Metabolic fingerprint of serum in first trimester of healthy pregnancy permits the prediction of macrosomia

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INTRODUCTION: Macrosomia is associated with pregnancy complications and is suggested to predict child's and mother's health. High birth weight (>4,000 g) has been associated to the risk of several major chronic diseases in future life including diabetes, cardiovascular disease or cancer. Additionally delivery of a large baby carries a risk of perinatal complications. The aim of this study was to obtain serum fingerprints of healthy pregnant women to identify early biomarkers of macrosomia and to understand the mechanisms leading to abnormal fetal growth not related to mother's BMI or presence of GDM.

MATERIALS & METHODS: Study was performed on serum samples collected at 12th-14th gestational week from 48 pregnant women (20 with high (HBW) and 28 with normal (NBW) birth weight). Samples were fingerprinted by LC-QTOF-MS and level of adipocyte fatty acid binding protein (A-FABP) enzyme in each sample was measured with ELISA kit. Statistical analysis was performed to find differences between metabolic profiles of women who deliver NBW or HBW neonates. Metabolites were also correlated with the level of A-FABP and birth weight.

QTOF 6540

Data analysis:
Feature finding - Mass Hunter Qualitative Analysis B.06.00 (Agilent).
Alignment and data filtering – Mass Profiler Professional 12.1 (Agilent).
Univariate analysis (t-test) - Excel (Microsoft) - p-value≤ 0.05. ±
Multivariate analysis (S-plot, PLS-DA model) – Simca 13.0 (Umetrics).

LC-MS parameters:
Column: Zorbax Extended-C18
Rapid Res., 2.1 × 50 mm, 1.8 μm;
column temperature: 60°C,
flow rate: 0.6 ml/min, inj. vol.: 0.5 μl,
scan range: 50 - 1000 m/z, capillary voltage: 3000 V

Identification:
Identification of significant compounds was performed by LC-MS/MS analysis using QTOF 6540. Experiments were repeated with chromatographic conditions identical to the primary analysis. Ions were targeted for CID fragmentation on the fly based on the previously determined accurate mass and retention time. Accurate mass data and isotopic distributions for the precursor and product ions were compared to spectral data of reference compounds available in public databases (METLIN, LIPIDMAPS).

RESULTS

Figure 1. PLS-DA score plots of the serum fingerprints of pregnant women.

ESI (+) $R^2=0.883$, $Q^2=0.505$

ESI (-) $R^2=0.931$, $Q^2=0.536$
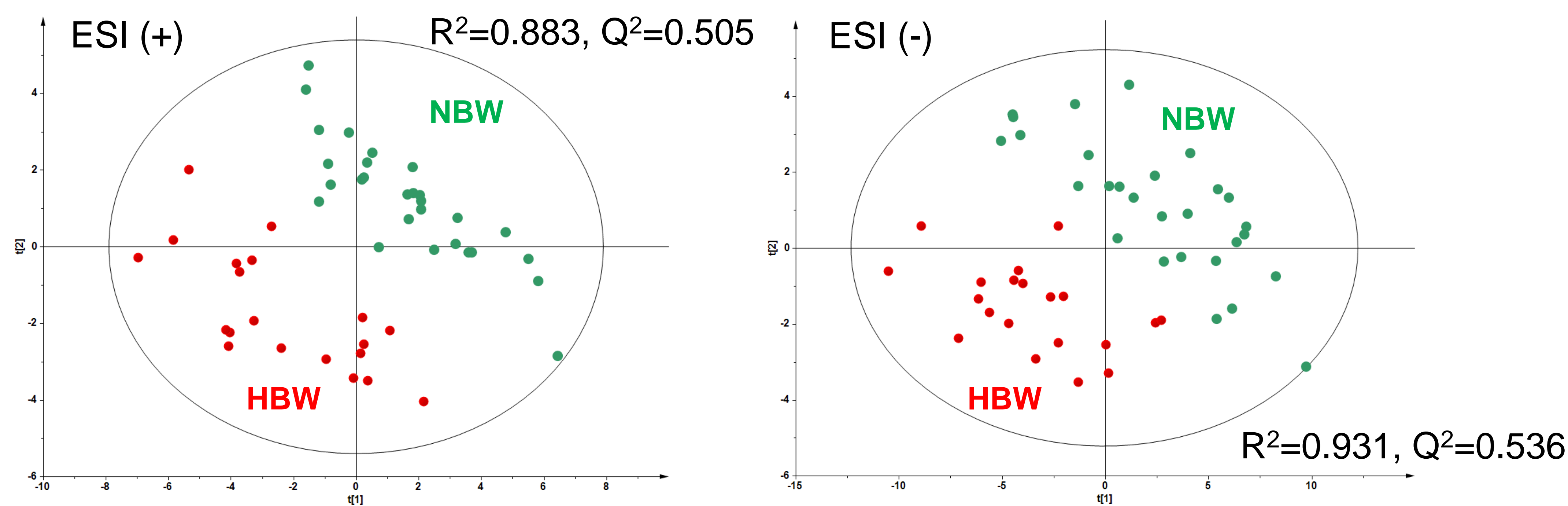
Figure 2. A-FABP level in serum of mothers in relation to newborn birth weight.
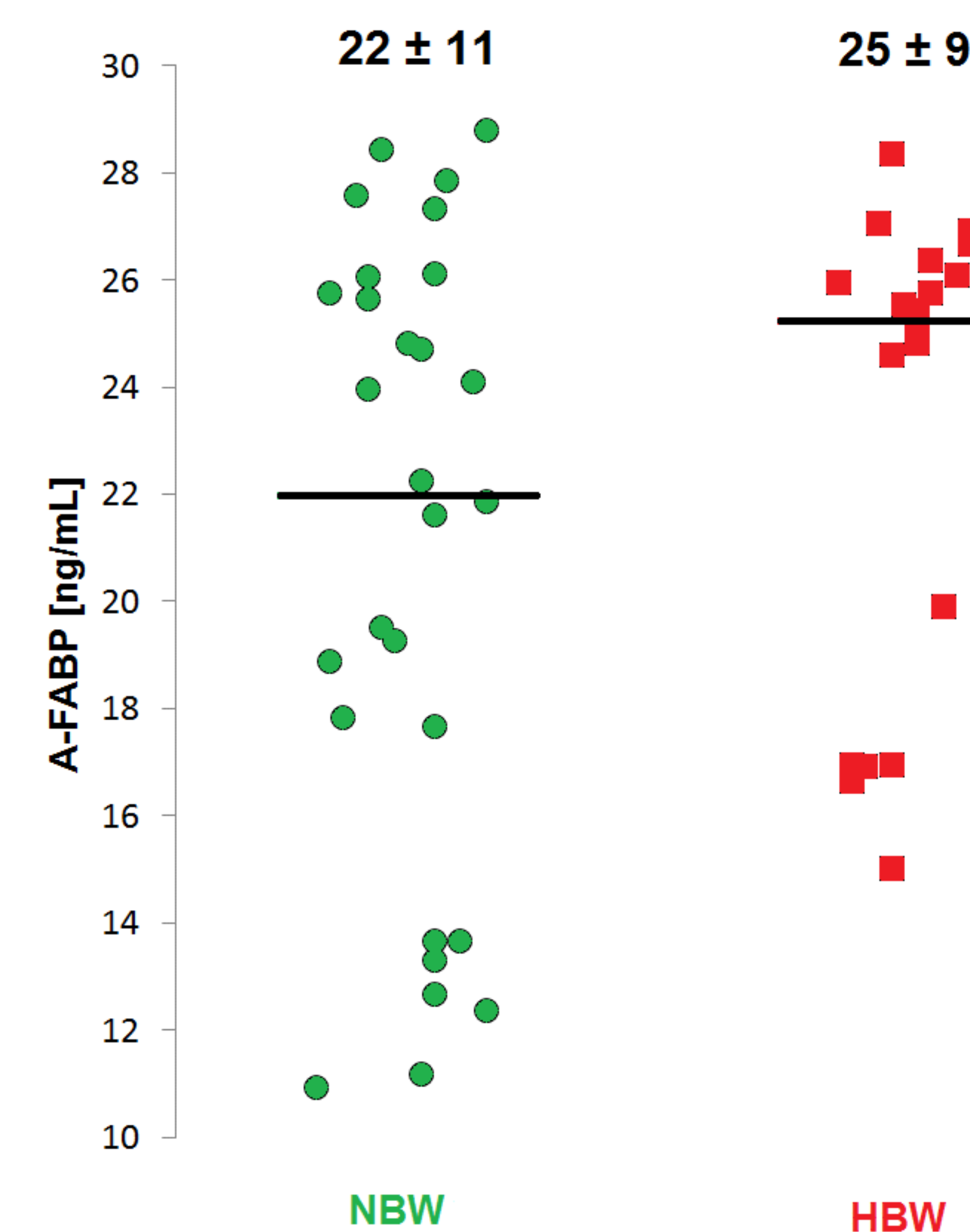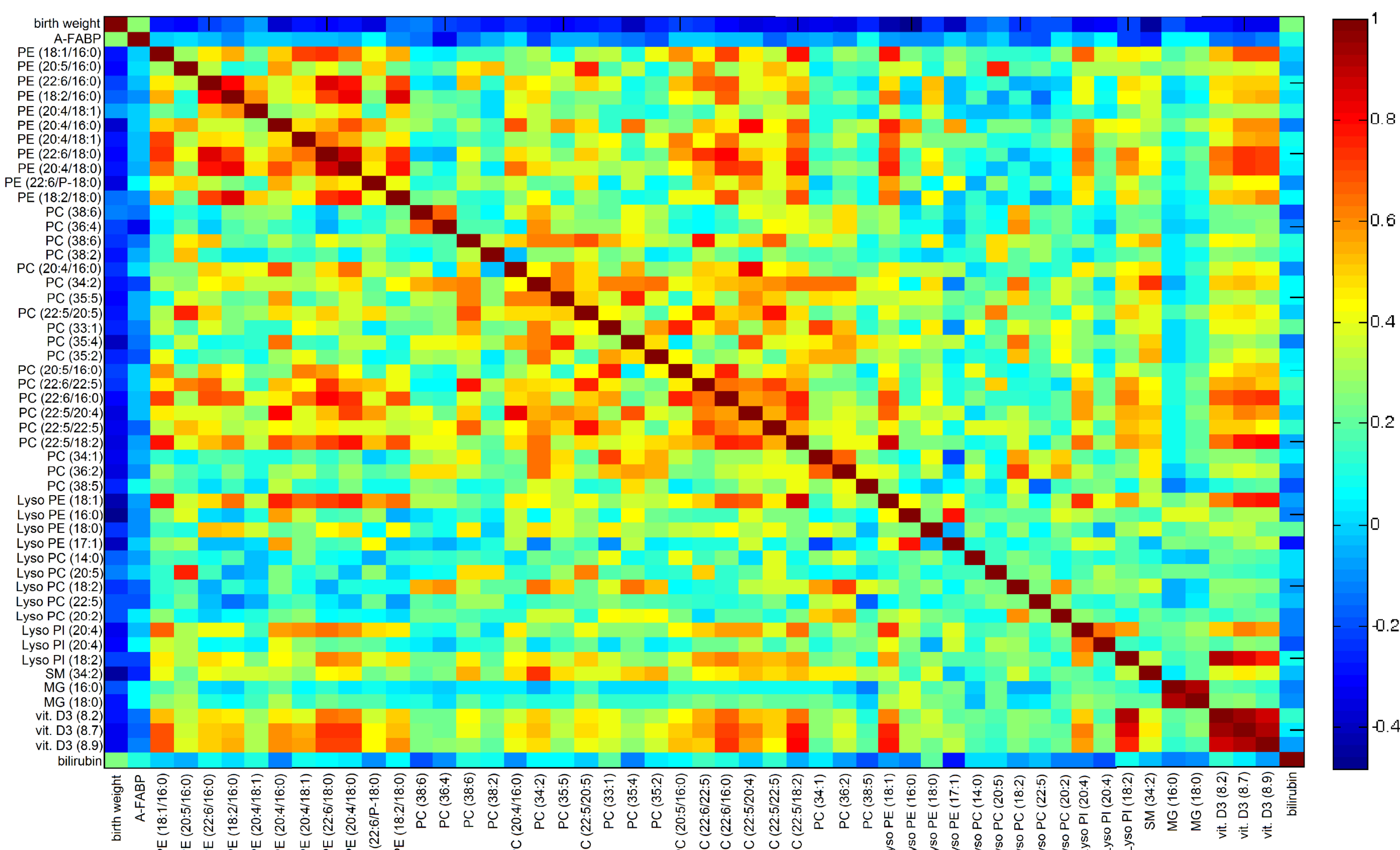

22 ± 11   25 ± 9

Figure 3. Heat-map matrix of correlations of metabolites, A-FABP level and newborn's birth weight

CONCLUSIONS

Fetal macrosomia at delivery was found to be associated to:
➤ low levels of lysophospholipids and phospholipids,
➤ low level of monoacylglycerols,
➤ low level of vitamin D3 metabolites,
➤ high level of bilirubin,
➤ high level of A-FABP.

A-FABP in the serum of the mother is positively correlated with the birth weight of the neonate and negatively correlated with the level of serum lipids. Enhanced transport of lipids by A-FABP from the mother to the fetus could provoke negative effects on fetal pancreatic β-cells being responsible for future diabetes development in individuals with high birth weight.