Energy Deficiency in Soldiers: The Risk of the Athlete Triad and Relative Energy Deficiency in Sport Syndromes in the Military

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Military personnel experience episodes of energy deficit (total energy expenditure higher than energy intake), particularly during combat training and field exercises where exercising energy expenditures are high and energy intake is reduced. Low energy availability (energy intake minus exercising energy expenditure expressed relative to fat free mass) impairs endocrine function and bone health, as recognized in female athletes as the Female Athlete Triad syndrome. More recently, the Relative Energy Deficiency in Sport (RED-S) syndrome encompasses broader health outcomes, physical and cognitive performance, non-athletes, and men. This review summarizes the evidence for the effect of low energy availability and energy deficiency in military training and operations on health and performance outcomes. Energy availability is difficult to measure in free-living individuals but doubly labeled water studies demonstrate high total energy expenditures during military training; studies that have concurrently measured energy intake, or measured body composition changes with DXA, suggest severe and/or prolonged energy deficits. Military training in energy deficit disturbs endocrine and metabolic function, menstrual function, bone health, immune function, gastrointestinal health, iron status, mood, and physical and cognitive performance. There are more data for men than women, and little evidence on the chronic effects of repeated exposures to energy deficit. Military training impairs indices of health and performance, indicative of the Triad and RED-S, but the multi-stressor environment makes it difficult to isolate the independent effects of energy deficiency. Studies supplementing with energy to attenuate the energy deficit suggest an independent effect of energy deficiency in the disturbances to metabolic, endocrine and immune function, and physical performance, but randomized controlled trials are lacking.

Keywords: energy availability, energy deficit, endocrinology, physical performance, reproductive function, bone

INTRODUCTION

Military personnel experience episodes of energy deficit (total energy expenditure higher than energy intake) throughout their career. High exercising energy expenditures and restricted food intake, either due to logistical constraints, suppressed appetite, or as part of a training objective, are contributing factors (1–8). Prolonged periods of energy deficit can negatively impact health
and performance (9–11) and potentially impair military effectiveness. The Female Athlete Triad (Triad) (11) and Relative Energy Deficiency in Sport (RED-S) (9, 10) syndromes describe the effects of chronic low energy availability (energy intake minus exercise energy expenditure expressed relative to fat free mass (FFM)) on health and performance outcomes. The Triad reflects the effect of low energy availability on menstrual disturbances and low bone mineral density (BMD) (11); RED-S describes the effects of low energy availability on a range of wider health and performance outcomes in "at risk" sporting and some non-sporting (e.g., dancers) civilian populations (9, 10). The relevance of the Triad and RED-S in a military context has not been comprehensively reviewed.

The physical and psychological challenges faced by military personnel are inherently different than those faced by athletes. The implications of impaired performance are also different between military and sporting populations; military tasks require a unique combination of physical and cognitive effort in unpredictable and stressful environments, and the consequences of underperformance can be catastrophic. The predisposing factors leading to, and health and performance implications of, low energy availability in sport, may, therefore, not be applicable to the military. Training for sport is focussed on optimizing performance and often a desire for "leaness," whereas military training prepares individuals for the hostile physical and psychological conditions of combat (e.g., concomitant periods of prolonged exercise, food restriction, sleep deprivation, extreme environments, and psychological stress). Evidence for the effects of low energy availability in the Triad (11) and RED-S (9, 10) mostly originates from short-term laboratory studies and cross-sectional studies comparing amenorrheic and eumenorrheic female athletes. Longitudinal prospective assessment of low energy availability is possible in military populations in the field, where energy restriction is often induced purposively as a training objective or due to logistical constraints. Whilst military field studies are not designed for this purpose, and involve exposure to several stressors, data from these studies contribute to an understanding of the implications of low energy availability on health and performance. Most evidence for the effects of low energy availability presented within the Triad (11) and RED-S (9, 10) are for clinical outcomes, and a better understanding of performance outcomes has important implications for the military. The aim of this article is to review the evidence for the effect of energy deficiency on health and performance outcomes implicated in the Triad and RED-S in military populations.

**ENERGY AVAILABILITY AND ENERGY BALANCE**

Energy availability is the dietary energy available for metabolic function after exercise, defined as energy intake minus exercise energy expenditure expressed relative to fat free mass (FFM) (Equation 1) (12). Dietary energy is essential for physiological processes, including locomotion, thermoregulation, reproduction, and growth (13). High exercise energy expenditures (locomotion) during athletic or military training use energy that is no longer available for other processes (12). Low energy availability partitions metabolic fuels toward processes essential for survival (i.e., circulation and neural activity) over non-essential processes (i.e., reproduction and growth) (13). The mechanism is through altered endocrine signaling from the central nervous system (i.e., decreased release of gonadotropin releasing hormone to suppress reproductive function) in response to acute changes in cellular fuel oxidation and peripheral hormones (13). This altered endocrine signaling can be harmful to health and performance.

Energy availability exists on a spectrum from optimal to low, with or without disordered eating, as highlighted by the Triad (11). Energy availability for normal metabolic function is 45 kcal·kg FFM–1·d–1 (12, 14–18). Energy availability below 30 kcal·kg FFM–1·d–1, equivalent to resting metabolic rate (12), decreases luteinising hormone (LH) pulse frequency, oestradiol, 3,3,5-triiodothyronine (T3), insulin-like growth factor-1 (IGF-1), and leptin, and increases cortisol, growth hormone (GH), and bone resorption, in women (14, 15, 17). Low energy availability has, therefore, been considered as < 30 kcal·kg FFM–1·d–1 in the Triad (11, 19) and RED-S (9, 10). Although defining a threshold for low energy availability is practically useful, the effect of differing severities of low energy availability is likely dependent on the physiological system, and an individual's body size, age, and sex (10); further validation of this threshold against other clinical outcomes is required.

Energy Availability [kcal·kg FFM–1·d–1] = (Energy Intake [kcal·d–1]−Exercise Energy Expenditure [kcal·d–1])/Fat Free Mass [kg].

**Equation 1. Calculation of energy availability (12).**

Energy balance is defined as energy intake minus total energy expenditure (i.e., exercise and all other physiological processes) and is distinctly different from energy availability; energy availability is the input to physiological processes, whereas energy balance is the net change in total body energy stores resulting from the output from physiological processes (12). The acute metabolic adaptations that occur with low energy availability reduce resting metabolic rate and total energy expenditure, and can result in an individual having low energy availability despite being in energy balance and body mass stable (12, 19). Most military studies have measured energy balance or body mass to estimate energy status (reviewed in Demands of Military Training and Employment); for the purpose of this review, energy deficit is used to reflect a negative energy balance rather than low energy availability. Findings from these military studies must, therefore, be interpreted in context of these definitions and physiological implications.

**Female Athlete Triad and Relative Energy Deficiency in Sport**

The observation that disordered eating in female athletes, particularly in sports emphasizing “leanness,” leads to functional hypothalamic amenorrhea and osteoporosis, was first summarized by the American College of Sports Medicine with the Triad framework in the 1990s (20). The Triad was updated in...
2007 to reflect the inter-relationship of energy availability (with or without disordered eating), menstrual disturbance (with or without functional hypothalamic amenorrhoea) and low BMD (with or without osteoporosis) on a spectrum (11).

Subsequent to the Triad, the International Olympic Committee defined RED-S in 2014 (9), with further updates in 2015 and 2018 (10, 21). The RED-S syndrome expands the Triad to include men, populations other than athletes (e.g., dancers), and other clinical and performance outcomes affected by low energy availability (9, 10), although the evidence surrounding some of the outcomes in RED-S and their clinical relevance has been questioned (22). In brief, the RED-S syndrome highlights that low energy availability can have effects on endocrine and metabolic function, menstrual function, bone health, immune function, hematological function, gastrointestinal health, psychological well-being, and physical and cognitive performance (9, 10):

The syndrome of RED-S refers to impaired physiological function including, but not limited to, metabolic rate, menstrual function, bone health, immunity, protein synthesis, cardiovascular health caused by relative energy deficiency (9).

Disordered eating and/or the desire to be lean for aesthetic or performance reasons are considered pre-dispositions for the Triad (11) and RED-S (9). Unlike some sports, a specific body composition is not a prerequisite to successful military performance (23), however, leanness may be desired by some military personnel; militaries have body mass employment standards, and there is evidence of disordered eating in military women (24, 25). Environments with unavoidable extreme exercise and insufficient energy intake also likely contribute to the development of RED-S (9), and there is evidence of the Triad in non-athletes as well as athletes (26) and in men as well as women (27). It, therefore, seems prudent to question whether components of the Triad and RED-S are evident in military personnel, considering: (i) periods of sustained high exercising energy expenditures with restricted food intake (either as a training objective, due to limited food availability in hostile environments, or suppressed appetite) are imposed on military personnel, particularly in the more arduous combat roles; (ii) all military roles, including these arduous combat roles, are now open to both men and women in many militaries, and; (iii) military occupational tasks require the performance components proposed within RED-S.

DEMANDS OF MILITARY TRAINING AND EMPLOYMENT

Physical Demands

Military tasks are diverse (e.g., combat field exercises, casualty extraction, weapon handling, repetitive lifting, prolonged load carriage) and impose a wide range of physiological stresses. Aerobic capacity and muscle strength, power, and endurance are all important for performing military tasks (28). Basic military training prepares new recruits for these tasks, and, therefore, consists of a range of activities including physical training (aerobic training, strength and conditioning, circuit training, obstacle courses, agility training, and swimming), field exercises, adventure training, and training on a variety of military specific skills including load carriage, marching, military drill, and weapon and equipment handling (29). Basic military training is physically demanding, and total energy expenditures can exceed ~3,400 and ~4,400 kcal·d⁻¹ for female and male recruits (29–32); however, food is usually eaten ad libitum. Beyond basic military training, trained soldiers undertake specialist military training courses and field exercises in preparation for the hostile nature of combat; selection and field exercises, therefore, impose the added stressors of energy restriction, sleep deprivation, and psychological stress (2, 33). For the purpose of this review, basic military training refers to training courses completed by new recruits upon entry to the military, and specialist military training refers to advanced combat or promotional courses, or field exercises, completed by trained soldiers throughout their careers.

Energy Availability and Energy Balance

The direct measurement of energy availability in free-living individuals is challenging, with no consensus on measurement protocols (e.g., defining what qualifies as exercise energy expenditure) and inherent inaccuracies with the required techniques (e.g., self-reported energy intake) (10, 34). The uniform nature of military training (e.g., same equipment, physical activity, and eating and sleeping patterns) may help standardize measurement of energy availability, but exercise energy expenditure is difficult to define in military training. There are various ambiguous definitions of exercise energy expenditure (i.e., purposeful training, other leisure activities, or activity above a certain intensity) (34), and unlike athletic training, military training does not comprise discrete bouts of physical activity.

Most military studies have measured energy balance rather than energy availability, likely due to the relative simplicity of measurement. Numerous studies have measured total energy expenditure and/or energy balance in military training and on operations with either doubly labeled water or dual energy X-ray absorptiometry (DXA). A comprehensive overview of these studies is presented in Table 1. These studies demonstrate that total energy expenditures, measured using the doubly labeled water method, are high, and largely differ between individuals as a function of body mass (29, 31, 49). Studies that have measured both total energy expenditure and energy intake have observed energy deficits (i.e., negative energy balance), but the measurement of energy intake is inherently inaccurate. Some studies have calculated energy deficits using DXA, which measures the change in fat mass and FFM based on the known energy densities of the two tissues (2, 4, 33, 53, 61). Food, either served in canteens or in ration packs, is often provided in standard portions or must be consumed within restricted times, and, therefore, some heavier individuals may not meet their energy requirements (1). In addition to high total energy expenditures, restricted energy intake, as the result of logistical barriers to eating or as a training objective (6), a hesitancy to carry extra weight (71), sub-optimal dietary practices (72, 73), or suppressed appetite or menu fatigue (6), may all contribute to energy deficits. The remainder of this review discusses the
### TABLE 1 | Field studies measuring total energy expenditure and/or energy balance in military training and operations with doubly labeled water or dual energy X-ray absorptiometry.

| Military activity | Participants | Measurements | Total energy expenditure (kcal·d⁻¹) | Energy intake (kcal·d⁻¹) | Energy balance (kcal·d⁻¹) |
|-------------------|--------------|--------------|--------------------------------------|--------------------------|---------------------------|
| **Australian Air Defense Guard training (12 days)** (35) | 10 men provided full rations; 10 men provided half rations; 11 men provided fresh food | TEE: doubly labeled water over 7 days (n = 8); EI: weighed-food, estimations, and ration pack discards; EB: not assessed | 3,650 ± 1,060 | Full ration: 2,197 ± 549; half ration: 1,576 ± 191; fresh feeding: 2,866 ± 310 | Not assessed |
| **Australian Army jungle warfare training (12 days)** (36) | 34 men | TEE: doubly labeled water over 7 days (n = 4); EI: weighed-food, estimations, and ration pack discards; EB: not assessed | 4,750 ± 531 | 4,040 (mess: 5,135; field: 2,582) | Not assessed |
| **British Army basic training (12 weeks)** (31) | 7 women; 7 men | TEE: doubly labeled water over 10 days across week 1 to 2 and week 9 to 10; EI: not assessed; EB: not assessed | Women: 2,964 ± 263 and 2,988 ± 143; men: 3,633 ± 359 and 3,537 ± 335 | Not assessed | Not assessed |
| **British Army basic training (14 weeks)** (32) | 10 women; 9 men | TEE: doubly labeled water over 10 days across week 1 to 2 and week 13 to 14; EI: not assessed; EB: not assessed | Women: 2,988 ± 382 and 3,227 ± 454; men: 4,159 ± 621 and 4,350 ± 478 | Not assessed | Not assessed |
| **British Army basic training (14 weeks)** (29) | 17 women; 16 men | TEE: doubly labeled water over 10 days across week 1 to 2 and week 12 to 13; EI: not assessed; EB: not assessed | Women: 2,847 ± 323 and 3,390 ± 344; men: 4,020 ± 620 and 4,253 ± 556 | Not assessed | Not assessed |
| **British Army Infantry basic training (14 weeks)** (37) | 14 men | TEE: doubly labeled water over 10 days across week 1 and 2; EI: not assessed; EB: not assessed | 4,419 ± 430 | Not assessed | Not assessed |
| **British Army Officer basic training (44 weeks)** (38) | 10 women; 10 men | TEE: doubly labeled water over 10 days; EI: not assessed; EB: not assessed | 4,112 ± 652 | Not assessed | Not assessed |
| **British Army Parachute Regiment basic training (24 weeks)** (30) | 6 men | TEE: doubly labeled water over 10 days across week 1 to 2 and week 19 to 20; EI: not assessed; EB: not assessed | 4,735 ± 700 and 4,698 ± 545 | Not assessed | Not assessed |
| **British Army Section Commanders battle course (8 weeks)** (1) | 27 men | TEE: doubly labeled water over 10 days across week 2 to 3 and week 6 to 7; EI: estimated from TEE and EB; EB: estimated from changes in FFM and FM measured with doubly labeled water | 4,693 ± 424 and 5,094 ± 471 | 4,235 | −644 |
| **British Army Section Commanders battle course (8 weeks)** (4) | 15 male controls; 15 men provided extra 1,218 kcal·d⁻¹ | TEE: not assessed; EI: not assessed; EB: estimated from changes in FFM and FM measured by DXA | Not assessed | Not assessed | Normal training: −526 ± 263; supplemented training: −167 ± 263 |

(Continued)
| Military activity                                                                 | Participants | Measurements                                                                 | Total energy expenditure (kcal·d⁻¹) | Energy intake (kcal·d⁻¹) | Energy balance (kcal·d⁻¹) |
|----------------------------------------------------------------------------------|--------------|------------------------------------------------------------------------------|-------------------------------------|--------------------------|--------------------------|
| British Royal Marines on deployment to Afghanistan (6 months) (39)              | 18 men       | TEE: doubly labeled water over 7 days mid-deployment; EI: 7-day food record mid-deployment; EB: not assessed | 3,626 ± 450                        | Patrolling days: 2,194 ± 630; non-patrolling days: 2,095 ± 613 | Not assessed             |
| Canadian Infantry arctic field exercise (10 days) (40)                          | 10 men       | TEE: doubly labeled water over 7 days; EI: food records; EB: EI/TEE × 100     | 4,317 ± 927                        | 2,633 ± 499                | EI was 61% of TEE        |
| Finish Defense Force basic training (8 weeks) (41)                               | 24 men       | TEE: doubly labeled water over 15 days during last 2 weeks of training; EI: food records over 7 days; EB: (EI—TEE)/TEE × 100 | 3,697 ± 394                        | 2,752 ± 771                | −26 ± 18%                |
| Finish Defense Force basic training (8 weeks) (42)                               | 24 men       | TEE: doubly labeled water over 8 days during field exercise; EI: not assessed; EB: not assessed | 3,965 ± 502                        | Not assessed                | Not assessed             |
| Gulf Cooperation Council country Army, Air Force and Navy Officer training (2 to 3 years) (43) | 119 men      | TEE: doubly labeled water over 7 days; EI: not assessed; EB: not assessed     | 3,057 ± 429 to 3,507 ± 504         | Not assessed                | Not assessed             |
| Israeli Defense Force winter and summer Infantry training (44)                  | 18 men in winter; 12 men in summer | TEE: doubly labeled water over 12 days (winter, n = 14; summer, n = 10); EI: food records; EB: EI—TEE | Winter: 4,281 ± 170; summer: 3,937 ± 159 | Training: 2,792 ± 108; ski march: 2,857 ± 179 | Winter: −1,422 ± 183; summer: −924 ± 232 |
| Royal Netherlands Army submarine deployment (3 months) (45)                     | 10 men       | TEE: doubly labeled water over 2 weeks (weeks 4 to 5); EI: estimated from TEE and EB; EB: estimated from changes in FFM and FM measured with doubly labeled water | 2,937 ± 498                        | Training: 3,098 ± 236; ski march: 3,461 ± 586 | −2,899 ± 498 (training: −2,382 ± 499; ski march: −3,390 ± 669) |
| Norwegian Army winter training (4 days training, 3 days ski march) (46)        | 21 men       | TEE: doubly labeled water; EI: discards from ration packs; EB: EI—TEE        | 6,140 ± 394                        | Training: 3,098 ± 236; ski march: 3,461 ± 586 | −2,899 ± 498 (training: −2,382 ± 499; ski march: −3,390 ± 669) |
| Norwegian Army winter training (4 days) (47)                                    | 2 women and 71 men (18 controls; 27 provided additional carbohydrate; 28 provided additional protein [both ∼1,000 kcal·d⁻¹]) | TEE: doubly labeled water (controls, n = 14; carbohydrate, n = 14; protein, n =14); EI: food records; EB: EI—TEE | Control: 6,096 ± 412; carbohydrate: 6,181 ± 505; protein: 6,167 ± 592 | Control: 2,506 ± 410; carbohydrate: 3,131 ± 633; protein: 2,825 ± 599 | Control: −3,595 ± 606; carbohydrate: −3,050 ± 888; protein: −3,402 ± 687 |
| Norwegian Defense Cyber Academy field exercise (10 days) (48)                   | 4 women and 15 men provided low protein (1 g·kg⁻¹·d⁻¹), and 3 women and 16 men provided high protein (2 g·kg⁻¹·d⁻¹) diet | TEE: not assessed; EI: food provided; EB: estimated from changes in FFM and FM measured by DXA | Not assessed                        | Low protein: 1,183 ± 168; high protein: 1,174 ± 170 | Low protein: −4,373 ± 1,250; high protein: −4,271 ± 1,075 |

(Continued)
| Military activity | Participants | Measurements | Total energy expenditure (kcal·d⁻¹) | Energy intake (kcal·d⁻¹) | Energy balance (kcal·d⁻¹) |
|------------------|--------------|--------------|------------------------------------|--------------------------|---------------------------|
| Norwegian Ranger training (7 day field exercise) (49) | 6 women; 10 men | TEE: doubly labeled water over 7 days; EI: estimated from food provided; EB: not assessed | Women: 5,234 ± 478; men: 6,358 ± 478 | Women: 48 to 454; men: 48 to 526 | Not assessed |
| US Army basic combat training (10 weeks) (50) | 14 women; 30 men | TEE: doubly labeled water over 5 days during weeks 5 and 10; EI: not assessed; EB: not assessed | Women: 3,412 ± 350 and 3,325 ± 493; men: 4,279 ± 445 and 4,096 ± 500 | Not assessed | Not assessed |
| US Army construction and humanitarian tasks at altitude (15 days) (51) | 35 male controls; 32 men provided additional carbohydrate | TEE: doubly labeled water (n = 11); EI: visual estimations and food records; EB: not assessed | Women: 3,549 ± 608 | Control: 2,140 ± 94; carbohydrate: 2,265 ± 119 | Not assessed |
| US Army Ranger selection and assessment programme (6 weeks) (52) | 131 men | TEE: doubly labeled water over 5 days during week 1 (n = 16); EI: estimated as food provided from menus (canteen) and ration packs (field); EB: not assessed | 4,264 ± 342 | 2,919 ± 331 | Not assessed |
| US Army Ranger training (8 weeks) (33, 53) | 50 to 55 men | TEE: estimated from EB and EI; EI: estimated from rations provided; EB: estimated from changes in FFM and FM measured by DXA | 2,796 to 3,220 | 3,991 to 4,200 | −1,195 ± 390 to −900 ± 390 |
| US Army Ranger training (8 weeks) (2) | 49 male controls; 48 men provided extra 400 kcal·d⁻¹ | TEE: not reported; EI: estimated as food provided from menus (canteen) and ration packs (field); EB: estimated from changes in FFM and FM measured by DXA | Figure not reported | Figure not reported | Controls: −1,195 ± 478; supplemented: −980 ± 392 |
| US Marine cold weather field exercise (11 days) (54) | 23 men | TEE: doubly labeled water; EI: food records; EB: estimated from changes in FFM and FM measured with doubly labeled water | 4,919 ± 190c | 3,132 ± 165c | −1,872 ± 293c |
| US Marine desert field exercise (11 days) (55) | 11 men provided carbohydrate drink; 8 men provided placebo drink | TEE: doubly labeled water; EI: food records and visual estimation; EB: not assessed | Carbohydrate: 4,397 ± 1,051; placebo: 3,950 ± 645 | Carbohydrate: 3,415 ± 143; placebo: 3,057 ± 191 | Not assessed |
| US Marine Infantry Officer training (7 day field course) (56) | 8 men | TEE: doubly labeled water over 50 h; EI: empty food wrappers from rations; EB: not assessed | 3,647 ± 394 | 1,366 ± 272 | Not assessed |
| US Marine Infantry Officer training (8 day field course) (57, 58) | 29 to 34 men | TEE: doubly labeled water (n = 12); EI: empty food wrappers from rations; EB: not assessed | 3,834 ± 200 to 3,862 ± 200 | 1,540 ± 300 to 1,540 ± 235 | Not assessed |
| US Marine Infantry Officer training (8 day field course) (59) | 18 men provided low protein (0.5 g·kg⁻¹·d⁻¹) and 17 men provided moderate protein (0.9 g·kg⁻¹·d⁻¹) rations | TEE: doubly labeled water (low protein, n = 6; moderate protein, n = 12); EI: empty food wrappers from rations; EB: EI − TEE | Low protein: 3,941 ± 478; moderate protein: 3,798 ± 502 | Low protein: 1,552 ± 143; moderate protein: 1,529 ± 167 | Both groups: −2,317 |
| US Marines Special Operation Command individual training (four phases [each 7 to 23 days] over 9 months) (60) | 9 to 13 men | TEE: doubly labeled water; EI: 24 h dietary recalls and food records; EB: EI − TEE | 3,754 ± 314 to 6,376 ± 712 | 346 ± 0 to 2,819 ± 488 | −1,027 ± 740 to −3,966 ± 776 |

(Continued)
| Military activity | Participants | Measurements | Total energy expenditure (kcal·d⁻¹) | Energy intake (kcal·d⁻¹) | Energy balance (kcal·d⁻¹) |
|------------------|--------------|--------------|------------------------------------|------------------------|--------------------------|
| US Marine survival, evasion, resistance, escape training (18 days) | 63 men | TEE: not assessed; EI: not assessed; EB: estimated from changes in FFM and FM measured by DXA | Not assessed | Not assessed | −4,203 ± 1,866 |
| US Marine winter field exercise (54 h) | 20 women; 30 men | TEE: doubly labeled water; EI: empty food wrappers from rations; EB: EI−TEE | Women: 4,729 ± 143; men: 6,138 ± 191 | Women: 1,146 ± 430; men: 1,433 ± 478 | −10,318 ± 2,484 over 54 h |
| US Natick Soldier Research, Development and Engineering Center personnel during normal duties (7 days) | 2 women; 24 men | TEE: doubly labeled water; EI: written or personal digital assistant food records; EB: (EI−TEE)/TEE | Written record group: 3,141 ± 647; personal digital assistant group: 3,158 ± 614 | Written record group: 3,266 ± 635; personal digital assistant group: 2,865 ± 716 | −10,318 ± 2,484 over 54 h |
| US Navy Sailors on amphibious assault ship (8 days) | 10 women; 7 men | TEE: doubly labeled water; EI: not assessed; EB: not assessed | Full ration: 3,480 ± 220; lightweight ration: 3,320 ± 280 | Full ration: first 14 days 2,840 ± 280, second 14 days 3,080 ± 630; lightweight ration: first 14 days 1,900 ± 130, second 14 days 1,960 ± 120 | −10,318 ± 2,484 over 54 h |
| US Special Forces field training (28 days) | 8 men provided full rations (4,020 kcal·d⁻¹); 8 men provided lightweight rations (1,980 kcal·d⁻¹) | TEE: doubly labeled water over 28 days; EI: daily food records; EB: not assessed | Pre-deployment training: 3,901 ± 521; combat diver training: 4,564 ± 351 | Pre-deployment training: 3,901 ± 521; combat diver training: 4,564 ± 351 | Not assessed |
| US Special Forces hot and cold climate training (4 to 5 days) | 21 men in hot environment; 8 men in cold environment | TEE: doubly labeled water; EI: food recall; EB: EI−TEE | Hot: 4,664 ± 1,339; cold: 4,549 ± 1,221 | Hot: 2,200 ± 711; cold: 3,001 ± 900 | −2,464 ± 1,696; cold: −1,548 ± 1,607 |
| US Special Forces pre-deployment and combat diver training (7 days) | 29 men | TEE: doubly labeled water; EI: not assessed; EB: not assessed | Pre-deployment training: 3,901 ± 521; combat diver training: 4,564 ± 351 | Pre-deployment training: 3,901 ± 521; combat diver training: 4,564 ± 351 | Not assessed |
| US Special Forces training (6 day mountainous field exercise) | 6 men | TEE: doubly labeled water; EI: daily food records; EB: estimated from changes in FFM and FM, predicted from underwater weighing and total body water | 4,554 ± 566 | 2,357 ± 860 | −2,280 ± 368 |
| US Special Forces training (four phases over 64 days) | 36 men | TEE: doubly labeled water over 10 days; EI: visual estimation (canteen) or discards from ration packs (field); EB: EI−TEE | 3,633 ± 980 to 5,210 ± 717 | Minimum of 2,510 ± 884; maximum not reported | Up to −2,700 ± 540 |
| US Special Forces training (routine garrison training) | 32 men in special forces; 13 male support soldiers | TEE: doubly labeled water over 9 days (special forces, n = 9; support soldiers, n = 9); EI: visual estimation and food records; EB: not assessed | Special forces: 4,099 ± 740; support soldiers: 3,136 ± 652 | Special forces: 3,204 (2,838, 3,676); support soldiers: 2,968 ± 632 | Not assessed |
| Zimbabwean Commando heat-stress field exercise | 8 men | TEE: doubly labeled water over 10 days; EI: food records; EB: not assessed | 5,493 ± 358² | 4,060 ± 358² | −10,318 ± 2,484 over 54 h |

Data are mean ± SD unless otherwise stated.

a Data estimated from figures; b median and interquartile range; c mean ± standard error.

DXA, dual energy X-ray absorptiometry; EB, energy balance; EI, energy intake; FFM, fat free mass; FM, fat mass; Mess, military canteen; TEE, total energy expenditure.
evidence for the health and performance implications of this energy deficiency in military personnel.

**ENERGY DEFICIENCY AND HEALTH**

**Endocrine and Metabolic Function**

Low energy availability decreases reproductive (gonadotropins and sex steroids), thyroid (T3), and metabolic (IGF-1, leptin) hormone concentrations, and increases cortisol and GH (14–17). Widespread disturbances in endocrine and metabolic function are evident in energy deficient soldiers during specialist military training. In Norwegian military cadets, 5 days of combat training increased circulating cortisol and GH, and decreased thyroid (T3 and thyroxine [T4]) and reproductive (follicle-stimulating hormone [FSH], testosterone, and oestradiol) hormone concentrations (74–79). The energy deficit was severe—estimated energy intake ≤ 1,600 kcal·d⁻¹ and energy expenditure ≥ 8,500 kcal·d⁻¹—and total sleep was ~2h across the 5 days. Subsequent studies of male US Army Rangers support these findings, and demonstrate that 8 weeks of combat training in energy deficit (~1,000 kcal·d⁻¹) increased cortisol, and decreased T3, IGF-1, and reproductive hormones (decreased LH and testosterone, increased sex hormone binding globulin [SHBG]) (2, 80–82). Disturbances to endocrine and metabolic function were also evident following a wide range of other specialist military training courses (4, 48, 57, 59, 83–85). Limited studies on operational deployment show decreased (with body mass losses) (86) or unchanged (with stable body mass) (87) reproductive hormone concentrations in men following deployment. The long-term effects of acute changes in endocrine function are unclear, but a cross-sectional analysis of experienced naval operators completing normal duties reported low testosterone suggesting chronic implications for gonadal function (88). Further work on the implications of these changes in sex steroids on reproductive function in men is required.

There are fewer studies on military women, likely due, in part, to their historic exclusion from combat roles and there is a greater proportion of men in the military. During a 5.5 day Norwegian Special Forces field exercise, women had a greater increase in cortisol and greater reduction in IGF-1 than men (89). The men and women did not, however, complete the same activities and further data comparing the response of men and women to the same military training are warranted. There is emerging evidence that female military personnel can experience low energy availability without effects on hypothalamic-pituitary-gonadal and adrenal axis function, assessed using clinically relevant dynamic testing (90). Six women who lost 13% body mass during a 61 day Antarctic crossing had largely unchanged responsiveness of the gonadal and adrenal axes, and metabolic status (90, 91). Results from this study provide important insight into extreme energy deficit in women but most outcomes were underpowered. For example, Korean female military cadets lost ~5% of body mass after 4 and 8 weeks of training and had decreased oestradiol (92). Assessment of hypothalamic-pituitary-adrenal axis responsiveness after adrenocorticotrophic hormone administration showed no mal-adaptation in women after 28 weeks of the 44 week British Army Officer training course, but increases in hair and saliva cortisol were observed in the initial weeks of training (93). Markers of psychological stress were also increased and so it is likely that increased cortisol was due, in part, to psychological stress. Whilst these observational studies in men and women demonstrate disturbed endocrine function, high levels of physical activity, sleep deprivation, and psychological stress could contribute to these responses and the role of energy deficit cannot be confirmed.

Several studies have examined differing severities of energy deficit and these studies provide support for a relationship between energy status and endocrine disturbance. Finnish male trained soldiers had increased GH and cortisol, and decreased testosterone and LH, following a 7 day field exercise in an energy deficit of ~4,000 kcal·d⁻¹ (94). These markers of endocrine function recovered during the subsequent 2 weeks of field exercise when the energy deficit was decreased to < 1,000 kcal·d⁻¹. Similarly, endocrine function was preserved in Norwegian special forces soldiers during 3 weeks of training with ad libitum food intake, but a subsequent 7 day field exercise in ~4,000 kcal·d⁻¹ energy deficit increased cortisol and SHGB, and decreased IGF-1, T3, T4, and testosterone (95). The periods of most severe energy deficit likely coincide with periods of highest physical activity, sleep deprivation, and psychological stress. It is, therefore, not possible to identify the independent effects of energy status in these studies and randomized supplementation trials are required.

The few studies that have provided supplementary energy in addition to the habitual dietary intake during training provide further support for energy status as the mechanism for endocrine disturbances. An additional intake of 6,000–8,500 kcal·d⁻¹ during the 5 day Norwegian Ranger course attenuated disturbances to GH, cortisol and thyroid hormones, but not reproductive hormones (74, 77, 78), whereas the provision of 3–6 h extra sleep per night had no protective effect (74, 76, 79). Increasing energy intake from 1,800 kcal·d⁻¹ to 3,200 kcal·d⁻¹ or 4,200 kcal·d⁻¹ did not prevent the decrease in testosterone after a 5 day combat course, but estimated energy expenditure was > 5,000 kcal·d⁻¹ and so the supplementary energy was insufficient to eliminate the energy deficit (96). Periods of refeeding throughout US Army Ranger training resulted in the recovery of cortisol, IGF-1, T3, SHBG, and testosterone, but the provision of an extra 400 kcal·d⁻¹ had no effect on these markers, which was also insufficient to eliminate the energy deficit (2). Supplementation with 1,218 kcal·d⁻¹ during an 8 week British Army combat course did not prevent the increase in cortisol, or decrease in IGF-1 and testosterone compared with a control group, but only 66% of the supplement was consumed resulting in only a small attenuation of the energy deficit (4). Disturbances to adrenal, thyroid, reproductive, and metabolic hormones may depend on the severity of energy deficit, and some of these disturbances can be attenuated by additional energy intake, supporting a role of energy deficit, at least in part, in the endocrine disturbances observed with military activities.

**Menstrual Function**

Chronic low energy availability can result in functional hypothalamic amenorrhoea in women. Functional hypothalamic
amenorrhoea is the absence of menses due to suppression of the hypothalamic-pituitary-ovarian axis (97). The suppressed pulsatile release of gonadotropin-releasing hormone from the hypothalamus, decreases LH pulse frequency from the pituitary, and results in low circulating oestradiol (15, 16). Several studies have investigated menstrual disturbances in the military (24, 98–101), but inconsistencies with definitions of, and screening methods used for, menstrual disturbances, limit robust conclusions [see Gifford et al. (102) for a comprehensive review of menstrual dysfunction in the military]. Cross-sectional studies in the US Army identified the prevalence of menstrual disturbances was 11–15% (amenorrhoea, oligomenorrhoea, or delayed menarche) (24, 99). More than 90% of women reported menstrual irregularities during 1 year of basic military training at the US military academy, with almost half of the female cohort reporting decreased menstrual frequency (98, 100). A similarly high prevalence (70%) of menstrual disturbances were reported after starting Korean basic military training (92). Although these studies demonstrate basic military training can disturb menstrual function, the role of energy availability is not clear. Hormonal contraceptive use is also higher in servicewomen than their civilian counterparts, possibly due to an increased desire to suppress menses (103). A high use of hormonal contraception in servicewomen may mask changes in menstrual function in military training. To our knowledge, there are no prospective data examining the relationship between energy status and menstrual function in military women, and other factors such as psychological stress may contribute to menstrual function disturbances (92, 101, 102).

Bone

Poor skeletal health is a widely recognized clinical outcome associated with chronic low energy availability, and forms part of the Triad (11) and RED-S (9). Low energy availability decreases bone formation, possibly mediated by increased cortisol and decreased T3, leptin, and IGF-1, and can increase bone resorption by decreasing oestradiol production in women (9, 11, 14, 102, 104). Amenorrhoeic athletes have lower whole-body, axial, and appendicular areal BMD (105–108), poorer bone microarchitecture and/or mechanical strength (105, 107, 109, 110), and increased stress fracture risk (105) compared with their eumenorrhoeic counterparts. Low energy availability and low oestradiol may have independent and combined effects on bone (110, 111). The relationship between low energy availability and bone in men is less well-described, but endocrine disturbances, including decreases in sex steroids and IGF-1, likely disturb bone health (27, 112, 113).

Male US Army Rangers had decreased markers of bone formation (bone-specific alkaline phosphatase) and increased markers of bone resorption (tartrate-resistant acid phosphatase) after 8 weeks of training with energy deficits of ∼1,000 kcal·d⁻¹ (114). Bone-specific alkaline phosphatase is indicative of bone mineralisation and tartrate-resistant acid phosphatase reflects osteoclast number (115), whereas C-telopeptide cross-links of type 1 collagen, a marker of type I collagen breakdown, was unchanged. Bone-specific alkaline phosphatase was still decreased 2–6 weeks after the cessation of training and when body mass had returned to pre-training values, whereas tartrate-resistant acid phosphatase had returned to baseline, indicating a lag in bone formation and a vulnerable period for overloading bone. This reduction in bone formation coincided with decreases in whole-body bone mineral content (2). Whole-body bone mineral content and areal BMD losses were also evident after 7–10 months of operational deployment, during which time a 1.9% loss in body mass was observed (116). Six female soldiers who lost 13% body mass over a 61 day crossing of the Antarctic had decreased bone formation and areal BMD at the axial skeleton (117). Tibial macro and microstructure were unchanged suggesting mechanical loading was protective during energy deficiency. These studies demonstrate that specialist military training and deployment in energy deficit results in decreased bone formation, increased bone resorption, and loss of bone mass from the axial skeleton.

Stress fractures at weight-bearing sites are common during basic military training (25, 118, 119), more so in women than in men (120, 121). Skeletal injuries are indicative of the high mechanical stresses of military activities, but decreased bone formation and increased bone resorption with low energy availability could decrease mechanical strength of bone and increase the propagation of microcracks with repeated loading. The evidence for low energy availability in basic military training is mixed, and bone adapts favorably in response to 8–13 weeks basic military training programmes at appendicular sites (122–126). Increased incidence of stress fractures (25, 99, 127–129) and musculoskeletal injuries (130), and lower bone mass (131), are seen in servicewomen with menstrual disturbances (oligomenorrhoea, amenorrhoea, or delayed menarche), although these findings are not supported by all studies (24, 132–136). Disordered eating (25, 134, 136) and self-reported dietary intake (133, 137) are also not predictive of stress fracture, but these studies must be interpreted with consideration for the limitations of measuring dietary behaviors. Studies have also demonstrated a greater decrease in body mass (136) and IGF-1 (138), indicative of energy deficiency, in stress fracture cases compared with non-injured controls during basic military training. Decreased bone formation, increased bone resorption, and bone loss from the axial skeleton are observed during specialist military training, field exercises, and operational deployment in military personnel experiencing energy deficit, but the link between energy deficit and stress fracture in this population is unclear.

Immune Function

Cell-mediated and humoral immune function is disturbed by specialist military training in energy deficit (5 days to 8 weeks) (35, 139–149). High levels of physical activity, insufficient micronutrient intake, exposure to environmental extremes, sleep deprivation, and psychological stress may have contributed to these responses (150, 151), but providing an energy supplement attenuates some of these effects. Eight weeks of US Army Ranger training in energy deficit suppressed in vitro T-lymphocyte function and resulted in a high incidence of infection, which were both attenuated with an additional ∼400 kcal·d⁻¹ of energy intake (140, 152). The provision of an extra 1,218 kcal·d⁻¹ during
an 8 week British Army combat course maintained circulating leukocytes, lymphocytes, and monocytes, and increased the secretory rate of salivary immunoglobulin A compared with a control group (139). Similarly, increasing energy intake by providing fresh food rather than a ration pack maintained salivary immunoglobulin A during an Australian Air Force 12-day tropical field exercise (35). The clinical relevance of these acute changes in immune function is unclear, however, post-exercise protein supplementation throughout US Marine basic military training decreased the number of visits to the medical center for illness (153), providing some support for energy status in clinical outcomes. Basic military training (19–20 weeks) with high total energy expenditures and psychological stress, but stable body mass, had minimal effect on markers of immune function and the incidence of upper respiratory tract infection (154, 155), further supporting an independent role of energy status on immune function. These studies provide some support for a role of energy deficiency in disturbed immune function during military training.

Gastrointestinal
Gastrointestinal distress is common during specialist military training (156) and operational deployment (157). Restricting the gut of essential nutrients places stress on the microbiota, and changes in gut microbiota may contribute to decrements in gut health during energy deficit (158). Increased intestinal permeability and marked changes in gut microbiota and gut microbiota derived metabolites were observed after 4 days of severe energy deficit in Norwegian soldiers (159). An increase in intestinal permeability is consistently reported following specialist military training and could contribute to the increase in gastrointestinal symptoms (156, 160). Changes to the gut microbiota could be important in the etiology of several other clinical outcomes including musculoskeletal injury, illness and infection, and psychological impairments (158), but the role of energy deficit on these outcomes is not clear. High levels of physical activity, inflammation, environmental extremes, sleep deprivation, psychological stress, and changes to diet composition could all contribute to these gastrointestinal changes (158).

Hematological
Low energy availability may play a role in iron deficiency commonly seen in female athletes (10). Iron status is determined by the measurement of a combination of biochemical markers including ferritin, transferrin saturation, soluble transferrin receptor, and hemoglobin (161, 162). Widespread disturbances in these markers of iron status were reported in men and women following 7–26 weeks of basic military training (137, 163–169) and 12–26 weeks of operational deployment (39, 170). Stable or small losses in body mass in these studies, and similar self-reported habitual energy intake between recruits with and without iron deficiency (171), suggest energy deficit was not a primary mechanism in impaired iron status. Specialist military training in energy deficit does not affect iron status in trained male soldiers, although small decreases in hemoglobin have been observed (162, 172). Ferritin and hepcidin, a regulator of iron status, increased during specialist military training courses in energy deficit in trained male soldiers (57, 81, 162, 173, 174), indicative of increased inflammation rather than improved iron status (162). These studies suggest that changes in iron status with military training and operations are independent of energy deficits; increased physical activity and inflammation, decreased iron intake, gastrointestinal bleeding, iron sweat loss, and an increase in iron turnover are potential mechanisms (163, 166).

Psychological
Numerous studies have reported mood disturbances, as measured by the Profile of Mood States, in response to specialist military training of several days to 8 weeks in energy deficit (35, 147, 173, 175–183). The 8 week US Army Ranger course increased tension, depression, anger, fatigue, and confusion, and decreased vigor (176); similar disturbances to mood have been reported following just 3 days of sustained military activities in severe energy deficit (∼3,000 kcal·d⁻¹) (175, 178). US basic military training improved mood for both men and women (166, 184–186), where energy intake was more likely matched to energy expenditure (124, 187). Conversely, women undergoing the 44-week British Army Officer basic military training course had decreased resilience and increased depression (93). Additional carbohydrate improved vigor and decreased confusion during a day of military activities, but other mood constructs were not affected and overall energy status was not measured (188). Supplementary energy during field exercises in an energy deficit had limited impact on mood disturbance (182, 189, 190), but the provision of fresh feeding rather than ration packs, which also resulted in increased energy intake, attenuated feelings of fatigue during a 12 day field exercise in energy deficit (35). Although controlled laboratory trials provide some support for a role of energy deficiency in mood disturbances (191, 192), psychological stress is a fundamental component of military training, and combined with sleep deprivation and the potential for dehydration, mood disturbances cannot be attributed solely to energy deficit.

ENERGY DEFICIENCY AND PERFORMANCE
Physical Performance
Muscle strength and power is decreased following specialist military training courses of 3 days to 8 weeks in energy deficits of ∼500–4,000 kcal·d⁻¹ (4, 46, 48, 58, 80, 81, 89, 95, 175, 189, 193). Lower limb muscle power, assessed by jump performance, is decreased by 9–28% (4, 48, 58, 80, 81, 89). Not all studies report a decrease in lower limb muscle performance (189, 194, 195) and muscle fatigue and/or damage likely contributes to some of these effects (29, 46, 196). The maximal weight that can be lifted during whole-body exercise is decreased by 14–21% (4, 80, 81, 193) and upper body strength is decreased by up to 10% (48, 95, 189). An impairment in upper body strength and endurance is not consistently observed (35, 175, 194), but occupational task performance (repetitive lifting, obstacle course, and wall building) can still decrease despite maintained upper body strength (175), demonstrating the importance of testing relevant
aspects of military occupational performance. It is not possible to identify the direct role of energy deficit on impaired muscle performance from these studies, and military activities will result in some exercise-induced muscle fatigue and damage. Several days of fasting decreased upper body strength in male soldiers in the absence of other stressors (197), providing support for an independent effect of energy deficiency on muscle performance. A meta-regression demonstrated that muscle performance is impaired in proportion to the energy deficit, and limiting energy deficits to absolute values of \( -5.686 \) to \( -19.109 \) kcal, or \( \leq 3\% \) of body mass, for an entire operation will limit muscle performance decrements to \( \leq 2\% \) (198).

There are fewer data on endurance performance parameters. Decreased aerobic performance is seen after several days of field exercise in energy deficit (96, 181) but anaerobic performance is generally protected (96). Longer periods of operational deployment (6–13 months) result in unchanged (39, 199) or decreased (5–13%) (116, 200) aerobic capacity, and unchanged or increased muscle performance (39, 87, 116, 199). Modest decreases, or even increases in body mass, following deployment suggests the energy deficit was not severe in these studies. The delay between the end of deployment and the measurement of physical performance, the potential for de-conditioning (116, 200) or increased physical training volume (199), differences in operational role performed (199), and the temporal nature of combat activity, make studies on deployments difficult to interpret.

The provision of an additional 1,218 kcal·d\(^{-1}\) during an 8 week British Army combat course attenuated the energy deficit from \( -500 \) kcal·d\(^{-1}\) to 150 kcal·d\(^{-1}\) and prevented the loss in FFM and muscle performance (4). Another study found no effect of supplementary energy on physical performance and FFM, although the energy failed to offset the energy deficit compared with a control group (189). Muscle performance decreases in proportion to the loss in FFM (4, 80, 193), with energy deficit resulting in negative whole-body protein balance (47, 201). Other energy supplementation studies demonstrated that aerobic performance loss is attenuated following a 5 day field exercise (96), and performance on military physical fitness tests is augmented (202) and musculoskeletal injury incidence is decreased (153, 203) in basic military training. These studies support energy deficiency as a contributing factor in impaired muscle performance, and to a lesser extent aerobic endurance, during military training.

**Cognitive Performance**

Impaired vigilance, choice and simple reaction time, pattern recognition, short-term working memory, logical reasoning, and marksmanship are reported following several days to 8 weeks of specialist military training in energy deficit (173, 176–180, 182, 204), although other studies report unchanged (35) or improved (192) cognitive performance. Although impaired cognitive performance coincided with severe energy deficits (173, 176, 178), and demonstrated recovery with re-feeding (176), laboratory studies demonstrated that 2 days of isolated energy deficit only decreases cognitive performance during exercise (205) and not at rest (191, 206). In contrast, components of logical reasoning, working memory, visual reaction time, and vigilance improved in US Army basic military training (185). Additional energy in the form of carbohydrate supplementation maintained vigilance during 1 day of sustained simulated military activity compared with a placebo (188), and promoted recovery of Stroop test performance following special forces survival training (207), although energy status was unreported. Shooting performance decreased during a 21 day field exercise, and although energy balance was not measured, decreased IGF-1 suggests an energy deficit (194). Shorter periods (4 days) of field training in severe energy deficit (\( -2,900 \) kcal·d\(^{-1}\)) had no effect on shooting performance (175) and high energy intakes did not improve shooting performance (208) or protect against decrements in other constructs of cognitive performance (182, 209) during field exercises in energy deficit. The multi-stressors of military training, including sleep deprivation and dehydration, may contribute to impaired cognitive performance, with sleep deprivation and energy restriction likely to have independent effects (210).

**ENERGY DEFICIENCY IN FEMALE SOLDIERS**

Most evidence for the effect of low energy availability on health and performance is in female athletes (9–11, 19), whereas most of the military studies presented here were conducted in men. The effect of low energy availability in male athletes is being increasingly recognized (27, 112), and these military data make an important contribution to this field. The lack of data on military women is likely due, in part, to their previous exclusion from combat roles, and, therefore, lack of exposure to severe energy deficits. Men make-up most of the military, and women have only recently been permitted to enter combat roles in several countries including the UK and US. Women in these combat roles are likely to experience higher physical demands (29, 196, 211), have poorer physical performance (211), a higher incidence of musculoskeletal injuries and stress fractures (121), and increased risk of reproductive disturbances with low energy availability (102), compared with men. Better understanding of the effects of low energy availability on the health and performance of women in military roles, including combat roles, is an important area of future study.

**CONCLUSIONS**

Military personnel are exposed to energy deficits of varying severities during training and on operational deployment. These energy deficits are largely experienced by trained soldiers during specialist military combat training courses and field exercises, rather than recruits in basic military training. Military training in energy deficit results in many components of the Triad and RED-S, notably disturbances to endocrine and metabolic function, bone turnover, immune function, gastrointestinal health, mood, and physical and cognitive performance (Figure 1). Military training is a multi-stressor environment, so it is difficult to isolate the independent effects of energy status. Energy supplementation
studies suggest that energy deficiency contributes to impaired metabolic, endocrine, and immune function, and physical performance. Further randomized controlled trials are required to better identify the role of feeding and energy deficiency on health and performance outcomes. Most studies examined the short-term effects of arduous military training courses, but the long-term health effects of cyclical phases of energy deficiency and recovery, characteristic of military training and employment, require further study. More prospective longitudinal studies are also important to better understand the effect of energy deficiency on female soldiers’ health and performance.

**AUTHOR CONTRIBUTIONS**

TO’L performed the literature search and produced the manuscript. SW and JG edited the manuscript for intellectual content. All authors made contributions to the conception of the review and approved the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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