.16–1.42</td>
<td>1.25–5.72</td>
<td>0.17–1.50</td>
<td>1.32–6.68</td>
<td>0.16–1.49</td>
<td>1.24–6.75</td>
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<tr>
<td>Inflammatory markers</td>
<td></td>
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<tr>
<td>C-reactive protein: &gt;90%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.90</td>
<td>2.91</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.99</td>
<td>3.17</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.61</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.84–4.28</td>
<td>1.23–6.74</td>
<td>0.87–4.56</td>
<td>1.31–7.68</td>
<td>0.68–3.81</td>
<td>0.73–4.80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen: &gt;90%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.38</td>
<td>1.78</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.33</td>
<td>1.65</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.21</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.62–3.05</td>
<td>0.77–4.13</td>
<td>0.59–2.97</td>
<td>0.68–4.00</td>
<td>0.54–2.74</td>
<td>0.53–3.29</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6: &gt;90%ile</td>
<td>OR</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.42</td>
<td>1.81</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.43</td>
<td>1.85</td>
<td>1&lt;sup&gt;Ref&lt;/sup&gt;</td>
<td>1.29</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.63–3.18</td>
<td>0.77–4.25</td>
<td>0.63–3.24</td>
<td>0.75–4.52</td>
<td>0.57–2.95</td>
<td>0.55–3.51</td>
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</tbody>
</table>

OR, odds ratio; 95% CI, 95% confidence interval.

<sup>a</sup>Abnormal concentrations are defined as ≥90th percentile (leptin, C-reactive protein, fibrinogen, IL-6, apoB, Lp-PLA<sub>2</sub>) or ≤10th percentile (adiponectin, apoA1).
Conflict of interest:
Funding technical assistance and Holger Knebel for documentation and
Acknowledgements
8. Leary SD, Smith GD, Rogers IS, Reilly JJ, Wells JC, Ness AR. Smoking during preg-
percentile (adiponectin, apoA1).
/C21 concentrations are defined as ≥90th percentile (leptin, C-reactive protein, fibrinogen, IL-6, apoB, Lp-PLA2) or ≤10th percentile (adiponectin, apoA1).

Figure 1 Percentage of children with clustering of abnormal cardiometabolic markers by ETS exposure (n = 383). Abnormal concentrations are defined as ≥90th percentile (leptin, C-reactive protein, fibrinogen, IL-6, apoB, Lp-PLA2) or ≤10th percentile (adiponectin, apoA1).

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References
An innocent bystander in the coronary tree

Andrew S.P. Sharp* and Antonio Colombo
Centro Cuore, Columbus Hospital and San Raffaele Scientific Institute, Milan, Italy

*Corresponding author. Tel: +39 02 4812920, Fax: +39 02 48193433, Email: andrewsharp@doctors.org.uk

A 58-year-old man presented to his local doctor with 30 min of chest pain and inferior ST-segment elevation on his ECG (Panel A). He was transferred immediately for primary angioplasty.

On arrival, his ECG became normal and pain had eased (Panel B). Left coronary injection (Panel C) showed a 70% stenosis of the posterolateral branch of the circumflex (arrow). Right coronary injection showed only minor atheroma (Panel D). The diagnosis was presumed to be ischaemia due to the stenosis involving the posterolateral circumflex branch and therefore a guiding catheter was taken in order to perform angioplasty to this lesion.

After first injection into the left coronary artery with the guide, the patient developed chest pain and ST elevation (Panel E). However, the circumflex appearance was identical to that seen in Panel C, with TIMI 3 flow. The right coronary was accessed again and this time showed three areas of significant coronary artery vasospasm (Panel G). Intracoronary nitroglycerin was administered and the chest pain abated with resolution of the ECG and angiographic changes (Panels F and H). The following day, blood tests showed no enzyme rise and he was discharged uneventfully on vasodilators. At 1 month clinical follow-up, the patient has been entirely asymptomatic on aspirin and calcium-channel blocker.

In this case, the operator almost succumbed to the ‘oculo-stenotic reflex’. Only coincidental chest pain with new ECG changes alerted him to the fact that the acute problem lay elsewhere, sparing this patient an unnecessary procedure. This case serves as a useful reminder that a ‘culprit lesion’ may occasionally have a very respectable appearance on coronary angiography, while the apparently attractive target may simply be an innocent bystander with respect to the acute presentation.