**Appendix**

**Metabolomic profiling substantiates adrenal suppression due to inhaled corticosteroid therapy in asthma**

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**Supplementary Tables**

**Supplementary Table 1.** Plasma metabolites significantly associated with prevalent asthma outcome (n=35, FDR < 5.14x10-5) in discovery EPIC-Norfolk cohort.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Metabolite** | **Names from metabolon\*** | **HMDB** | **N** | **Ncase** | **se** | **p** | **or** | **or\_95l** | **or\_95h** |
| dehydroisoandrosterone sulfate (DHEA-S) |  | HMDB0001032 | 10,751 | 661 | 0.04 | 1.42E-27 | 0.65 | 0.60 | 0.70 |
| X - 21364 | possibly a steroid conjugate |  | 10,665 | 642 | 0.04 | 2.24E-22 | 0.66 | 0.61 | 0.72 |
| X - 11444 | tetrahydrocortisol glucuronide |  | 10,717 | 648 | 0.04 | 2.93E-21 | 0.68 | 0.63 | 0.74 |
| X - 12846 | retired for 11beta-hydroxyandrosterone glucuronide |  | 10,342 | 607 | 0.04 | 1.45E-20 | 0.67 | 0.62 | 0.73 |
| cortisone |  | HMDB0002802 | 10,712 | 649 | 0.04 | 7.77E-20 | 0.72 | 0.67 | 0.77 |
| Pregn steroid monosulfate |  |  | 10,751 | 660 | 0.05 | 1.56E-17 | 0.68 | 0.62 | 0.74 |
| 4-androsten-3beta,17beta-diol disulfate (2) |  | HMDB0003818 | 10,739 | 658 | 0.04 | 1.75E-17 | 0.70 | 0.65 | 0.76 |
| X - 12844 | possibly a steroid conjugate |  | 10,744 | 656 | 0.04 | 5.47E-17 | 0.73 | 0.68 | 0.78 |
| 21-hydroxypregnenolone disulfate |  | HMDB0004026 | 10,655 | 642 | 0.04 | 4.54E-16 | 0.71 | 0.65 | 0.77 |
| 4-androsten-3beta,17beta-diol monosulfate (1) |  | HMDB0003818 | 10,711 | 653 | 0.04 | 2.26E-14 | 0.71 | 0.65 | 0.78 |
| epiandrosterone sulfate |  | HMDB0000365 | 10,720 | 656 | 0.04 | 1.06E-13 | 0.74 | 0.69 | 0.80 |
| 16a-hydroxy DHEA 3-sulfate |  |  | 10,696 | 647 | 0.04 | 1.12E-13 | 0.72 | 0.66 | 0.79 |
| X - 17359 | retired for cortolone glucuronide |  | 10,382 | 615 | 0.04 | 5.63E-13 | 0.73 | 0.67 | 0.79 |
| pregnenolone sulfate |  | HMDB0000774 | 10,187 | 593 | 0.05 | 3.21E-12 | 0.73 | 0.66 | 0.79 |
| androsterone sulfate |  | HMDB0002759 | 10,741 | 661 | 0.04 | 2.15E-11 | 0.77 | 0.72 | 0.83 |
| cortisol |  | HMDB0000063 | 10,738 | 657 | 0.04 | 3.32E-11 | 0.78 | 0.72 | 0.84 |
| X - 11440 | retired for pregnenetriol disulfate |  | 10,738 | 661 | 0.04 | 8.15E-11 | 0.75 | 0.69 | 0.82 |
| X - 22379 | retired for androsterone glucuronide |  | 10,524 | 617 | 0.05 | 2.81E-10 | 0.73 | 0.66 | 0.80 |
| X - 24544 | 17-hydroxypregnenolone sulfate | HMDB0000416 | 9,580 | 547 | 0.05 | 7.44E-10 | 0.74 | 0.68 | 0.82 |
| etiocholanolone glucuronide |  | HMDB0004484 | 10,468 | 623 | 0.04 | 1.29E-09 | 0.77 | 0.71 | 0.84 |
| X - 17357 | possibly a steroid conjugate |  | 8,923 | 502 | 0.05 | 3.65E-09 | 0.76 | 0.69 | 0.83 |
| pregnen-diol disulfate |  |  | 10,754 | 661 | 0.04 | 5.43E-09 | 0.77 | 0.70 | 0.84 |
| X - 17340 | possibly a steroid conjugate |  | 9,992 | 593 | 0.05 | 6.04E-09 | 0.76 | 0.70 | 0.84 |
| 4-androsten-3alpha,17alpha-diol monosulfate (2) |  |  | 9,775 | 563 | 0.05 | 2.15E-08 | 0.77 | 0.70 | 0.84 |
| 4-androsten-3beta,17beta-diol disulfate (1) |  | HMDB0003818 | 10,750 | 660 | 0.04 | 2.66E-08 | 0.78 | 0.72 | 0.85 |
| X - 21470 | 5-androstenetriol disulfate |  | 10,099 | 581 | 0.04 | 1.51E-07 | 0.79 | 0.72 | 0.86 |
| 5alpha-pregnan-3beta,20alpha-diol monosulfate (2) |  |  | 9,551 | 547 | 0.05 | 2.98E-07 | 0.78 | 0.71 | 0.86 |
| 4-androsten-3beta,17beta-diol monosulfate (2) |  |  | 10,462 | 628 | 0.04 | 3.75E-07 | 0.80 | 0.74 | 0.87 |
| 5alpha-pregnan-3beta,20alpha-diol disulfate |  |  | 10,257 | 611 | 0.04 | 5.61E-07 | 0.80 | 0.74 | 0.87 |
| 4-androsten-3alpha,17alpha-diol monosulfate (3) |  |  | 10,675 | 647 | 0.05 | 6.48E-07 | 0.80 | 0.73 | 0.87 |
| X - 11470 | tetrahydrocorticosterone glucuronide |  | 10,069 | 589 | 0.04 | 9.95E-07 | 0.81 | 0.74 | 0.88 |
| glycosyl-N-palmitoyl-sphingosine |  |  | 10,742 | 659 | 0.04 | 7.64E-06 | 1.20 | 1.11 | 1.30 |
| X - 15492 | possibly a steroid conjugate |  | 10,612 | 635 | 0.05 | 1.49E-05 | 0.82 | 0.75 | 0.90 |
| 5alpha-androstan-3beta,17alpha-diol disulfate |  |  | 8,839 | 505 | 0.05 | 1.78E-05 | 0.81 | 0.74 | 0.89 |
| X - 24546 | 16a-hydroxy-DHEA-disulfate |  | 8,880 | 500 | 0.05 | 2.50E-05 | 0.81 | 0.73 | 0.89 |

Abbreviations: N, total number of subjects; Ncase, number of asthma cases; se, standard error, p, p-value; or, odds ratio; or\_95l, lower bound of the 95% confidence interval; or\_95h, upper bound of the 95% confidence interval. Multivariable logistic regression models were used to obtain odds ratio and p-values comparing asthma cases with controls.

**Supplementary Table 2.** Steroid metabolite associations based on logistic regression models (adjusted for confounders) between asthma cases and controls; asthma cases with ICS intake and controls; asthma cases with no ICS and controls; and asthma cases with and without ICS intake in MGBB-Asthma.

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Metabolite** | **Metabolite Subclass** | **Asthma vs. Control** | | | **Asthma ICS vs. Control** | | | **Asthma NO ICS vs. Control** | | | **Asthma ICS vs. Asthma NO ICS** | | |
| OR  (95% CI) | P-Value | FDR | OR  (95% CI) | P-Value | FDR | OR  (95% CI) | P-Value | FDR | OR  (95% CI) | P-Value | FDR |
| androstenediol (3beta,17beta) monosulfate (1) | Androgenic Steroids | 0.84 (0.79, 0.88) | 5.5x10-11 | 1.9x10-9 | 0.81 (0.77, 0.86) | 1.8x10-14 | 6.0x10-13 | 0.92 (0.86, 0.98) | 0.006 | 0.07 | 0.92 (0.86, 0.99) | 0.029 | 0.14 |
| androstenediol (3beta,17beta) disulfate (2) | Androgenic Steroids | 0.84 (0.79, 0.89) | 4.6x10-9 | 3.2x10-8 | 0.81 (0.77, 0.86) | 3.2x10-12 | 2.0x10-11 | 0.92 (0.85, 0.99) | 0.03 | 0.13 | 0.93 (0.86, 1.00) | 0.040 | 0.14 |
| androstenediol (3beta,17beta) disulfate (1) | Androgenic Steroids | 0.84 (0.80, 0.89) | 8.0x10-9 | 4.5x10-8 | 0.81 (0.77, 0.86) | 6.4x10-13 | 7.3x10-12 | 0.93 (0.87, 1.00) | 0.06 | 0.15 | 0.93 (0.86, 1.00) | 0.049 | 0.14 |
| androstenediol (3alpha, 17alpha) monosulfate (3) | Androgenic Steroids | 0.84 (0.80, 0.90) | 1.8x10-8 | 7.6x10-8 | 0.82 (0.78, 0.87) | 3.0x10-11 | 1.3x10-10 | 0.93 (0.86, 0.99) | 0.03 | 0.13 | 0.93 (0.86, 1.01) | 0.094 | 0.18 |
| androstenediol (3beta,17beta) monosulfate (2) | Androgenic Steroids | 0.85 (0.80, 0.89) | 4.5x10-10 | 7.6x10-9 | 0.84 (0.80, 0.88) | 2.0x10-11 | 9.7x10-11 | 0.91 (0.86, 0.97) | 0.003 | 0.07 | 0.95 (0.89, 1.02) | 0.186 | 0.28 |
| 5alpha-androstan-3beta,17beta-diol disulfate | Androgenic Steroids | 0.85 (0.80, 0.90) | 1.3x10-8 | 6.3x10-8 | 0.83 (0.79, 0.88) | 1.0x10-10 | 3.5x10-10 | 0.92 (0.86, 0.98) | 0.02 | 0.13 | 0.95 (0.88, 1.02) | 0.164 | 0.27 |
| epiandrosterone sulfate | Androgenic Steroids | 0.85 (0.81, 0.90) | 4.7x10-9 | 3.2x10-8 | 0.83 (0.79, 0.87) | 3.0x10-12 | 2.0x10-11 | 0.93 (0.87, 1.00) | 0.04 | 0.13 | 0.94 (0.88, 1.01) | 0.096 | 0.18 |
| dehydroisoandrosterone sulfate (DHEA-S) | Androgenic Steroids | 0.86 (0.81, 0.90) | 3.6x10-8 | 1.2x10-7 | 0.83 (0.79, 0.87) | 3.6x10-12 | 2.0x10-11 | 0.95 (0.89, 1.02) | 0.16 | 0.24 | 0.91 (0.85, 0.98) | 0.017 | 0.14 |
| androsterone sulfate | Androgenic Steroids | 0.86 (0.81, 0.91) | 1.0x10-7 | 3.2x10-7 | 0.84 (0.80, 0.89) | 3.9x10-10 | 1.1x10-9 | 0.93 (0.87, 1.00) | 0.04 | 0.14 | 0.95 (0.89, 1.03) | 0.211 | 0.29 |
| androstenediol (3alpha, 17alpha) monosulfate (2) | Androgenic Steroids | 0.87 (0.83, 0.92) | 4.2x10-7 | 1.1x10-6 | 0.84 (0.80, 0.89) | 1.3x10-10 | 3.9x10-10 | 0.95 (0.89, 1.02) | 0.13 | 0.24 | 0.93 (0.86, 0.99) | 0.033 | 0.14 |
| 5alpha-androstan-3beta,17beta-diol monosulfate (2) | Androgenic Steroids | 0.88 (0.84, 0.93) | 6.0x10-7 | 1.5x10-6 | 0.87 (0.83, 0.91) | 3.8x10-8 | 7.1x10-8 | 0.94 (0.89, 0.99) | 0.03 | 0.13 | 0.95 (0.89, 1.03) | 0.218 | 0.29 |
| androsterone glucuronide | Androgenic Steroids | 0.88 (0.84, 0.93) | 4.0x10-6 | 7.2x10-6 | 0.86 (0.82, 0.91) | 2.3x10-8 | 4.9x10-8 | 0.95 (0.90, 1.02) | 0.15 | 0.24 | 0.94 (0.87, 1.01) | 0.088 | 0.18 |
| etiocholanolone glucuronide | Androgenic Steroids | 0.88 (0.84, 0.93) | 3.5x10-7 | 9.8x10-7 | 0.86 (0.82, 0.90) | 4.3x10-10 | 1.1x10-9 | 0.95 (0.90, 1.01) | 0.10 | 0.22 | 0.94 (0.88, 1.00) | 0.058 | 0.14 |
| 5alpha-androstan-3alpha,17beta-diol monosulfate (1) | Androgenic Steroids | 0.89 (0.85, 0.93) | 9.0x10-7 | 2.1x10-6 | 0.89 (0.85, 0.93) | 4.5x10-7 | 7.7x10-7 | 0.93 (0.88, 0.98) | 0.006 | 0.07 | 0.99 (0.93, 1.05) | 0.717 | 0.78 |
| 5alpha-androstan-3beta,17alpha-diol disulfate | Androgenic Steroids | 0.90 (0.86, 0.94) | 1.8x10-6 | 3.4x10-6 | 0.89 (0.85, 0.92) | 3.5x10-8 | 7.0x10-8 | 0.96 (0.92, 1.01) | 0.12 | 0.23 | 0.95 (0.89, 1.01) | 0.129 | 0.22 |
| 5alpha-androstan-3alpha,17alpha-diol monosulfate | Androgenic Steroids | 0.90 (0.86, 0.95) | 1.3x10-4 | 1.9x10-4 | 0.88 (0.84, 0.93) | 1.8x10-6 | 2.7x10-6 | 0.98 (0.92, 1.03) | 0.39 | 0.46 | 0.95 (0.88, 1.03) | 0.209 | 0.29 |
| 5alpha-androstan-3alpha,17beta-diol disulfate | Androgenic Steroids | 0.91 (0.87, 0.95) | 1.2x10-4 | 1.9x10-4 | 0.89 (0.85, 0.93) | 1.2x10-6 | 1.8x10-6 | 0.97 (0.92,1.02) | 0.30 | 0.39 | 0.96 (0.89, 1.03) | 0.276 | 0.36 |
| 16a-hydroxy DHEA 3-sulfate | Androgenic Steroids | 0.92 (0.87, 0.97) | 0.003 | 0.005 | 0.89 (0.84, 0.94) | 8.8x10-6 | 1.3x10-5 | 1.01 (0.95, 1.07) | 0.76 | 0.78 | 0.92 (0.85, 0.99) | 0.025 | 0.14 |
| 5alpha-androstan-3alpha,17beta-diol monosulfate (2) | Androgenic Steroids | 0.93 (0.88, 1.00) | 0.04 | 0.05 | 0.91 (0.86, 0.97) | 0.007 | 0.008 | 0.98 (0.92, 1.05) | 0.64 | 0.68 | 0.92 (0.82, 1.04) | 0.185 | 0.28 |
| andro steroid monosulfate C19H28O6S (1) | Androgenic Steroids | 0.94 (0.89, 0.98) | 0.006 | 0.008 | 0.91 (0.87, 0.95) | 7.1x10-5 | 9.2x10-5 | 1.00 (0.95, 1.06) | 0.88 | 0.88 | 0.92 (0.86, 0.98) | 0.016 | 0.14 |
| pregnenediol sulfate (C21H34O5S) | Pregnenolone Steroids | 0.84 (0.79, 0.89) | 2.2x10-8 | 8.2x10-8 | 0.82 (0.77, 0.87) | 3.9x10-11 | 1.5x10-10 | 0.91 (0.85, 0.99) | 0.02 | 0.13 | 0.93 (0.85, 1.00) | 0.058 | 0.14 |
| pregnenolone sulfate | Pregnenolone Steroids | 0.85 (0.81, 0.90) | 2.6x10-9 | 3.0x10-8 | 0.82 (0.78, 0.86) | 1.4x10-13 | 2.4x10-12 | 0.93 (0.87, 0.99) | 0.02 | 0.13 | 0.93 (0.87, 1.00) | 0.043 | 0.14 |
| pregnenediol disulfate (C21H34O8S2) | Pregnenolone Steroids | 0.86 (0.81, 0.91) | 1.0x10-6 | 2.1x10-6 | 0.84 (0.79, 0.89) | 3.4x10-9 | 8.3x10-9 | 0.95 (0.88, 1.02) | 0.13 | 0.24 | 0.92 (0.85, 0.99) | 0.036 | 0.14 |
| 21-hydroxypregnenolone disulfate | Pregnenolone Steroids | 0.87 (0.83, 0.92) | 1.1x10-6 | 2.2x10-6 | 0.85 (0.81, 0.90) | 4.0x10-9 | 9.0x10-9 | 0.94 (0.88, 1.01) | 0.09 | 0.21 | 0.93 (0.87, 1.00) | 0.065 | 0.15 |
| 17alpha-hydroxypregnenolone 3-sulfate | Pregnenolone Steroids | 0.92 (0.87, 0.97) | 1.4x10-3 | 2.0x10-3 | 0.89 (0.84, 0.94) | 2.2x10-5 | 3.0x10-5 | 0.98 (0.93, 1.04) | 0.48 | 0.54 | 0.89 (0.82, 0.98) | 0.012 | 0.14 |
| cortisone | Corticosteroids | 0.89 (0.83, 0.94) | 5.8x10-5 | 9.8x10-5 | 0.86 (0.81, 0.91) | 8.3x10-8 | 1.5x10-7 | 0.95 (0.87, 1.04) | 0.28 | 0.39 | 0.93 (0.86, 1.00) | 0.039 | 0.14 |
| cortisol | Corticosteroids | 0.89 (0.84, 0.95) | 4.0x10-4 | 6.0x10-4 | 0.86 (0.81, 0.91) | 5.9x10-7 | 9.5x10-7 | 0.97 (0.90, 1.06) | 0.53 | 0.59 | 0.92 (0.85, 0.99) | 0.036 | 0.14 |
| pregnanediol-3-glucuronide | Progestin Steroids | 0.95 (0.90, 0.99) | 0.02 | 0.03 | 0.94 (0.90, 0.99) | 0.02 | 0.02 | 0.97 (0.91, 1.03) | 0.27 | 0.38 | 0.97 (0.91, 1.03) | 0.294 | 0.37 |
| 5alpha-pregnan-3beta,20beta-diol monosulfate (1) | Progestin Steroids | 0.95 (0.90, 0.99) | 0.02 | 0.03 | 0.95 (0.91, 1.00) | 0.04 | 0.05 | 0.96 (0.90, 1.01) | 0.14 | 0.24 | 0.98 (0.92, 1.04) | 0.568 | 0.65 |
| 5alpha-pregnan-diol disulfate | Progestin Steroids | 0.96 (0.92, 1.00) | 0.06 | 0.07 | 0.98 (0.94, 1.02) | 0.22 | 0.25 | 0.96 (0.92, 1.00) | 0.07 | 0.17 | 1.01 (0.96, 1.07) | 0.721 | 0.78 |
| 5alpha-pregnan-3beta,20alpha-diol disulfate | Progestin Steroids | 0.96 (0.92, 1.01) | 0.14 | 0.15 | 0.97 (0.93, 1.02) | 0.21 | 0.23 | 0.97 (0.92, 1.03) | 0.33 | 0.40 | 0.99 (0.94, 1.06) | 0.828 | 0.83 |
| pregnanolone/allopregnanolone sulfate | Progestin Steroids | 0.97 (0.92, 1.01) | 0.13 | 0.15 | 0.98 (0.94, 1.03) | 0.44 | 0.44 | 0.95 (0.90, 1.00) | 0.06 | 0.15 | 1.01 (0.95, 1.07) | 0.770 | 0.80 |
| 5alpha-pregnan-3beta,20alpha-diol monosulfate (2) | Progestin Steroids | 0.97 (0.93, 1.02) | 0.19 | 0.19 | 0.97 (0.93, 1.02) | 0.25 | 0.27 | 0.97 (0.92, 1.03) | 0.32 | 0.40 | 0.99 (0.94, 1.05) | 0.779 | 0.80 |
| 5alpha-pregnan-3beta-ol,20-one sulfate | Progestin Steroids | 1.00 (0.95, 1.06) | 0.93 | 0.93 | 1.03 (0.98, 1.08) | 0.33 | 0.34 | 0.96 (0.91, 1.02) | 0.21 | 0.32 | 1.03 (0.97, 1.11) | 0.326 | 0.40 |

Abbreviations: ICS, Inhaled Corticosteroid Use; OR, odds ratio; CI, confidence interval; FDR, false discovery rate. Multivariable logistic regression models using pairwise comparisons were used to obtain odds ratio and p-values comparing metabolite levels between groups. To control for confounding due to asthma severity, the analysis comparing asthma cases with and without ICS treatment was adjusted for asthma severity and oral corticosteroid use (OCS) in the past year in addition to other covariates.

**Supplementary Table 3.** Metabolite-ICS associations for the replicated metabolites cortisol and cortisone in CAMP data

|  |  |  |
| --- | --- | --- |
| **Models for ICS intake as predictor and metabolite levels as outcome (metabolite~ICS intake)** | **Estimate (95% CI)** | **P-valueadj** |
| **Cortisol** |  |  |
| Base model | -0.87 (-1.50, -0.24) | 6.8e-03 |
| Base model + FEV1 | -0.86 (-1.50, -0.23) | 7.5e-03 |
| Base model + Cumulative hospitalizations | -0.87 (-1.51, -0.24) | 6.7e-03 |
| Base model + emergency room visits | -0.88 (-1.51, -0.25) | 6.3e-03 |
| Base model + total eosinophils | -0.78 (-1.42, -0.15) | 0.02 |
| Base model + total IgE | -0.88 (-1.52, -0.25) | 6.4e-03 |
| Base model + FEV1 + Cumulative hospitalizations + emergency room visits + total eosinophils + total IgE | -0.79 (-1.43, -0.15) | 0.02 |
| **Cortisone** |  |  |
| Base model | -0.60 (-1.20, -0.01) | 0.04 |
| Base model + FEV1 | -0.59 (-1.19, -0.0001) | 0.05 |
| Base model + Cumulative hospitalizations | -0.61 (-1.20, -0.02) | 0.04 |
| Base model + emergency room visits | -0.62 (-1.22, -0.03) | 0.04 |
| Base model + total eosinophils | -0.54 (-1.14, 0.06) | 0.079 |
| Base model + total IgE | -0.61 (-1.20, -0.01) | 0.045 |
| Base model + FEV1 + Cumulative hospitalizations + emergency room visits + total eosinophils + total IgE | -0.53 (-1.13, 0.07) | 0.08 |

Multivariable linear regression models were used adjusted for age, gender, race, BMI, and an interaction variable between age and randomized ICS-use for the end of the trial model. These covariates were included in the base model. Base model was further evaluated for robustness after adjusting for additional asthma severity confounders both individually and in combination: FEV1, cumulative hospitalizations, emergency room visits, total eosinophils and total IgE.

Abbreviations: CI: confidence interval; IgE: Immunoglobulin E; CAMP: Childhood Asthma Management Program

**Supplementary Table 4.** Mass General Brigham Biobank (MGBB), electronic medical health record (EMR) data on clinical symptoms of adrenal insufficiency (AI) in mild asthma cases in the presence and absence of ICS use.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Clinical symptoms | Absence of ICS (n=200) # | Presence of ICS (n=555) # | OR (95% CI) | P-valueadj\* |
| Fatigue, n (%) |  |  | 2.27 (1.61, 3.22) | 3.2e-06 |
| Presence | 70 (35.0) | 316 (56.9) |  |  |
| Absence | 130 (65.0) | 239 (43.1) |  |  |
| Weight loss, n (%) |  |  | 1.41 (0.88, 2.31) | 0.16 |
| Presence | 26 (13.0) | 100 (18.0) |  |  |
| Absence | 174 (87.0) | 455 (82.0) |  |  |
| Hyperpigmentation, n (%) |  |  | 1.07 (0.64, 1.87) | 0.79 |
| Presence | 21 (10.5) | 75 (13.5) |  |  |
| Absence | 179 (89.5) | 480 (86.5) |  |  |
| Anemia, n (%) |  |  | 2.28 (1.57, 3.35) | 2.0e-05 |
| Presence | 50 (25.0) | 240 (43.2) |  |  |
| Absence | 150 (75.0) | 315 (56.8) |  |  |

\*P-valueadj: Adjusted P-values. For the adjusted analysis, a logistic regression model was used for clinical symptoms (Fatigue, weight loss, hyperpigmentation and anemia) with a binary outcome of presence and absence and linear regression model was used for continuous outcomes (quantitative measure of ICS prescriptions) adjusted for age, sex (male and female), race (African Americans, Hispanics, Asian and Others), body mass index (BMI), smoking (former and current) and severity scale. Presence of ICS intake was defined for subjects taking four or more prescriptions and absence of ICS was defined for subjects with no ICS prescriptions. Subjects with prescription counts of 1-3 were removed from the analysis to avoid any chance of misclassification in this analysis. These results were even more robust at 10 or more prescriptions, however led to removal of many subjects therefore have not been shown here. #All these individuals had been tested for adrenal insufficiency within the last five years and had information available on the reported clinical symptoms in this table.

**Supplementary Table 5.** Distribution of metabolites in MGBB-Asthma by platform and by super-pathway (n=904)

|  |  |  |
| --- | --- | --- |
| Platform | n | % |
| LC/MS Neg | 508 | 56.2 |
| LC/MS Polar | 83 | 11.9 |
| LC/MS Pos Early | 242 | 2.7 |
| LC/MS Pos Late | 71 | 19.7 |
|  |  |  |
| Super-pathway | n | % |
| Lipid | 184 | 20.4 |
| Xenobiotics | 108 | 11.9 |
| Carbohydrate | 24 | 2.7 |
| Amino Acid | 178 | 19.7 |
| Cofactors and Vitamins | 29 | 3.2 |
| Nucleotide | 31 | 3.4 |
| Energy | 9 | 1 |
| Peptide | 29 | 3.2 |
| Partially Characterized molecules | 3 | 0.3 |
| Unannotated metabolites | 309 | 34.2 |

**Supplementary Table 6.** Inclusion and exclusion definitions and data dictionary for asthma and asthma medications from Mass General Brigham Biobank electronic medical health record (MGBB EMR) data. Since the data in biobank is dynamic, the data download was restricted till March 24, 2020 (the date at the time of last pull for final analysis)

|  |  |  |
| --- | --- | --- |
| **Diagnosis/Medications** | **Folder one level up in MGBB** | **International Classification of Diseases (ICD)-9 and ICD-10 codes where applicable/available** |
| Asthma - current or past history (custom PPV) [>= 0.80PPV] | Asthma (AST) | NA |
| Asthma - current or past history (PPV 0.90) | Asthma (AST) | NA |
| Asthma - no history (NPV 0.99) | Asthma (AST) | Absence of J45 |
| Plasma | Biobank Sample Types | NA |
| Asthma | Chronic lower respiratory diseases (J40-J47) | J45 |
| Chronic obstructive pulmonary disease with (acute) exacerbation | Other chronic obstructive pulmonary disease | J44.1 |
| Prednisone | Glucocorticoids | RXNORM:8640 |
| Methylprednisolone | Glucocorticoids | RXNORM:6902 |
| Dexamethasone | Glucocorticoids | RXNORM:3264 |
| Dexamethasone | Anti-inflammatories, inhalation | RXNORM:3264 |
| Ipratropium | Bronchodilators, anticholinergic | RXNORM:7213 |
| Tiotropium | Bronchodilators, anticholinergic | RXNORM:69120 |
| Omalizumab | Immune Suppressants | RXNORM:302379 |
| Beclomethasone dipropionate | Anti-inflammatories, inhalation | RXNORM:1348 |
| Triamcinolone | Glucocorticoids | RXNORM:10759 |
| Triamcinolone | Anti-inflammatories, inhalation | RXNORM:10759 |
| Fluticasone | Anti-inflammatories, inhalation | RXNORM:41126 |
| Budesonide | Glucocorticoids | RXNORM:19831 |
| Budesonide | Anti-inflammatories, inhalation | RXNORM:19831 |
| Mometasone | Anti-inflammatories, inhalation | RXNORM:108118 |
| Ciclesonide | Anti-inflammatories, inhalation | RXNORM:274964 |
| Flunisolide | Anti-inflammatories, inhalation | RXNORM:25120 |
| Fluticasone/salmeterol | Antiasthma, other | RXNORM:284635 |
| Budesonide/formoterol | Antiasthma, other | RXNORM:389132 |
| Formoterol/mometasone | Antiasthma, other | RXNORM:1002293 |
| Fluticasone/vilanterol | Antiasthma, other | RXNORM:1424888 |
| Montelukast | Antiasthma, other | RXNORM:88249 |
| Zafirlukast | Antiasthma, other | RXNORM:114970 |
| Zileuton | Antiasthma, other | RXNORM:40575 |
| Albuterol | Bronchodilators, sympathomimetic, inhalation | RXNORM:435 |
| Albuterol | Bronchodilators, sympathomimetic, oral | RXNORM:435 |
| Levalbuterol | Bronchodilators, sympathomimetic, inhalation | RXNORM:237159 |
| Ipratropium/albuterol 3ml | Antiasthma, antileukotrienes | B00913606 |
| Albuterol/ipratropium | Antiasthma, other | RXNORM:214199 |