|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Wheezer | Healthy children < 6 y | Asthmatic children | Healthy children | Adults | Healthy adults |
| Eotaxin | 60.3 | 57.2 | 51.0 | 50.7 | 48.3 | 55.0 |
| bFGF | 14.9 | 39.9 | 63.1 | 63.5 | 4.0 | 3.8 |
| G-CSF | 77.3 | 66.8 | 83.8 | 84.6 | 57.4 | 50.4 |
| GM-CSF | 8.9 | 3.3 | 6.4 | 3.7 | 12.1 | 10.7 |
| IFN-y | 160.2 | 156.7 | 124.5 | 99.8 | 50.1 | 46.6 |
| IL-10 | 13.5 | 12.4 | 13.7 | 12.3 | 3.8 | 3.5 |
| IL-12(p70) | 23.2 | 21.4 | 44.3 | 32.9 | 10.1 | 2.6 |
| IL-13 | 4.8 | 4.6 | 6.4 | 4.5 | 1.7 | 1.7 |
| IL-15 | 5.1 | 5.9 | 5.1 | 5.1 | 6.2 | 6.2 |
| IL-17 | 63.3 | 172.9 | 89.1 | 85.0 | 47.0 | 41.4 |
| IL 1β | 5.0 | 4.3 | 3.3 | 3.0 | 3.4 | 3.2 |
| IL-1ra | 104.2 | 101.6 | 100.0 | 94.3 | 66.6 | 56.2 |
| IL-2 | 3.6 | 3.6 | 4.6 | 4.1 | 2.1 | 2.1 |
| IL-4 | 7.1 | 7.9 | 5.1 | 5.2 | 5.6 | 5.8 |
| IL-5 | 11.1 | 10.6 | 15.2 | 9.8 | 4.3 | 4.5 |
| IL-6 | 12.9 | 11.9 | 6.6 | 7.2 | 9.3 | 8.5 |
| IL-7 | 10.2 | 10.3 | 11.9 | 9.2 | 7.6 | 7.1 |
| IL-8 | 35.0 | 32.7 | 27.9 | 26.4 | 34.7 | 35.1 |
| IL-9 | 30.2 | 47.1 | 52.1 | 40.5 | 12.6 | 12.4 |
| IP-10 | 349.6 | 282.4 | 258.4 | 217.7 | 262.4 | 240.2 |
| MCP-1 | 16.5 | 9.7 | 12.7 | 8.1 | 3.8 | 3.9 |
| MIP-1a | 6.2 | 5.6 | 5.9 | 5.9 | 5.5 | 4.5 |
| MIP-1b | 116.3 | 100.6 | 83.7 | 81.9 | 86.3 | 89.4 |
| PDGF-BB | 3281.0 | 3031.8 | 3055.3 | 2556.7 | 2924.5 | 3042.8 |
| RANTES | 11223.9 | 17086.2 | 4812.8 | 19862.3 | 8984.5 | 14586.2 |
| TNF-a | 60.9 | 66.6 | 44.0 | 46.2 | 46.9 | 45.7 |
| VEGF | 32.3 | 44.9 | 41.4 | 27.5 | 9.9 | 2.8 |

Supplement Table S1: Mean cytokine concentration [pg/ml] in children and adults with wheeze or asthma and in healthy controls, respectively. Statistical significant differences between the groups (Mann–Whitney U test p< 0.05) are marked in green (corrected for multiple testing) and red (not corrected for multiple testing), respectively. bFGF: Basic Fibroblast Growth Factor; G-CSF: Granulocyte-colony stimulating factor; Granulocyte-macrophage colony-stimulating factor; IFN: Interferon; IL: interleukin; IP-10: Interferon gamma-induced protein 10; MCP-1: Monocyte Chemoattractant Protein 1; MIP: Macrophage inflammatory protein; PDGF: Platelet-derived growth factor; RANTES: Regulated upon activation, normal T-cell expressed, and secreted; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor.

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| --- | --- | --- | --- | --- |
|  | **A** | **B** | **C** | **D** |
|  | **GLM**  **case-control + age** | **GLM**  **age + cosinor** | **GLM**  **case-control + age + cosinor** | **GLM**  **case-control + age + month** |
| Interleukins | | | | |
| IL 1β | 0.843 (0.973) | 0.024 (0.052) | NA | 0.631(0.779) |
| IL 1ra | 0.251 (0.470) | 0.001 (0.007) | 0.187 (0.261) | 0.136 (0.290) |
| IL 4 | 0.225 (0.470) | 0.008 (0.019) | 0.146 (0.256) | 0.155 (0.29) |
| IL 7 | 0.311 (0.518) | 0.036 (0.057) | NA | 0.457 (0.623) |
| IL 9 | 0.975 (0.987) | < 0.001 (< 0.001) | 0.968 (0.968) | 0.923 (0.923) |
| IL 13 | 0.065 (0.242) | 0.119 (0.153) | NA | 0.109 (0.272) |
| IL 17A | 0.006 (0.046) | < 0.001 (< 0.001) | 0.002 (0.015) | 0.002 (0.028) |
| Tumor Necrosis Factor | | | | |
| TNF-α | 0.081 (0.243) | 0.002 (0.008) | 0.042 (0.146) | 0.034 (0.159) |
| Growth Factors | | | | |
| G-CSF | 0.356 (0.533) | 0.513 (0.550) | NA | 0.228 (0.379) |
| PDGF-bb | 0.006 (0.046) | 0.961 (0.961) | NA | 0.006 (0.047) |
| Chemokines | | | | |
| MIP 1α | 0.137 (0.343) | 0.004 (0.011) | 0.136 (0.256) | 0.096 (0.272) |
| MIP 1β | 0.631 (0.789) | 0.03 (0.056) | NA | 0.675 (0.779) |
| IL 8 | 0.391 (0.534) | 0.038 (0.057) | NA | 0.304 (0.456) |
| Eotaxin | 0.987 (0.987) | 0.304 (0.35) | NA | 0.851 (0.912) |
| IP 10 | 0.026 (0.130) | 0.123 (0.153) | NA | 0.042 (0.159) |

Supplement Table S2: Overview of the tested cytokine associations with > 80% values within the quantification limits. All nominal p-values and p-values that are adjusted for multiple testing (in brackets) are listed. Four different GLMs were conducted, all accounting for age: A) testing group difference without adjusting for seasonality; B) testing for sinusoidal seasonality; C) testing group difference accounting for sinusoidal seasonality; D) testing group difference accounting for any monthly variation. The p-values were adjusted columnwise with the Bonferroni-Holm method. The GLM (age + cosinor) column lists the smallest p-value of the cosinor coefficients indicating sinusoidal seasonal variation. All adjusted p-values being smaller than the significance level for tests for group differences and for sinusoidal seasonality are marked green. Cytokines showing no sinusoidal seasonality are marked red.

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| --- | --- | --- | --- | --- |
|  | **A** | **B** | **C** | **D** |
|  | **GLM**  **case-control + age** | **GLM**  **age + cosinor** | **GLM**  **case-control + age + cosinor** | **GLM**  **case-control + age + month** |
| Interleukins | | | | |
| IL 1β | -0.021  [-0.237; 0.193] | 0.142  [0.019; 0.264] | -0.044  [-0.258; 0.171] | -0.052  [-0.265; 0.161] |
| IL 1ra | -0.121  [-0.329; 0.086] | 0.190  [0.075; 0.305] | -0.139  [-0.344; 0.067] | -0.1526  [-0.353; 0.048] |
| IL 4 | -0.377  [-0.987; 0.232] | 0.473  [0.127; 0.819] | -0.451  [-1.058; 0.156] | -0.4421  [-1.050; 0.166] |
| IL 7 | 0.171  [-0.160; 0.503] | 0.120  [0.014; 0.385] | NA | 0.1238  [-0.202; 0.448] |
| IL 9 | 0.003  [-0.181; 0.188] | 0.241  [0.139; 0.343] | -0.004  [-0.185; 0.178] | -0.0088  [-0.188, 0.170] |
| IL 13 | 0.273  [-0.016; 0.562] | 0.130  [-0.33; 0.293] | NA | 0.2339  [-0.052; 0.519] |
| IL 17A | -1.076  [-1.836; -0.317] | 1.356  [0.944; 1.769] | -1.146  [-1.875; -0.418] | -1.1522  [-1.874; -0.430] |
| Tumor Necrosis Factor | | | | |
| TNF-α | -0.484  [-1.028; 0.059] | 0.488  [0.180; 0.796] | -0.562  [-1.101; -0.022] | -0.5795  [-1.113; -0.046] |
| Growth Factors | | | | |
| G-CSF | -0.274  [-0.856; 0.307] | 0.110  [-0.219; 0.438] | NA | -0.349  [-0.915: 0.217] |
| PDGF-bb | 13.464  [3.879; 23.094] | 0.136  [-5.315; 5.587] | NA | 13.5292  [3.88; 23.178] |
| Chemokines | | | | |
| MIP 1α | -0.150  [-0.348; 0.048] | 0.166  [0.055; 0.277] | -0.150  [-0.348; 0.047] | -0.1679  [-0.365; 0.029] |
| MIP 1β | 0.060  [-0.185; 0.305] | 0.155  [0.015; 0.294] | NA | 0.0526  [-0.193; 0.298] |
| Eotaxin | -0.008  [-1.017; 1.000] | 0.303  [-0.274; 0.879] | NA | -0.097  [-1.109; 0.915] |
| IL 8 | -0.517  [-1.699; 0.664] | 0.715  [0.042; 1.389] | NA | -0.625  [-1.815; 0.565] |
| IP 10 | 0.150  [0.018; 0.283] | 0.059  [-0.016; 0.134] | NA | 0.1392  [0.005; 0.273] |

Supplement Table S3: Overview of the tested cytokine effect estimates with > 80% values within the quantification limits. All estimates for the case-control coefficients and their 95%-confidence intervals are shown. Four different GLMs were conducted, all accounting for age: A) testing group difference without adjusting for seasonality; B) testing for sinusoidal seasonality; C) testing group difference accounting for sinusoidal seasonality; D) testing group difference accounting for any monthly variation. The GLM (age + cosinor) column lists the cosinor coefficient and 95%-confidence interval with the smallest p-value. All effect estimates with a confidence interval that does not include the 0 are marked green. Cytokines showing no sinusoidal seasonality are marked red.