Effects of prenatal exposure to perfluoroalkyl acids on prevalence of allergic diseases among 4-year-old children

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Figure S1. Flow chart of study participant selection.

1,558 participants completed follow-up questionnaires at 48 months

2,056 participants

6,335 participants completed follow-up questionnaires at 4, 12 and 24 months

Excluded: congenital malformations (N = 17), blood samples taken <26 weeks of gestation (N = 15), extremely high PFOS levels (n=1)

Excluded due to withdrawal (n=6)

300 participants were randomly selected yearly between 2003 and 2008,

and 295 in 2009 (total: 2,095 subjects)

Excluded: miscarriage and stillbirth (N = 19), congenital malformations (N = 143), multiple births (N = 162)

Baseline questionnaires, 3rd trimester blood samples, and birth records were obtained from 12,847 participants

17,869 participants agreed to join the Hokkaido Study on Environment and Children’s Health between 2003 and 2009

Supplementary data, Table S1. Prenatal PFAA concentrations and risk of eczema at 4 years of age in the Hokkaido Study on Environment and Children's Health, Japan, 2003–2013 (n= 1558).

|  |  |  |  |
| --- | --- | --- | --- |
| Compound | Total (n = 1558) | Male children (n = 793) | Female children (n = 765) |
| n\* | Crude | Adjusted a | n\* | Crude | Adjusted a | n\* | Crude | Adjusted a |
| ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d |
| PFHxS |  |  |  |  |  | 　 | 　 | 　 | 　 | 　 |  |  |  |  |  |
|  Quartile 1 | 76 | 1 |  | 1 |  | 41 | 1 | 　 | 1 |  | 35 | 1 |  | 1 |  |
|  Quartile 2 | 77 | 0.975 | (0.685, 1.38) | 0.953 | (0.658, 1.38) | 39 | 0.951 | (0.582, 1.55) | 0.894 | (0.535, 1.48) | 38 | 1.00 | (0.603, 1.67) | 0.996 | (0.574, 1.73) |
|  Quartile 3 | 71 | 0.899 | (0.627, 1.28) | 0.910 | (0.623, 1.32) | 35 | 0.827 | (0.501, 1.36) | 0.797 | (0.471, 1.33) | 36 | 0.982 | (0.586, 1.64) | 1.07 | (0.612, 1.87) |
|  Quartile 4 | 72 | 0.906 | (0.633, 1.29) | 0.917 | (0.626, 1.34) | 38 | 0.91 | (0.556, 1.48) | 0.854 | (0.509, 1.42) | 34 | 0.904 | (0.536, 1.52) | 1.00 | (0.567, 1.77) |
| p for trend |  | 0.513 |  | 0.618 |  | 　 | 0.596 | 　 | 0.478 |  |  | 0.697 |  | 0.929 |  |
| P for Sex interaction |  | 0.960 |  | 0.920 |  |  |  |  |  |  |  |  |  |  |  |
| PFOS |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 87 | 1 |  | 1 |  | 47 | 1 | 　 | 1 |  | 40 | 1 |  | 1 |  |
|  Quartile 2 | 65 | 0.690 | (0.482, 0.986) | 0.640 | (0.439, 0.928) | 31 | 0.628 | (0.379, 1.03) | 0.584 | (0.341, 0.985) | 34 | 0.760 | (0.457, 1.26) | 0.728 | (0.422, 1.25) |
|  Quartile 3 | 66 | 0.707 | (0.495, 1.01) | 0.650 | (0.445, 0.946) | 33 | 0.693 | (0.422, 1.13) | 0.590 | (0.344, 0.995) | 33 | 0.724 | (0.434, 1.20) | 0.742 | (0.428, 1.28) |
|  Quartile 4 | 78 | 0.865 | (0.613, 1.22) | 0.853 | (0.591, 1.22) | 42 | 0.882 | (0.551, 1.41) | 0.839 | (0.508, 1.38) | 36 | 0.847 | (0.511, 1.40) | 0.907 | (0.524, 1.56) |
| p for trend |  | 0.439 |  | 0.427 |  | 　 | 0.675 | 　 | 0.502 |  |  | 0.498 |  | 0.761 |  |
| P for Sex interaction |  | 0.935 |  | 0.896 |  |  |  |  |  |  |  |  |  |  |  |
| PFOA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 76 | 1 |  | 1 |  | 38 | 1 | 　 | 1 |  | 38 | 1 |  | 1 |  |
|  Quartile 2 | 83 | 1.10 | (0.781, 1.56) | 1.10 | (0.760, 1.59) | 54 | 1.41 | (0.881, 2.26) | 1.31 | (0.802, 2.18) | 29 | 0.788 | (0.463, 1.34) | 0.883 | (0.497, 1.55) |
|  Quartile 3 | 74 | 0.964 | (0.675, 1.37) | 0.915 | (0.623, 1.34) | 35 | 0.854 | (0.513, 1.42) | 0.742 | (0.432, 1.27) | 39 | 1.08 | (0.660, 1.79) | 1.16 | (0.667, 2.03) |
|  Quartile 4 | 63 | 0.791 | (0.547, 1.14) | 0.843 | (0.556, 1.27) | 26 | 0.623 | (0.361, 1.07) | 0.592 | (0.319, 1.08) | 37 | 0.974 | (0.589, 1.61) | 1.21 | (0.683, 2.17) |
| p for trend |  | 0.159 |  | 0.287 |  | 　 | **0.025** |  | **0.022** |  |  | 0.791 |  | 0.356 |  |
| P for Sex interaction |  | **0.031** |  | **0.039** |  |  |  |  |  |  |  |  |  |  |  |
| PFNA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 78 | 1 |  | 1 |  | 43 | 1 | 　 | 1 |  | 35 | 1 |  | 1 |  |
|  Quartile 2 | 77 | 0.987 | (0.694, 1.40) | 1.03 | (0.718, 1.48) | 44 | 1.05 | (0.657, 1.70) | 1.07 | (0.654, 1.75) | 33 | 0.913 | (0.540, 1.54) | 1.03 | (0.594, 1.78) |
|  Quartile 3 | 75 | 0.949 | (0.667, 1.35) | 0.901 | (0.620, 1.30) | 32 | 0.735 | (0.442, 1.22) | 0.668 | (0.387, 1.13) | 43 | 1.21 | (0.737, 1.99) | 1.29 | (0.763, 2.22) |
|  Quartile 4 | 66 | 0.810 | (0.563, 1.16) | 0.782 | (0.528, 1.15) | 34 | 0.722 | (0.438, 1.18) | 0.686 | (0.400, 1.16) | 32 | 0.920 | (0.542, 1.56) | 0.976 | (0.543, 1.74) |
| p for trend |  | 0.254 |  | 0.175 |  | 　 | 0.098 | 　 | 0.068 |  |  | 0.935 |  | 0.826 |  |
| P for Sex interaction |  | 0.300 |  | 0.280 |  |  |  |  |  |  |  |  |  |  |  |
| PFDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 79 | 1 |  | 1 |  | 41 | 1 | 　 | 1 |  | 38 | 1 |  | 1 |  |
|  Quartile 2 | 72 | 0.880 | (0.616, 1.25) | 0.854 | (0.589, 1.23) | 39 | 0.934 | (0.572, 1.52) | 0.875 | (0.524, 1.45) | 33 | 0.824 | (0.491, 1.38) | 0.872 | (0.504, 1.50) |
|  Quartile 3 | 71 | 0.868 | (0.607, 1.24) | 0.819 | (0.563, 1.18) | 35 | 0.848 | (0.514, 1.40) | 0.832 | (0.491, 1.40) | 36 | 0.887 | (0.534, 1.47) | 0.854 | (0.495, 1.47) |
|  Quartile 4 | 74 | 0.901 | (0.633, 1.28) | 0.926 | (0.637, 1.34) | 38 | 0.927 | (0.566, 1.51) | 0.887 | (0.527, 1.48) | 36 | 0.876 | (0.527, 1.45) | 1.03 | (0.596, 1.78) |
| p for trend |  | 0.567 |  | 0.641 |  | 　 | 0.684 | 　 | 0.619 |  |  | 0.692 |  | 0.939 |  |
| P for Sex interaction |  | 0.971 |  | 0.985 |  |  |  |  |  |  |  |  |  |  |  |
| PFUnDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 78 | 1 |  | 1 |  | 34 | 1 | 　 | 1 |  | 44 | 1 |  | 1 |  |
|  Quartile 2 | 78 | 0.994 | (0.699, 1.41) | 1.01 | (0.703, 1.46) | 55 | 1.62 | (1.007, 2.63) | 1.61 | (0.984, 2.68) | 23 | 0.512 | (0.295, 0.891) | 0.544 | (0.302, 0.962) |
|  Quartile 3 | 77 | 0.968 | (0.681, 1.37) | 0.958 | (0.663, 1.38) | 36 | 1.14 | (0.681, 1.92) | 1.15 | (0.668, 1.98) | 41 | 0.831 | (0.514, 1.34) | 0.857 | (0.515, 1.42) |
|  Quartile 4 | 63 | 0.763 | (0.529, 1.10) | 0.704 | (0.477, 1.03) | 28 | 0.780 | (0.452, 1.34) | 0.759 | (0.428, 1.33) | 35 | 0.750 | (0.456, 1.23) | 0.657 | (0.382, 1.12) |
| p for trend |  | 0.163 |  | 0.077 |  | 　 | 0.183 | 　 | 0.181 |  |  | 0.530 |  | 0.314 |  |
| P for Sex interaction |  | 0.006 |  | 0.022 |  |  |  |  |  |  |  |  |  |  |  |
| PFDoDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 85 | 1 |  | 1 |  | 44 | 1 | 　 | 1 |  | 41 | 1 |  | 1 |  |
|  Quartile 2 | 75 | 0.829 | (0.585, 1.17) | 0.815 | (0.565, 1.17) | 46 | 0.924 | (0.578, 1.47) | 0.877 | (0.536, 1.43) | 29 | 0.707 | (0.418, 1.19) | 0.732 | (0.418, 1.27) |
|  Quartile 3 | 79 | 0.885 | (0.627, 1.24) | 0.862 | (0.601, 1.23) | 39 | 0.824 | (0.506, 1.34) | 0.828 | (0.500, 1.36) | 40 | 0.951 | (0.583, 1.55) | 0.926 | (0.546, 1.56) |
|  Quartile 4 | 57 | 0.591 | (0.408, 0.856) | 0.566 | (0.383, 0.831) | 24 | 0.452 | (0.262, 0.779) | 0.451 | (0.253, 0.785) | 33 | 0.755 | (0.454, 1.25) | 0.731 | (0.423, 1.25) |
| p for trend |  | **0.012** |  | **0.008** |  |  | **0.004** |  | **0.008** |  |  | 0.485 |  | 0.419 |  |
| P for Sex interaction |  | 0.239 |  | 0.351 |  |  |  |  |  |  |  |  |  |  |  |
| PFTrDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 91 | 1 |  | 1 |  | 44 | 1 | 　 | 1 |  | 47 | 1 |  | 1 |  |
|  Quartile 2 | 67 | 0.679 | (0.477, 0.966) | 0.687 | (0.474, 0.990) | 44 | 0.884 | (0.55, 1.42) | 0.874 | (0.533, 1.43) | 23 | 0.471 | (0.272, 0.813) | 0.489 | (0.273, 0.858) |
|  Quartile 3 | 68 | 0.693 | (0.488, 0.986) | 0.671 | (0.463, 0.968) | 32 | 0.620 | (0.374, 1.02) | 0.602 | (0.352, 1.02) | 36 | 0.776 | (0.476, 1.26) | 0.763 | (0.452, 1.28) |
|  Quartile 4 | 70 | 0.698 | (0.493, 0.990) | 0.672 | (0.465, 0.968) | 33 | 0.675 | (0.408, 1.11) | 0.695 | (0.409, 1.17) | 37 | 0.72 | (0.444, 1.16) | 0.666 | (0.395, 1.11) |
| p for trend | 　 | 0.054 | 　 | **0.037** |  | 　 | 0.057 | 　 | 0.082 |  | 　 | 0.411 | 　 | 0.300 |  |
| P for Sex interaction |  | 0.127 |  | 0.165 |  |  |  |  |  |  |  |  |  |  |  |

a Adjusted for maternal age, maternal educational level, parental allergic history, number of older siblings, children gender, breast feeding, day care attendance and ETS exposure at 4 years of age. In addition to the mentioned confounders, we included children gender in adjusted models for total children before sex stratification.

\*Indicates number of cases with eczema symptoms.

Supplementary data, Table S2. Association between PFAA concentrations in maternal plasma and rhinoconjunctivitis at 4 years of age in the Hokkaido Study on Environment and Children's Health, Japan, 2003–2013 (n= 1558).

|  |  |  |  |
| --- | --- | --- | --- |
| Compound | Total (n = 1558) | Male children (n = 793) | Female children (n = 765) |
| n\* | Crude | Adjusted a | n\* | Crude | Adjusted a | n\* | Crude | Adjusted a |
| ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d | ORc | (95% CI)d |
| PFHxS |  |  |  |  |  | 　 | 　 | 　 | 　 | 　 |  |  |  |  |  |
|  Quartile 1 | 24 | 1 |  | 1 |  | 15 | 1 | 　 | 1 |  | 9 | 1 |  | 1 |  |
|  Quartile 2 | 25 | 1.00 | (0.565, 1.79) | 0.900 | (0.494, 1.63) | 11 | 0.725 | (0.325, 1.62) | 0.616 | (0.257, 1.41) | 14 | 1.47 | (0.621, 3.48) | 1.44 | (0.596, 3.65) |
|  Quartile 3 | 15 | 0.598 | (0.309, 1.15) | 0.586 | (0.293, 1.13) | 8 | 0.516 | (0.214, 1.24) | 0.536 | (0.208, 1.28) | 7 | 0.736 | (0.268, 2.01) | 0.691 | (0.233, 1.96) |
|  Quartile 4 | 20 | 0.802 | (0.435, 1.47) | 0.675 | (0.348, 1.28) | 12 | 0.787 | (0.359, 1.72) | 0.700 | (0.298, 1.59) | 8 | 0.836 | (0.315, 2.21) | 0.682 | (0.228, 1.95) |
| p for trend |  | 0.242 |  | 0.128 |  | 　 | 0.414 | 　 | 0.346 |  |  | 0.404 |  | 0.238 |  |
| P for Sex interaction |  | 0.631 |  | 0.555 |  |  |  |  |  |  |  |  |  |  |  |
| PFOS |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 26 | 1 |  | 1 |  | 15 | 1 | 　 | 1 |  | 11 | 1 |  | 1 |  |
|  Quartile 2 | 14 | 0.517 | (0.266, 1.00) | 0.460 | (0.224, 0.900) | 8 | 0.536 | (0.222, 1.29) | 0.480 | (0.176, 1.19) | 6 | 0.499 | (0.181, 1.37) | 0.418 | (0.138, 1.14) |
|  Quartile 3 | 20 | 0.755 | (0.414, 1.37) | 0.687 | (0.365, 1.27) | 10 | 0.692 | (0.303, 1.58) | 0.642 | (0.259, 1.50) | 10 | 0.841 | (0.349, 2.03) | 0.774 | (0.308, 1.92) |
|  Quartile 4 | 24 | 0.913 | (0.515, 1.62) | 0.799 | (0.435, 1.45) | 13 | 0.871 | (0.404, 1.88) | 0.871 | (0.383, 1.95) | 11 | 0.972 | (0.411, 2.3) | 0.747 | (0.291, 1.88) |
| p for trend |  | 0.991 |  | 0.690 |  | 　 | 0.826 | 　 | 0.838 |  |  | 0.812 |  | 0.839 |  |
| P for Sex interaction |  | 0.981 |  | 0.961 |  |  |  |  |  |  |  |  |  |  |  |
| PFOA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 17 | 1 |  | 1 |  | 10 | 1 | 　 | 1 |  | 7 | 1 |  | 1 |  |
|  Quartile 2 | 26 | 1.55 | (0.830, 2.91) | 1.42 | (0.742, 2.77) | 15 | 1.40 | (0.616, 3.21) | 1.30 | (0.541, 3.20) | 11 | 1.73 | (0.658, 4.57) | 1.64 | (0.613, 4.65) |
|  Quartile 3 | 19 | 1.12 | (0.573, 2.19) | 1.04 | (0.520, 2.11) | 12 | 1.15 | (0.487, 2.74) | 1.12 | (0.456, 2.83) | 7 | 1.04 | (0.359, 3.03) | 1.00 | (0.321, 3.11) |
|  Quartile 4 | 22 | 1.304 | (0.682, 2.49) | 1.27 | (0.625, 2.61) | 9 | 0.881 | (0.35, 2.21) | 0.968 | (0.349, 2.64) | 13 | 1.928 | (0.752, 4.94) | 1.78 | (0.637, 5.27) |
| p for trend |  | 0.696 |  | 0.767 |  | 　 | 0.677 | 　 | 0.872 |  |  | 0.309 |  | 0.453 |  |
| P for Sex interaction |  | 0.684 |  | 0.691 |  |  |  |  |  |  |  |  |  |  |  |
| PFNA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 27 | 1 |  | 1 |  | 13 | 1 | 　 | 1 |  | 14 | 1 |  | 1 |  |
|  Quartile 2 | 22 | 0.806 | (0.451, 1.44) | 0.774 | (0.422, 1.39) | 16 | 1.27 | (0.598, 2.73) | 1.20 | (0.547, 2.70) | 6 | 0.403 | (0.152, 1.07) | 0.401 | (0.138, 1.03) |
|  Quartile 3 | 23 | 0.840 | (0.473, 1.49) | 0.731 | (0.395, 1.33) | 9 | 0.711 | (0.297, 1.70) | 0.598 | (0.225, 1.49) | 14 | 0.946 | (0.438, 2.04) | 0.798 | (0.349, 1.80) |
|  Quartile 4 | 12 | 0.425 | (0.212, 0.851) | 0.409 | (0.192, 0.825) | 8 | 0.581 | (0.236, 1.43) | 0.578 | (0.215, 1.46) | 4 | 0.276 | (0.089, 0.856) | 0.259 | (0.070, 0.722) |
| p for trend |  | **0.026** |  | **0.019** |  | 　 | 0.127 | 　 | 0.129 |  |  | 0.105 |  | 0.064 |  |
| P for Sex interaction |  | 0.099 |  | 0.153 |  |  |  |  |  |  |  |  |  |  |  |
| PFDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 23 | 1 |  | 1 |  | 13 | 1 | 　 | 1 |  | 10 | 1 |  | 1 |  |
|  Quartile 2 | 26 | 1.12 | (0.632, 2.01) | 1.04 | (0.576, 1.89) | 17 | 1.32 | (0.628, 2.81) | 1.18 | (0.545, 2.62) | 9 | 0.880 | (0.349, 2.21) | 0.873 | (0.335, 2.23) |
|  Quartile 3 | 17 | 0.721 | (0.379, 1.37) | 0.672 | (0.341, 1.29) | 11 | 0.860 | (0.376, 1.96) | 0.783 | (0.320, 1.86) | 6 | 0.562 | (0.200, 1.57) | 0.540 | (0.178, 1.50) |
|  Quartile 4 | 18 | 0.758 | (0.402, 1.42) | 0.724 | (0.370, 1.39) | 5 | 0.375 | (0.131, 1.07) | 0.370 | (0.114, 1.02) | 13 | 1.25 | (0.534, 2.92) | 1.15 |  |
| p for trend |  | 0.209 |  | 0.183 |  | 　 | 0.050 | 　 | 0.053 |  |  | 0.751 |  | 0.923 |  |
| P for Sex interaction |  | 0.062 |  | 0.111 |  |  |  |  |  |  |  |  |  |  |  |
| PFUnDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 27 | 1 |  | 1 |  | 19 | 1 | 　 | 1 |  | 8 | 1 |  | 1 |  |
|  Quartile 2 | 17 | 0.609 | (0.327, 1.13) | 0.591 | (0.304, 1.11) | 8 | 0.358 | (0.153, 0.838) | 0.338 | (0.127, 0.808) | 9 | 1.255 | (0.473, 3.32) | 1.26 | (0.467, 3.46) |
|  Quartile 3 | 27 | 0.986 | (0.567, 1.71) | 0.986 | (0.558, 1.74) | 13 | 0.700 | (0.335, 1.46) | 0.680 | (0.308, 1.46) | 14 | 1.668 | (0.684, 4.07) | 1.57 | (0.650, 4.07) |
|  Quartile 4 | 13 | 0.46 | (0.234, 0.905) | 0.420 | (0.200, 0.838) | 6 | 0.289 | (0.113, 0.741) | 0.285 | (0.099, 0.714) | 7 | 0.870 | (0.309, 2.44) | 0.713 | (0.227, 2.12) |
| p for trend |  | 0.102 |  | 0.081 |  | 　 | **0.027** | 　 | **0.030** |  |  | 0.978 |  | 0.758 |  |
| P for Sex interaction |  | 0.195 |  | 0.221 |  |  |  |  |  |  |  |  |  |  |  |
| PFDoDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 23 | 1 |  | 1 |  | 18 | 1 | 　 | 1 |  | 5 | 1 |  | 1 |  |
|  Quartile 2 | 18 | 0.753 | (0.4, 1.419) | 0.656 | (0.334, 1.26) | 10 | 0.475 | (0.214, 1.05) | 0.394 | (0.156, 0.912) | 8 | 1.73 | (0.558, 5.41) | 1.66 | (0.538, 5.67) |
|  Quartile 3 | 23 | 0.976 | (0.538, 1.77) | 0.859  | (0.464, 1.58) | 9 | 0.460 | (0.201, 1.05) | 9.427  | (0.175, 0.970) | 14 | 2.89 | (1.021, 8.19) | 2.61 | (0.950, 8.39) |
|  Quartile 4 | 20 | 0.835 | (0.451, 1.546) | 0.808 | (0.429, 1.50) | 9 | 0.450 | (0.197, 1.02) | 0.430 | (0.176, 0.985) | 11 | 2.24 | (0.766, 6.59) | 2.19 | (0.768, 7.16) |
| p for trend |  | 0.765 |  | 0.683 |  | 　 | 0.050 | 　 | **0.045** |  |  | 0.092 |  | 0.115 |  |
| P for Sex interaction |  | 0.024 |  | 0.033 |  |  |  |  |  |  |  |  |  |  |  |
| PFTrDA |  |  |  |  |  | 　 | 　 | 　 |  |  |  |  |  |  |  |
|  Quartile 1 | 16 | 1 |  | 1 |  | 12 | 1 | 　 | 1 |  | 4 | 1 |  | 1 |  |
|  Quartile 2 | 30 | 1.94 | (1.041, 3.62) | 1.89 | (1.01, 3.64) | 14 | 1.06 | (0.479, 2.36) | 1.11 | (0.487, 2.58) | 16 | 4.73 | (1.551, 14.43) | 4.50 | (1.59, 16.03) |
|  Quartile 3 | 18 | 1.13 | (0.568, 2.25) | 0.964 | (0.468, 1.98) | 12 | 0.932 | (0.408, 2.12) | 0.860 | (0.355, 2.06) | 6 | 1.62 | (0.451, 5.85) | 1.27 | (0.328, 5.23) |
|  Quartile 4 | 20 | 1.23 | (0.629, 2.41) | 1.17 | (0.594, 2.34) | 8 | 0.634 | (0.253, 1.58) | 0.634 | (0.239, 1.59) | 12 | 3.06 | (0.971, 9.66) | 2.82 | (0.951, 10.32) |
| p for trend | 　 | 0.944 | 　 | 0.762 |  | 　 | 0.318 | 　 | 0.288 |  | 　 | 0.337 | 　 | 0.302 |  |
| P for Sex interaction |  | 0.064 |  | 0.072 |  |  |  |  |  |  |  |  |  |  |  |

a Adjusted for maternal age, maternal educational level, parental allergic history, number of older siblings, breast-feeding period, day care attendance and ETS exposure at 4 years of age. In addition to the mentioned confounders, we included children gender in adjusted models for total children before sex stratification.

\*Indicates number of cases with rhinoconjunctivitis symptoms.

Supplementary data Table S3. Characteristics of mother-child pairs assessed at 4 years compare with first 2 years of age and loss of follow up population.

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristics | Assessment during the first 2 years of age (n=2062),mean±SD or No. (%) | Assessment at 4-years of age (n=1558),mean±SD or No. (%) | Loss of follow up population between assessment during first 2 years of life and 4 years (n=498), mean±SD or No. (%) |
| **Parental characteristics** |  |  |  |
| Maternal age (years) (mean ± SD) | 30.4±4.5 | 31.1±4.4 | 30.1±4.4 |
| Maternal educational level (less than ≤12 years) | 911 (44.2) | 660 (42.4) | 251 (50.4) |
| Parity (nulliparous) | 944 (45.8) | 702 (45.7) | 226 (45.3) |
| Maternal smoking during pregnancy | 150 (7.3) | 90 (5.7) | 53 (10.6) |
| Maternal allergic history (yes) | 652 (31.6) | 484 (31.0) | 168 (33.7) |
| Paternal allergic history (yes) | 385 (18.7) | 307 (19.7) | 92 (18.4) |
| **Children characteristics** |  |  |  |
| Gender (male) | 1044 (50.6) | 793 (50.9) | 249 (50.0) |
| Day care attendance (yes) | 583 (28.3) | 1373 (90.3) | 　　　- |
| ETS exposure (yes) | 947 (45.9) | 724 (48.0) |  - |