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Individual effects of a nutritional supplementation blend on sleep in professional under-17 footballers: a replicate crossover trial

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ABSTRACT

To estimate sleep-related mean and individual effects of a supplementation blend comprising 15,000 mg cherry juice concentrate, 220 mg cherry extract, 250 mg cocoa extract, 200 mg of tryptophan, 100 mg of L-5-hydroxytryptophan, 3000 mg of glycine, 300 mg of magnesium, and 200 mg of theanine in youth Middle Eastern football players. Using a two-cycle replicate crossover design, 12 male youth football players (age = 16.1 ± 0.4 years, body mass = 70 ± 8.5 kg, stature = 179 ± 7.5 cm) completed two identical supplementation and two identical placebo (40-g dual-source carbohydrate gel) conditions, each lasting 2 days and in randomized sequences following the rest days subsequent to official match-play. Wrist-worn actigraphy measured time asleep, wake-after-sleep onset, sleep onset latency, and sleep efficiency in free-living conditions. Between-cycle Pearson's correlation coefficients quantified the consistency of the placebo-adjusted sleep responses to active supplementation for the first night and two-night averaged administration effects, respectively. Within-person linear mixed models and random-effects meta-analyses quantified person-by-supplementation response variability. For all administration comparisons and sleep outcomes, the between-cycle correlations were trivial (r range = -0.25 to 0.17 , all $p \geq 0.43$), with linear mixed modelling and meta-analytic approaches indicating trivial replicate-averaged supplementation effects. Participant-by-supplementation variability in sleep responses was trivial, indicated by the individual treatment estimates showing strong shrinkage toward the mean. Aggregated sets of n -of-1 trials revealed trivial replicate-averaged treatment effects and a lack of meaningful individual differences in placebo-adjusted sleep responses to blend supplementation in male youth Middle Eastern football players.

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KEYWORDS

Sleep; recovery; tryptophan; precision nutrition; replicate crossover

Introduction

Optimal recovery following training and competition is essential to maintain high-performance in professional sports (Halsen 2014, 2019). In this process, adequate sleep duration and consistent timing are critical for athletes to be prepared for, and recover from, training and competition (Fox et al. 2020; Walsh et al. 2021). Sleep is central to maintain psychophysiological processes and health in humans of all ages (Van Someren et al. 2015). We adopted Doherty et al.'s definition of sleep requirement (sleep need) as '*the optimum amount of sleep required to remain alert and function throughout the day*' (Doherty et al. 2024). The National Sleep Foundation recommends that sleep length should be 8–10 h for teenagers, 7–9 h for adults, and 7–8 h for older adults (Hirshkowitz et al. 2015). Young people are vulnerable to problems of sleep deprivation (Fox et al.

2020), with adverse implications for carbohydrate metabolism, appetite, energy intake, and protein synthesis that, ultimately, influence learning, cognition, immunity, and inflammation (Halsen 2014). Sleep disorders and disruption are particularly common in people from the Middle East throughout the Gregorian year (Reilly and Waterhouse 2007; Qasrawi et al. 2017; Arora et al. 2018; Lolli et al. 2021).

Research on recovery strategies in professional sports has focussed upon many different approaches to enhance sleep duration in athletes, including cognitive behaviour therapy, sleep hygiene education, light therapy, and nutritional interventions (Halsen 2014, 2019). The latter use of nutritional interventions to improve sleep duration has been investigated in general and clinical populations (St-Onge et al. 2016; Smith et al. 2019; Charest and Grandner 2024). Nutritional

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interventions for promoting good sleep can involve alterations of dietary intake *per se* or, more directly, administrations of nutritional supplementations that can stimulate brain neurotransmitters involved in the sleep–wake cycle regulation (Smith et al. 2019; Charest and Grandner 2024; Doherty et al. 2024). Dietary substances such as L-tryptophan (Wyatt et al. 1970; Hartmann and Spinweber 1979; van Zyl et al. 2018), glycine (Yamadera et al. 2007; Bannai and Kawai 2012), magnesium (Zhang et al. 2022), L-theanine (Lyon et al. 2011), and tart cherry (Howatson et al. 2012) have received particular attention because of their sleep-promoting effects via stimulation of the rate of serotonin synthesis and melatonin secretion (Halsen 2014, 2019).

Information regarding the isolated or combined effects of the above dietary supplementations on sleep in youth and senior sports athletes is, nevertheless, still sparse – the few randomized parallel-arm or single-cycle crossover trials have been conducted primarily on populations of healthy adults or those with clinical disorders from Western countries (Wyatt et al. 1970; Hartmann and Spinweber 1979; Yamadera et al. 2007; Lyon et al. 2011; Bannai and Kawai 2012; Howatson et al. 2012; van Zyl et al. 2018; Zhang et al. 2022). In this context, the Union of European Football Associations expert group statement on nutrition in professional football advised that the development of nutrition strategies (including the use of supplements) in preparation for, or to recover from, training and match demands should involve *individualized* protocols (Collins et al. 2021). The notion that nutritional strategies should be *individualized* or *personalized* for athletes is informed by the idea of *precision nutrition*, which encompasses the notion that individualizing nutritional advice, products, or services is more effective than more generic ‘*average-effect*’ approaches (Ordovas et al. 2018). Evidence for personalized nutrition is mostly based on observational studies with a low level of reproducibility (Ordovas et al. 2018). Individualized recommendations can be provided as part of service provision *only if* underpinned by evidence from appropriately designed studies adopting relevant statistical analysis approaches (Lolli et al. 2025).

As a form of *n*-of-1 trial, a replicate crossover study design is optimum for quantifying individual treatment effect heterogeneity (Senn 2001, 2018). By definition, a replicate crossover trial involves the repeated administration of control and dietary interventions, in a randomized order, to isolate the crucial component of variation corresponding to the athlete-by-supplement effects interaction (Lolli et al. 2025). Studies on the effects of L-tryptophan, glycine, magnesium, L-theanine, and tart cherry administered in combination as a nutritional blend have provided contrasting findings

regarding their sleep-related effects in samples of healthy adults (Langan-Evans et al. 2023; Morrison et al. 2025). Langan-Evans et al. (2023) conducted a conventional randomized single-cycle crossover trial. In this investigation, the combined administration of L-tryptophan, glycine, magnesium, L-theanine, and tart cherry reduced sleep onset latency by 24 min and increased total sleep time by 22 minutes per night (Langan-Evans et al. 2023). Conversely, Morrison et al. (2025) reported trivial effects of two nutritional interventions with differing glycaemic index and differential whey protein, tryptophan, and theanine content. Nevertheless, none of these studies adopted a replicate crossover design to determine whether the nutritional interventions may have worked consistently or not for all participants, which is the central tenet of personalized nutrition (Ordovas et al. 2018). The replicate crossover design can also provide increased statistical power to detect mean treatment effects compared with a single-cycle crossover trial. Therefore, we aimed to investigate the mean treatment effects and whether inter-individual variability exists in objective sleep responses to nutritional blend supplementation of L-tryptophan, glycine, magnesium, L-theanine, and tart cherry in professional male youth football players from the Middle East using a replicate crossover research design.

Methods

The protocol for this trial was registered on ClinicalTrials.gov (identifier: NCT07190989). The study received ethics approval by the Aspire Zone Foundation Institutional Review Board, Doha, State of Qatar (protocol number: F202501089).

Participants

Participants were eligible if injury-free and fully available for training and official match-play at the time of the trial administration. Study methods and reporting followed the CONSORT (Consolidated Standards of Reporting Trials) extension for *N*-of-1 trials (Shamseer et al. 2015). All procedures and potential risks were explained to both the student-athletes and their parents/guardians. Participant assent and written informed parental/guardian consent were obtained for participants eligible for this study.

Overall study design

Using a replicate crossover design (Senn 2016), participants received two identical supplementation and two identical placebo administrations over two consecutive

days in randomized sequences following the off days subsequent to official match-play, all over a 4-week period between September 2025 (Rabi ul Awal 1447) and October 2025 (Rabi Al-Akhar 1447). During this period, calendar prayer times ranged from 04:05 to 04:14 for the Fajr, 11:20 to 11:27 for the Dhuhr, 14:40 to 14:54 for the Asr, 17:08 to 17:32 for the Maghrib, and 18:38 to 19:02 for the Isha. Sunrise timings ranged from 05:22 to 05:31.

Sample size estimation

We adopted a pragmatic approach to statistical power for this quite onerous investigation and, therefore, estimated minimum detectable between-cycle correlation coefficient for the sample size of 12 participants, who were feasible to recruit (Figure 1; Supplementary File 1). In the absence of an established target difference value (Cook et al. 2018) and design-specific variance values (Senn 2019) applicable to each outcome measure considered in this two-cycle, four-period replicate crossover trial, a minimum sample size of 12 participants would translate to a one-tailed between-cycle correlation of 0.5, with a 90% confidence interval for this correlation ranging from 0.00 to 0.80, assuming both a null and a negative correlation would suggest non-rejection of the null hypothesis ($r \leq 0$). A sensitivity analysis involving a methodologically alternative and more advanced procedure to sample size estimation to examine the effects of the supplementation administration following a fixed-effects philosophy (Senn 2019) indicated that, assuming a minimum number of repeat cycles in a replicate crossover of two (Senn et al. 2011), a Type I error rate of 0.05, a Type II error rate of 0.2, a minimum clinically important

difference corresponding to an increase of 30 min limited to time asleep as primary outcome of interest (Youngstedt 2003; de Zambotti et al. 2019), an expected lack of meaningful treatment-by-participant interaction variability and a within-cycle standard deviation of 35 min (Langan-Evans et al. 2023), approximately 13 participants over a minimum of two cycles would be required for investigating whether the supplementation can have an effect in the sample being recruited.

Main trials

Our randomized replicate crossover trial was embedded into routine service provision to youth football players enrolled as part of a national federation development programme. Official match-play was scheduled on a Friday afternoon followed by 1 day off during first trial cycle, and on a Thursday followed by 2 days off during the second trial cycle. The general schedule for the student-athletes taking part to this study consisted of six school classes from 07:30 to 15:30 and double training sessions from 10:30 to 12:00 and 16:00 to 18:00 on the 2 days of the trial period. Breakfast was scheduled at 8:30, lunch at 12:30, and dinner at 19:00.

The randomization sequence for the four experimental trials was performed within paired cycles and generated by one researcher using the PLAN procedure available in SAS (Deng and Graz 2002). In keeping with the planned training and preparation microcycle, the supplementation and placebo were administered by the team nutritionist at dinner time to participants following the afternoon training session across each study period. The participants and

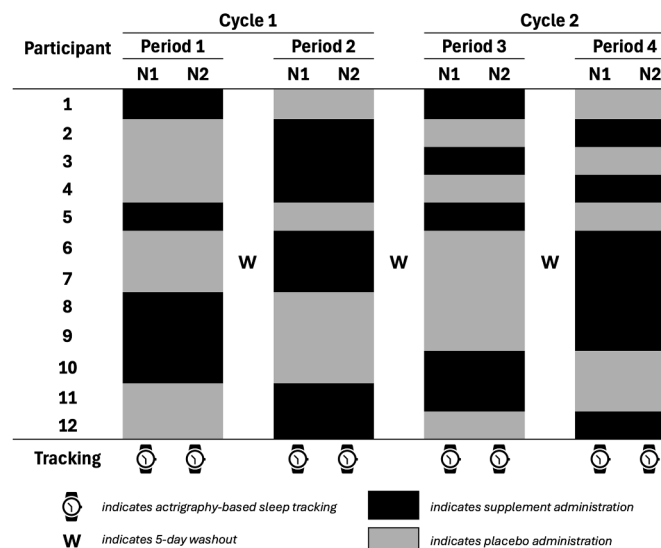


Figure 1. Set of sequences for trial participants who completed both administration cycles.

team nutritionist were all blinded as to the specific supplementation/placebo administration. Each trial was separated by at least 5 days as washout across the study periods within and between each cycle (Figure 1).

The supplementation involved the administration of 15,000 mg cherry juice concentrate, 220 mg cherry extract, 250 mg cocoa extract, 200 mg of tryptophan, 100 mg of L-5-hydroxytryptophan, 3000 mg of glycine, 300 mg of magnesium, and 200 mg of theanine as a nutritional blend in the form of a mixed juice. The placebo consisted of a 40-g dual-source carbohydrate gel, having a 1:0.8 ratio of maltodextrin and fructose, as an alternative supplementation known for having trivial effects on sleep-related outcome measures (St-Onge et al. 2016). Both the active supplementation (batch: F4213) and placebo (batch: F5005) were manufactured by Science in Sport and Informed Sport Tested for appropriate and certified administration of dietary substances to professional athletes. Participants followed a routine eat-as-usual dietary protocol consistent with the recommendations provided by the team nutritionist, and they were not habitual users of caffeine and nicotine, which they were asked to refrain from in principle as part of this 4-week trial administration procedures. Any experience of potential gastrointestinal symptoms was tracked on a routine basis over the course of the trial. In the case of late-phase trials as in the present investigation (Senn 1993), any suspension of supplementation was considered if a minimum of three participants or more in the study sample had experienced grade 2 severity or moderate adverse reactions to each administration (Coates et al. 2019). The supplementation dosing regimen was consistent with the safety ranges for metabolic tolerance and adequate administration to children and adolescents (Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference I 1997; Bruni et al. 2004; Lyon et al. 2011; Fernstrom 2012; Barrett et al. 2013; Cynober et al. 2016; van Zyl et al. 2018; Elango 2023). A schematic of the set of sequences relevant to participants who completed both trial cycles is illustrated in Figure 1.

Measured outcomes

Wrist-worn actigraphy (Ametris, Pensacola, FL, USA) tracked time asleep (min), wake-after-sleep-onset (min), sleep onset latency, and sleep efficiency (%) as proxy measures of objective night-time sleep in free-living conditions. The ActiGraph GT9X Link (Ametris, Pensacola, FL, USA) activity monitors were set for date of birth, stature, body mass, and non-dominant wrist.

Devices tracked all activities during the surveillance period outside of training and official matches only. The ActiGraph GT9X Link monitors (35 mm × 35 mm × 100 mm, and a weight of 14 g) were configured as per the manufacturer recommendations, using the Cole-Kripke sleep scoring algorithm to analyze the data and the Tudor-Locke algorithm (Tudor-Locke et al. 2014) set as default for automated sleep period detection (Cole et al. 1992). The primary outcome measure of this investigation was time asleep representing '*the time spent in bed asleep*' (Reed and Sacco 2016). Secondary outcome measures were wake-after-sleep-onset as '*periods of wakefulness occurring after defined sleep onset*' (Lolli et al. 2021), sleep onset latency as the time between lights out to the first epoch (Morrison et al. 2025), and sleep efficiency as time asleep divided by time in bed and multiplied by 100 (Reed and Sacco 2016). Participants completed a sleep diary following each trial administration night with the objective to collect the information supplementary to actigraphy-based sleep outcome measures as follows: *time someone went to bed*; *time someone thought fell asleep*; *time someone woke up* (Short et al. 2017).

Subjective ratings of perceived exertion (RPE) and in-training distances covered represented other secondary outcome measures assessed for descriptive purposes only. Student-athletes rated the global intensity (RPE) of all sessions using level-anchored semi-ratio Borg CR-100® scale (Borg and Borg 2001). Total and very high-speed running intensity ($>20 \text{ km} \cdot \text{h}^{-1}$) distances were monitored during all training sessions with 10-Hz global positioning system (OHCOACH Cell Y; Fitogether, South Korea). Daily energy and macronutrient intakes were assessed using the remote food photography method on the days of the trial administration (Martin et al. 2009). Participants were instructed on how to capture photographs at 45 ° and 90 ° angles before and after each eating and/or drinking occasion, which were captured and time stamped via WhatsApp (WhatsApp Inc., Mountain View, CA). The data were assessed by two accredited sports nutrition practitioners using dietary analysis software to establish daily energy and macronutrients values (Nutritics V5, Nutritics Ltd, Swords, Co. Dublin, Ireland).

Statistical analysis

Descriptive statistics relevant to dietary intake training were summarized as mean and standard deviation (SD), apart from ratings of perceived exertion and distances covered during training, which were summarized with median and interquartile range (IQR).

The statistical analysis framework involved a complementary five-step approach (Lolli et al. 2025) partly informed by existing research for appropriate examination of continuous data from a replicate cross-over experiment (Senn et al. 2011; Senn 2016, 2024). Response pairs were formulated by calculating the placebo-adjusted supplementation effects for the first supplementation and placebo pair in each participants' sequence (response 1; supplementation 1 *minus* placebo 1) along with the second supplementation and placebo pair (response 2; supplementation 2 *minus* placebo 2). Our trial design and analysis were informed by applied issues relevant to the study context (Di Salvo et al. 2023), especially the requirement that any interventions have a rapid onset of action (Charest and Grandner 2024; Chatters et al. 2024). Considering methodological issues relevant to the analysis of repeated measurements that may be collected within a single trial period (Ciminera and Wolfe 1953; Putt and Chinchilli 1999; Senn et al. 2000; Senn 2001; Araujo et al. 2016), the first and second replicates were calculated as the difference between the supplementation and placebo raw measurement scores in two distinct comparisons:

- (1) The immediate impact of supplementation *minus* placebo on the first administration night;
- (2) The immediate impact of supplementation *minus* placebo for the outcome averaged over the two administration nights as a summary measure (Senn et al. 2000; Lolli et al. 2025).

First, Pearson's product-moment correlation coefficients between the two cycles of the supplementation and placebo differences for each sleep outcome were estimated to explore the consistency of the supplementation effect between the replicate trials as an adjunct to the scatterplot approach reported by Senn (2016), with thresholds of 0.1, 0.3 and 0.5 indicating small, moderate and large coefficients, respectively. Second, a naïve estimate of the true (placebo-adjusted) individual differences SD was determined for exploratory purposes by calculating the difference in SDs of the raw scores between the supplementation and placebo trials for each cycle (Atkinson and Batterham 2015; Atkinson et al. 2019, 2026). A positive standard deviation of the individual responses (SD_{IR}) was considered as suggestive of greater heterogeneity in the supplementation response compared to any random within-subject variability (Atkinson and Batterham 2015; Atkinson et al. 2019, 2026). Third, the Pitman-Morgan test was conducted as supplementary to

comparisons of variances from paired (correlated) samples (Cohen 1990; Lolli et al. 2025). The test consisted of calculating the Pearson's product-moment correlation coefficient between supplementation *plus* placebo (x-axis) and supplementation *minus* placebo (y-axis) responses for primary and secondary sleep outcome measures on each cycle, respectively (Cohen 1990). Fourth, separate within-participant linear mixed modelling was conducted in SAS OnDemand for Academics for each outcome to derive the participant-by-condition interaction. Each model included condition, period (trial sequence) and the period-by-condition interaction adjustment (Spiegelhalter 1988) as fixed effects, plus participant and the participant-by-condition interaction modelled as random effects (Lolli et al. 2025). Standard residual diagnostics was performed to assess the adequacy and stability of the modelled covariance parameter estimates (Schabenberger 2004; Schall et al. 2010). Sensitivity analyses were conducted if outliers that were >3 times higher or lower than the sample SD were detected (Lolli et al. 2025). Fifth, a sample estimate of within-subjects variance was calculated and converted to a standard error given the completed number of cycles to derive per participant replicate-averaged supplementation effects (Senn 2024). A random-effects meta-analysis with Hartung-Knapp adjustment (IntHout et al. 2014) summarized individual-participant replicate-averaged supplementation effects and respective sampling errors (Senn 2024) using the *metagen()* function. The restricted maximum-likelihood estimation method determined the tau-statistic (τ) value describing the between-participant replicate-averaged supplementation effect response variability across the distribution of true supplementation-related effects (Veroniki et al. 2016; Langan et al. 2019). The uncertainty surrounding the point τ -statistic estimate was described using a 95% CI derived using the generalized Q-statistic method (Viechtbauer 2007). Weighted raw replicate-averaged supplementation effects were reported as descriptive statistics alongside the respective 95% prediction interval (PI) describing the range for the distribution of true mean differences expected for 95% of similar trials (IntHout et al. 2016; Borenstein 2024). Accordingly, the phenomenon of statistical shrinkage of supplementation effects toward the sample-level mean was assessed by deriving best linear unbiased predictor, or shrunk, estimates using the *blup()* function available in the *metafor* package following random effects meta-analysis (Senn 2024). Visual inspection of unadjusted (or naïve) estimates (x-axis) against shrunk estimates (y-

axis) informed judgements relevant to interpreting the clinical meaningfulness of the estimated sleep-response heterogeneity (Araujo et al. 2016; Gewandter et al. 2019; Senn 2024). A minimum clinically important difference (MCID) of ± 30 minutes informed interpretations for time asleep (Youngstedt 2003; de Zambotti et al. 2019). Meta-analyses were conducted in R (version 4.5.2, R Foundation for Statistical Computing). Mean differences and correlation coefficients were reported with their corresponding 95% confidence intervals (CI).

Results

Fifteen male youth football players volunteered to take part in this study (age = 16.1 ± 0.4 years, body mass = 70 ± 8.5 kg, stature = 179 ± 7.5 cm). Of this sample, two participants experienced a soft-tissue injury, and one participant did not comply with the supplementation administration regimen (Supplementary File 1). The final analysis included data for 12 participants who completed both administration cycles (Figure 1). Daily energy nutrient intakes for these participants were generally stable across the trial administration, with average intakes ranging from $2508 \text{ kcal} \cdot \text{day}^{-1}$ to $2880 \text{ kcal} \cdot \text{day}^{-1}$ and carbohydrate average intake ranging from $282 \text{ g} \cdot \text{day}^{-1}$ to $348 \text{ g} \cdot \text{day}^{-1}$ (Table 1). Total, and very high-speed, running distances covered during training were relatively longer during the second compared to the first trial cycle. The median total and very high-speed running distance was 3510 m (IQR, 3048 to 4576 m) and 67 m (IQR, 35 to 213 m) in the first period, 3958 m (IQR, 2974 to 5428 m) and 63 m (IQR, 35 to 302 m) in the second period, 6389 m (IQR, 5709 to 6638 m) and 141 m (IQR, 48 to 615 m) in the third period, and 6174 m (IQR, 5408 to 7022 m) and 130 m (IQR, 51 to 375 m) in the fourth period, respectively. Perceived exertion remained stable across the trial administration, with a median of 45 AU (IQR, 25 to 45 AU) in the first period, 20 AU (IQR, 11 to 34 AU) in the second period, 35 AU (IQR, 26 to 45 AU) in the third period, and 33 AU (IQR, 25 to 50 AU) in the fourth period.

Mean treatment effects on sleep

Placebo-adjusted replicate-averaged supplementation effects from linear mixed-effects modelling were trivial and prone to uncertainty as reflected by the width of the 95% CIs (Table 2). These intervals overlapped with zero for all comparisons and sleep outcome measures under investigation (all $p \geq 0.226$), consistent with results from the random-effects meta-analyses.

Inter-individual variability in sleep responses to blend supplementation

Table 2 illustrates summary statistics relevant to examining supplementation response heterogeneity. For the placebo-adjusted supplementation effects on the first night only, the between-cycle Pearson's correlation coefficients were not statistically significant and the 95% CIs described negative-to-positive relationships (all $p \geq 0.5616$). Three participants exhibited replicate-averaged time asleep responses to supplementation exceeding the target MCID (Figure 2). The SD_{IR} for time asleep over cycle 1 and cycle 2 were similar in magnitude, and were indicative of smaller response variability under the supplementation *versus* placebo condition (Table 2). These effects were consistent with the observed direction of the moderate yet not statistically significant Pitman-Morgan correlation coefficients (Supplementary File 2). The person-by-supplement interaction variation from linear mixed-effects modelling (Table 2) and the τ -statistic from random-effects meta-analysis (Figure 3) approaches indicated a general lack of substantial individual sleep responses to blend supplementation, consistent with the shrinkage-adjusted estimates providing evidence of strong shrinkage toward the mean (Figure 4).

For the placebo-adjusted supplementation effects over the two-night averaged measurements, the between-cycle Pearson's correlation coefficients were not statistically significant and the 95% CIs described negative-to-positive relationships (all $p \geq 0.5616$). Two participants exhibited replicate-averaged time asleep

Table 1. Estimated daily energy and macronutrient intakes of participants during the trial administration.

Cycle	Episode	Energy intake ($\text{kcal} \cdot \text{day}^{-1}$)		CHO intake ($\text{g} \cdot \text{day}^{-1}$)		Protein intake ($\text{g} \cdot \text{day}^{-1}$)		Fat intake ($\text{g} \cdot \text{day}^{-1}$)	
		μ	SD	μ	SD	μ	SD	μ	SD
1	1	2710	600	339	137	144	53	60	26
1	2	2530	637	319	138	140	52	51	24
1	3	2880	473	340	127	148	54	74	29
1	4	2865	423	348	121	138	60	74	31
2	5	2508	536	282	117	128	56	69	26
2	6	2596	604	332	131	112	39	66	37
2	7	2675	398	327	112	136	48	65	27
2	8	2687	768	338	142	137	58	60	32

CHO indicates carbohydrate; μ indicates mean; SD indicates standard deviation.

Table 2. Estimated marginal means and uncertainty for primary outcomes under supplement and placebo conditions with relevant statistics for examining supplement response heterogeneity.

Outcome	Supplement mean effect	Placebo mean effect	Mean difference (Δ)	Between-cycle r	Person-by-supplement interaction SD	τ -statistic	SD _{IR} (cycle 1)	SD _{IR} (cycle 2)	Pitman–Morgan r (cycle 1)	Pitman–Morgan r (cycle 2)
First night only										
Time asleep	348 min (322 to 374)	339 min (313 to 365)	9 min (–18 to 37) $p = 0.4733$	–0.16 (–0.67 to 0.46) $p = 0.6313$	–19 min (–38 to 27) $p = 0.5319$	0 min (0 to 10)	–41 min	–46 min	–0.35 (–0.77 to 0.28) $p = 0.2666$	–0.30 (–0.75 to 0.33) $p = 0.3403$
Wake-after-sleep-onset	75 min (61 to 89)	73 min (60 to 87)	2 min (–17 to 20) $p = 0.8523$	0.17 (–0.43 to 0.69) $p = 0.5616$	11 min (–17 to 22) $p = 0.5616$	15 min (0 to 42)	23 min	–16 min	0.36 (–0.27 to 0.77) $p = 0.2486$	–0.16 (–0.67 to 0.46) $p = 0.6203$
Sleep onset latency	35 min (19 to 51)	38 min (22 to 54)	–3 min (–31 to 25) $p = 0.8281$	–0.01 (–0.58 to 0.57) $p = 0.9703$	12 min (–28 to 33) $p = 0.7659$	9 min (0 to 30)	22 min	–30 min	0.18 (–0.44 to 0.68) $p = 0.5689$	–0.26 (–0.73 to 0.36) $p = 0.4055$
Sleep efficiency	82% (80 to 85)	82% (80 to 84)	0% (–4 to 3) $p = 0.8935$	–0.07 (–0.62 to 0.52) $p = 0.8238$	–1% (–4 to 4) $p = 0.7717$	0% (0 to 7)	4%	2%	0.32 (–0.32 to 0.75) $p = 0.3173$	0.09 (–0.51 to 0.63) $p = 0.7785$
Two-night average										
Time asleep	365 min (345 to 384)	359 min (339 to 378)	6 min (–25 to 36) $p = 0.6815$	0.04 (–0.54 to 0.60) $p = 0.8927$	17 min (–28 to 37) $p = 0.5914$	19 min (0 to 60)	–30 min	33 min	–0.21 (–0.70 to 0.42) $p = 0.519$	0.36 (–0.27 to 0.77) $p = 0.2491$
Wake-after-sleep-onset	73 min (60 to 87)	73 min (59 to 87)	0 min (–16 to 16) $p = 0.9595$	0.17 (–0.44 to 0.68) $p = 0.5911$	12 min (–11 to 21) $p = 0.3016$	14 min (0 to 37)	18 min	7 min	0.24 (–0.39 to 0.72) $p = 0.4482$	–0.04 (–0.60 to 0.55) $p = 0.9024$
Sleep onset latency	33 min (23 to 44)	42 min (31 to 52)	–9 min (–25 to 7) $p = 0.2599$	–0.16 (–0.67 to 0.45) $p = 0.6141$	3 min (–18 to 18) $p = 0.9525$	0 min (0 to 10)	13 min	–25 min	0.13 (–0.48 to 0.66) $p = 0.6774$	–0.53 (–0.85 to 0.06) $p = 0.07664$
Sleep efficiency	83% (81 to 86)	83% (81 to 86)	0% (–2 to 2) $p = 0.9716$	–0.25 (–0.72 to 0.38) $p = 0.4311$	–1% (–3 to 2) $p = 0.6652$	0% (0 to 4)	4%	1%	0.30 (–0.33 to 0.75) $p = 0.3369$	–0.02 (–0.59 to 0.56) $p = 0.9522$

SD_{IR}, standard deviation of the individual responses calculated as $SD_{IR} = \sqrt{SD_S^2 - SD_P^2}$, where SD_S and SD_P are the SDs of the primary and secondary outcome measures under the supplementation and placebo administrations, respectively; 95% confidence intervals in parentheses.

responses to supplementation exceeding the target MCID (Figure 5). The degree and direction of the SD_{IR} estimates were inconsistent between cycle 1 and cycle 2 (Table 1), and in line with the observed direction of the Pitman–Morgan correlation coefficients found to be not statistically significant (Supplementary File 3). The person-by-supplement interaction variation from linear mixed-effects modelling (Table 2) and the τ -statistic from the meta-analytic approach (Figure 6) suggested a general lack of consistent individual sleep responses to blend supplementation. This was in line with the observed shrinkage of the individual supplementation effects toward the overall mean (Figure 7). Post-estimation regression diagnostics for all comparisons and sleep outcome measures under examination indicated model residuals were well-behaved for adequate covariance parameter estimation.

Discussion

We adopted a replicate crossover research design to investigate actigraphy-based sleep responses to nutritional blend supplementation administered in free-living conditions. Our objective was to explore how nutritional interventions may aid in addressing sleep-related

problems that are common in Muslim adolescents. Aggregated sets of n -of-1 trials in our study revealed trivial replicate-averaged (mean treatment) supplementation effects and a lack of meaningful individual differences in actigraphy-derived placebo-adjusted sleep responses to blend supplementation in male youth football players from the Middle East. Our study also illustrates that the development of protocols that may seek the *personalization* or *individualization* of nutritional plans or supplementations provided to individual athletes should be underpinned by evidence of meaningful and clinically relevant inter-individual differences in response to a nutritional intervention from an appropriately designed replicate crossover trial. Only this research design allows the quantification of the crucial person-by-treatment interaction variance component.

Single-participant or sets of n -of-1 of trials to explore treatment effectiveness are not new in nutrition research (Schork and Goetz 2017), nor in other fields of research (Hawthornth et al. 2024). Historically, the non-randomized experiment by Cushny and Peebles (1905) is probably the first investigation to examine the effects of the repeated administration of different interventions on hours of sleep gained per night. However, Cushny and Peebles (1905) did not consider randomization, the

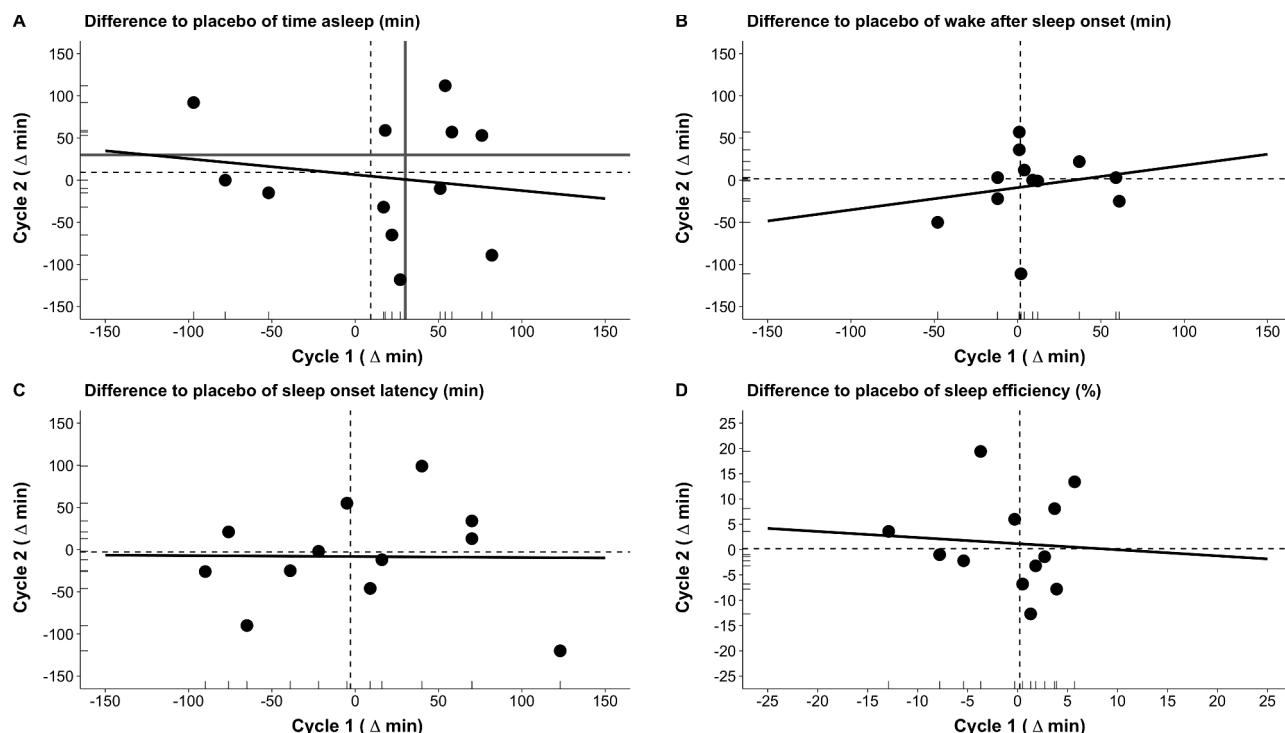


Figure 2. Scatterplots showing the between-cycle associations for individual responses in time asleep (A), wake after sleep onset latency (B), sleep onset latency (C), and sleep efficiency (D) on the first administration night. The supplementation minus placebo responses for the first cycle are plotted on the x-axis against those for the second cycle on the y-axis.

definition of washout periods, adequate blinding, and the rationalization of trial cycles with suitable alternation of active treatment and comparator conditions as the keystones for a principled assessment of individual responses to a treatment (Chatters et al. 2024). In nutrition, similar replicate research designs were used to investigate the effects of changes in diet on individual responses in serum cholesterol concentrations (Keys et al. 1965). In this context, replicate crossover designs can be useful to inform sports nutritionists regarding whether personalized strategies may be necessary or not for athletes preparing for or recovering from training and competition.

The dietary substances within the nutritional blend that was administered to participants in our study have well-known mechanisms of action for enhancing sleep, and are considered plausible alternatives to pharmaceutical-grade treatments that can have unwanted side effects if administered on a long-term basis in humans (Silber and Schmitt 2010; Fernstrom 2012; Halson 2014; van Zyl et al. 2018; Smith et al. 2019; Charest and Grandner 2024; Doherty et al. 2024). Tryptophan is an amino acid that can be found in dietary sources such as milk, turkey, chicken, eggs, fish, pumpkin, and beans (Doherty et al. 2024). As for the large neutral amino acids (LNNAs) such as leucine, isoleucine, tyrosine, phenylalanine, and valine, L-tryptophan follows a specific

active transport pathway across the blood–brain barrier, where it is converted by the tryptophan hydroxalase and amino acid decarboxylase to serotonin (Silber and Schmitt 2010). The effects of tryptophan uptake for sleep promotion purposes depend primarily on higher plasma tryptophan concentrations relative to the sum of other LNAAs (Silber and Schmitt 2010), with a dose of at least 250 mg of L-tryptophan reported to have beneficial effects on night sleep in healthy adults (Hartmann and Spinweber 1979). Wyatt et al. (1970) undertook a semi-replicate crossover trial (i.e., two cycles with three periods only) and reported beneficial effects of tryptophan supplementation on sleep. Nevertheless, this and other studies may be prone to methodological limitations such as treatment carry-over problems (Lolli et al. 2025) – any tryptophan-related effect may have been biased by potential residual effects from a previous exposure to the active supplementation itself, with inevitable consequences on the robustness of evidence on this topic (Sutanto et al. 2022).

Glycine is a non-essential amino acid that can contribute to upregulating whole-body vasodilation and, accordingly, reduce core temperature to facilitate sleep onset (Bannai and Kawai 2012; Langan-Evans et al. 2023). A dose of 3000 mg is considered beneficial to sleep (Yamadera et al. 2007). L-theanine is a water-soluble, non-proteinogenic amino acid present in the leaves of

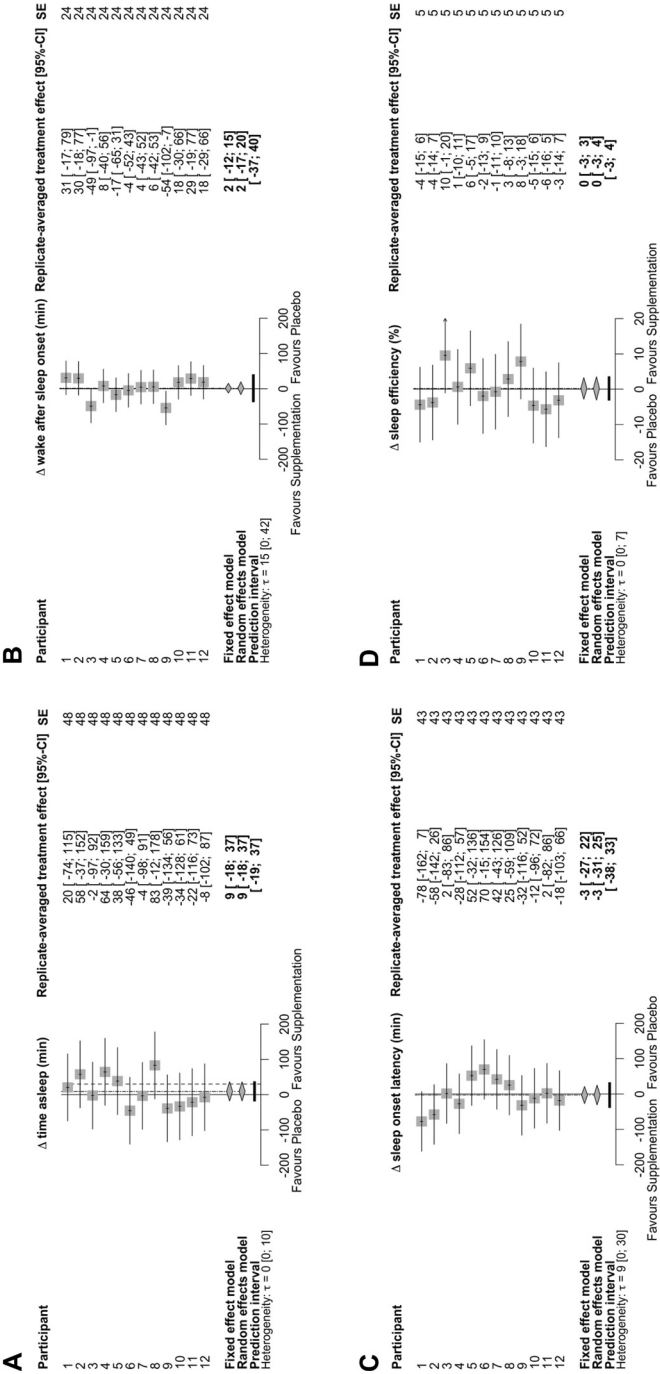


Figure 3. Forest plot showing the average difference in response of time asleep (A), wake after sleep onset latency (B), sleep onset latency (C), and sleep efficiency (D) for each participant in the replicate crossover randomized controlled trial on the first administration night.

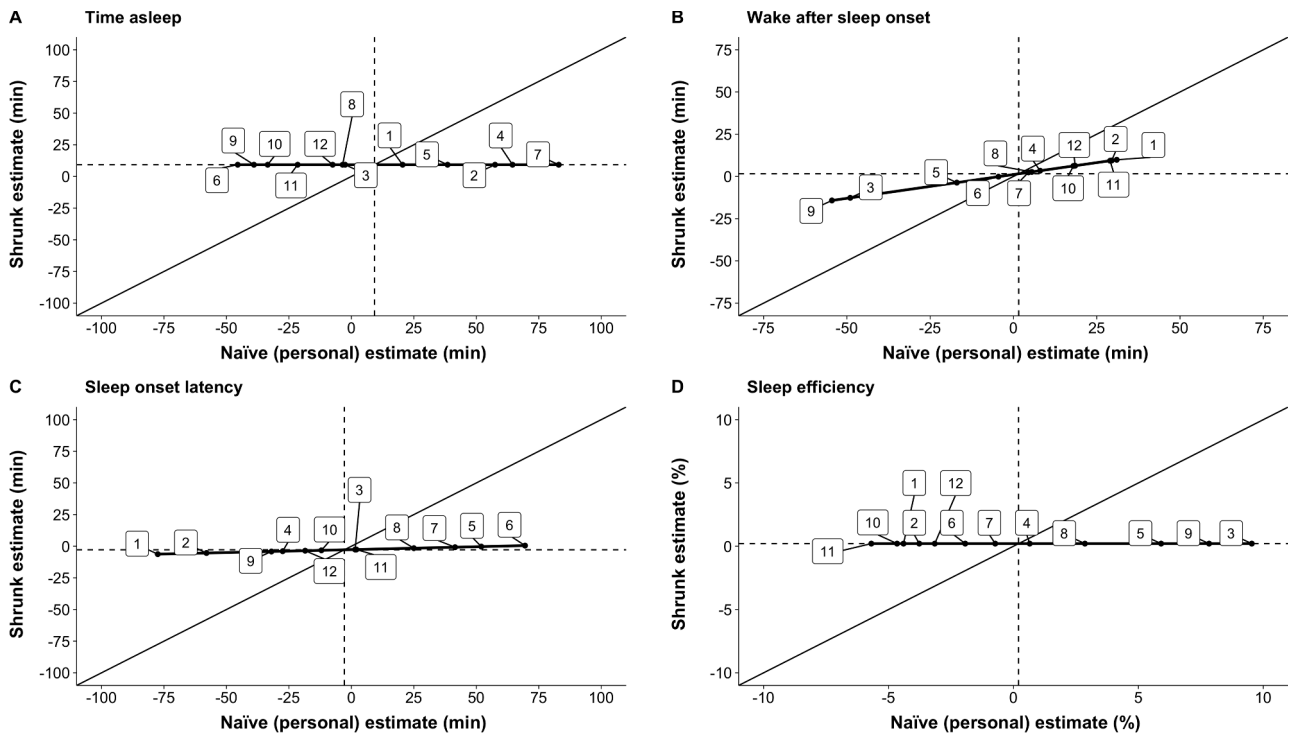


Figure 4. Shrunk and naïve estimates for time asleep (A), wake after sleep onset latency (B), sleep onset latency (C), and sleep efficiency (D) on the first administration night. The solid diagonal line indicates the line of equality, and the dashed lines represent the replicate-averaged supplementation effects. Boxes indicate labels for each individual participant estimate.

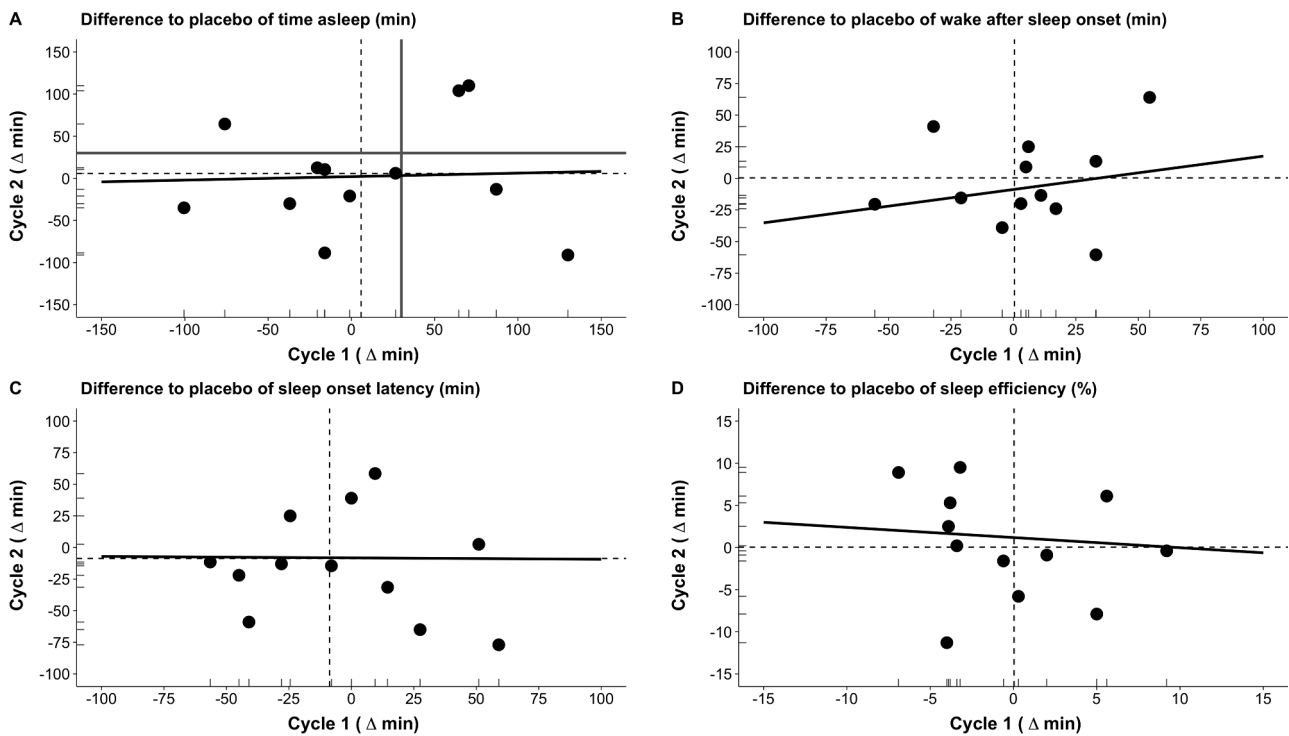


Figure 5. Scatterplots showing the between-cycle associations for individual responses in time asleep (A), wake after sleep onset latency (B), sleep onset latency (C), and sleep efficiency (D) averaged over the two administration nights. The supplementation minus placebo responses for the first cycle are plotted on the x-axis against those for the second cycle on the y-axis.

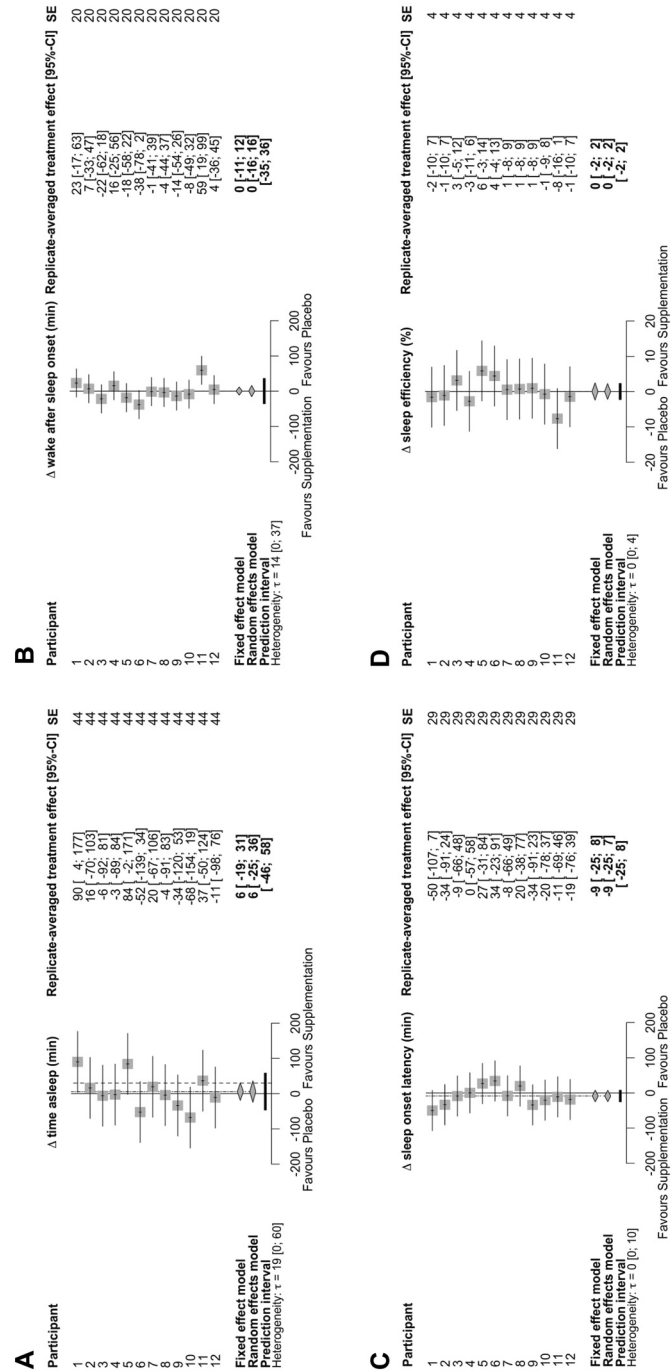


Figure 6. Forest plot showing the average difference in response of time asleep (A), wake after sleep onset latency (B), sleep onset latency (C), and sleep efficiency (D) for each participant in the replicate crossover randomized controlled trial averaged over the two administration nights.

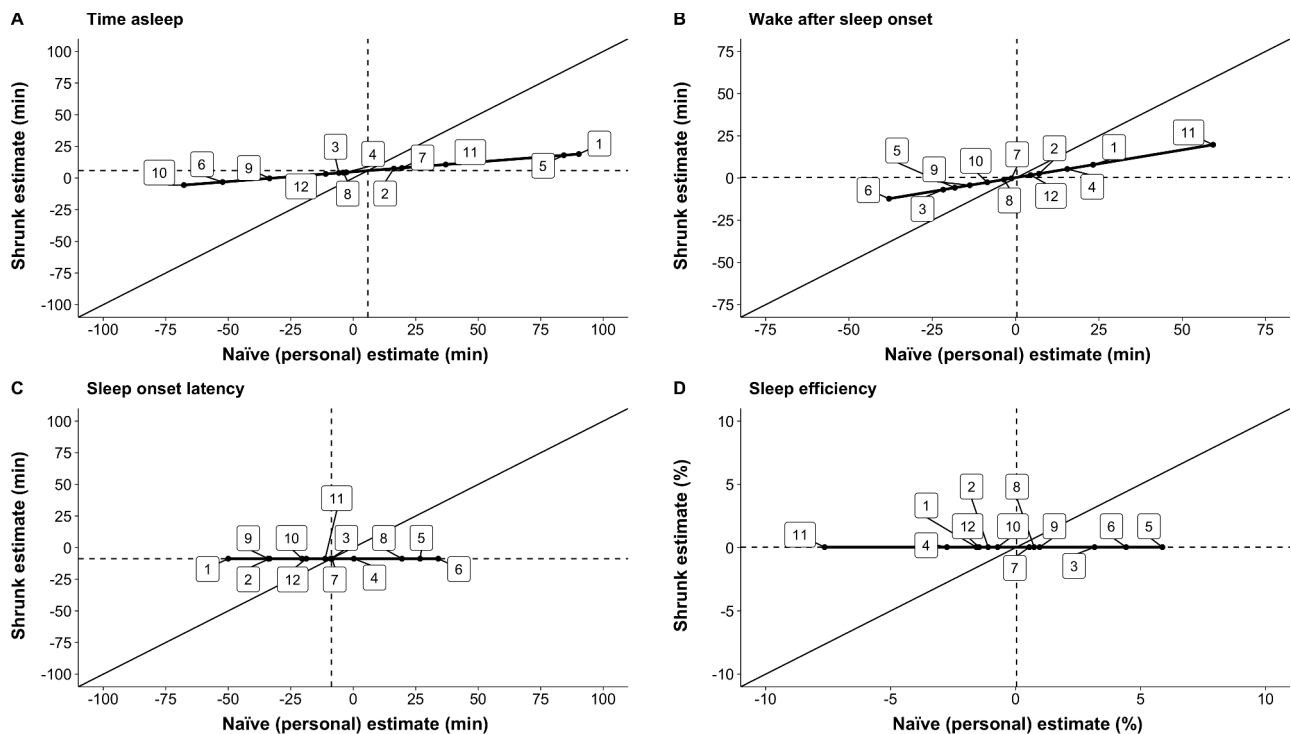


Figure 7. Shrunk and naïve estimates for time asleep (A), wake after sleep onset latency (B), sleep onset latency (C), and sleep efficiency (D) averaged over the two administration nights. The solid diagonal line indicates the line of equality, and the dashed lines represent the replicate-averaged supplementation effects. Boxes indicate labels for each individual participant estimate.

the tea plant (Bulman et al. 2025) and has been reported to enhance sleep in samples of healthy people and those with clinical disorders (Bulman et al. 2025). A recent systematic review and meta-analysis suggested beneficial effects of L-theanine on sleep onset latency (Bulman et al. 2025). Nevertheless, it remains unclear what might constitute adequate dosing and duration of L-theanine supplementation for improving sleep (Bulman et al. 2025). Magnesium is a mineral present in the human body that can be found in dietary sources as boiled spinach, brown rice, and plain, low-fat, yoghurt (Smith et al. 2019; Charest and Grandner 2024; Doherty et al. 2024). This mineral generally acts as a γ -aminobutyric acid (GABA) agonist to increase melatonin concentration together by stimulating serotonin *N*-acetyltransferase. Studies conducted in adults and elderly have suggested beneficial effects on sleep (Silber and Schmitt 2010; Fernstrom 2012; Halson 2014; van Zyl et al. 2018; Smith et al. 2019; Charest and Grandner 2024; Doherty et al. 2024). The melatonin-rich phytonutrient profile of tart Montmorency cherries (*Prunus cerasus*) has also been studied as a sleep-enhancing nutritional intervention, with 30 mL of tart cherry juice concentrate previously reported to increase actigraphy-measured sleep duration in healthy adults (Howatson et al. 2012). Overall, our findings extend knowledge in this field regarding

the sleep-related effects of these dietary supplements in male adolescents from the Middle East (Table 2).

Our investigation is the first to assess the potential for personalization of nutritional supplementation in youth football players using the necessary replicate crossover design. Previous studies adopted a conventional, single-cycle only, randomized crossover trial in participants of healthy adults from general populations (Langan-Evans et al. 2023) or sports athletes screened under laboratory conditions (Morrison et al. 2025) to examine the sleep-related effects of different formulations of the nutritional blend supplementation we investigated. The content of the active supplementation from our trial protocol was consistent with the nutritional blend formulation examined by Langan-Evans et al. (2023). This nutritional blend was reported to increase total sleep time on average by 22 minutes per night, and additional calculations from a detailed scrutiny of the summary statistics from the report of Langan-Evans et al. (2023) indicated a single-cycle SD_{IR} of -27 min. A decreased response variance under the supplementation *versus* placebo condition was indicative of systematic benefit from the supplementation intake for all participants, thereby precluding any potential for personalized advices (Lolli et al. 2025). The negative response variance that could be calculated from Langan-Evans et al. (2023) seemed in line with the time asleep

response variability estimates for the first night only comparison (Table 2), but not confirmed by the results from the necessary analyses of both trial cycles (Figures 2–4). Although the combined administration of these dietary substances may not permit drawing specific considerations regarding their isolated effectiveness, the estimated replicate-averaged supplement effects suggested minimal effects for enhancing sleep in participants from our study (Table 2) compared to what reported in adult samples from Western countries (Wyatt et al. 1970; Hartmann and Spinweber 1979; Yamadera et al. 2007; Lyon et al. 2011; Bannai and Kawai 2012; Howatson et al. 2012; van Zyl et al. 2018; Zhang et al. 2022).

Our study is novel for adopting a randomized replicate crossover design to examine the individual sleep responses to nutritional blend supplementation in youth football players, but certain aspects of our trial design and methods deserve attention. First, the length of supplementation and placebo administrations consisted of randomized sequences of two consecutive evenings only instead of 3-day or week-long administrations previously documented (Hartmann and Spinweber 1979; Silber and Schmitt 2010; Halson 2014; Langan-Evans et al. 2023; Bulman et al. 2025; Morrison et al. 2025). In keeping with the nature of replicate crossover trials suitable to examine the transient effects of an intervention, having rapid onset of action and cessation are fundamental criteria (Chatters et al. 2024) for any strategy intending to maximize sleep and other relevant proxy measures of recovery following competition in professional football (Di Salvo et al. 2023).

The length of administration in our protocol was consistent with a typical microcycle in professional football, which coincided with resumption of training activities following the off days subsequent to official competition. In this context, in-training running distances were longer during the second compared to the first trial cycle. Nevertheless, this seemed negligible given the effects observed under supplementation and placebo conditions (Table 2), also considering a lack of concomitant differences in perceived exertion, which remained stable for participants who completed both administration cycles. Second, both supplementation and placebo were provided to participants in our study following the afternoon training session at dinner time, taking place approximately at 7:00 pm. There is no established guidance on the most appropriate timing for administering the dietary supplementations we investigated. Participants in the single-cycle crossover from Langan-Evans et al. (2023) received both supplementation and placebo 2-h prior to bedtime. Chauffard-Alboucq et al. (1991) reported that sleep-promoting effects of dietary supplements as

tryptophan were found to peak 90 min after ingestion. Evidence from other studies indicated administration of sleep-enhancing was best recommended between 6:00 pm and 9:00 pm (Doherty et al. 2024), and our protocol was consistent with these procedures.

Third, the dosing in our study was compliant with the safety ranges for metabolic tolerance in children and adolescents (Institute of Medicine Standing Committee on the Scientific Evaluation of Dietary Reference I 1997; Bruni et al. 2004; Lyon et al. 2011; Fernstrom 2012; Barrett et al. 2013; Cynober et al. 2016; van Zyl et al. 2018; Elango 2023). However, any direct comparison with the report of Langan-Evans et al. (2023) may not be drawn given the nature of the nutritional blend composition in our protocol that was commercially available at the time of the present replicate crossover trial planning. Fourth, food containing a tryptophan-rich protein in combination with a high glycaemic carbohydrate may also have sleep-enhancing effects (St-Onge et al. 2016). Nevertheless, estimates for dietary intake tracked during the days of supplement and placebo provision indicated carbohydrate intake did not exceed thresholds found to have beneficial effects on sleep (St-Onge et al. 2016).

Conclusions

Our aggregated series of *n*-of-1 trials showed that sleep-related mean effects and individual responses to nutritional blend supplementation were trivial on repeated occasions in phases subsequent to the off days after official competition in male youth Middle Eastern football players. Randomized replicate crossover trials remain underused in sports and nutrition sciences, but these research designs are critical for exploring the potential to personalize dietary strategies for individual athletes who may or may not benefit from the administration of the same nutritional intervention.

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Author contributions

CRedit: **Thomas G. Jackson:** Conceptualization, Project administration, Supervision, Writing – original draft, Writing –

review & editing; **Valter Di Salvo:** Conceptualization, Resources, Writing – original draft, Writing – review & editing; **Lloyd J. F. Parker:** Conceptualization, Project administration, Writing – original draft, Writing – review & editing; **Theofanis Tzatzakis:** Supervision, Writing – original draft, Writing – review & editing; **Greg Atkinson:** Formal analysis, Methodology, Software, Writing – original draft, Writing – review & editing; **Lorenzo Lolli:** Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing.

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Data availability statement

Data not available due to [ethical/legal/commercial] restrictions.

Code availability statement

Supplementary File 4 includes the base R scripts and SAS codes.

Ethics approval statement and informed consent

The protocol for this trial was registered on ClinicalTrials.gov (identifier: NCT07190989). The study received ethics approval by the Aspire Zone Foundation Institutional Review Board, Doha, State of Qatar (protocol number: F202501089). Participant assent and written informed parental/guardian consent were obtained for participants eligible for this study.

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