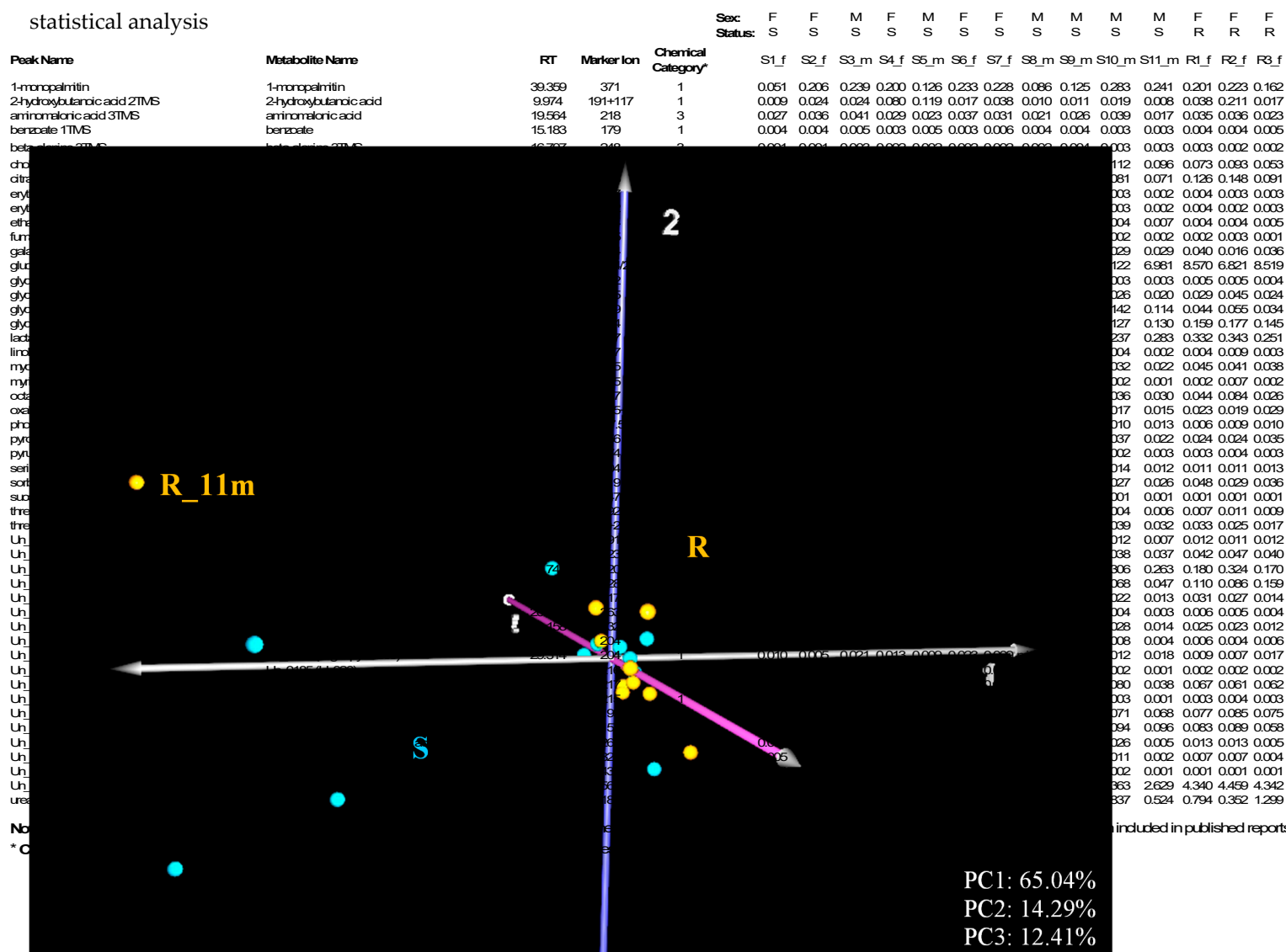

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Supplementary Table 1: The normalized blood plasma metabolomic dataset of the 22 participants used in multivariate statistical analysis

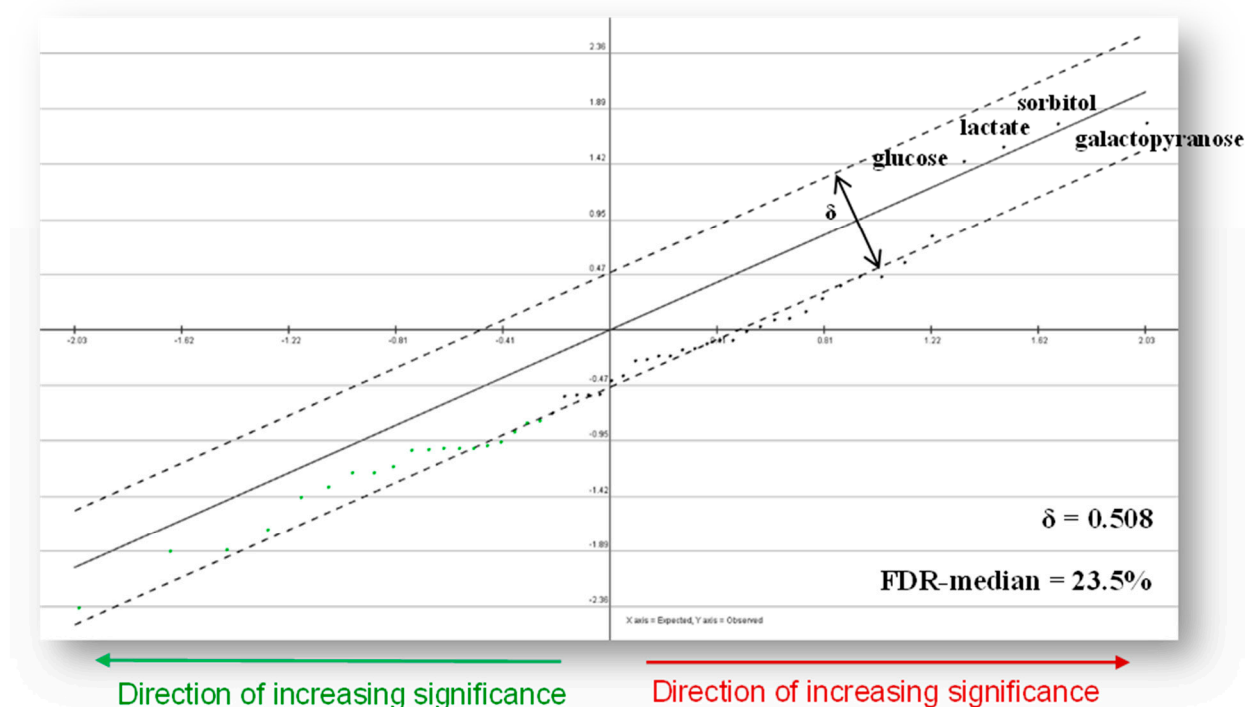


Supplementary Figure 1: The PCA graph of the metabolomic dataset of all 22 samples. The profile of the glucocorticoid resistant participant 11 (male; R_11m) exhibits a substantially different metabolic profile from all other samples (see also Suppl. Table 1) and has been excluded from further analysis. R (yellow) and S (light blue) depict, respectively, the plasma metabolic profiles of the glucocorticoid resistant and glucocorticoid sensitive participants.

Supplementary Table 2: Clinical characteristics, biochemical and endocrinological parameters of the most glucocorticoid sensitive (S) and most glucocorticoid resistant (R), in the absence of R11_m, healthy subjects one month after the very-low dexamethasone suppression test.

	Glucocorticoid Sensitive (S), n=11	Glucocorticoid Resistant (R) but R11_m, n=10	<i>p-value</i>
Age (years)	25.3 ± 3.9	27.5 ± 6.7	0.478
Weight (kg)	62.8 ± 12.3	60.5 ± 12.9	0.646
Height (cm)	1.7 ± 0.1	1.7 ± 0.1	0.276
BMI (kg/m ²)	21.1 ± 2.0	21.6 ± 2.5	0.944
25-Hydroxy-Vitamin D (ng/mL)	16.0 ± 7.9	13.1 ± 5.3	0.652
ACTH (pg/mL)	33.2 ± 18.8	27.4 ± 16.3	0.459
Androstenedione (ng/mL)	2.9 ± 0.9	3.2 ± 1.2	0.748
Anti-TG (IU/mL)	20 ± 0.0	20 ± 0.0	0.999
Anti-TPO (IU/mL)	10.4 ± 0.7	11.1 ± 2.6	0.652
ApoA1 (mg/dl)	158.4 ± 8.0	167.6 ± 15.0	0.237
ApoB (mg/dl)	75.5 ± 14.4	71.4 ± 7.7	0.515
Total Cholesterol (mg/dl)	157.4 ± 16.9	156. ± 15.0	0.965
Cortisol (nmol/L)	664.2 ± 148.5	502.6 ± 286.0	0.270
DHEAS (µg/dL)	238.6 ± 146.0	264.6 ± 107.6	0.308
E2 (pg/mL)	103.0 ± 106.4	63.3 ± 78.1	0.857
FSH (mUI/mL)	5.2 ± 2.7	4.0 ± 2.3	0.246
FT4 (ng/dL)	1.1 ± 0.1	1.1 ± 0.1	0.484
Glucose (mg/dl)	73.2 ± 6.3	74.7 ± 13.6	0.965
HDL (mg/dl)	49.5 ± 7.0	52.9 ± 8.1	0.315
IGFBP-3 (µg/mL)	5.3 ± 1.0	5.1 ± 1.3	0.418
IGF-I (ng/mL)	259.2 ± 79.5	256.5 ± 68.1	0.857
Insulin (µUI/mL)	6.7 ± 2.7	14.3 ± 14.6	0.114
LDL (mg/dl)	90.7 ± 17.8	87.6 ± 13.5	0.762
LH (mUI/mL)	10.1 ± 14.9	6.4 ± 2.3	0.802
Lpa (mg/dl)	21.8 ± 37.4	25.8 ± 27.3	0.460
Prolactin (ng/mL)	24.9 ± 8.8	22.6 ± 8.8	0.275
PTH (pg/mL)	34.1 ± 15.2	38.9 ± 18.8	0.548
SHBG (nmol/L)	65.1 ± 27.9	45.5 ± 16.2	0.173
T3 (ng/dL)	102.3 ± 27.6	98.4 ± 21.8	1
Testosterone (ng/dL)	187.8 ± 231.6	292.2 ± 280.8	0.478
Triglycerides (mg/dl)	69.4 ± 30.0	74.2 ± 16	0.315
TSH (µUI/mL)	2.8 ± 0.9	2.1 ± 1.1	0.131

Note: The parameters for the two groups are expressed as mean ± SD.



Supplementary Fig. 2: The SAM curve of the metabolic profile data of the S (Group B) compared to the R (Group A) groups. Each point corresponds to a particular metabolite. The axes of the graph correspond to the observed (y axis) and the expected (x axis) values calculated by the method for the analyzed metabolites; the expected value refers to the case in which the difference in the metabolite abundance between the two compared groups would have been based only on random error. The dashed lines define the strictest threshold of significance δ for which significant metabolites were obtained in this study; FDR (median) depicts the false discovery rate (%) for the particular δ . If the difference between the measured and the expected value for a metabolite concentration is in absolute value larger than δ , then if it is positive or negative, this metabolite is, respectively, identified of significantly higher (red) or lower (green) concentration in the S compared to the R group. The further a significant metabolite is from the origin (0,0) of the graph, the higher the statistical significance of the metabolite. The list of the negatively significant metabolites depicted as green points in this figure is shown in Table 3 in decreasing significance. Here indicated are the four metabolites, which exhibit higher abundance in the S compared to the R groups, but are just below the positive significance threshold. Finally, the negative intercept of the SAM curve indicates an overall lower abundance of all 50 analyzed metabolites in the S compared to the R group.