Perceived stress and related conditioning indices following fursultiamine and B-complex supplementation in recreational runners: a single-arm pilot study

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Headline

Recreational runners experience cumulative psychological and physiological strain from training and daily life stressors, which can impair recovery and increase fatigue. Stress monitoring strategies integrate objective autonomic and sleep-related variables captured via wearable devices (1, 2) and subjective indices, such as Hooper's questionnaire assessing sleep quality, fatigue, stress, and muscle soreness (3-6). B-group vitamins, particularly fursultiamine (thiamine tetrahydrofurfuryl disulfide, TTFD), play a vital role in energy metabolism and neuromuscular function. This lipid-soluble thiamine derivative has been shown to improve energy metabolism and endurance performance under fatigue loading in animal models (7, 8). In preclinical models, fursultiamine modulates carbohydrate and lactate metabolism (9) and promotes voluntary physical activity via dopaminergic activation (10). In trained male athletes, fursultiamine combined with B vitamins attenuated exercise-induced fatigue and subjective symptoms (11). Furthermore, B-complex supplementation combining multiple B vitamins has been shown to reduce perceived stress and exercise-induced fatigue in healthy adults and active populations (12-14). While B-complex supplementation has been reported to attenuate stress and fatigue, evidence evaluating integrated subjective wellness, objective wearable-derived sleep/training parameters, and urinary vitamin absorption in active recreational runners remains limited.

Aim

This single-arm pilot study examined the feasibility of an integrated monitoring framework and evaluated the associations between 4 weeks of fursultiamine-containing B-complex supplementation and changes in subjective wellness, wearable-derived sleep/training parameters, and urinary vitamin absorption in recreational runners.

Methods

Design and Ethical Approval

This was an exploratory, single-arm, open-label pilot study consisting of a 2-week observation (control) period followed by a 4-week intake (intervention) period. The study protocol was approved by the Ethics Committee of the Shiba Palace Clinic (158191_rn-39613) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. Data collection took place between March and May 2025. Participants maintained their habitual training routines without experimental restrictions.

Participants

Healthy male recreational runners aged 18–49 years who trained regularly and owned a Garmin smartwatch were recruited nationwide. The sample size was chosen based on guidance for pilot studies (15, 16) to estimate outcome variance and feasibility. Out of 23 recruited runners, 4 were excluded for failing to meet the prespecified 75% or greater response rate for daily wellness surveys or due to missing smartwatch training logs. Consequently, $n = 19$ participants were included in the final analysis ($n < 19$ for specific sleep metrics due to an 80% wear-time compliance threshold).

Intervention and Investigational Product

The investigational product was identical in formulation to a marketed B-vitamin complex quasi-drug in Japan and provided by Alinamin Pharmaceutical Co., Ltd. (Tokyo). The daily dose of two tablets contained fursultiamine hydrochloride (21.83 mg), vitamin B2 (12 mg), vitamin B6 (10 mg), vitamin B12 (40 μg), and dl-α-tocopherol succinate (20 mg). During the intake period, participants were instructed to take two tablets (maximum daily dosage) every morning, immediately after a meal with regular or hot water. Adherence was recorded using a web-based system, and all participants maintained an intake rate of over 80%. They were instructed to avoid initiating any new dietary supplements, over-the-counter drugs, or quasi-drugs aimed at fatigue recovery during the period.

Data Collection and Measurements

Throughout both periods, participants were required to complete Hooper's questionnaire daily and wear their smartwatches continuously. These data were collected either through direct input into a web-based system (One Tap Sports, Euphoria Co., Ltd., Tokyo, Japan) or via the Application Programming Interface (API) provided by Garmin. Subjective wellness indices were assessed using Hooper's questionnaire (3), comprising 4 items (sleep quality, fatigue, stress, and muscle soreness). Participants were asked to rate each variable on a 7-point scale (1 representing "very, very good" and 7 representing "very, very bad"). Hooper's questionnaire was administered in the participants' native language (Japanese). Objective sleep-related metrics (total sleep duration, nocturnal heart rate [HR], and heart rate variability [HRV; mean RMSSD]) as well as training metrics (running distance, duration, speed, and HR) were captured continuously using participants' Garmin smartwatches and aggregated via an API system.

To evaluate estimated vitamin absorption, urine tests were conducted to measure urine-based estimated absorption of vitamins B1, B2, and B6 at four time points: the start and end of the observation period (week 0 and 2, respectively), and midpoint and end of the intake period (week 4 and 6, respectively). The timing of urine collection was designed to evaluate the effects of sustained daily supplementation rather than acute fluctuations following a single dose, thereby reflecting stable vitamin status during each study period. Urine samples were collected using a mail-in nutritional testing kit (VitaNote; Yukashikado Inc., Tokyo, Japan) at the four time points. These algorithm-derived mg-equivalent indices reflect the metabolic state following intestinal absorption and serve as surrogate markers of systemic vitamin availability. According to the manufacturer, the analytical precision of the urinary assay, expressed as the coefficient of variation, was 1.4% for B1, 2.2% for B2, and 5.6% for B6. To minimize dietary influence, age-specific standardized meals with identical compositions were provided for approximately 36 h preceding each sampling point, starting from dinner 2 days prior through all meals on the day before urine collection.

Statistical analysis

Analyses were performed in R (version 4.5.1). In alignment with SPSR guidelines, statistical hypothesis testing (p-values) was omitted, and outcomes were evaluated using magnitude-based effect sizes and 95% confidence intervals (95% CI). Primary comparisons for wellness, sleep, and training variables were made between the final week of observation (Week 2) and the final week of intake (Week 6). Cohen's d_z was calculated for normally distributed continuous variables, and rank-biserial correlation r (with Hodges-Lehmann 95% CI) was used for non-normally distributed data. For urinary biomarkers, Weeks 0 and 2 were averaged as baseline; changes across baseline, Week 4, and Week 6 were evaluated using Kendall's W. Effect size magnitudes were interpreted according to Cohen's benchmarks (17): small ($|d_z| \geq 0.2$), medium ($|d_z| \geq 0.5$), and large ($|d_z| \geq 0.8$). Exploratory correlation analyses between changes (Delta, Week 6 minus baseline/Week 2) in perceived stress and urinary vitamin absorption were conducted using Pearson's r or Spearman's rho following the exclusion of influential outliers identified via Cook's distance with a cutoff of 4/N (18).

Results

Perceived stress decreased from Week 2 to Week 6, with a mean change of -0.34 (95% CI [-0.67, -0.02]; Cohen's d_z = -0.508). For the remaining three Hooper items (sleep quality, fatigue, and muscle soreness), 95% CI spanned across zero (Table 1). Objective sleep variables (total sleep duration, sleep HR, and sleep HRV) all demonstrated 95% CI spanning across zero (Table 1). Training variables (running distance, duration, speed, and running HR) similarly presented 95% CI spanning across zero (Table 1). Urinary indices of estimated absorption for vitamins B1, B2, and B6 demonstrated overall main effects of time across baseline, Week 4, and Week 6, with marked increases from baseline to Weeks 4 and 6 across all three biomarkers (Table 2).

In the primary sample (n = 19), correlations between changes in urinary vitamins and perceived stress were unclear. However, after removing influential outliers based on Cook's distance, large negative correlations emerged between changes in perceived stress and urinary vitamin B1 (n = 17, r = -0.556, 95% CI [-0.818, -0.102]; Figure 1) and vitamin B6 (n = 16, r = -0.507, 95% CI [-0.802, -0.016]; Figure 2).

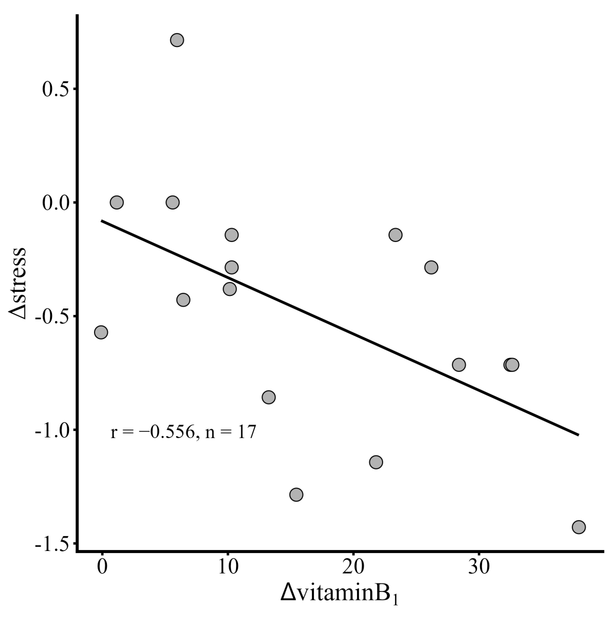

Fig. 1. Sensitivity analysis of the correlation between changes (Delta) in estimated urinary vitamin B1 absorption and perceived stress. The scatter plot illustrates the relationship between changes in vitamin B1 (Week 6 minus the baseline mean of Weeks 0 and 2) and perceived stress (Week 6 minus Week 2). Influential observations based on Cook's distance (n = 2) were excluded. The solid line represents the linear regression (n = 17, r = -0.556, 95% CI [-0.818, -0.102]).

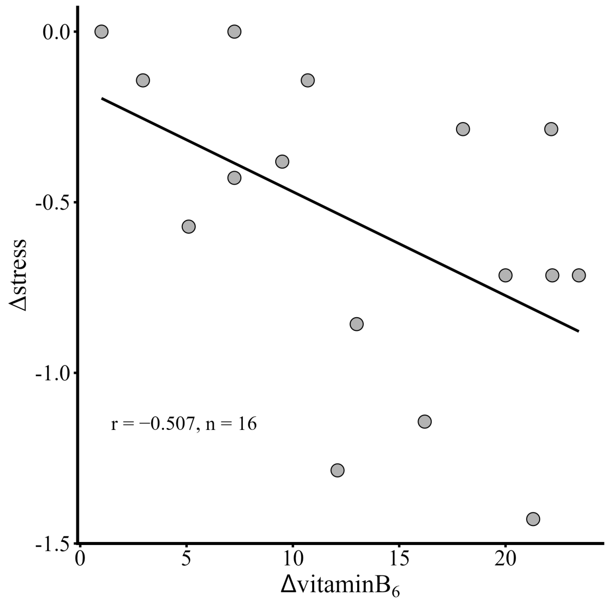

Fig. 2. **Sensitivity analysis of the correlation between changes (Delta) in estimated urinary vitamin B_6 absorption and perceived stress. The scatter plot illustrates the relationship between changes in vitamin B6 (Week 6 minus the baseline mean of Weeks 0 and 2) and perceived stress (Week 6 minus Week 2). Influential observations based on Cook's distance (n = 3) were excluded. The solid line represents the linear regression (n = 16, r = -0.507, 95% CI [-0.802, -0.016]).**

Table 1. **Subjective wellness indices, sleep-related variables, and training variables during the observation and intervention periods. Values are presented as mean ± SD for normally distributed variables and median [IQR] for non-normally distributed variables. Change represents the difference between Week 2 and Week 6, expressed as mean change or Hodges–Lehmann estimate with 95% confidence interval (CI). Effect sizes are reported as Cohen's d_z (parametric) or rank-biserial correlation r (non-parametric).**

Variables	Observation period	Intervention period	Change [95% CI]	Effect Size
Sleep quality (n = 19)	3.72 ± 0.60	3.70 ± 0.54	-0.02 [-0.28, 0.24]	d_z =-0.044
Fatigue (n =19)	3.86 ± 0.66	3.81± 0.71	-0.05 [-0.46,0.36]	d_z =-0.060
Stress (n = 19)	3.68 ± 0.65	3.34 ± 0.72	-0.34 [-0.67, -0.02]	d_z =-0.508
Muscle soreness (n = 19)	3.11 ± 0.92	3.49 ± 1.05	0.38 [-0.03,0.78]	d_z =0.450
Total sleep duration (min) (n = 17)	371.4 ± 52.9	381.3 ± 50.0	10.0 [-9.29,29.19]	d_z =0.266
Sleep HRV (ms) (n = 17)	64.03 ± 19.24	64.62 ± 16.86	0.59 [-4.25,5.42]	d_z =0.062
Sleep HR (bpm) (n = 15)	46.39 ± 5.52	45.75 ± 5.31	-0.64 [-2.10, 0.82]	d_z =-0.243
Running distance (km) (n = 19)	35.9 [14.5,59.3]	33.1 [10.4,60.8]	-6.69 [-17.52,6.10]	r =-0.647
Running duration (min) (n = 19)	192 [94,312]	178.0 [55.5–344.0]	-41.0 [-112.5,35.0]	r =-0.653
Running speed (m/s) (n = 16)	3.28 [2.92,3.50]	3.19 [2.91,3.60]	-0.05 [-0.20,0.15]	r =-0.132
Running HR (bpm) (n = 16)	134.5 ± 14.9	137.0 ± 16.9	2.49 [-4.12,9.11]	d_z =0.201

Discussion

Our preliminary findings indicate that 4 weeks of fursultiamine-containing B-complex supplementation was accompanied by lower perceived stress in recreational runners. As no corresponding shifts were observed in training variables, fluctuations in training load alone may not fully account for this observed change.

The efficacy of B-vitamin supplementation is highly contingent on factors such as supplement composition, dosage, intervention duration, and training status. For instance, supplementation with thiamine does not typically influence high-intensity performance when the baseline thiamine status is already adequate (19). In contrast, a 4-week intervention with a multicomponent B-complex improved endurance performance and reduced exercise-induced fatigue in healthy adult non-athletes (13). These findings suggest that although high doses of thiamine alone may not enhance endurance performance, a prolonged, synergistic B-complex approach is effective, particularly in recreational or non-athlete populations who may have more physiological room for improvement. B-complex supplementation can influence subjective and recuperative outcomes. Our findings extend this logic, suggesting that in a real-world environment, multi-week B-complex supplementation appears to align primarily with lower perceived stress. This study used a preparation centered on TTFD, which shows superior intestinal absorption and efficient conversion to active thiamine compared with conventional thiamine. Although causal inference is limited by the single-arm design, our findings that vitamins B1 and B6 were associated with lower perceived stress are consistent with these converging neurometabolic roles and with prior reports linking B-vitamin supplementation to reduced perceived stress (12-14).

Table 2. Urine-based estimated absorption of vitamins B1, B2, and B6 at baseline and during the intervention period. Values are shown as medians [IQR]. Change represents the difference from baseline, expressed as Hodges–Lehmann estimates with 95% CI. Main effects across time were assessed via the Friedman test (χ^2 and Kendall's W). Pairwise effect sizes are reported as rank-biserial correlation r.

Variables	Baseline (0-2)	Week 4	Week 6	Friedman results	Change [95% CI]	Effect size
Vitamin B_1 (n=19)	1.00[0.78,1.33]	14.50[10.35,26.90]	16.70[11.10,31.40]	χ^2=22.84, W=0.60	Week 4: 16.26[10.38,23.80]	Week 4: r =0.868
					Week 6: 19.25[10.95,29.88]	Week 6: r =0.868
Vitamin B2 (n=19)	4.25[2.98,6.95]	12.80[8.10,15.20]	27.10[15.75,32.00]	χ^2=32.32, W=0.85	Week 4: 7.64[4.90,10.88]	Week 4: r =0.868
					Week 6: 19.59[13.95,25.60]	Week 6: r =0.877
Vitamin B_6 (n=19)	3.55[2.70,5.23]	16.60[13.20,20.65]	20.50[12.85,26.60]	χ^2=26.53, W=0.70	Week 4: 11.45[8.62,15.10]	Week 4: r =0.868
					Week 6: 14.34[9.68,21.08]	Week 6: r =0.877

Practical Applications

- Supplementation with a fursultiamine-containing B-complex may serve as a practical nutritional strategy to lower perceived psychological stress in recreational runners during habitual training.
- Combining subjective daily surveys with wearable tracking provides a feasible, low-burden framework for monitoring stress and recovery in free-living environments for recreational runners.

Limitations

- The single-arm, open-label design lacks a placebo control group, making it impossible to rule out expectancy (placebo) effects or temporal regression to the mean.
- Wear-time thresholds for nocturnal smartwatch tracking reduced the effective sample size for sleep HRV and HR, limiting the precision of objective physiological estimates.
- Participants used personal Garmin smartwatches with varying sensor generations and firmware versions.

Author Contribution Statements

FT: Conceptualization, Investigation, Methodology, Project administration, Writing - original draft, Writing - review and editing. HI: Formal analysis, Visualization, Writing - original draft, Writing – review and editing. RT: Conceptualization, Funding acquisition, Project administration, Writing – review and editing. YU: Investigation, Data curation, Writing – review and editing. EN: Conceptualization, Writing – review and editing. YN: Conceptualization, Writing – review and editing. TN: Conceptualization, Writing – review and editing. YT: Investigation, Supervision, Writing – review and editing.

Conflicts of Interest

EN, YN, and TN are employees of Alinamin Pharmaceutical Co., Ltd., which provided funding for this study. As individual authors, they contributed scientifically to the work (see Author Contributions), and their company responsibilities were limited to matters concerning this study. At the organizational level, the sponsor was not involved in on-site investigations, formal statistical analyses, or data curation. FT, HI, RT, and YU are employees of Euphoria Co., LTD., which received research funding from Alinamin Pharmaceutical Co., Ltd. for this study. YT is the Medical Investigator (responsible physician) for this study and received an honorarium for medical supervision from Alinamin Pharmaceutical Co., Ltd. The authors affirm that the results are reported transparently and accurately without fabrication, falsification, or inappropriate manipulation.

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