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Validated predictive risk analyses for neonatal brain injury before birth

Dear Editor.

Neonatal cerebral hemorrhage and white matter damage condition psychomotor development and educational success during childhood and adolescence [1]. Prediction of neonatal brain damage before birth would therefore enhance risk stratification of clinical management to ameliorate or prevent harm, helps with patient counselling, and would allow for precautionary cord blood banking for potential stem cell treatment of the newborn infant [2]. We therefore set out to calculate a weighted pregnancy risk score (the sum of odds ratios) based on odds ratios to quantify the adverse effects of risk factors on overall *predicted* psychomotor development using a large prospective cranial ultrasound screening database (n = 5,301) and validation cohort(n = 508,926) and related the weighted pregnancy risk score to *predicted* brain damage [1].

A prospective cranial ultrasound screening(CUS) study was carried out in a level III perinatal center on 5,301 live-born babies with complete records (1984–1988, analysed in 2024) at discharge of the mother after 5–8 days [1]. All neonates(51.0 % male) underwent CUS to detect cerebral hemorrhage and/or white matter damage. In a previous study, we established that growth variables and obstetrical risk factors predict overall psychomotor development at 4 years of preschool age [1]. We now explored the capacity of weighted pregnancy risk factors to predict neonatal brain damage *before* birth. Standard statistical methods, stepwise multiple regression analysis, ANOVA, ROC curve analysis, and a validation procedure (as follows) were used. The predictive risk analyses for neonatal brain injury *before* birth were validated by relating the Pregnancy risk score to the Morphometric vitality index at birth, combining hard growth variables with Apgar score at 10 mins (cMVI = [zWeight + zLength + zHead circumference + zWeight/Length + zApgar_10]/5) in the prospective Cranial ultrasound screening (CUS) database (n = 5,301) and a validation cohort derived from a population based National survey (Perinatalerhebung) from various german counties (n = 508,926).

The comparison revealed that the relations between these variables were similar:

CUS: cMVI = 0.297–0.041*pregnancy risk score, SE estimate 0.001, r = 0.743, n = 5,246, P < 0.001.

National survey: cMVI = 0.158–0.036*pregnancy risk score, SE estimate 0.000, r = 0.479, n = 502,993, P < 0.001.

The study was approved by the local institutional review board. This report follows the STROBE reporting guideline for observational studies.

There were 278/5,301(5.2 %) neonates presenting cerebral hemorrhage and/or white matter damage, and in 2,479/5,301(46.8 %) of the pregnancies at least one risk factor was documented. The odds ratios related to the risk factors varied depending on their adverse effects on *predicted* overall psychomotor development at 4.3(SD 0.8) of age between 1.10 for sex and 42.73 for preterm birth < = 36 weeks gestation [1]. The mean pregnancy risk score, i.e., the sum of odds ratios from all documented risk factors, was 7. 3(SD 16.0), range 0–85.4, n = 5,267 and 15.5(SD 20.4), range 1.1–85.4, n = 2,479 for the entire and risk cohort, respectively. The mean *predicted* brain damage was 0.06(SD 0.09), range −0.08–0.75, n = 5,298.

The key result is that neonatal brain damage *predicted before* birth correlates closely with the weighted pregnancy risk score (r = 0.796, n = 5,266, P < 0.001)(Fig. 1). The Receiver operating characteristics (ROC) of Predicted brain damage vs Pregnancy risk score revealed a sensitivity of 84.1 % at a specificity of 65.9 %, AUC 0.831, n = 5,301(P < 0.001), and a positive predictive value (PPV) of 79.4 % and negative predictive value (NPV) of 72.3 %, respectively(Fig. 2).

This prospective study first demonstrates in 5,301 newborns with complete obstetrical records that weighted pregnancy risk scores bear predictive capacity for brain damage in newborn infants *before* birth [1, 3]. The prediction of brain damage *before* birth is important clinically to enhance risk stratification for a timely gentle and safe delivery, helps with patient counselling regarding preventive early intervention strategies, and provides the opportunity for precautionary cord blood banking as a basis for potential stem cell treatments in the newborn period to ameliorate brain damage [4,5]. This will improve childhood psychomotor development in the long term. To ease introduction of this novel methodology into clinical practice, a smartphone application as been developed (https://www.brainprotect.de).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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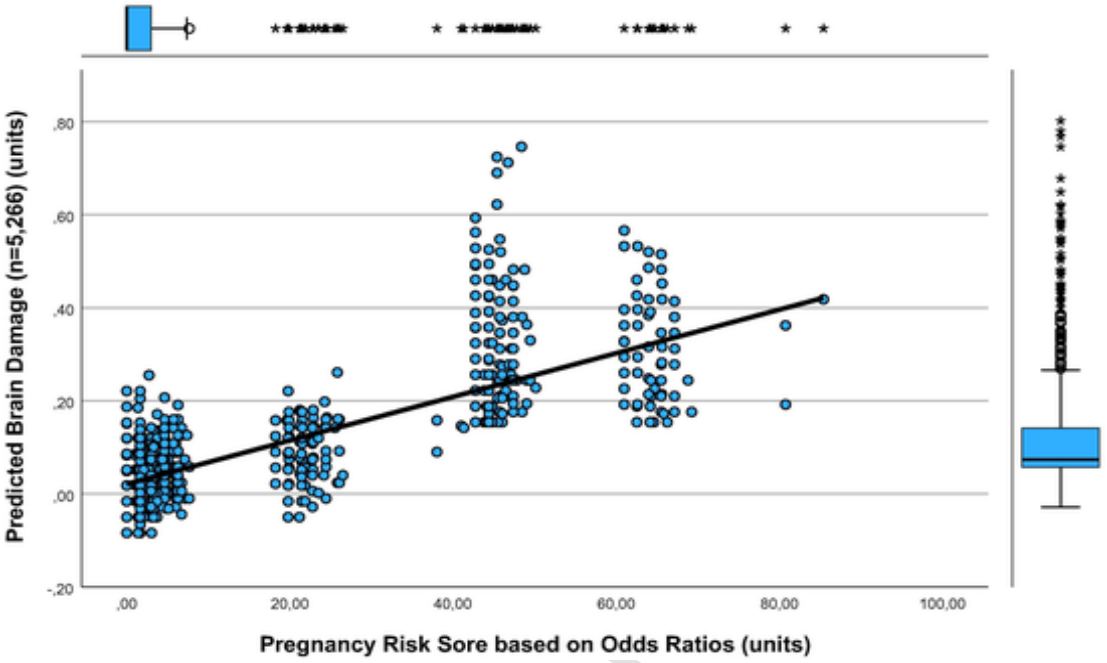

Fig. 1. Relation between *predicted* Brain damage and Pregnancy risk score The correlation between *predicted* Brain damage and Pregnancy risk score in 5,301 newborns is depicted [1] (Brain damage = 0.021 + 0.005*pregnancy risk score, SE estimate 0.000, r = 0.80, n = 5,266, P < 0.001). Stepwise multiple regression analysis with documented neonatal brain damage, i.e., cerebral hemorrhage and/or white matter damage, as dependent variable was used to determine the predictors (Brain damage = 1.38–0.034*gestational age + 0.038*multiples + 0.022*cardiotocogram pathologic + 0.264*amnion infection + 0.065*maternal fever > 38 °C + 0.018*prolonged or arrested labor + 0.135*malformation, r = 0.426, n = 5,095, P < 0.001). The individual overall pregnancy risk score was generated by addition of each documented risk factor multiplied by the respective odds ratio for adverse overall *predicted* (*p*) psychomotor development (*p*Total psychomotor development score = (*p*Intelligence quotient + *p*Porteus maze test + *p*Neurological examination optimality score)/3)) at 4.3 (SD 0.8) years of age [1]. The rational for using odds ratios calculated to quantify the adverse effects of pregnancy risk factors on the overall psychomotor development resides in the fact that beyond sonographically visible brain damage like hemorrhage and white matter damage, there are microstructural changes during growth restriction not visible by cranial ultrasound resulting in poor neurocognitive performance [3,5]. This invisible burden of brain damage has been accounted for by the weighted score.

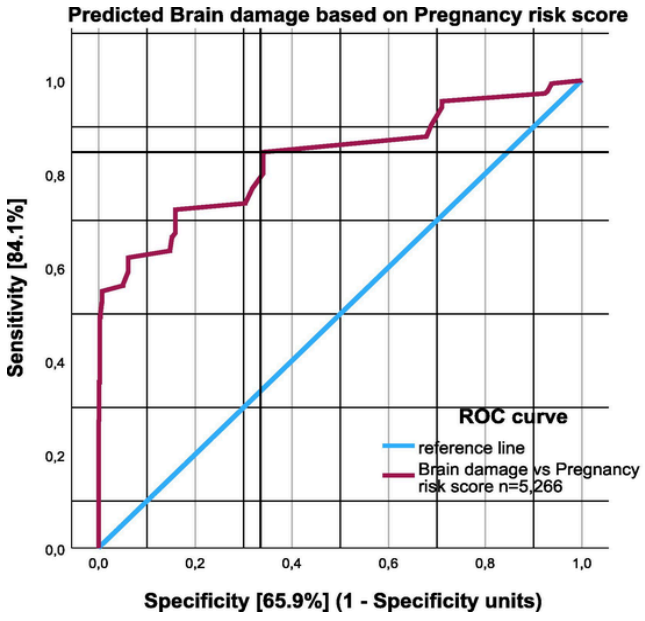

Fig. 2. Receiver operating characteristics of *predicted* Brain damage vs. Pregnancy risk score (ROC curve analysis) Using the weighted Pregnancy risk score to detect Brain damage *before* birth, the sensitivity and specificity yielded 84.1 % and 65.9 %, respectively (n = 5,266, P > 0.001). The positive predictive value (PPV) and the negative predicted value (NPV) were 79.4 % and 72.3 %, respectively. Thus, neonatal brain damage can be predicted *before* birth with substantial certainty using weighted pregnancy risk scores as a solid basis for the decision to bank cord blood for potential stem cell treatment in the newborn to improve neurocognition [4].

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