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Integration of suboptimal health status evaluation as a criterion for prediction of preeclampsia is strongly recommended for healthcare management in pregnancy: A prospective cohort study in a Ghanaian population

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1 **Title page**

2 **Integration of Suboptimal Health Status evaluation as a criterion for prediction of**

3 **preeclampsia is strongly recommended for healthcare management in pregnancy: a**

4 **prospective cohort study in a Ghanaian population**

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Abstract

Background: Normotensive pregnancy may develop into preeclampsia (PE) and other adverse pregnancy complications (APCs), for which the causes are still unknown. Suboptimal Health Status (SHS), a physical state between health and disease, might contribute to the development and progression of PE. By integration of a routine health measure in this Ghanaian Suboptimal Health Cohort Study, we explored the usefulness of a 25-question item SHS questionnaire (SHSQ-25) for early screening and prediction of normotensive pregnant women (NTN-PW) likely to develop PE.

Methods: We assessed the overall health status among a cohort of 593 NTN-PW at baseline (10-20 weeks gestation) and followed them at 21-31 weeks until 32-42 weeks. After an average of 20 weeks follow-up, 498 participants returned and were included in the final analysis. Haematobiochemical, clinical, and socio-demographic data were obtained.

Results: Of the 498 participants, 49.8% (248/498) had 'high SHS' at baseline [61.7% (153/248) later developed PE] and 38.3% (95/248) were NTN-PW whereas 50.2% (250/498) had 'optimal health' [17.6% (44/250) later developed PE] and 82.4% (206/250) were NTN-PW. At baseline, high SHS score yielded a significantly ($p<0.05$) increased adjusted odds ratio, a wider area under the curve (AUC), and a higher sensitivity and specificity for the prediction of PE (3.67; 0.898; 91.9% and 87.8%), PE coexisting with intrauterine growth restriction (2.86, 0.838; 91.5% and 75.9%), stillbirth (2.52; 0.783; 96.6% and 60.0%), haemolysis elevated liver enzymes and low platelet count (HELLP) syndrome (2.08; 0.800; 97.2% and 63.8%), acute kidney injury (2.20; 0.825; 95.3% and 70.0%) and dyslipidaemia (2.80; 0.8205; 95.7% and 68.4%) at 32-42 weeks gestation.

Conclusions: High SHS score is associated with increased incidence of PE; hence, SHS can be used independently as a risk stratification tool for adverse pregnancy outcomes thereby creating an opportunity for predictive, preventive and personalised medicine.

59

Introduction

61   Given the advances in research and technology, one would expect that pregnancy and

62   childbirth should be safe without mortalities. To date, however, this expectation has

63   largely been a mirage [1]. An estimation from the United Nations Maternal

64   Mortality Estimation Inter-Agency Group and the current World Health Organisation

65   (WHO), shows that the regional maternal mortality rate was estimated at 546 deaths per

66   100,000 live births in sub-Saharan Africa (SSA) [1]. One of the main causes of these

67   disturbing estimates is preeclampsia (PE).

68   Preeclampsia (PE) (ICD-10-014) is a disorder of pregnancy characterised by a

69   combination of measurable proteinuria and hypertension after 20 weeks of gestation, in

70   pregnant women who were previously normotensive [2]. PE is associated with multi-

71   organ dysfunction and other adverse pregnancy complications (APCs) such as stillbirth,

72   intrauterine growth restriction (IUGR), fetal distress and death, abruptio placenta and

73   HELLP syndrome [3, 4]. PE afflicts about 5 to 8 percent of all pregnancies worldwide [1]

74   and is responsible for up to 4% of all maternal morbidities and mortalities in sub-Saharan

75   Africa (SSA) [5, 6].

76   Despite its positive association with maternal morbidities and mortalities, the

77   aetiology of PE is not fully understood. The unclear pathogenesis of PE is now a dilemma

78   for clinicians and researchers working to develop appropriate therapeutic and diagnostic

79   measures, aside from delivery of the placenta and the baby under intensive care which

80   remain the major protective measures for PE [2]. The stressful demands of pregnancy

3

81 may cause pregnant mothers to present with poor health complaints and this has led to an

82 unexpected onset of PE and delayed therapeutic intervention among normotensive

83 pregnant women (NTN-PW) who were previously devoid of a diagnosable condition [7].

84 Since an early detection coupled with appropriate therapeutic intervention is important in

85 preventing the clinical manifestation of diseases, there is the need for clinicians to shift

86 from the perspective of delayed intervention approach to predictive, preventive and

87 personalised medicine (PPPM) [8-10]. A paradigm shift from reactive to PPPM would

88 allow screening of patients at the preclinical or suboptimal stage before the onset of a

89 disease [11]. PPPM has over the past few years adopted environmental, traditional and

90 behavioural factors to solving public health conditions, and this approach has impacted

91 significantly on the prevention and treatment of chronic diseases [11]. The perspective of

92 PPPM if integrated into maternal and neonatal health screening may inform early

93 detection of PE onset and improve diagnosis, prevention, and therapeutics. There is an

94 urgent need to screen and identify normotensive pregnant women who may be

95 experiencing poor health prior to the onset of PE.

96   In recent public health studies, a search for an inexpensive, less turnaround time

97 and a non-invasive health screening measure has yielded a 25-question item of suboptimal

98 health status questionnaire (SHSQ-25) [12]. SHSQ-25 represents a new PPPM, which can

99 be used in both health care and field/community settings to identify individuals who

100 complain of poor health without a diagnosable condition [12, 13]. Over the past few years,

101 SHSQ-25 has made a significant impact on the field PPPM and has been used to explain

102 the concept of suboptimal health status (SHS), which is defined as the overall physical

103 state between health and disease [12, 14, 13]. The SHSQ-25 expresses the overall health

104 of an individual from five domains- including fatigue, cardiovascular, digestive, immune

105 and mental health [12, 13]. SHS represents a subclinical reversible stage of chronic

106 disease and is typified by health complaints, low energy, and general weakness within

4

107   three months [14, 15]. The SHSQ-25 has been previously used in our previous studies as

108   a potential risk stratification measure for cardiovascular and other chronic diseases in

109   different populations including Asia [16-18] and Africa [19]. Also, SHSQ-25 was used

110   along with the endothelial dysfunction (ED) index to predict the onset of cardiovascular

111   disease in an European population [20]. Furthermore, SHS was found to be associated

112   with telomere length [21], psychosocial stress, plasma cortisol and mRNA expression of

113   glucocorticoid receptor a/b in lymphocytes in a Chinese population [22].

114   Although SHS has been associated with blood pressure disorders, no study to date

115   has explored the usefulness of SHSQ-25 in pregnancy and childbirth. While previous

116   studies extensively explored SHS from the perspective of PPPM in several chronic

117   conditions, its relevance as a predictive measure PE onset has not been reported. Thus,

118   we examined the potential of the subjective tool, SHSQ-25 along with clinical biochemical

119   measures for prediction and early identification of suboptimal health in normotensive pregnant

120   women likely to develop PE coexisting with and without other adverse pregnancy

121   complications (APCs). The findings of this study is expected to increase our knowledge of

122   the pathogenesis of PE and create a window of opportunity for predictive, preventive and

123   personalised medicine (PPPM) specific measures such as risk assessment, screening

124   programmes and targeted prevention [8-10].

125

126   **Methods**

127   **Study design/study participants**

128   This prospective cohort study included 593 normotensive pregnant women (NTN-PW)

129   aged from 18 to 45 years who had no history of a clinically diagnosed disease in the last three

130   months and were visiting the antenatal clinic at the Komfo Anokye Teaching Hospital

131   (KATH), Kumasi, Ghana from June 2017 to December 2018. Pregnant women were

132 initially contacted through a letter of introduction and were invited via a phone call for

133 an interview as well as clinical and biochemical evaluation. Both nulliparous and

134 multiparous pregnant women with a singleton pregnancy were contacted. After written

135 informed consent and ethical consideration, all participants were physically examined and

136 assessed by a qualified consultant obstetrician/gynaecologist before inclusion in the

137 study. Exclusion criteria were women with a twin pregnancy, those below 18 years,

138 advanced maternal age (>45years), previous history of preeclampsia, gestational diabetes,

139 gestational hypertension, obesity, hyperlipidaemia, cancers, smoking, alcoholism,

140 sexually transmitted infections, sickle cell anaemia, cerebrovascular conditions and

141 cardiovascular conditions of any form.

142 **Baseline assessment of SHS**

143 At baseline [10-20 weeks gestation (average gestation of 17 weeks)] the overall health

144 status of 593 NTN-PW was measured using a validated SHSQ-25. The SHSQ-25 is made

145 up of five domains namely; fatigue, cardiovascular system, digestive system, immune

146 system and mental health (**Fig. 1**). These questions were explained to each participant in

147 the native Ghanaian language and their responses were translated into English by the

148 consultant obstetrician/gynaecologist with 100% accuracy. Based on how often each

149 pregnant woman had experienced a particular health complaint in the last three months,

150 they were asked to rate a health statement on a 5-point Likert scale: never or almost never

151 (1), occasionally (2), often (3), very often (4) and always (5). These scores were recoded

152 as 0-4 followed by a summation of the codes for the 25 answered items. The median of

153 the total score was recorded as the cut-off point and values ≥ the cut-off represented 'high

154 SHS' (Poor health) and those < the cut-off indicates 'optimal health' [14, 15, 13]. In this

155 study, a median score ≥ 19 depicted high SHS and <19 depicted optimal health status

156 (OHS). A Cronbach's alpha coefficient value of 0.95 was found after testing the reliability

157 of SHSQ-25. SHS was measured for all participants at baseline (10-20 weeks) only.

Sociodemographic, obstetric and clinical assessment

Information regarding socio-demographic characteristics such as age, highest level of education attained, occupational history, household income as well as obstetric data such as parity, gravidity, gestational age, contraceptive use, family history of hypertension and previous pregnancy complications were obtained via the antenatal folder and the participant's record in the hospital database. Blood pressure (BP) in mmHg was measured by trained personnel and midwives using mercury sphygmomanometers (Accoson, England) and a stethoscope following recommendations by the National High Blood Pressure Education Program (NHBEP) working group (2000). The procedure was performed twice at a 5 to 10-minute interval for each participant after the first measurement. The average values of the two measurements were recorded as the BP. Participants were classified as normotensive pregnant women if their pregnancy was without measurable proteinuria and blood pressure was $\leq 120/80$ mmHg on two (2) occasions at least four (4) hours apart. Weight and height were read and recorded to the nearest 0.1 kilogram and 0.1 centimetres, respectively. Briefly, pregnant women were made to stand on a weighing scale (Seca 762 Mechanical Personal Scale, Hamburg, Germany) and against the stadiometer (Seca 213 Portable Height Measuring Rod Stadiometer, Hamburg, Germany) without their shoes, belongings or any extraneous weight. The body mass index (BMI) was calculated with the formula (weight/height^2) and written in kg/m² units. Pre-gestation BMI was recorded. Proteinuria was measured using a urine reagent dipstick (a semi-quantitative colour scale on the URIT 2VPG Medical electronic Co., Ltd. China). The absence of proteinuria was recorded as 'negative'. The presence of protein in urine was recorded as ≥ 0.3g/l on microalbuminuria or $\geq 1+$ on dipstick urinalysis. For each pregnant woman, the BP, BMI, and proteinuria were measured at three (3) time points (10-20 weeks, 21-31 weeks and 32-41 weeks) and data recorded.

Follow-up and the events of preeclampsia

After an average period of 20 weeks follow-up from baseline until birth, 498 out of 593 participants returned for delivery and were included in the final assessment. By the time of delivery, 301 had normal blood pressure without proteinuria (i.e. NTN-PW) and were classified as control, whereas 197 developed PE and were classified as cases. Of the 498 participants, 248 of them had 'high SHS' at baseline (153 later developed PE and 95 were NTN-PW) whereas 250 had 'optimal health' at baseline (44 developed PE and 206 were NTN-PW). Of the initial 593 participants, 95 women comprising 89 and 6 participants were lost to follow-up and thus did not partake in the first (21-31 weeks gestation) and second (32-42 weeks gestation) follow-ups, respectively **(Fig. 2)**. The reasons for these losses were unwillingness to continue (n=32), relocation (n=48), spontaneous abortion (n=4) and self-induced abortion (n=11).

Participants were physically examined and diagnosed in addition to the examination of selection criteria by a qualified consultant Obstetrician/Gynaecologist. Preeclampsia (ICD-10-CM-014) was defined as the presence of proteinuria ($\geq$ 1+ or 0.3g/l) and hypertension ($\geq$ 140/90 mmHg) on two (2) occasions at least four (4) hours apart detected after the 20th week of gestation in pregnant women who were previously normotensive. Alternatively, high blood pressure combined with multisystemic manifestations such as HELLP syndrome, renal insufficiency, pulmonary oedema, and visual or cerebral disturbances supported the diagnosis of PE even in the absence of proteinuria [23].

Biochemical evaluation

Fasting venous blood samples were collected in the morning hours (8 am to 11 am) from each pregnant woman into vacutainer® tubes. Plasma and serum were separated into two cryovials and stored at -80°C (Thermo Scientific™ Freezers, USA) until analysis. Biochemical measures including fasting blood glucose (FBG), triglyceride (TG), and total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein

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210 cholesterol (LDL-c), alanine aminotransferase (ALT), aspartate aminotransferase (AST),

211 gamma-glutamyl transferase (GGT), total protein (TP), albumin (ALB), lactate

212 dehydrogenase (LDH), alkaline phosphatase (ALP), urea, creatinine (Cr), uric acid (UA),

213 sodium (Na), potassium (K), chloride (Cl-), magnesium (Mg), and calcium (Ca) were

214 measured using an automatic chemistry analyser (Roche Diagnostics, COBAS INTEGRA

215 400 Plus, USA). Haemoglobin and red blood cell distribution width (RDW) were analysed

216 using the Mindray Haematology Analyzer BC 2800. These haematobiochemical

217 determinations were performed at three-time points (10-20 weeks, 21-31 weeks and 32-

218 41 weeks) for each participant.

219 **Diagnostic criteria for adverse pregnancy complications**

220 IUGR, stillbirth, HELLP syndrome and acute kidney injury (AKI) were diagnosed by a

221 qualified consultant obstetrician/gynaecologist following the criteria of ICD-10-O36.5990

222 [24], ICD-10-Z37.1 [24], ICD-10-O14.2 [25] and ICD-10-N17 [26], respectively.

223 Dyslipidaemia was classified based on the National Cholesterol Education Programme Adult

224 Treatment Panel III (NCEP-ATP III) criteria as reduced HDL-c <1.29 mmol/L or specific

225 treatment for this lipid abnormality, raised TG ≥1.7 mmol/L or specific treatment for this lipid

226 abnormality, TC >6.2 mmol/l, and LDL-c >3.37 mmol/l [27].

227 **Statistical analysis**

228 Data were analysed using SPSS version 24 (IBM Corp, NY, USA), XLSTAT Premium

229 version 2018.1 and R version 3.4.3 (R core Team 2017). The normality of the data was

230 performed using the Kolmogorov-Smirnov test. Data was presented as mean ± SD for

231 parametric continuous variables, median (interquartile ranges) for non-parametric

232 continuous variables and frequency (percentages) for categorical variables. A Chi-square

233 test was used to test the association between the proportion of high SHS and optimal

234 health status normotensive pregnant women. Mean comparison between three

235 independent variables was performed using one-way ANOVA followed by Bonferroni

236 post-hoc multiple comparison test. Median comparison between three independent

237 variables was performed using Kruskal Wallis one-way ANOVA followed by Bonferroni

238 post-hoc multiple comparison test. Since neither the SHS nor PE incidence data meets the

239 assumptions for Pearson's correlation, Spearman Rho correlation was used to test

240 association between the individual SHS-specific domains scores and the incidence of PE.

241 Benjamini Hochberg correction was performed to adjust for false discovery rates. A

242 multivariate logistic regression model was performed to test the association between SHS

243 and PE with and without adverse pregnancy complications and adjusted odds ratios (aOR)

244 were recorded. A receiver operating characteristic (ROC) curve and area under the curve

245 (AUC) were generated to evaluate the diagnostic performance of the model. $P < 0.05$ was

246 considered statistically significant.

247

248 **Results**

249

250 A total of 593 normotensive pregnant women (NTN-PW) were assessed at baseline. Of

251 these, 498 of them returned and were included in the final analysis. At baseline, a higher

252 proportion of NTN-PW had completed secondary education (41.8%), were married

253 (83.5%), were Akan (81.7%) by ethnicity, had an informal occupation (66.1%), had low

254 basic monthly income (38.4%), were nulliparous (36.9%), were primigravida (46.8%),

255 and had no history of family hypertension (77.9%), spontaneous abortion (72.1%) and

256 caesarean section (80.1%). When the 498 NTN-PW were stratified into high SHS and

257 optimal health status (OHS) from baseline, NTN-PW with high SHS had a significantly

258 increased percentage history of spontaneous abortion (36.7% vs. 19.2%; $p = 0.0001$),

259 nulliparity (41.1% vs. 32.8%; $p = 0.0202$) and primigravidity (62.9% vs. 30.8%; p

260 <0.0001) compared to those with optimal health. None of the NTN-PW had proteinuria

261 at baseline. There was a statistically significant difference between the mean level of SBP

262 among NTN-PW with high SHS compared to those with optimal health (116.0 vs. 113.2;

263 p =0.0036). Meanwhile, there was no statistically significant difference between the mean

264 age, gestational age, DBP, pre-gestational and gestational BMI among high SHS NTN-

265 PW compared to those with optimal health (p >0.05) (**Table 1**).

266 A total of the 498 participants completed the study. Of the 498 participants, 248 of them

267 representing 49.8% (248/498) had 'high SHS' at baseline (10-20 weeks gestation). Of the

268 248 high SHS participants, 61.7% (153/248) later developed PE whereas 38.3% (95/248)

269 were NTN-PW. Conversely, 250 of the 498 participants representing 50.2% (250/498) had

270 'optimal health' at baseline. Of the 250 optimal health participants, 17.6% (44/250) later

271 developed PE whereas 82.4% (206/250) were NTN-PW. When the high SHS and optimal

272 health participants were stratified into pregnant women who later developed PE (PWLD-

273 PE) and NTN-PW at baseline, high SHS PWLD-PE had significantly increased SBP

274 (118.3 vs. 112.4; p <0.0001), DBP (75.05 vs. 69.91; p =0.0002), ALT (14.3 vs 10.7; p

275 <0.0001), ALP (97 vs 70; p =0.0002), urea (4.34 vs. 3.55; p =0.0011), creatinine (65.61

276 vs. 56.92; p <0.0001), uric acid (326.0 vs 286.0; p =0.0034) and triglyceride (1.56 vs.

277 1.21; p =0.0003) but significantly lower levels of serum Mg (0.88 vs. 0.96; p =0.0082)

278 and albumin-adjusted calcium (2.03 vs. 2.20; p =0.0004) compared to high SHS NTN-

279 PW. Optimal health PWLD-PE had significantly higher ALP (95 vs. 91.5; p =0.0006),

280 UA (304.9 vs. 275.3; p =0.0039) and TG (1.44 vs 1.16; p =0.0031) compared to optimal

281 health NTN-PW (**Table 2**).

282 As depicted in **Table 3**, when the high SHS were stratified into PE and NTN-PW at 32-

283 42 weeks gestation, there were significantly (p <0.0001) elevated levels of SBP, DBP,

284 Na, LDH, AST, ALT, ALP, GGT, urea, creatinine, UA, and TG among PE women

285 compared to NTN-PW, who previously had high SHS at baseline. Conversely, PE women

286 were at an increased risk of preterm delivery as depicted by a significantly lower

287 gestational age than NTN-PW who previously had high SHS at baseline. Additionally,

288 levels of Mg, Ca, total protein, albumin, and platelet (PLT) count were significantly

289 reduced among PE women compared to NTN-PW, who previously had high SHS at

290 baseline sampling.

291 At 32-42 weeks gestation when participants who previously had optimal health were

292 stratified into PE and NTN-PW, there were a significantly (p <0.0001) elevated levels of

293 SBP, DBP, LDH, AST, ALT, ALP, GGT, urea, creatinine, UA, and TG but a reduced GA,

294 Mg, Ca, total protein, albumin, platelet (PLT) count and baby birthweight in PE

295 compared to the NTN-PW.

296 Furthermore, when PE women who previously had high SHS were compared to PE

297 women who previously had optimal health, there were a statistically significantly (p

298 <0.05) lower GA, Mg, Ca, total protein, and albumin levels, but elevated levels of SBP,

299 LDH, AST, ALT, ALP. Also, when NTN-PW who previously had high SHS were

300 compared to NTN-PW who previously had optimal health at 32-42 weeks gestation, there

301 were statistically significantly (p <0.05) lower levels of serum Mg and Ca, but elevated

302 levels of SBP **(Table 3)**.

303 On exploring the association between the incidence of PE and the individual SHS domain

304 score **(Table 4)**, there was a significant positive correlation between PE incidence and

305 Fatigue (r=0.300; p =0.0038), Cardiovascular system (r=0.291; p =0.0174), digestive

306 system (r=0.287; p =0.0291), immune system (r=0.342; p =0.0010), mental health status

307 (r=0.442; p <0.0001) and the overall SHS score (r=0.509; p <0.0001) **(Table 4).**

308 The univariate logistic regression analysis explained that, high BP, low Mg, low Ca, low

309 Hb, low HDL, high LDH, high AST levels, high creatinine and high TG levels yielded a

310 significantly increased odds ratio for predicting high SHS among NTN-PW at baseline

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who later developed PE. After adjusting for confounding factors on multivariate analysis, the association remained significant and the odds ratios were only slightly attenuated if at all. Overall, high BP [aOR=2.84, 95% CI (1.94-5.40), p =0.0314], low Mg [aOR= 2.99, 95% CI (1.29-6.20), p =0.0038] and low Ca [aOR=4.20, 95% CI (1.57-5.63), p <0.0001], high TG [aOR= 2.08, 95% CI (1.12-4.27), p =0.0151] and low HDL-c [aOR= 2.30, 95% CI (1.20-6.83), p =0.03071] were significant independent risk factors associated with baseline high SHS PWLD-PE **(Table 5).**

To explore the usefulness of SHS in predicting PE and other APCs, we performed a multivariate logistic regression model and use the cut-off to generate sensitivity, specificity and area under the ROC curve. Using high SHS alone as a screening measure yielded significantly increased odds, a wider area under the ROC curve (AUC), and a high sensitivity and specificity for identifying PE (aOR= 3.67, AUC= 0.8987, 91.9% and 87.8%), PE coexisting with IUGR (aOR=2.86, AUC= 0.8378, 91.5% and 75.9%), and stillbirth (aOR= 2.52, AUC= 0.7832, 96.6% and 60.0%) compared to its combination with Mg and Ca **(Table 6).**

Also using high SHS alone as a screening measure yielded a better predictive and diagnostic accuracies for identifying PE coexisting with HELLP syndrome (aOR=2.08, AUC= 0.8009, 97.2% and 63.8%), AKI (aOR= 2.2, AUC= 0.8246, 95.3% and 70.0%) and dyslipidaemia (aOR=2.80, AUC= 0.8205, 95.7% and 68.4%) compared to its combination with Mg and Ca (**Table 7**).

Meanwhile, a novel combination of SHS, Mg and Ca levels yielded a fair discriminating power, sensitivity and specificity for identifying PE coexisting with APCs. Particularly, a combination of high SHS and low Ca levels yielded a better predictive power and diagnostic performance compared to the combination of high SHS and low Mg. Overall, SHS is an independent predictive and screening measure for PE and its associated APCs **(Tables 6 and 7).**

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336

As shown in **Fig. 3**, high SHS yielded a significantly high discriminating power (area under the ROC curve) for identifying all PE women (AUC= 0.7832; p <0.0001) (Fig. 3a), PE coexisting with IUGR (AUC= 0.8378; p <0.0001) (Fig. 3b), stillbirth (AUC=0.8205; p <0.0001) (Fig. 3c), HELLP syndrome (AUC= 0.8009; p <0.0001) (Fig. 3d), AKI (AUC= 0.8378; p <0.0001) (Fig. 3e), and dyslipidaemia (AUC= 0.8987; p <0.0001) (Fig. 3f)

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Discussion

For the first time in a Ghanaian Suboptimal Health Cohort Study (GHOACS), the present study determined the usefulness of SHSQ-25 for prediction and early identification of normotensive pregnant women (NTN-PW) likely to develop PE and other adverse pregnancy complications (APCs).

One major finding of the present study indicated that 61.7% of high SHS NTN-PW developed PE compared to 17.6% for optimal health NTN-PW (Tables 2 and 3). At baseline (10-20 weeks), normotensive pregnant women who had high SHS were at approximately 4-fold increased odds of developing PE after adjusting for maternal age, gestational age, parity, gravidity, family history of hypertension, maternal BP, history of spontaneous abortion, pre-gestational BMI, high TG and low HDL. This signifies that the association between SHS and PE is independent of these confounders. Moreover, high SHS at baseline (10-20 weeks gestation) yielded a sensitivity of 91.9%, a specificity of 87.8% and an area under the ROC curve (AUC)/ discriminating power of 89.9% (Fig. 3a), indicating the power of high SHS for predicting the onset of PE. The ability of high SHS

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362   at baseline to predict the onset of PE signifies that SHSQ-25 may be an important measure

363   in predictive, preventive and personalise medicine (PPPM).

364   In the present study, the link between SHS and PE onset was further supported by

365   a significant relationship between the individual SHS-specific domains and the incidence

366   of PE. Particularly, the incidence of PE increased with increasing SHS-specific domains

367   score for fatigue, cardiovascular complaints, digestive system disorder, immune health

368   disorder and mental health complaints (Table 4). The probable reason(s) for this

369   relationship between SHS and the onset of PE are not currently understood. PE which is

370   a multi-systemic and multi-organ syndrome, however, may share a common biological

371   and/or physiological pathway to SHS. Particularly, SHS is associated with hypertension

372   and other cardiovascular-related disorders [17, 18, 20] which links to PE. SHSQ-25

373   evaluates the general health status via five specific domains: fatigue, cardiovascular

374   system, digestive system, immune system and mental health. Although the exact

375   aetiology of PE is still unknown, previous studies have linked PE onset to immune [28,

376   29] and cardiovascular disease [30, 31]. Additionally, the clinical symptoms of PE have

377   also been associated with digestive disorders such as hyperemesis gravidarum (severe

378   vomiting), nausea, and constipation [32], fatigue [32] and mental health [33]. All these

379   symptoms are significant components of SHS and thus uncover the hidden link between

380   SHS and the onset of PE, although we are the first to study the factors together. The

381   probable explanation for the association between PE and the five SHS-specify domains

382   may be due to the common symptoms, biological and/or physiological pathway both share

383   [32, 33, 30, 29, 28, 31]. Hence, integration of SHSQ-25 as a SHS screening tool in

384   antenatal care will generate a new approach with potential for early identification of

385   normotensive pregnant women likely to develop PE, thereby creating a window of

386   opportunity for PPPM. Here, PPPM intervention will promote adequate patients

387 surveillance, risk stratification, optimal diagnosis, prediction of adverse drug to drug

388 interactions and early disease identification [9, 10, 8].

389   Previous case-control studies by Ephraim et al. [34] among a Ghanaian population

390 and Guo et al. [35] among a Chinese population [34, 35] have observed several serum

391 biochemical changes including reduced levels of magnesium and calcium in preeclamptic

392 pregnancies at the point of diagnosis, although these imbalances are not commonly

393 reported in early normotensive pregnancies prior to the onset of PE. However, at baseline

394 (10-20 weeks gestation) in the present longitudinal cohort study, high SHS NTN-PW who

395 later developed PE at 32-42 weeks gestation had significantly reduced levels of

396 magnesium and calcium compared to optimal health NTN-PW (Table 2). High SHS NTN-

397 PW had low serum magnesium and calcium levels with 3- and 4-fold increased odds

398 respectively, compared to those with optimal health status (Table 5). This relationship is

399 novel. This novel finding signifies that SHS can represent a tool for PPPM by predicting

400 an early risk of low dietary magnesium and calcium intake. A cross-sectional study in a

401 Ghanaian population observed significantly low Mg and Ca levels among NTN-PW

402 compared to non-pregnant women [36]. The low calcium levels at baseline may have led

403 to hypertension by stimulating an increased release of renin and parathyroid hormone,

404 which in turn increases intracellular calcium in smooth muscle, culminating in

405 vasoconstriction [34]. The observed low magnesium levels may also be due to increased

406 clearance by the renal system, reduced dietary intake, haemodilution caused by expansion

407 of the extracellular space and high consumption of minerals by the growing foetus [35,

408 34]. From the PPPM perspective, SHS can be used to predict early signs of calcium and

409 magnesium malnutrition and also inform therapeutic options needed for high SHS NTN-

410 PW likely to develop PE.

411   Preeclampsia is a multifactorial syndrome, indicating that it can co-exist with

412 other adverse pregnancy complications (APCs) such as intrauterine growth restriction

413 (IUGR), stillbirth, haemolysis elevated liver enzymes and low platelet count (HELLP)

414 syndrome [3, 37], dyslipidaemia [38, 39] and acute kidney injury (AKI) [40]. These

415 reports agree with the findings of the present study although the identification of these

416 APCs is mostly delayed and diagnosis occurs late in gestation which highly supports

417 earlier PPPM approach. For this purpose, we performed a predictive model using baseline

418 high SHS scores alone as well as an algorithm of high SHS score, low magnesium and/or

419 calcium and generated an area under ROC curve (AUC)/ discriminating power, sensitivity

420 and specificity to predict and identify the risk of PE co-existing with other APCs. Our

421 findings indicated that using high SHS score alone can yield a better predictive odds ratio,

422 sensitivity and specificity than its combination with low magnesium and calcium levels.

423 Conversely, a combination of SHS with Mg and Ca levels yielded a significantly high

424 specificity but low sensitivity compared to using SHS alone (Tables 6 and 7). This

425 confirms our findings that SHS is an independent predictor of PE and other APCs that

426 supports the paradigm shift of clinical medicine from delayed medical intervention to

427 PPPM.

428   Particularly in the present study, high SHS NTN-PW at baseline were at 3-fold

429 increased odds of developing PE-coexisting with IUGR at 32-42 weeks gestation. This

430 occurred at 83.8% discriminating power (Fig. 3b), a sensitivity of 91.5% and a specificity

431 of 75.9% (Table 6). The occurrence of IUGR may be due to endothelial dysfunction [41].

432 Our previous cross-sectional study among adult European population found an

433 association between SHS and endothelial dysfunction, and thus the relationship between

434 SHS and IUGR, may possibly be due to endothelial dysfunction [20]. Endothelial

435 dysfunction may be caused by placental hypoxia, oxidative stress and nitric oxide

436 deficiency originating from poor extravillous trophoblast invasion and incomplete

17

437 maternal artery remodeling [42]. Another factor that may explain PE coexisting with

438 IUGR is maternal psychosocial stress [43, 7, 44], previously shown by a cross-sectional

439 study among a Chinese population that found an association between SHS and

440 psychosocial stress [22] potentially associated with fatigue which is one of the SHS-

441 specific domains.

442 Another novel finding of the present study was a significant association between

443 SHS and PE coexisting with stillbirth. Normotensive pregnant women who had high SHS

444 at baseline (10-20 weeks gestation) were 2.5 times more likely to develop PE-coexisting

445 with stillbirth during birth (32-42 weeks gestation). At 2.5-fold predictive odds ratio for

446 high SHS, a sensitivity of 96.6%, specificity of 60.0% (Table 6) and a discriminating

447 power of 78.3% (Fig. 3c) was observed. Preeclampsia is known to complicate the

448 development of stillbirth and the underlying cause has been linked to placental

449 insufficiency and incomplete maternal arteries remodeling [3, 42, 45]. Thus, SHSQ-25

450 suggests a non-invasive subjective measure for the identification of stillbirth strongly

451 emphasizes the advantage of PPPM to prevent this fatal outcome.

452 SHS and PE-coexisting HELLP syndrome in this study is another novel finding. In the

453 present study, HELLP syndrome identified by haemolysis (high levels of LDH), elevated

454 liver enzymes (ALP, AST, ALT, and GGT) and low platelet count was observed at a

455 higher rate in PE women compared to NTN-PW. Pregnant women who had high SHS at

456 baseline (10-20 weeks) were 2.08 times more likely to develop PE-coexisting HELLP

457 syndrome at 32-42 weeks (Table 7). This syndrome, which is characterised by

458 microangiopathic anaemia, thrombocytopaenia and periportal hepatic necrosis [25] is a

459 known cause of eclampsia-associated mental health problems in pregnancy [33]. Our

460 findings indicated that high SHS can identify PE-coexisting HELLP syndrome at 97.2%

461 sensitivity, 63.8% specificity and a discriminating power (AUC) (Fig. 3d) of 80.1%.

462 Hepatic involvement in PE may be explained by precipitation of fibrin within the portal

463 and periportal areas of the liver lobule and hepatic arterial vasospasm resulting in hepatic

464 cell necrosis and lobular ischaemia [25]. The link between SHS and PE-coexisting with

465 HELLP syndrome could be also related to the mental health phenomenon both share,

466 though this mechanism is speculative. Early detection of mental health complaints using

467 SHSQ-25 in pregnancy will inform clinicians of the likelihood of HELLP syndrome

468 developments.

469 Acute kidney injury (AKI) is not commonly associated with normotensive

470 pregnancy, but can occur in pregnancies potentially associated with severe PE, HELLP

471 syndrome [26, 40], intrauterine fetal death, and stillbirth [46]. In the present study, AKI

472 was diagnosed based on either a sudden increase in serum creatinine $\geq 88.4\mu mol/l$ or

473 oligoanuria or the need for dialysis [46]. Our present study found that increased creatinine

474 levels were associated with high SHS women who developed PE compared to

475 normotensive pregnant women. Using high SHS score at baseline as a predictive measure,

476 a discriminating power of 82.5% (Fig. 3e), a sensitivity of 95.3%, aspecificity of 70.0%

477 and a predictive odds ratio of 2.2 were generated to identify the risk of PE co-existing

478 with AKI. Since high SHS score was associated with high creatinine levels, which is the

479 hallmark of AKI, early detection of abnormal creatinine will inform clinicians the

480 likelihood of AKI in pregnancy and thus supporting the integration and use of SHSQ-25

481 as a potential SHS measure in antenatal care.

482 In a previous prospective cohort study among NTN-PW in a Turkish population,

483 early dyslipidaemia (10-20 weeks) was found to be a significant risk factor for PE [39].

484 This agrees with the present study findings, as a low HDL-c and high TG at baseline (10-

485 20 weeks gestation) were associated with high SHS NTN-PW who later developed PE.

486 Thus hypertriglyceridaemia [47] is ideal for early PE detection and management. Using

487 high SHS score as an independent measure a high predictive odds ratio (2.8),

488   discriminating power of 82.1% (Fig. 3f) and diagnostic performance (sensitivity of 95.7%

489   and specificity of 68.4%) was observed for the prediction of PE-coexisting with

490   dyslipidaemia (Table 7). An association between SHS and cardiovascular and/or

491   cardiometabolic risk has been established in our previous studies [18, 20]. Although

492   pregnancy-induced hyperlipidaemia may be physiologic, dyslipidaemia may predispose

493   the mother to atherosclerosis and directly contributes to cardiovascular disease (CVD)

494   [27, 47]. The development of dyslipidaemia may be associated with systemic

495   inflammation originating from *N*-glycosylation-induced changes in immunoglobulin G (IgG)

496   structure and function [48]. Since, dyslipidaemia remains one of the predisposing factors

497   PE [30], early identification of women at risk of dyslipidaemia would be an opportunity

498   for selective monitoring and management. This supports the need to integrate SHSQ-25

499   in antenatal care as a dynamic screening tool for PE complicated by dyslipidaemia. Since

500   SHS correlates with cardiovascular index like dyslipidaemia it will generate an early risk

501   stratification for PE participants at risk of cardiovascular disease as well as promote an

502   opportunity personalised medicine.

503   To our knowledge, this is the first study integrating SHS as a screening tool in

504   pregnancy and childbirth, and the largest prospective cohort study in a Ghanaian

505   population. Nevertheless, there were some limitations. First, the recruitment of

506   participants in this present study was single-hospital centred, in the sense that only one

507   teaching hospital was involved, thus, there was a possibility of ethnic bias as most of the

508   participants were Akan's and few were distributed across other ethnic groups. Second,

509   this study could not recruit baseline participants at early but rather late first trimester of

510   pregnancy, hence we could not perform SHS evaluation at 21-31 weeks gestation to see

511   the changes in health status over time in relation to the risk of PE. The findings of this

512   study, however, is novel and, thus, further studies are needed in another population to

513 establish the observed association. The relationship between SHS and PE as well as PE

514 coexisting with APCs, although not well-understood, may have an interconnection with

515 placenta-derived factors (angiogenic growth mediators) and oxidative stress, which are

516 key factors contributing to the pathogenesis of PE. Our next study will address this by

517 evaluating an association between SHS, angiogenic growth mediators and oxidative stress

518 among NTN-PW in this on-going Ghanaian Suboptimal Health Cohort Study (GHOACS).

519 **Conclusion**

520 In summary, a higher percentage of high SHS NTN-PW at baseline are more likely

521 to developed PE. The incidence of PE increased with increasing SHS-specific domain

522 scores. This association was supported by a significantly deranged haematobiochemical

523 profile, an increased adjusted odds ratio, a wider area under the ROC curve, and a better

524 sensitivity and specificity in favour of high SHS NTN-PW compared to optimal health

525 participants. Overall, high SHS in early pregnancy is an independent risk factor of PE as

526 well as PE coexisting with IUGR, stillbirth, HELLP syndrome, AKI and dyslipidaemia.

527 Integration of SHSQ-25 as a screening tool in both early antenatal care and follow-

528 up of pregnant women will allow early detection of adverse pregnancy complications

529 whilst creating an opportunity for PPPM policies such as screening programmes,

530 education, risk assessment and targeted prevention. The idea of SHS (Sub optimal Health

531 Status) profile – highly correlated with biochemical/ physiological risk factors – implies

532 that we can "feel" the inside pathologies – though usually perceived as "subjective", is

533 very important for self-education/responsibility, suggesting a potential for "subjective"

534 PPPM approach. Hence, SHSQ-25 can be used as an alternative health pre-screening

535 measure in clinical laboratory-limited communities, fields and community health centres

536 in sub-Saharan African countries on emergency situations.

537 **Acknowledgement**

21

557
558 **Authors Contribution**

559 EOA, PR, DC and WW conceived the study. EOA and CAT performed the investigation

560 collected the data. EOA performed the statistical analysis. EOA, PR, DC, EA, YW, and WW

561 wrote the paper. All authors read and approved the final manuscript.

562

563   **Compliance and ethical standards**

564   **Conflict of interest**

565   The authors declare that they have no conflict of interest.

566   **Consent for publication**

567   Not applicable

568   **Ethical approval and consent to participants**

569   Approval for this study was obtained from the Committee on Human Research

570   Publication and Ethics (CHRPE) of the School of Medical Science (SMS) /KNUST and

571   Komfo Anokye Teaching Hospital (KATH) (CHRPE/AP/146/17) and the Human

572   Research Ethics Committee of Edith Cowan University (ECU) (17509). This study was

573   conducted in accordance with the guidelines of the Helsinki Declaration. Written

574   informed consent in the form of a signature and fingerprint was obtained from all

575   participants and Legally Authorised Representatives after the protocol of the study was

576   explained to them in plain English language and native Ghanaian language where

577   appropriate.

578   **Abbreviations**

579   SHS, suboptimal health status; OHS, optimal health status; SHSQ-25, 25-question based

580   Suboptimal Health Status questionnaire; GHOACS, Ghanaian Suboptimal Health Cohort

581   Study; PE, preeclampsia; APCs, adverse pregnancy complications; PPPM, preventive,

582   predictive and personalised medicine; IUGR, intrauterine growth restriction; HELLP,

583   haemolysis, elevated liver enzymes and low platelet count; SBP, systolic blood pressure; DBP,

584   diastolic blood pressure; Mg, magnesium, Ca, calcium, Na: sodium; K: potassium; Cl-:

585   chloride; LDH: lactate dehydrogenase; UA: uric acid; RDW: red cell distribution width; FBG,

586   fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL-c, high density

587 lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; ALT, alanine

588 aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase;

589 TP, total protein; ALB, albumin; LDH, lactate dehydrogenase; ALP, alkaline

590 phosphatase; aOR, adjusted odds ratio, CI, confidence interval; ROC, receiver's operating

591 characteristics, AUC, area under the ROC curve.

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740

Table 1. Baseline (10-20 weeks gestation) sociodemographic characteristics of normotensive pregnant women stratified by high SHS and optimal health status (OHS)

Characteristics	Total (N=498)	High SHS (N=248)	OHS (N=250)	Statistics	*p*-value
Highest Level of Education				1.794, 3	0.6163
Unschooled	3(0.4)	1(0.4)	2(0.8)		
Primary	168(33.7)	82(33.1)	86(34.4)		
Secondary	208(41.8)	110(44.4)	98(39.2)		
Tertiary	119(23.9)	55(22.2)	64(25.6)		
Marital Status				0.207, 2	0.9018
Never married	78(15.7)	37(14.9)	41(16.4)		
Married	416(83.5)	209(84.3)	207(82.8)		
De-facto	4(0.8)	2(0.8)	2(0.8)		
Ethnicity				2.768, 3	0.4288
Akan	407(81.7)	196(79.0)	211(84.4)		
Ga-Adangbe	9(1.8)	6(2.4)	3(1.2)		
Mole Dagbani	75(15.1)	42(16.9)	33(13.2)		
Ewe	7(1.4)	4(1.6)	3(1.2)		
Occupation				0.199, 2	0.3687
Unemployed	47(9.4)	28(11.3)	19(7.6)		
Formal	122(24.5)	59(23.8)	63(25.2)		
Informal	329(66.1)	161(64.9)	168(67.2)		
Basic income (GH₵)				2.777, 3	0.4273
None	47(9.4)	28(11.3)	19(7.6)		
Low (<500.0)	191(38.4)	92(37.1)	99(39.6)		
Middle (500.0-1000.0)	170(34.1)	87(35.1)	83(33.2)		
High (>1000.0)	90(18.1)	41(16.5)	49(19.6)		
Parity				7.706, 2	**0.0212**
Nulliparous	184(36.9)	102(41.1)	82(32.8)		
Primiparous	135(27.1)	54(21.7)	81(32.4)		
multiparous	179(36.0)	92(37.1)	87(34.8)		
Gravidity				51.54, 1	**<0.0001**
Primigravida	233(46.8)	156(62.9)	77(30.8)		
Multigravida	265(53.2)	92(37.1)	173(69.2)		
FH of Hypertension				0.230,1	0.6314
Yes	110(22.1)	57(23.0)	53(21.2)		
No	388(77.9)	191(77.0)	197(78.8)		
History of spontaneous Abortion				5.083, 1	**0.0001**
Yes	139(27.9)	91(36.7)	48(19.2)		
No	359(72.1)	157(63.3)	202(80.8)		
Previous CS				0.085, 1	0.7701
Yes	99(19.9)	48(19.4)	51(20.4)		
No	399(80.1)	200(80.6)	199(79.6)		
Dipstick proteinuria (<0.3g/g/24hr)	498(100.0)	248(100.0)	250(100.0)		1.0000
Age (years)	29.64 ± 5.98	29.42 ± 5.92	29.60 ± 6.08	0.667	0.5049
Gestational age (weeks)	16.98 ± 2.01	16.97 ± 2.08	17.04 ± 1.98	0.060	0.9586
SBP (mmHg)	114.7 ± 10.57	116.0 ± 11.00	113.2 ± 10.01	2.703	**0.0036**
DBP (mmHg)	72.58 ± 9.26	73.0 ± 8.78	71.8 ± 8.42	1.618	0.1341
Pre-gestational BMI (Kg/m^2)	27.04 ± 4.83	26.86 ± 4.74	27.07 ± 4.92	0.405	0.6887
Gestational BMI (Kg/m^2)	27.33 ± 4.81	27.32 ± 4.74	27.2 ± 4.92	0.298	0.7658

Values are presented as mean ± SD, frequency (percentage), CS: caesarean section; GH₵: Ghana cedi; SBP: systolic blood pressure; DBP: diastolic blood pressure. OHS: optimal health status

Table 2. Baseline (10-20 weeks gestation) clinical and haematobiochemical profile among high SHS and OHS normotensive pregnant women who later developed preeclampsia (PWLD-PE) compared to NTN-PW who did not develop PE

Parameter	High SHS at 10-20 weeks (Baseline)			OHS at 10-20 weeks (Baseline)		
	PWLD-PE (N=153)	NTN-PW(N=95)	*p*-value	PWLD-PE (N=44)	NTN-PW (N=206)	*p*-value
Age (years)	28.86 ± 6.08	30.24 ± 5.11	0.0664	28.07 ± 7.21	30.03 ± 5.76	0.0531
Gestational age (weeks)	16.93 ± 1.95	17.04 ± 2.26	0.9768	17.11 ± 1.76	17.02 ± 1.98	0.9933
SBP (mmHg)	118.3 ± 10.84	112.4 ± 10.52	**<0.0001**	114.0 ± 10.95	115.1 ± 9.54	0.9641
DBP (mmHg)	75.05 ± 9.49	69.91 ± 8.93	**0.0002**	72.70 ± 9.45	71.61 ± 9.29	0.8932
Pre-gestational BMI (Kg/m^2)	26.95 ± 4.68	27.12 ± 4.44	0.7712	26.64 ± 5.04	27.15 ± 5.01	0.9186
Gestational BMI (Kg/m^2)	27.45 ± 4.64	27.11 ± 4.39	0.9475	27.01 ± 5.10	27.25 ± 5.00	0.9910
Mg (mmol/l)	0.88 ± 0.24	0.96 ± 0.22	**0.0082**	0.94 ± 0.12	0.99 ± 0.13	0.2867
Adjusted Ca (mmol/l)	2.03 ± 0.37	2.20 ± 0.31	**0.0004**	2.13 ± 0.44	2.26 ± 0.31	0.0573
Na (mmol/l)	136.4 ± 2.0	136.2 ± 1.96	0.9652	136.5 ± 2.17	136.2 ± 2.01	0.9441
K (mmol/l)	4.18 ± 0.41	4.20 ± 0.48	0.9605	4.12 ± 0.35	4.17 ± 0.31	0.8641
Cl-(mmol/l)	105.6 ± 2.19	105.5 ± 2.42	0.9987	105.8 ± 2.40	105.6 ± 2.33	0.9394
LDH (IU/L)	187(138.5-198.0)	168(139-196)	0.6822	192(147.5-198)	187(139-196)	0.3045
AST (IU/L)	17.2(14.30-27.1)	16.1(13.8-29.4)	0.9324	15.7(13.7-19.3)	15.2(13.6-19.30)	0.9918
ALT (IU/L)	14.3(10.7-28.4)	10.7(10.2-15.3)	**<0.0001**	12.6(10.2-17.3)	11.3(10.3-14.6)	0.9997
ALP (IU/L)	97(77.3-105)	70(56.3-100)	**0.0002**	95(90.8-111.8)	91.5(65-105)	**0.0006**
GGT (IU/L)	10.9(10.1-15.1)	11.3(10.1-15.4)	0.9991	10.3(9.51-12.2)	10.3(9.8-12.2)	0.9999
Total Protein (g/L)	68.08 ± 2.21	67.76 ± 2.20	0.6943	67.74 ± 2.46	67.97 ± 2.23	0.9283
Albumin (g/L)	37.0 ± 1.26	36.81 ± 1.26	0.6741	36.84 ± 1.38	36.91 ± 1.29	0.9870
Urea (mmol/l)	4.34 ± 2.08	3.55 ± 1.36	**0.0011**	3.58 ± 1.55	3.61 ± 1.33	0.9996
Creatinine (µmol/l)	65.61 ± 16.49	56.92 ± 10.75	**<0.0001**	63.84 ± 11.22	59.47 ± 11.0	0.1753
UA (µmol/l)	326.0 ± 39.77	286.0 ± 44.8	**0.0034**	304.9 ± 38.21	275.3 ± 48.98	**0.0039**
Hb (g/dL)	10.92 ± 0.62	11.57 ± 0.63	0.0573	11.74 ± 0.56	11.70 ± 0.57	0.9705
RDW-CV (%)	13.70 ± 1.34	13.67 ± 1.31	0.9989	13.56 ± 1.34	13.64 ± 1.24	0.9802
PLT (X10^9/L)	284.5 ± 85.3	300.4 ± 85.56	0.5006	292.3 ± 88.78	301.7 ± 89.18	0.9154
FBG (mmol/L)	4.85 ± 0.76	4.930 ± 0.79	0.0854	5.21 ± 0.76	5.08 ± 0.71	0.6785
TC (mmol/L)	4.76 ± 1.30	4.70 ± 1.15	0.9801	4.63 ± 1.18	4.65 ± 1.11	0.9997
TG (mmol/L)	1.56 ± 0.91	1.21 ± 0.48	**0.0003**	1.44 ± 0.94	1.16 ± 0.41	**0.0031**
HDL-c (mmol/L)	1.38 ± 0.31	1.46 ± 0.31	0.1062	1.50 ± 0.27	1.48 ± 0.35	0.9753
LDL-c (mmol/L)	2.86 ± 1.19	2.93 ± 1.00	0.9709	2.73 ± 1.02	2.79 ± 0.98	0.9801

Values are presented as mean ± SD; median (IQR); PWLD-PE: Pregnant women who later developed PE.

748 **Table 3. Clinical and haematobiochemical profile at 32-42 weeks gestation (Birth) among high SHS and OHS participants who developed PE**
749 **compared to NTN-PW**

| Parameter | High SHS | | | OHS | | |
	PE (N=153)	NTN-PW (N=95)	*p*-value	PE (N=44)	NTN-PW (N=206)	*p*-value
Age (years)	28.94 ± 6.10	30.28 ± 5.09	0.1718	28.37 ± 7.33	30.46 ± 5.82	0.1480
Gestational age (weeks)	33.99 ± 2.43	38.12 ± 1.52	**<0.0001**	35.0 ± 2.25 ‡	37.98 ± 1.52	**<0.0001**
SBP (mmHg)	172.7 ± 16.76	119.8 ± 8.74	**<0.0001**	160.2 ± 12.29 ‡	115.1 ± 9.54†	**<0.0001**
DBP (mmHg)	109.9 ± 10.05	76.34 ± 9.29	**<0.0001**	109.2 ± 7.89	74.78 ± 8.69	**<0.0001**
Pre-gestational BMI (Kg/m^2)	26.95 ± 4.68	27.12 ± 4.44	0.7712	26.64 ± 5.04	27.15 ± 5.01	0.9186
Gestational BMI (Kg/m^2)	28.37 ± 4.58	27.99 ± 4.35	0.5230	28.17 ± 4.85	27.98 ± 4.92	0.9948
Mg (mmol/l)	0.57 ± 0.21	0.99 ± 0.24	**<0.0001**	0.69 ± 0.19 ‡	1.11 ± 0.16†	**<0.0001**
Adjusted Ca (mmol/l)	1.74 ± 0.37	2.25 ± 0.41	**<0.0001**	1.97 ± 0.23 ‡	2.49 ± 0.31†	**<0.0001**
Na (mmol/l)	145.7 ± 3.18	141.2 ± 1.96	**<0.0001**	143.0 ± 3.66	143.2 ± 2.01	0.0682
K (mmol/l)	3.56 ± 0.32	3.58 ± 0.35	0.8041	3.60 ± 0.44	3.66 ± 0.38	0.8787
Cl-(mmol/l)	110.6 ± 2.19	110.5 ± 2.42	0.8767	110.9 ± 2.29	110.6 ± 2.33	0.8471
LDH (IU/L)	264(227-330.0)	175(146.0-203.0)	**<0.0001**	238(223.5-301.8) ‡	174.4(146.0-203.0)	**<0.0001**
AST (IU/L)	31.9(25.6-47.4)	23.5(19.9-25.7)	**<0.0001**	29.1(24.9-38.58) ‡	22.5(20.35-25.70)	**<0.0001**
ALT (IU/L)	52.0(39.8-72.4)	31.1(24.0-39.2)	**<0.0001**	40.3(37.8-70.0) ‡	30.5(23.8-39.2)	**<0.0001**
ALP (IU/L)	383(335-423)	238(195-275)	**<0.0001**	344(263.8-382)	235(203-253)	**<0.0001**
GGT (IU/L)	20.4(17.9-47.3)	18.8(17.6-22.9)	**<0.0001**	19.3(17.2-35.6)	17.8(17.3-19.7)	**<0.0001**
Total Protein (g/L)	57.90 ± 3.07	62.71 ± 2.20	**<0.0001**	60.51 ± 2.98 ‡	62.97 ± 2.23	**<0.0001**
Albumin (g/L)	30.93 ± 1.73	33.91 ± 1.26	**<0.0001**	32.73 ± 1.69 ‡	34.01 ± 1.25	**<0.0001**
Urea (mmol/l)	9.17 ± 2.46	5.67 ± 1.27	**<0.0001**	8.94 ± 2.10	5.42 ± 1.33	**<0.0001**
Creatinine (µmol/l)	107.8 ± 43.43	68.45 ± 11.21	**<0.0001**	102.0 ± 15.17	66.6 ± 11.0	**<0.0001**
UA (µmol/l)	413.5 ± 73.9	314.0 ± 37.3	**<0.0001**	398.8 ± 72.66	301.6 ± 43.91	**<0.0001**
Hb (g/dL)	11.02 ± 0.63	10.97 ± 0.62	0.5212	11.14 ± 0.56	11.10 ± 0.57	0.9705
RDW-CV (%)	16.40 ± 1.34	16.37 ± 1.31	0.8868	16.26 ± 1.34	16.34 ± 1.24	0.9802
PLT (X10^9/L)	247.7 ± 90.6	292.4 ± 85.56	**0.0007**	268.5 ± 86.01	293.2 ± 88.76	0.3354
FBG (mmol/L)	5.58 ± 0.68	5.50 ± 0.70	0.6198	5.67 ± 0.59	5.65 ± 0.71	0.9981
TC (mmol/L)	5.64 ± 1.29	5.33 ± 0.97	0.1330	5.63 ± 1.16	5.23 ± 0.94	0.1236
TG (mmol/L)	1.84 ± 0.96	1.42 ± 0.52	**<0.0001**	1.78 ± 0.79	1.35 ± 0.41	**0.0010**
HDL-C (mmol/L)	1.11 ± 0.29	1.18 ± 0.35	0.3284	1.14 ± 0.27	1.19 ± 0.35	0.7798
LDL-C (mmol/L)	3.59 ± 1.12	3.57 ± 0.98	0.9984	3.49 ± 1.16	3.39 ± 0.87	0.9218
Birthweight (kg)	1.97 ± 0.01	2.83 ± 0.01	**<0.0001**	2.69 ± 0.01	2.87 ± 0.01	0.0812

750 Values are presented as mean ± SD; median (IQR); † Significant difference compared to high SHS NTN-PW; ‡ Significant difference compared to high SHS PE. Mg: magnesium; Ca: calcium;
751 Na: sodium; K: potassium; Cl-: chloride; LDH: lactate dehydrogenase; UA: uric acid; RDW: red blood cell distribution width

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Table 4. Association between the individual and overall SHS domain scores among participants at baseline (10-20 weeks gestation) and PE incidence at 32-42 weeks gestation (n=498)

SHS domains	PE incidence	
	r	*p*-value
Fatigue	0.300	0.0038
Cardiovascular system	0.291	0.0174
Digestive system	0.287	0.0291
Immune system	0.342	0.0010
Mental health status	0.442	<0.0001
Overall SHS	0.509	<0.0001

r: Spearman Rho correlation coefficient. *P*-values are adjusted for the false discovery rate using Benjamini Hochberg correction

Table 5. Univariate and multivariate logistic regression model of baseline clinical and haematobiochemical profile for risk stratification of high SHS among pregnant women who later developed-PE (PWLD-PE)

Characteristics	Model 1 cOR (95% CI)	p-value	Model 2 aOR (95% CI)	p-value
BP (mmHg)				
Optimal	1.00		1.00	
High-normal	2.96(2.39-4.85)	**< 0.0001**	2.84(1.94-5.40)	**0.0314**
Mg (mmol/l)				
Low	3.47(3.16-7.15)	**<0.0001**	2.99(1.29-6.20)	**0.0038**
Normal	1.00		1.00	
Adj. Ca (mmol/l)				
Low	4.19(1.19-5.03)	**<0.0001**	4.20(1.57-5.63)	**<0.0001**
Normal	1.00		1.00	
LDH (IU/L)				
High	2.75(0.60-5.07)	0.0818	1.94(0.76-4.98)	0.2104
Normal	1.00		1.00	
AST (IU/L)				
High	1.82(0.68-8.14)	0.0518	1.10(0.37-24.2)	0.4613
Normal	1.00		1.00	
ALP (IU/L)				
High	1.08(0.78-1.93)	0.8054	0.78(0.39-1.57)	0.5944
Normal	1.00		1.00	
Urea (IU/L)				
High	1.03(0.73-10.51)	0.0910	1.22(0.41-16.55)	0.4729
Normal	1.00		1.00	
Creatinine (IU/L)				
High	1.15(0.55-7.04)	0.258	1.39(1.04-6.33)	0.1449
Normal	1.00		1.00	
Uric Acid (µmol/l)				
High	1.18(0.41-3.88)	0.8531	0.48(0.15-1.53)	0.3138
Normal	1.00		1.00	
Hb (g/dl)				
Anaemia	1.58(1.01-2.62)	0.0597	1.81(0.74-4.38)	0.2276
Non-anaemia	1.00		1.00	
FBG (mmol/L)				
High Normal	1.85(0.81-3.85)	0.1068	0.84(0.31-2.28)	0.7942
Normal	1.00		1.00	
TC (mmol/L)				
High	1.30(0.94-2.03)	0.2750	1.82(0.81-4.10)	0.1884
Normal	1.00		1.00	
TG (mmol/L)				
High	2.14(1.08-4.79)	**0.0206**	2.08(1.12-4.27)	**0.0151**
Normal	1.00		1.00	
HDL (mmol/L)				
Low	2.44(1.15-7.05)	**0.0418**	2.30(1.20-6.83)	**0.0307**
Normal	1.00		1.00	
LDL (mmol/L)				
High	1.38(0.689-2.67)	0.0890	1.23(0.50-3.05)	0.8252
Normal	1.00		1.00	

cOR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence interval; 1.00: reference category; Model 2 adjusted for maternal age, parity, gravidity, family history of hypertension, maternal blood pressure, history of spontaneous abortion, pre-gestational BMI

Table 6. Predictive performance of baseline high SHS score with serum Mg and Ca levels for prediction and diagnosis of PWLD-PE and PE-coexisting IUGR and stillbirth at 32-42 weeks gestation

Baseline SHS	Model 1 cOR (95% CI)	Model 2 aOR (95% CI)	p-value	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	LR+	AUC
Overall PE									
High SHS	3.51 (2.18-9.41)*	3.67 (2.73- 8.32)	**<0.0001**	91.9 (87.6-94.8)	87.8 (83.2-91.3)	87.1	92.4	7.55	0.8987
OHS	1.00	1.00							
High SHS + Low Mg	3.00 (2.51-7.33)*	2.58 (1.15- 5.95)	**0.0381**	66.5 (59.6-72.7)	90.9 (86.3-94.4)	52.4	81.9	2.67	0.6212
OHS + Normal Mg	1.00	1.00							
High SHS + Low Ca	2.82 (2.06- 8.41)*	2.22 (1.51- 6.72)	**0.0461**	70.6 (61.1-78.9)	93.9 (90.4-99.7)	58.3	82.9	2.71	0.7559
OHS + Normal Ca	1.00	1.00							
PE+ IUGR									
High SHS	3.19 (2.01-8.87)*	2.86 (1.62- 8.87)	**<0.0001**	91.5 (86.6-94.8)	75.9 (70.8-80.4)	70.1	93.6	3.81	0.8378
OHS	1.00	1.00							
High SHS + Low Mg	1.04 (0.57-7.35)	1.37 (0.92- 6.09)	0.0934	22.2 (10.1-39.2)	80.3 (79.2-93.7)	33.3	82.6	2.06	0.5211
OHS + Normal Mg	1.00	1.00							
High SHS + Low Ca	2.33 (2.26-8.07)*	2.08 (1.68- 8.32)	**0.0328**	62.5 (48.6-75.1)	89.2 (83.2-89.5)	46.7	83.2	2.25	0.6462
OHS + Normal Ca	1.00	1.00							
PE + Stillbirth									
High SHS	2.61 (2.60-9.00)*	2.52 (2.34-10.12)	**<0.0001**	96.6(89.8-99.1)	60.0(55.3-64.7)	33.9	99.8	2.41	0.7832
OHS	1.00	1.00							
High SHS + Low Mg	1.87 (1.61- 9.38)*	1.91 (1.53- 11.92)	**0.0430**	37.5 (15.2-64.6)	90.8 (86.1-94.3)	23.1	95.2	4.06	0.5805
OHS + Normal Mg	1.00	1.00							
High SHS + Low Ca	2.35 (1.85-10.56)*	2.67 (2.40- 9.74)	**<0.0001**	72.7 (49.8-89.3)	86.2 (84.6-89.9)	62.8	96.3	2.82	0.7203
OHS + Normal Ca	1.00	1.00							

cOR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence interval; 1.00: reference category; Model 1: unadjusted odds ratio. Model 2: Model adjusted for adjusted for maternal age, parity, gravidity, family history of hypertension, maternal blood pressure, history of spontaneous abortion, pre-gestational BMI, low HDL, and high TG. HSHS: high SHS; OHS: optimal health status; Mg: magnesium; Ca: albumin-adjusted calcium; IUGR: intrauterine growth restriction. * indicates significant crude odds ratio ($p < 0.05$).

Table 7. Predictive performance of baseline high SHS score with serum Mg and Ca levels for prediction and diagnosis of PE-coexisting with HELLP syndrome, acute kidney injury (AKI) and dyslipidaemia at 32-42 weeks gestation

Baseline SHS	Model 1	Model 2							
	cOR (95% CI)	aOR (95% CI)	p-value	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	LR+	AUC
PE+ HELLP syndrome									
High SHS	2.47 (1.88- 9.25)*	2.08 (1.95- 6.83)	**0.0001**	97.2 (91.5-99.4)	63.8 (58.1-67.6)	41.5	98.8	2.62	0.8009
OHS	1.00	1.00							
High SHS + Low Mg	1.59 (1.09- 6.32)*	1.97 (1.30- 8.14)	**0.0225**	66.5 (59.6-72.7)	90.9 (86.3-94.3)	13.1	97.6	4.11	0.6437
OHS + Normal Mg	1.00	1.00							
High SHS + Low Ca	1.75 (1.31- 7.04)*	2.05 (1.39- 5.36)	**0.0013**	74.3 (44.9-92.2)	78.3 (62.7-73.5)	16.7	97.5	2.80	0.7310
OHS + Normal Ca	1.00	1.00							
PE + AKI									
High SHS	2.15 (1.33- 5.31)*	2.20 (1.58- 6.03)	**0.0051**	95.3(90.4-97.8)	70.0(64.6-74.2)	57.3	97.1	3.14	0.8246
OHS	1.00	1.00							
High SHS + Low Mg	1.61 (1.53- 8.47)*	1.84 (1.36- 7.58)	**0.0330**	31.0(15.3-50.8)	91.1(86.6-94.5)	31.0	91.1	3.49	0.5023
OHS + Normal Mg	1.00	1.00							
High SHS + Low Ca	2.08 (1.74- 4.82)*	2.13 (1.50- 5.10)	**0.0018**	72.6(58.3-84.1)	73.8(67.3-79.6)	40.2	91.7	2.77	0.7630
OHS + Normal Ca	1.00	1.00							
PE + dyslipidaemia									
High SHS	2.77(1.80- 9.07)*	2.80 (2.30- 10.35)	**0.0004**	95.7 (90.7-98.2)	68.4 (63.3-72.9)	54.5	97.6	3.02	0.8205
OHS	1.00	1.00							
High SHS + Low Mg	1.29 (1.02- 4.16)	1.18 (0.80- 7.20)	0.0599	50.0(6.7-93.2)	90.8(86.2-94.3)	9.1	99.0	5.45	0.6321
OHS + Normal Mg	1.00	1.00							
High SHS + Low Ca	1.64 (1.00- 7.13)	1.52 (0.79- 9.06)	0.1244	60.0(14.7-94.7)	73.7(67.2-79.5)	5.1	98.7	2.28	0.6594
OHS + Normal Ca	1.00	1.00							

cOR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence interval; 1.00: reference category; Model 1: unadjusted odds ratio. Model 2: Model adjusted for maternal age, gestational age, parity, gravidity, family history of hypertension, maternal blood pressure, history of spontaneous abortion, pre-gestational BMI, low HDL and high TG. HSHS: high SHS; OHS: optimal health status; Mg: magnesium; Ca: albumin-adjusted calcium; HELLP: haemolysis elevated liver enzymes and low platelet count. * indicates significant crude odds ratio ($p <0.05$).