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# НЕВРОЛОГИЧЕСКИЕ КОРРЕЛЯТЫ СУБКЛИНИЧЕСКОЙ НАГРУЗКИ ОТ КРОВОТЕЧЕНИЙ У ЗДОРОВЫХ МЕНСТРУИРУЮЩИХ ЖЕНЩИН

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# NEUROLOGICAL CORRELATES OF SUBCLINICAL BLEEDING BURDEN IN HEALTHY MENSTRUATING FEMALES

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**Резюме.** Изучена взаимосвязь между нагрузкой кровотечений и неврологической симптоматикой у здоровых менструирующих женщин. В исследовании приняли участие 143 участницы. Выявлена статистически значимая умеренная корреляция ($r = 0{,}358$; $p < 0{,}0001$). Медиационный анализ показал, что клиническая анемия объясняет лишь 0,8 % этой взаимосвязи, что свидетельствует о субклиническом механизме, обусловленном тканевым дефицитом железа.

**Ключевые слова:** субклиническая нагрузка кровотечений, неврологические симптомы, дефицит железа, когнитивный туман, меноррагия, патофизиология.

**Resume.** The association between bleeding burden and neurological symptom load was examined in healthy menstruating females ($n = 143$). A statistically significant moderate correlation was identified ($r = 0.358$; $p < 0.0001$). Mediation analysis revealed that clinical anaemia explained only 0.8 % of the relationship, implicating subclinical tissue-level iron depletion as the primary driver.

**Keywords:** subclinical bleeding burden, neurological symptoms, iron deficiency, cognitive fog, menorrhagia, pathophysiology.

**Relevance.** Heavy menstrual bleeding affects 10-20 % of reproductive-age females, and up to 30 % of women have an undiagnosed bleeding disorder [3]. Despite this, the neurological consequences of repeated subclinical blood loss remain largely unexplored. Fatigue, brain fog, dizziness, and restless leg phenomena worsen during menstruation yet are routinely dismissed as unrelated to bleeding. We hypothesise that subclinical bleeding burden drives neurological symptoms through iron depletion, cerebral hypoperfusion, and hormonal modulation, mechanisms operating below the threshold of standard haematological markers.

**Aim:** to characterise the association between bleeding burden and neurological symptom load in healthy menstruating females, and to explore potential underlying pathophysiological mechanisms.

**Objectives:**

1. Construct a Bleeding Symptom Index (BSI) integrating menstrual and systemic haemostatic features.
2. Construct a Neurological Symptom Index (NSI) capturing period-specific neurological symptoms using delta-scoring.
3. Determine the BSI–NSI correlation and test whether clinical anaemia mediates the relationship.

**Materials and methods.** A cross-sectional online survey was distributed in English and Russian languages via social and academic networks (March 2026) to menstruating females aged 16–55 without a known bleeding disorder. Of 173 initial responses, 30 were excluded: 15 who did not meet the inclusion criteria and 15 using hormonal contraceptives (which suppress the menstrual cycle and confound both indices). The primary analysis comprised n = 143 (Sri Lankan 42.8 %; Nigerian 28.3 %; other 28.9%).

BSI scoring: Ten items summed across two domains: menstrual symptoms (period duration 0-3 pts; change frequency 0-2 pts; clot frequency 0-4 pts; clot size 0-3 pts; self-reported heavy period 0-2 pts) and systemic haemostatic markers (easy bruising 0–4 pts; unexplained bruises 0–1 pt; nosebleeds 0-4 pts; prolonged wound bleeding 0-4 pts; post-dental bleeding 0-1 pt). Maximum BSI = 28. Cronbach's $\alpha = 0.431$, reflecting intentional multi-domain construction: menstrual and systemic bleeding co-occur in undiagnosed haemostatic disorders such as von Willebrand disease.

NSI scoring: Nine items capturing period-specific neurological burden. For four paired domains (restless leg sensations, urge to move, RLS nocturnal worsening, concentration), a delta score was computed (during - off-period, clamped at 0), isolating period-attributable worsening from baseline. Remaining items were scored directly: fatigue, dizziness, cognitive fog, word-finding (each 0 - 4 pts); headache frequency (0 - 3 pts); menstrual headache link (0 - 2 pts). Cronbach's $\alpha = 0.60$.

Statistical analysis: Spearman rank correlation with Fisher z-transformation (95 % CI); Kruskal-Wallis for NSI across BSI tiers; mediation analysis with logistic regression for path a (BSI → anaemia) and linear regression for path b (anaemia → NSI | BSI). All analyses were conducted in R v4.5.3.

**Results and their discussion.** In the primary sample (n = 143), mean BSI was 7.05 (SD 2.90, range 1–14) and mean NSI was 11.11 (SD 4.81, range 2–25). A statistically significant moderate positive correlation was identified between BSI and NSI: Spearman $r = 0.358$, 95 % CI [0.216–0.489], $p < 0.0001$. The 95 % CI does not cross zero, confirming statistical significance.

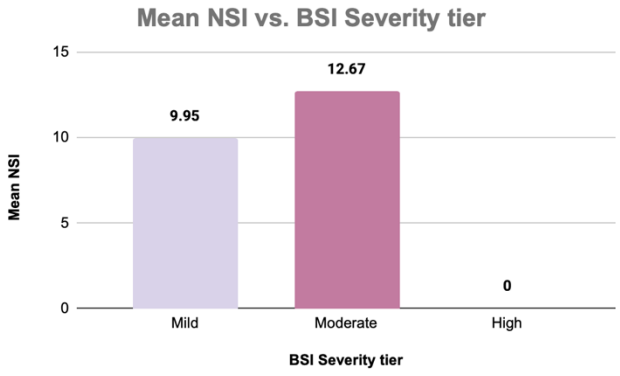


**Fig. 1** – Mean NSI vs. BSI severity tier

A dose-response gradient was observed across BSI severity tiers: mean NSI rose from 9.95 (Mild, BSI 1–6, n = 82) to 12.67 (Moderate, BSI 7–13, n = 61), indicating that neurological symptom burden scales proportionally with bleeding severity. Symptom

clustering revealed the fatigue-dizziness-cognitive fog triad as the strongest individual correlates (mean scores 2.74, 1.67, and 2.08 respectively), consistent with a systemic mechanism involving oxygen delivery and mitochondrial energetics rather than a purely dopaminergic pathway.

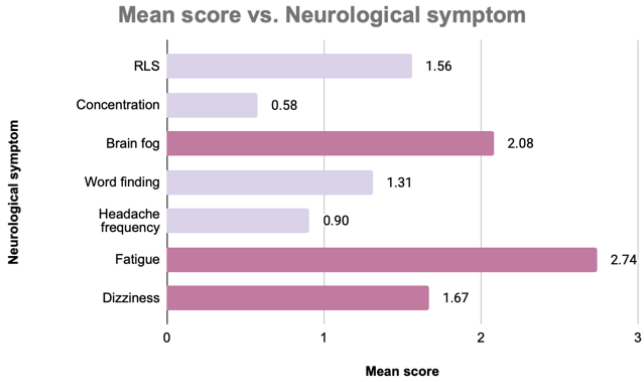


**Fig. 2** – Mean score vs. neurological symptom

Mediation analysis demonstrated that clinical anaemia accounts for only 0.8 % of the BSI–NSI relationship (indirect $\beta = 0.002$, 95 % CI [−0.231, 0.260], $p = 0.982$). The confidence interval crosses zero, confirming the indirect pathway is non-significant. The direct effect ($\beta = 0.319$) is virtually unchanged after adjusting for anaemia. This is the central finding: the neurological pathway exists and is statistically significant, but does not require clinical anaemia to operate.

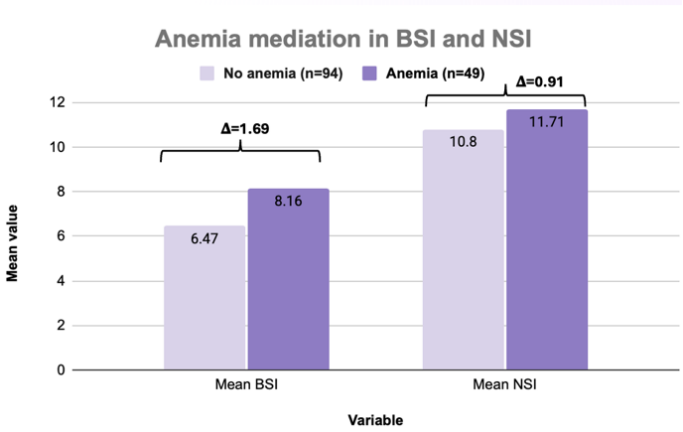


**Fig. 3** – Anemia mediation in BSI and NSI

Three complementary pathophysiological mechanisms explain this subclinical relationship.

Iron-Dopamine Axis: Iron is the rate-limiting cofactor for tyrosine hydroxylase, which converts L-tyrosine to L-DOPA → dopamine. Tissue-level iron depletion, occurring before haemoglobin falls to anaemic thresholds; pairs dopaminergic signalling in the basal ganglia and prefrontal cortex, manifesting as brain fog and executive dysfunction [2].

Haemodynamic & Metabolic Constraints: Cyclic hypovolaemia from menstrual blood loss transiently reduces cerebral perfusion (orthostatic dizziness), while iron-dependent cytochrome oxidase depletion impairs mitochondrial oxidative phosphorylation,

producing the profound fatigue that was the strongest BSI correlate in our data (r = 0.347) [2].

Neuroendocrine Modulation: Cyclic oestrogen and progesterone fluctuations modulate dopaminergic and serotonergic receptor sensitivity. When iron stores are already marginal, these hormonal shifts act as a second hit, amplifying neurological symptom expression specifically during menstruation [1].

Limitations: Convenience sample (71% Sri Lankan or Nigerian); self-report only with no serum ferritin or haemostatic workup; novel unvalidated composite indices (BSI $\alpha = 0.431$, NSI $\alpha = 0.60$); cross-sectional design precludes causal inference.

**Conclusions:**

1. Undiagnosed bleeding burden is significantly and dose-dependently associated with neurological symptom load in healthy menstruating females ($r = 0.358$, $p < 0.0001$).

2. Clinical anaemia mediates only 0.8 % of the relationship, demonstrating that the mechanism operates through subclinical iron depletion, impaired mitochondrial energetics, and cerebral hypoperfusion, all below standard diagnostic thresholds. Ferritin-based, rather than haemoglobin-based, screening is warranted.

3. Bleeding burden is not solely a gynaecological problem. It is a neurological one too.

**Literature**

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