***Supplementary Material***

**Men have higher cytokine production response upon stimulation with lipopolysaccharide than women: a pooled-analysis including 15 study populations.**

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| Name study population | Key ref. for methods |  | Cytokine production response | | | | | | | | | | |
|  | TNF-α, pg/ml | |  | IL-6, pg/ml | |  | IL-12, pg/ml | |  | IL-1β, pg/ml | |
|  | Women | Men |  | Women | Men |  | Women | Men |  | Women | Men |
| LPS, ng/ml | Median | Median |  | Median | Median |  | Median | Median |  | Median | Median |
| (IQR) | (IQR) |  | (IQR) | (IQR) |  | (IQR) | (IQR) |  | (IQR) | (IQR) |
| **General population** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Myoage young | n/a | 10 | 5.1 | 7.5 |  | 73.4 | 87.9 |  | 2.3 | 3.3 |  | 10.1 | 13.8 |
|  |  |  | (3.3-6.9) | (5.1-10.0) |  | (54.4-89.7) | (76.6-94.7) |  | (1.7-2.9) | (2.2-4.3) |  | (8.2-12.0) | (9.6-15.7) |
| YNTR | [[9](#_ENREF_8)] | 10000 | 7.0  (5.5-9.9) | 7.2  (6.0-10.4) |  | 64.4  (53.0-90.5) | 72.2  (61.0-95.8) |  |  |  |  | 5.8  (4.0-7.5) | 6.6  (4.6-8.9) |
| Meningitis relatives | [[10](#_ENREF_9)] | 10 | 4.4∞  (3.1-6.2) | 5.0∞  (3.7-7.1) |  |  |  |  |  |  |  |  |  |
| MS-SLE relatives | [[1](#_ENREF_11)2] | 1000 | 7.6  (5.3-10.6) | 9.3  (6.7-13.2) |  | 26.5  (17.1-38.2) | 35.7  (22.9-55.9) |  | 8.9  (5.6-12.7) | 9.6  (6.7-15.2) |  | 1.8  (1.0-3.3) | 2.7  (1.6-5.1) |
| Ghana | [[4](#_ENREF_44)7] | 10 | 18.6  (12.9-25.8) | 20.5  (13.3-28.6) |  |  |  |  |  |  |  |  |  |
| ANTR | [[9](#_ENREF_8)] | 10000 | 5.9  (4.8-7.9) | 7.3  (5.4-10.3) |  | 63.8  (52.3-80.1) | 71.4  (57.8-105.7) |  |  |  |  | 4.8  (3.5-6.8) | 6.2  (4.5-8.5) |
| LLS | [[3](#_ENREF_31)3] | 10 | 8.1  (5.7-11.0) | 9.1  (6.4-13.7) |  | 82.8  (67.2-103.4) | 94.1  (78.5-120.1) |  | 4.6b  (3.5-5.9) | 5.0b  (3.9-6.7) |  | 10.1  (7.4-13.1) | 12.1  (9.4-16.0) |
| Myoage old | n/a | 10 | 7.0  (5.1-10.5) | 7.6  (5.9-9.5) |  | 72.1  (54.8-92.6) | 75.7  (60.0-93.1) |  | 2.3  (1.8-3.5) | 3.0  (1.9-4.0) |  | 9.7  (7.1-12.1) | 11,5  (9.9-14.7) |
| PROSPER | [[4](#_ENREF_45)8] | 10000 | 13.6  (8.6-20.1) | 15.1  (10.3-25.6) |  | 69.5  (52.1-92.7) | 73.8  (56.7-97.4) |  | 12.8  (8.3-19.9) | 12.6  (8.0-19.2) |  | 7.1  (4.8-10.6) | 9.1  (5.9-14.2) |
| Leiden 85-plus | [[4](#_ENREF_46)9] | 10 | 9.6  (6.7-12.7) | 11.3  (8.5-14.7) |  | 56.9  (40.8-78.4) | 70.5  (48.6-90.5) |  | 6.2  (3.8-9.4) | 8.1  (5.1-11.6) |  | 3.4  (1.9-5.5) | 4.5  (2.3-7.6) |
| **Specific diseases** |  |  |  |  |  |  |  |  |  |  |  |  |  |
| MS-SLE | [[1](#_ENREF_11)2] | 10 | 7.2  (4.7-10.8) | 11.0  (7.7-15.3) |  | 26.2  (13.8-45.1) | 23.8  (17.2-42.4) |  | 7.0ª  (4.4-14.7) | 14.6ª  (11.2-17.1) |  | 1.9  (1.0-3.6) | 1.6  (0.8-2.8) |
| BEST | [[5](#_ENREF_50)3] | 10 | 6.2  (3.9-9.5) | 9.0  6.4-10.8) |  | 108.3 | 102.5 |  |  |  |  | 1.4  (0.6-2.9) | 1.6  (0.8-4.2) |
| Cardiac surgery | n/a | 10 | 5.8  (3.5-8.4) | 7.1  (4.3-10.0) |  | 78.6  (61.7-100.6) | 94.2  (79.1-119.2) |  |  |  |  |  |  |
| GARP | [[3](#_ENREF_33)5] | 10 | 7.6  (5.8-9.6) | 7.7  (5.9-11.7) |  |  |  |  |  |  |  | 3.0  (1.9-4.7) | 3.6  (2.4-6.7) |
| PRALINE | n/a | 10 | 6.9  (3.7-11.7) | 5.5  (2.7-14.1) |  | 108.3  (75.7-128.8) | 102.5  (79.7-139.1) |  | 3.6  (2.1-4.7) | 3.9  (1.9-9.1) |  | 10.7  (7.7-20.6) | 11.4  (9.5-20.9) |
| Ref.: Reference, LPS concentration: whole blood samples were incubated for with lipopolysaccharide for 24 hours at 37°C. n/a: not available. \* LPS was incubated for 4 hours, ∞ LPS was incubated for 6 hours, ª 1000 ng/ml LPS was used, b 50000 ng/ml LPS was used. | | | | | | | | | | | | | |

**Supplementary table 1A:** Crude cytokine production response values in men and women in the included study populations.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Name study population | Key ref. for methods |  | Cytokine production response | | | | | | | | | | |
|  | IL-1RA, pg/ml | |  | IL-10, pg/ml | |  | IFN-γ, pg/ml | |  | GM-CSF, pg/ml | |
|  | Women | Men |  | Women | Men |  | Women | Men |  | Women | Men |
| LPS, ng/ml | Median | Median |  | Median | Median |  | Median | Median |  | Median | Median |
| (IQR) | (IQR) |  | (IQR) | (IQR) |  | (IQR) | (IQR) |  | (IQR) | (IQR) |
| **General population** | |  |  |  |  |  |  |  |  |  |  |  |  |
| Myoage young | n/a | 10 | 26.6  (21.8-30.9) | 34.3  (29.5-45.5) |  | 5.2  (4.8-6.6) | 6.7  (5.2-8.6) |  | 2.4  (1.4-8.8) | 3.3  (2.4-4.8) |  | 0.13  (0.09-0.22) | 0.16  (0.09-0.28) |
| YNTR | [[9](#_ENREF_8)] | 10000 | 31.4  (24.9-38.9) | 32.9  (26.0-39.9) |  | 2.3  (1.9-3.0) | 2.2  (1.8-2.7) |  |  |  |  |  |  |
| Meningitis relatives | [[10](#_ENREF_9)] | 10 |  |  |  | 2.2  (1.6-3.1) | 2.8  (1.6-3.9) |  |  |  |  |  |  |
| MS-SLE relatives | [[1](#_ENREF_11)2] | 1000 | 17.0  (11.8-27.5) | 19.6  (12.9-29.1) |  | 1.1  (0.7-1.5) | 1.2  (0.8-1.6) |  |  |  |  |  |  |
| Ghana | [[4](#_ENREF_44)7] | 10 |  |  |  | 3.6  (2.2-4.8) | 4.1  (2.4-6.1) |  | 2.7  (1.7-3.7) | 2.6  (1.8-3.7) |  |  |  |
| ANTR | [[9](#_ENREF_8)] | 10000 | 35.4  (27.8-41.8) | 33.6  (29.0-39.3) |  | 2.1  (1.7-2.5) | 1.9  (1.5-2.6) |  |  |  |  |  |  |
| LLS | [[3](#_ENREF_31)3] | 10 | 60.4  (49.4-77.2) | 68.9  (52.5-88.8) |  | 4.3  (3.2-5.4) | 4.3  (3.2-5.7) |  | 1.7  (0.8-4.1) | 1.8  (0.6-4.7) |  | 0.15b  (0.09-0.29) | 0.11b  (0.07-0.20) |
| Myoage old | n/a | 10 | 25.4  (20.4-31.3) | 37.0  (25.7-43.8) |  | 5.0  (3.6-7.6) | 5.3  (4.0-7.2) |  | 1.6  (0.7-2.6) | 1.4  (1.0-2.7) |  | 0.09  (0.06-0.14) | 0.07  (0.04-0.09) |
| PROSPER | [[4](#_ENREF_45)8] | 10000 | 32.9  (26.4-47.0) | 37.5  (29.7-53.8) |  | 1.5  (1.0-2.2) | 1.6  (1.2-2.3) |  |  |  |  |  |  |
| Leiden 85-plus | [[4](#_ENREF_46)9] | 10 | 35.8  (26.7-44.7) | 38.9  (31.3-49.4) |  | 0.7  (0.5-1.0) | 0.8  (0.5-1.2) |  | 0.13  (0.04-0.40) | 0.14  (0.05-0.51) |  |  |  |
| **Specific diseases** | |  |  |  |  |  |  |  |  |  |  |  |  |
| MS-SLE | [[1](#_ENREF_11)2] | 10 | 19.7  (12.0-34.4) | 20.7  (13.9-30.9) |  | 1.0  (0.5-1.4) | 1.0  (0.7-1.5) |  |  |  |  |  |  |
| BEST | [[5](#_ENREF_50)3] | 10 | 25.9  (18.7-31.0) | 37.1  (28.5-50.3) |  | 0.5  (0.3-0.9) | 0.8  (0.4-1.1) |  |  |  |  |  |  |
| Cardiac surgery | n/a | 10 |  |  |  | 4.2  (3.3-5.6) | 4.6  (3.6-6.3) |  |  |  |  |  |  |
| GARP | [[3](#_ENREF_33)5] | 10 | 23.0  (18.1-28.4) | 24.8  (19.6-30.4) |  | 0.7  (0.5-1.0) | 0.8  (0.6-1.1) |  |  |  |  |  |  |
| PRALINE | n/a | 10 | 50.8  (35.5-61.0) | 45.0  (31.6-61.6) |  | 4.6  (2.8-6.1) | 4.5  (2.4-5.2) |  | 0.6  (0.2-1.6) | 1.0  (0.6-2.6) |  | 0.05  (0.03-0.09) | 0.05  (0.03-0.14) |
| Ref.: Reference, LPS concentration: whole blood samples were incubated for with lipopolysaccharide for 24 hours at 37°C. n/a: not available. \* LPS was incubated for 4 hours, ∞ LPS was incubated for 6 hours, ª 1000 ng/ml LPS was used, b 50000 ng/ml LPS was used. | | | | | | | | | | | | | |

**Supplementary table 1B**: Crude cytokine production response values in men and women in the included study populations.

**Supplementary table 2**. Pooled leukocyte concentration and differentiation in men and women of three independent study populations (Myoage young, Myoage old and LLS).

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | Men  mean (95% CI) |  | Women  mean (95% CI) |  | p-value |
| Leukocytes \*109/L | 6.08 (5.34 to 6.82) |  | 5.87 (4.89 to 6.85) |  | 0.29 |
| Neutrophils \*109/L | 3.58 (3.08 to 4.08) |  | 3.25 (2.56 to 3.94) |  | 0.008 |
| Lymphocytes \*109/L | 1.79 (1.58 to 2.00) |  | 1.99 (1.73 to 2.25) |  | <0.001 |
| Monocytes \*109/L | 0.53 (0.49 to 0.57) |  | 0.46 (0.41 to 0.50) |  | <0.001 |
| Eosinophils \*109/L | 0.15 (0.15 to 0.17) |  | 0.15 (0.13 to 0.17) |  | 0.12 |
| Basophils \*109/L | 0.03 (0.02 to 0.03) |  | 0.03 (0.02 to 0.04) |  | 0.25 |
| Estimates were calculated using a meta-analysis model with random effects and corrected for age and family relationships between subjects, CI: confidence interval. | | | | | |