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Title page

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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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.

Keywords: Suboptimal Health Status, preeclampsia, pregnancy complications, patient stratification, primary healthcare, risk assessment, population screening, education, Predictive Preventive Personalised Medicine.

Introduction

Given the advances in research and technology, one would expect that pregnancy and childbirth should be safe without mortalities. To date, however, this expectation has largely been a mirage [1]. An estimation from the United Nations Maternal Mortality Estimation Inter-Agency Group and the current World Health Organisation (WHO), shows that the regional maternal mortality rate was estimated at 546 deaths per 100,000 live births in sub-Saharan Africa (SSA) [1]. One of the main causes of these disturbing estimates is preeclampsia (PE).

Preeclampsia (PE) (ICD-10-014) is a disorder of pregnancy characterised by a combination of measurable proteinuria and hypertension after 20 weeks of gestation, in pregnant women who were previously normotensive [2]. PE is associated with multi-organ dysfunction and other adverse pregnancy complications (APCs) such as stillbirth, intrauterine growth restriction (IUGR), fetal distress and death, abruptio placenta and HELLP syndrome [3, 4]. PE afflicts about 5 to 8 percent of all pregnancies worldwide [1] and is responsible for up to 4% of all maternal morbidities and mortalities in sub-Saharan Africa (SSA) [5, 6].

Despite its positive association with maternal morbidities and mortalities, the aetiology of PE is not fully understood. The unclear pathogenesis of PE is now a dilemma for clinicians and researchers working to develop appropriate therapeutic and diagnostic measures, aside from delivery of the placenta and the baby under intensive care which remain the major protective measures for PE [2]. The stressful demands of pregnancy

may cause pregnant mothers to present with poor health complaints and this has led to an unexpected onset of PE and delayed therapeutic intervention among normotensive pregnant women (NTN-PW) who were previously devoid of a diagnosable condition [7]. Since an early detection coupled with appropriate therapeutic intervention is important in preventing the clinical manifestation of diseases, there is the need for clinicians to shift from the perspective of delayed intervention approach to predictive, preventive and personalised medicine (PPPM) [8-10]. A paradigm shift from reactive to PPPM would allow screening of patients at the preclinical or suboptimal stage before the onset of a disease [11]. PPPM has over the past few years adopted environmental, traditional and behavioural factors to solving public health conditions, and this approach has impacted significantly on the prevention and treatment of chronic diseases [11]. The perspective of PPPM if integrated into maternal and neonatal health screening may inform early detection of PE onset and improve diagnosis, prevention, and therapeutics. There is an urgent need to screen and identify normotensive pregnant women who may be experiencing poor health prior to the onset of PE.

In recent public health studies, a search for an inexpensive, less turnaround time and a non-invasive health screening measure has yielded a 25-question item of suboptimal health status questionnaire (SHSQ-25) [12]. SHSQ-25 represents a new PPPM, which can be used in both health care and field/community settings to identify individuals who complain of poor health without a diagnosable condition [12, 13]. Over the past few years, SHSQ-25 has made a significant impact on the field PPPM and has been used to explain the concept of suboptimal health status (SHS), which is defined as the overall physical state between health and disease [12, 14, 13]. The SHSQ-25 expresses the overall health of an individual from five domains- including fatigue, cardiovascular, digestive, immune and mental health [12, 13]. SHS represents a subclinical reversible stage of chronic disease and is typified by health complaints, low energy, and general weakness within

three months [14, 15]. The SHSQ-25 has been previously used in our previous studies as a potential risk stratification measure for cardiovascular and other chronic diseases in different populations including Asia [16-18] and Africa [19]. Also, SHSQ-25 was used along with the endothelial dysfunction (ED) index to predict the onset of cardiovascular disease in an European population [20]. Furthermore, SHS was found to be associated with telomere length [21], psychosocial stress, plasma cortisol and mRNA expression of glucocorticoid receptor a/b in lymphocytes in a Chinese population [22].

Although SHS has been associated with blood pressure disorders, no study to date has explored the usefulness of SHSQ-25 in pregnancy and childbirth. While previous studies extensively explored SHS from the perspective of PPPM in several chronic conditions, its relevance as a predictive measure PE onset has not been reported. Thus, we examined the potential of the subjective tool, SHSQ-25 along with clinical biochemical measures for prediction and early identification of suboptimal health in normotensive pregnant women likely to develop PE coexisting with and without other adverse pregnancy complications (APCs). The findings of this study is expected to increase our knowledge of the pathogenesis of PE and create a window of opportunity for predictive, preventive and personalised medicine (PPPM) specific measures such as risk assessment, screening programmes and targeted prevention [8-10].

Methods

Study design/study participants

This prospective cohort study included 593 normotensive pregnant women (NTN-PW) aged from 18 to 45 years who had no history of a clinically diagnosed disease in the last three months and were visiting the antenatal clinic at the Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana from June 2017 to December 2018. Pregnant women were

initially contacted through a letter of introduction and were invited via a phone call for an interview as well as clinical and biochemical evaluation. Both nulliparous and multiparous pregnant women with a singleton pregnancy were contacted. After written informed consent and ethical consideration, all participants were physically examined and assessed by a qualified consultant obstetrician/gynaecologist before inclusion in the study. Exclusion criteria were women with a twin pregnancy, those below 18 years, advanced maternal age (>45years), previous history of preeclampsia, gestational diabetes, gestational hypertension, obesity, hyperlipidaemia, cancers, smoking, alcoholism, sexually transmitted infections, sickle cell anaemia, cerebrovascular conditions and cardiovascular conditions of any form.

Baseline assessment of SHS

At baseline [10-20 weeks gestation (average gestation of 17 weeks)] the overall health status of 593 NTN-PW was measured using a validated SHSQ-25. The SHSQ-25 is made up of five domains namely; fatigue, cardiovascular system, digestive system, immune system and mental health **(Fig. 1)**. These questions were explained to each participant in the native Ghanaian language and their responses were translated into English by the consultant obstetrician/gynaecologist with 100% accuracy. Based on how often each pregnant woman had experienced a particular health complaint in the last three months, they were asked to rate a health statement on a 5-point Likert scale: never or almost never (1), occasionally (2), often (3), very often (4) and always (5). These scores were recoded as 0-4 followed by a summation of the codes for the 25 answered items. The median of the total score was recorded as the cut-off point and values ≥ the cut-off represented 'high SHS' (Poor health) and those < the cut-off indicates 'optimal health' [14, 15, 13]. In this study, a median score ≥ 19 depicted high SHS and <19 depicted optimal health status (OHS). A Cronbach's alpha coefficient value of 0.95 was found after testing the reliability of SHSQ-25. SHS was measured for all participants at baseline (10-20 weeks) only.

158 **Sociodemographic, obstetric and clinical assessment**

159 Information regarding socio-demographic characteristics such as age, highest level of
160 education attained, occupational history, household income as well as obstetric data such as
161 parity, gravidity, gestational age, contraceptive use, family history of hypertension and
162 previous pregnancy complications were obtained via the antenatal folder and the participant's
163 record in the hospital database. Blood pressure (BP) in mmHg was measured by trained
164 personnel and midwives using mercury sphygmomanometers (Accoson, England) and a
165 stethoscope following recommendations by the National High Blood Pressure Education
166 Program (NHBEP) working group (2000). The procedure was performed twice at a 5 to
167 10-minute interval for each participant after the first measurement. The average values of
168 the two measurements were recorded as the BP. Participants were classified as
169 normotensive pregnant women if their pregnancy was without measurable proteinuria and
170 blood pressure was ≤ 120/80 mmHg on two (2) occasions at least four (4) hours apart.
171 Weight and height were read and recorded to the nearest 0.1 kilogram and 0.1 centimetres,
172 respectively. Briefly, pregnant women were made to stand on a weighing scale (Seca 762
173 Mechanical Personal Scale, Hamburg, Germany) and against the stadiometer (Seca 213
174 Portable Height Measuring Rod Stadiometer, Hamburg, Germany) without their shoes,
175 belongings or any extraneous weight. The body mass index (BMI) was calculated with
176 the formula (weight/height^2) and written in kg/m^2 units. Pre-gestation BMI was recorded.
177 Proteinuria was measured using a urine reagent dipstick (a semi-quantitative colour scale
178 on the URIT 2VPG Medical electronic Co., Ltd. China). The absence of proteinuria was
179 recorded as 'negative'. The presence of protein in urine was recorded as ≥ 0.3g/l on
180 microalbuminuria or ≥ 1+ on dipstick urinalysis. For each pregnant woman, the BP, BMI,
181 and proteinuria were measured at three (3) time points (10-20 weeks, 21-31 weeks and
182 32-41 weeks) and data recorded.

183

184 **Follow-up and the events of preeclampsia**

185 After an average period of 20 weeks follow-up from baseline until birth, 498 out of 593
186 participants returned for delivery and were included in the final assessment. By the time
187 of delivery, 301 had normal blood pressure without proteinuria (i.e. NTN-PW) and were
188 classified as control, whereas 197 developed PE and were classified as cases. Of the 498
189 participants, 248 of them had 'high SHS' at baseline (153 later developed PE and 95 were
190 NTN-PW) whereas 250 had 'optimal health' at baseline (44 developed PE and 206 were NTN-
191 PW). Of the initial 593 participants, 95 women comprising 89 and 6 participants were lost
192 to follow-up and thus did not partake in the first (21-31 weeks gestation) and second (32-
193 42 weeks gestation) follow-ups, respectively **(Fig. 2)**. The reasons for these losses were
194 unwillingness to continue (n=32), relocation (n=48), spontaneous abortion (n=4) and self-
195 induced abortion (n=11).

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

204 **Biochemical evaluation**

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

cholesterol (LDL-c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), total protein (TP), albumin (ALB), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), urea, creatinine (Cr), uric acid (UA), sodium (Na), potassium (K), chloride (Cl-), magnesium (Mg), and calcium (Ca) were measured using an automatic chemistry analyser (Roche Diagnostics, COBAS INTEGRA 400 Plus, USA). Haemoglobin and red blood cell distribution width (RDW) were analysed using the Mindray Haematology Analyzer BC 2800. These haematobiochemical determinations were performed at three-time points (10-20 weeks, 21-31 weeks and 32-41 weeks) for each participant.

Diagnostic criteria for adverse pregnancy complications

IUGR, stillbirth, HELLP syndrome and acute kidney injury (AKI) were diagnosed by a qualified consultant obstetrician/gynaecologist following the criteria of ICD-10-036.5990 [24], ICD-10-Z37.1 [24], ICD-10-014.2 [25] and ICD-10-N17 [26], respectively. Dyslipidaemia was classified based on the National Cholesterol Education Programme Adult Treatment Panel III (NCEP-ATP III) criteria as reduced HDL-c <1.29 mmol/L or specific treatment for this lipid abnormality, raised TG ≥1.7 mmol/L or specific treatment for this lipid abnormality, TC >6.2 mmol/l, and LDL-c >3.37 mmol/l [27].

Statistical analysis

Data were analysed using SPSS version 24 (IBM Corp, NY, USA), XLSTAT Premium version 2018.1 and R version 3.4.3 (R core Team 2017). The normality of the data was performed using the Kolmogorov-Smirnov test. Data was presented as mean ± SD for parametric continuous variables, median (interquartile ranges) for non-parametric continuous variables and frequency (percentages) for categorical variables. A Chi-square test was used to test the association between the proportion of high SHS and optimal health status normotensive pregnant women. Mean comparison between three

independent variables was performed using one-way ANOVA followed by Bonferroni post-hoc multiple comparison test. Median comparison between three independent variables was performed using Kruskal Wallis one-way ANOVA followed by Bonferroni post-hoc multiple comparison test. Since neither the SHS nor PE incidence data meets the assumptions for Pearson's correlation, Spearman Rho correlation was used to test association between the individual SHS-specific domains scores and the incidence of PE. Benjamini Hochberg correction was performed to adjust for false discovery rates. A multivariate logistic regression model was performed to test the association between SHS and PE with and without adverse pregnancy complications and adjusted odds ratios (aOR) were recorded. A receiver operating characteristic (ROC) curve and area under the curve (AUC) were generated to evaluate the diagnostic performance of the model. $P< 0.05$ was considered statistically significant.

Results

A total of 593 normotensive pregnant women (NTN-PW) were assessed at baseline. Of these, 498 of them returned and were included in the final analysis. At baseline, a higher proportion of NTN-PW had completed secondary education (41.8%), were married (83.5%), were Akan (81.7%) by ethnicity, had an informal occupation (66.1%), had low basic monthly income (38.4%), were nulliparous (36.9%), were primigravida (46.8%), and had no history of family hypertension (77.9%), spontaneous abortion (72.1%) and caesarean section (80.1%). When the 498 NTN-PW were stratified into high SHS and optimal health status (OHS) from baseline, NTN-PW with high SHS had a significantly increased percentage history of spontaneous abortion (36.7% vs. 19.2%; p =0.0001), nulliparity (41.1% vs. 32.8%; p =0.0202) and primigravidity (62.9% vs. 30.8%; p <0.0001) compared to those with optimal health. None of the NTN-PW had proteinuria

at baseline. There was a statistically significant difference between the mean level of SBP among NTN-PW with high SHS compared to those with optimal health (116.0 vs. 113.2; p =0.0036). Meanwhile, there was no statistically significant difference between the mean age, gestational age, DBP, pre-gestational and gestational BMI among high SHS NTN-PW compared to those with optimal health (p >0.05) (**Table 1)**.

A total of the 498 participants completed the study. Of the 498 participants, 248 of them representing 49.8% (248/498) had 'high SHS' at baseline (10-20 weeks gestation). Of the 248 high SHS participants, 61.7% (153/248) later developed PE whereas 38.3% (95/248) were NTN-PW. Conversely, 250 of the 498 participants representing 50.2% (250/498) had 'optimal health' at baseline. Of the 250 optimal health participants, 17.6% (44/250) later developed PE whereas 82.4% (206/250) were NTN-PW. When the high SHS and optimal health participants were stratified into pregnant women who later developed PE (PWLD-PE) and NTN-PW at baseline, high SHS PWLD-PE had significantly increased SBP (118.3 vs. 112.4; p <0.0001), DBP (75.05 vs. 69.91; p =0.0002), ALT (14.3 vs 10.7; p <0.0001), ALP (97 vs 70; p =0.0002), urea (4.34 vs. 3.55; p =0.0011), creatinine (65.61 vs. 56.92; p <0.0001), uric acid (326.0 vs 286.0; p =0.0034) and triglyceride (1.56 vs. 1.21; p =0.0003) but significantly lower levels of serum Mg (0.88 vs. 0.96; p =0.0082) and albumin-adjusted calcium (2.03 vs. 2.20; p =0.0004) compared to high SHS NTN-PW. Optimal health PWLD-PE had significantly higher ALP (95 vs. 91.5; p =0.0006), UA (304.9 vs. 275.3; p =0.0039) and TG (1.44 vs 1.16; p =0.0031) compared to optimal health NTN-PW (**Table 2**).

As depicted in **Table 3**, when the high SHS were stratified into PE and NTN-PW at 32-42 weeks gestation, there were significantly (p <0.0001) elevated levels of SBP, DBP, Na, LDH, AST, ALT, ALP, GGT, urea, creatinine, UA, and TG among PE women compared to NTN-PW, who previously had high SHS at baseline. Conversely, PE women

were at an increased risk of preterm delivery as depicted by a significantly lower gestational age than NTN-PW who previously had high SHS at baseline. Additionally, levels of Mg, Ca, total protein, albumin, and platelet (PLT) count were significantly reduced among PE women compared to NTN-PW, who previously had high SHS at baseline sampling.

At 32-42 weeks gestation when participants who previously had optimal health were stratified into PE and NTN-PW, there were a significantly (p <0.0001) elevated levels of SBP, DBP, LDH, AST, ALT, ALP, GGT, urea, creatinine, UA, and TG but a reduced GA, Mg, Ca, total protein, albumin, platelet (PLT) count and baby birthweight in PE compared to the NTN-PW.

Furthermore, when PE women who previously had high SHS were compared to PE women who previously had optimal health, there were a statistically significantly (p <0.05) lower GA, Mg, Ca, total protein, and albumin levels, but elevated levels of SBP, LDH, AST, ALT, ALP. Also, when NTN-PW who previously had high SHS were compared to NTN-PW who previously had optimal health at 32-42 weeks gestation, there were statistically significantly (p <0.05) lower levels of serum Mg and Ca, but elevated levels of SBP **(Table 3)**.

On exploring the association between the incidence of PE and the individual SHS domain score **(Table 4)**, there was a significant positive correlation between PE incidence and Fatigue (r=0.300; p =0.0038), Cardiovascular system (r=0.291; p =0.0174), digestive system (r=0.287; p =0.0291), immune system (r=0.342; p =0.0010), mental health status (r=0.442; p <0.0001) and the overall SHS score (r=0.509; p <0.0001) **(Table 4).**

The univariate logistic regression analysis explained that, high BP, low Mg, low Ca, low Hb, low HDL, high LDH, high AST levels, high creatinine and high TG levels yielded a significantly increased odds ratio for predicting high SHS among NTN-PW at baseline

311 who later developed PE. After adjusting for confounding factors on multivariate analysis,
312 the association remained significant and the odds ratios were only slightly attenuated if
313 at all. Overall, high BP [aOR=2.84, 95% CI (1.94-5.40), p =0.0314], low Mg [aOR= 2.99,
314 95% CI (1.29-6.20), p =0.0038] and low Ca [aOR=4.20, 95% CI (1.57-5.63), p <0.0001],
315 high TG [aOR= 2.08, 95% CI (1.12-4.27), p =0.0151] and low HDL-c [aOR= 2.30, 95%
316 CI (1.20-6.83), p =0.03071] were significant independent risk factors associated with
317 baseline high SHS PWLD-PE **(Table 5).**

318 To explore the usefulness of SHS in predicting PE and other APCs, we performed a
319 multivariate logistic regression model and use the cut-off to generate sensitivity, specificity
320 and area under the ROC curve. Using high SHS alone as a screening measure yielded
321 significantly increased odds, a wider area under the ROC curve (AUC), and a high sensitivity
322 and specificity for identifying PE (aOR= 3.67, AUC= 0.8987, 91.9% and 87.8%), PE
323 coexisting with IUGR (aOR=2.86, AUC= 0.8378, 91.5% and 75.9%), and stillbirth (aOR=
324 2.52, AUC= 0.7832, 96.6% and 60.0%) compared to its combination with Mg and Ca (**Table**
325 **6).**

326 Also using high SHS alone as a screening measure yielded a better predictive and diagnostic
327 accuracies for identifying PE coexisting with HELLP syndrome (aOR=2.08, AUC= 0.8009,
328 97.2% and 63.8%), AKI (aOR= 2.2, AUC= 0.8246, 95.3% and 70.0%) and dyslipidaemia
329 (aOR=2.80, AUC= 0.8205, 95.7% and 68.4%) compared to its combination with Mg and Ca
330 (**Table 7)**.

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

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)

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

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

surveillance, risk stratification, optimal diagnosis, prediction of adverse drug to drug interactions and early disease identification [9, 10, 8].

Previous case-control studies by Ephraim et al. [34] among a Ghanaian population and Guo et al. [35] among a Chinese population [34, 35] have observed several serum biochemical changes including reduced levels of magnesium and calcium in preeclamptic pregnancies at the point of diagnosis, although these imbalances are not commonly reported in early normotensive pregnancies prior to the onset of PE. However, at baseline (10-20 weeks gestation) in the present longitudinal cohort study, high SHS NTN-PW who later developed PE at 32-42 weeks gestation had significantly reduced levels of magnesium and calcium compared to optimal health NTN-PW (Table 2). High SHS NTN-PW had low serum magnesium and calcium levels with 3- and 4-fold increased odds respectively, compared to those with optimal health status (Table 5). This relationship is novel. This novel finding signifies that SHS can represent a tool for PPPM by predicting an early risk of low dietary magnesium and calcium intake. A cross-sectional study in a Ghanaian population observed significantly low Mg and Ca levels among NTN-PW compared to non-pregnant women [36]. The low calcium levels at baseline may have led to hypertension by stimulating an increased release of renin and parathyroid hormone, which in turn increases intracellular calcium in smooth muscle, culminating in vasoconstriction [34]. The observed low magnesium levels may also be due to increased clearance by the renal system, reduced dietary intake, haemodilution caused by expansion of the extracellular space and high consumption of minerals by the growing foetus [35, 34]. From the PPPM perspective, SHS can be used to predict early signs of calcium and magnesium malnutrition and also inform therapeutic options needed for high SHS NTN-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

maternal artery remodeling [42]. Another factor that may explain PE coexisting with IUGR is maternal psychosocial stress [43, 7, 44], previously shown by a cross-sectional study among a Chinese population that found an association between SHS and psychosocial stress [22] potentially associated with fatigue which is one of the SHS-specific domains.

Another novel finding of the present study was a significant association between SHS and PE coexisting with stillbirth. Normotensive pregnant women who had high SHS at baseline (10-20 weeks gestation) were 2.5 times more likely to develop PE-coexisting with stillbirth during birth (32-42 weeks gestation). At 2.5-fold predictive odds ratio for high SHS, a sensitivity of 96.6%, specificity of 60.0% (Table 6) and a discriminating power of 78.3% (Fig. 3c) was observed. Preeclampsia is known to complicate the development of stillbirth and the underlying cause has been linked to placental insufficiency and incomplete maternal arteries remodeling [3, 42, 45]. Thus, SHSQ-25 suggests a non-invasive subjective measure for the identification of stillbirth strongly emphasizes the advantage of PPPM to prevent this fatal outcome.

SHS and PE-coexisting HELLP syndrome in this study is another novel finding. In the present study, HELLP syndrome identified by haemolysis (high levels of LDH), elevated liver enzymes (ALP, AST, ALT, and GGT) and low platelet count was observed at a higher rate in PE women compared to NTN-PW. Pregnant women who had high SHS at baseline (10-20 weeks) were 2.08 times more likely to develop PE-coexisting HELLP syndrome at 32-42 weeks (Table 7). This syndrome, which is characterised by microangiopathic anaemia, thrombocytopaenia and periportal hepatic necrosis [25] is a known cause of eclampsia-associated mental health problems in pregnancy [33]. Our findings indicated that high SHS can identify PE-coexisting HELLP syndrome at 97.2% 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 ≥88.4μmol/lor
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),

discriminating power of 82.1% (Fig. 3f) and diagnostic performance (sensitivity of 95.7% and specificity of 68.4%) was observed for the prediction of PE-coexisting with dyslipidaemia (Table 7). An association between SHS and cardiovascular and/or cardiometabolic risk has been established in our previous studies [18, 20]. Although pregnancy-induced hyperlipidaemia may be physiologic, dyslipidaemia may predispose the mother to atherosclerosis and directly contributes to cardiovascular disease (CVD) [27, 47]. The development of dyslipidaemia may be associated with systemic inflammation originating from *N*-glycosylation-induced changes in immunoglobulin G (IgG) structure and function [48]. Since, dyslipidaemia remains one of the predisposing factors PE [30], early identification of women at risk of dyslipidaemia would be an opportunity for selective monitoring and management. This supports the need to integrate SHSQ-25 in antenatal care as a dynamic screening tool for PE complicated by dyslipidaemia. Since SHS correlates with cardiovascular index like dyslipidaemia it will generate an early risk stratification for PE participants at risk of cardiovascular disease as well as promote an opportunity personalised medicine.

To our knowledge, this is the first study integrating SHS as a screening tool in pregnancy and childbirth, and the largest prospective cohort study in a Ghanaian population. Nevertheless, there were some limitations. First, the recruitment of participants in this present study was single-hospital centred, in the sense that only one teaching hospital was involved, thus, there was a possibility of ethnic bias as most of the participants were Akan's and few were distributed across other ethnic groups. Second, this study could not recruit baseline participants at early but rather late first trimester of pregnancy, hence we could not perform SHS evaluation at 21-31 weeks gestation to see the changes in health status over time in relation to the risk of PE. The findings of this study, however, is novel and, thus, further studies are needed in another population to

establish the observed association. The relationship between SHS and PE as well as PE coexisting with APCs, although not well-understood, may have an interconnection with placenta-derived factors (angiogenic growth mediators) and oxidative stress, which are key factors contributing to the pathogenesis of PE. Our next study will address this by evaluating an association between SHS, angiogenic growth mediators and oxidative stress among NTN-PW in this on-going Ghanaian Suboptimal Health Cohort Study (GHOACS).

Conclusion

In summary, a higher percentage of high SHS NTN-PW at baseline are more likely to developed PE. The incidence of PE increased with increasing SHS-specific domain scores. This association was supported by a significantly deranged haematobiochemical profile, an increased adjusted odds ratio, a wider area under the ROC curve, and a better sensitivity and specificity in favour of high SHS NTN-PW compared to optimal health participants. Overall, high SHS in early pregnancy is an independent risk factor of PE as well as PE coexisting with IUGR, stillbirth, HELLP syndrome, AKI and dyslipidaemia.

Integration of SHSQ-25 as a screening tool in both early antenatal care and follow-up of pregnant women will allow early detection of adverse pregnancy complications whilst creating an opportunity for PPPM policies such as screening programmes, education, risk assessment and targeted prevention. The idea of SHS (Sub optimal Health Status) profile – highly correlated with biochemical/ physiological risk factors – implies that we can "feel" the inside pathologies – though usually perceived as "subjective", is very important for self-education/responsibility, suggesting a potential for "subjective" PPPM approach. Hence, SHSQ-25 can be used as an alternative health pre-screening measure in clinical laboratory-limited communities, fields and community health centres in sub-Saharan African countries on emergency situations.

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Authors Contribution

EOA, PR, DC and WW conceived the study. EOA and CAT performed the investigation collected the data. EOA performed the statistical analysis. EOA, PR, DC, EA, YW, and WW wrote the paper. All authors read and approved the final manuscript.

Compliance and ethical standards

Conflict of interest

The authors declare that they have no conflict of interest.

Consent for publication

Not applicable

Ethical approval and consent to participants

Approval for this study was obtained from the Committee on Human Research Publication and Ethics (CHRPE) of the School of Medical Science (SMS) /KNUST and Komfo Anokye Teaching Hospital (KATH) (CHRPE/AP/146/17) and the Human Research Ethics Committee of Edith Cowan University (ECU) (17509). This study was conducted in accordance with the guidelines of the Helsinki Declaration. Written informed consent in the form of a signature and fingerprint was obtained from all participants and Legally Authorised Representatives after the protocol of the study was explained to them in plain English language and native Ghanaian language where appropriate.

Abbreviations

SHS, suboptimal health status; OHS, optimal health status; SHSQ-25, 25-question based Suboptimal Health Status questionnaire; GHOACS, Ghanaian Suboptimal Health Cohort Study; PE, preeclampsia; APCs, adverse pregnancy complications; PPPM, preventive, predictive and personalised medicine; IUGR, intrauterine growth restriction; HELLP, haemolysis, elevated liver enzymes and low platelet count; SBP, systolic blood pressure; DBP, diastolic blood pressure; Mg, magnesium, Ca, calcium, Na: sodium; K: potassium; Cl-: chloride; LDH: lactate dehydrogenase; UA: uric acid; RDW: red cell distribution width; FBG, fasting blood glucose; TG, triglyceride; TC, total cholesterol; HDL-c, high density

lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transferase; TP, total protein; ALB, albumin; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; aOR, adjusted odds ratio, CI, confidence interval; ROC, receiver's operating characteristics, AUC, area under the ROC curve.

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740

741 **Table 1. Baseline (10-20 weeks gestation) sociodemographic characteristics of normotensive**
742 **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

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

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

	High SHS at 10-20 weeks (Baseline)			**OHS at 10-20 weeks (Baseline)**		
Parameter	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

747 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**

	High SHS			OHS		
Parameter	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

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)

	PE incidence	
SHS domains	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

	Model 1	Model 2							
Baseline SHS	cOR (95% CI)	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).