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Combined effects of creatine supplementation in women. A medical review

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Abstract

Introduction: Creatine plays an essential role in cellular bioenergetics via the creatine kinase/phosphocreatine phosphagen system. Historically, most studies have been conducted in male cohorts. However, contemporary evidence shows considerable sexual dimorphism, characterized by lower baseline endogenous creatine pools in females and by susceptibility to hormonal fluctuations spanning the menstrual cycle and over the lifetime.

Objective: The purpose of this medical review is to create current scientific evidence regarding the multi-systemic effects of creatine supplementation in the female organism. **Results:** In the context of physical exercise, integrating creatine into resistance training (RT) stimulates improvements in dynamic strength, although the hypertrophic potential and accretion of lean

body mass (LBM) are lower in females compared to males. A distinct neuroprotective potential has been demonstrated: supplementation increases total creatine concentrations in the frontal lobes, optimizes cognitive function under acute metabolic stress, and effectively supports the pharmacotherapy of major depressive disorder (MDD). In postmenopausal females, combining creatine with exercise is an effective countermeasure against sarcopenia and enhances skeletal structural strength parameters. In gynecology, population data (NHANES) correlate higher dietary creatine intake with regular menstrual cycling, while preclinical models suggest a crucial mediating role for creatine in uterine energetics as well as in protecting the fetus against perinatal hypoxia.

Conclusions: Creatine represents a safe, low-cost, and versatile strategy to promote metabolic, skeletal, and neurological health in females across all stages of ontogeny.

Keywords: creatine, sexual dimorphism, musculoskeletal system, neuroprotection, postmenopause, menstrual cycle

Highlights

Sexual Dimorphism: Females exhibit distinct creatine kinetics with lower baseline prefrontal pools, necessitating individualized supplementation protocols rather than extrapolating male data.

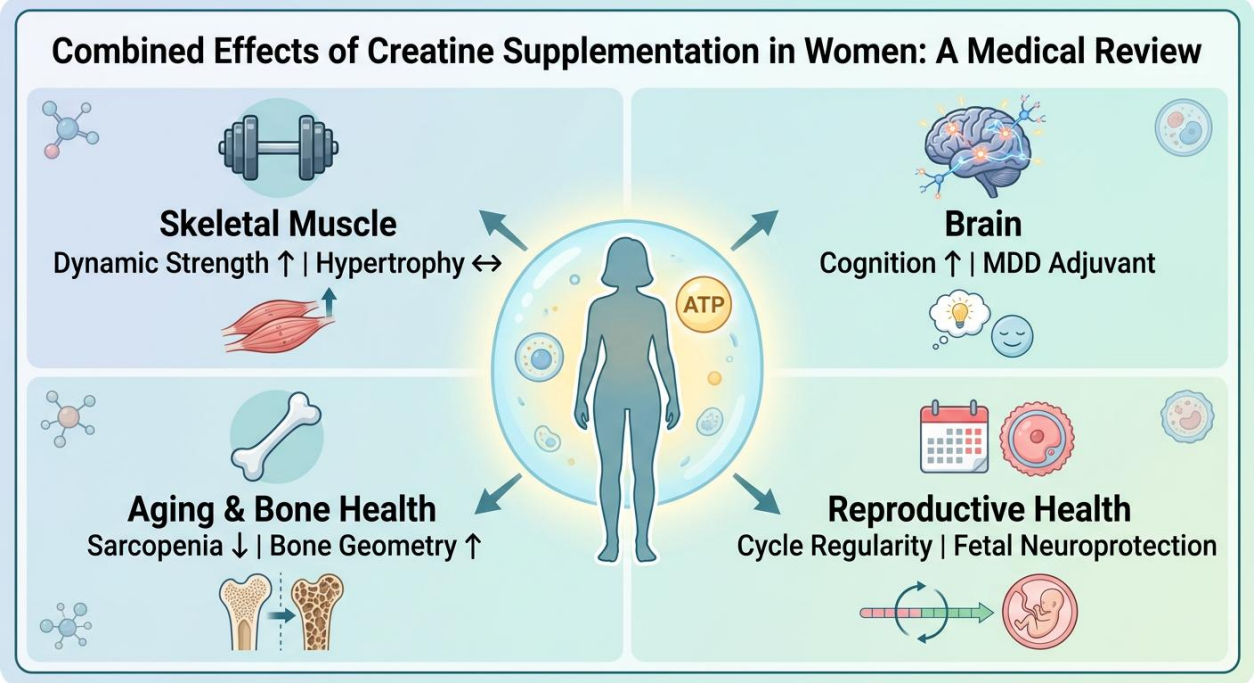
Musculoskeletal Adaptation: While the hypertrophic response in women is muted compared to men, creatine combined with resistance training significantly improves dynamic strength and counters postmenopausal sarcopenia.

Neuroprotection & Psychiatry: Supplementation enhances frontal lobe bioenergetics, optimizes cognition under metabolic stress, and acts as a highly effective adjuvant in major depressive disorder (MDD) pharmacotherapy.

Geriatric Prophylaxis: In aging women, creatine improves skeletal geometric strength and reduces osteoporotic fracture risk when paired with mechanical loading, despite neutral effects on areal BMD.

Reproductive Health: Higher dietary creatine intake correlates with menstrual regularity, and preclinical models highlight its crucial neuroprotective role against perinatal hypoxic injury.

Graphical Abstract



1. Introduction

Within the fields of sports medicine and clinical nutrition, creatine is among the most thoroughly investigated and empirically validated substances. Synthesized endogenously in the liver, kidneys, and pancreas, or acquired through the diet (predominantly via red meat and seafood), creatine plays a fundamental role in cellular bioenergetics. Upon entering target tissues via specific sodium- and chloride-dependent creatine transporters (CreaT), it is phosphorylated to phosphocreatine (PCr) [1, 2]. During intense, brief bouts of physical exertion, the enzyme creatine kinase (CK) rapidly transfers a phosphate group from PCr to adenosine diphosphate (ADP), thereby resynthesizing adenosine triphosphate (ATP) and buffering the acute depletion of cellular energy reserves [1, 3, 4, 5]. Beyond this primary phosphagen system, contemporary molecular physiology recognizes creatine as an important, dynamic energy shuttle between the mitochondria and the cytoplasm, supporting cells with exceptionally high metabolic demands, including skeletal muscle, myocardium, and the central nervous system (CNS) [3, 4]. Additionally, this compound exhibits therapeutic potential to mitigate oxidative stress, attenuate inflammatory cascades, and stabilize mitochondrial membranes, thereby accelerating post-exercise recovery [1, 2, 3, 8].

Historically, investigations concerning the efficacy, dosage regimens, and safety parameters of creatine have been predominantly conducted in male cohorts, with the resulting

data subsequently extrapolated to females without a critical appraisal of physiological differences. However, contemporary evidence-based medicine (EBM) recognizes that distinct sex-specific characteristics—including lower baseline endogenous creatine stores in females, smaller absolute muscle mass, and changing hormonal profiles throughout the lifespan—warrant a dedicated re-evaluation of creatine kinetics in females [6, 7]. Standard dosage protocols frequently do not account for the higher concentrations required to breach the blood-brain barrier for the optimization of neurological health, while pervasive misconceptions regarding adverse effects, such as pathological fluid retention, unnecessarily restrict its clinical implementation in female patients [5, 6, 9, 10]. This medical review aims to synthesize and present current scientific evidence on the biochemical mechanisms, standardized administration protocols, and combined physiological effects of creatine supplementation in females, thereby establishing a strong theoretical framework for clinical application.

2. Ergogenic Effects of Creatine on Muscle Mass and Resistance Training in Women

Integrating creatine supplementation with structured resistance training (RT) is a central strategy for improving neuromuscular function, stimulating skeletal muscle hypertrophy, and optimizing body composition. Although the ergogenic efficacy of creatine monohydrate is indisputably established in male athletes, recent clinical data from the 2025–2026 research cycle indicate clear, sex-specific differences in physiological responsiveness [11, 12, 13]. The female population exhibits a more muted and non-linear hypertrophic and anaerobic adaptation [11, 12]. This stems from the fact that the baseline biomechanical starting point of females—characterized by a lower absolute mass of striated muscle, a distinct distribution of fast-twitch (type II) fibers, and natural fluctuations in estrogen levels—implies that a simple transposition of male paradigms leads to an overestimation of potential lean body mass (LBM) gains [14, 15].

Systematic scientific evidence indicates substantial heterogeneity of outcomes within the cohort of active females. A comprehensive systematic review from 2025, evaluating 27 clinical trials, demonstrated that while creatine provision yielded limited improvements in isolated metrics of upper-body power and anaerobic capacity, the majority of the assessed cohorts failed to display statistically significant functional improvements compared to placebo [11]. Of eleven rigorously controlled trials evaluating maximal strength and explosive power, only three demonstrated objective superiority of the supplementation group [11]. This phenomenon corresponds with data tracking changes in body composition. The implementation of a 7-day loading phase (5 g/day) induced an immediate increase in LBM in females, driven by

intracellular hyperhydration [16]. However, upon completion of the subsequent resistance training program, both the creatine and control groups achieved an equivalent, parallel increase of approximately 2 kg of lean body mass, demonstrating that creatine does not exert as potent a synergism in stimulating long-term myofibrillar protein synthesis in females as observed in males [16].

This paradigm is further substantiated by macro-analyses from the 2025–2026 period. A large-scale meta-analysis of strength parameters in multi-joint exercises revealed that females achieve smaller or statistically non-significant gains in exercises such as the barbell squat, leg press, or vertical jump compared to young males [13]. Furthermore, studies evaluating alternative chemical variations, including creatine hydrochloride (Creatine HCl) versus classic monohydrate in trained females, showed no differences in mechanical adaptations, thereby limiting their performance to modifying circulating biomarkers of oxidative stress and the kinetics of muscle micro-damage [19]. The contemporary consensus, therefore, signifies that while females can successfully utilize creatine to support exercise adaptation, their outcome expectations should remain moderate [11, 15, 18].

3. Neuroprotective and Cognitive Implications of Creatine Supplementation in Women

Modern neurobiology is increasingly documenting the advanced neuroprotective functions of creatine within the central nervous system. The brain demonstrates an exceptionally high demand for ATP, and the localized CK/PCr system plays a critical function in maintaining the energetic homeostasis of neurons and glial cells [3, 9]. New scientific reports supply compelling arguments showing a distinct sexual dimorphism in brain bioenergetics. The female population is physiologically characterized by a lower baseline density of the creatine pool in cerebral structures, particularly in prefrontal cortex zones responsible for mood control, executive functions, and cognitive functioning [20]. This bioenergetic specificity suggests that females may exhibit greater responsiveness to exogenous supplementation, offering new avenues for the prevention of cognitive and affective disorders [20, 21].

The impact of supplementation on the cognitive integrity of females has been precisely documented in recent randomized controlled trials. In a 2025 clinical trial (the CONCRET-MENOPA project) evaluating perimenopausal and menopausal females, an 8-week intervention using a moderate dose of creatine hydrochloride (1.5 g/day) led to an objective increase in total creatine levels in the frontal lobes of approximately 16% [22]. These alterations were accompanied by a statistically significant improvement in reaction time and a beneficial

modulation of the lipid profile, along with a clear trend toward stabilizing mood fluctuations [22]. Meta-analyses of large adult cohorts confirm that creatine effectively optimizes short-term memory, attention span, and information processing speed [24, 25]. Crucially, subgroup analyses revealed that the improvement in mental function speed following the supplementation protocol was more pronounced in females than in males [24].

The most spectacular neuroprotective potential of creatine manifests under conditions of acute metabolic and cellular stress. Systematic literature reviews consistently indicate that exogenous and endogenous CNS energy deficits—induced by sleep deprivation, chronic mental exertion, or transient hypoxia—are effectively ameliorated by the administration of this compound [4, 26, 27]. In controlled clinical models involving a 21-hour period of continuous sleep deprivation, the application of a single, high dose of creatine (ranging from 0.2 g/kg to 0.35 g/kg of body weight) successfully prevented the metabolic degradation of brain tissue [26, 28]. This intervention considerably lessened declines in alertness and minimized deficits in logical and numerical tasks [28]. It is worth noting that in tests assessing neurobiological resilience to fatigue, females derived measurably greater cognitive benefits across a range of elaborate cognitive tasks, supporting the hypothesis of high plasticity in female cerebral metabolism in response to phosphagen restoration [28].

Keenly promising data emerge from the field of psychiatry and the treatment of affective disorders in females. A reduction in the density of the prefrontal phosphocreatine pool is strictly correlated in neurobiology with the pathophysiology of depressed mood and clinical depression [27]. Population studies find a direct negative correlation: higher dietary creatine intake in daily nutrition is associated with a linear decrease in the risk of developing depressive episodes [27]. In a group of female patients diagnosed with major depressive disorder (MDD), the adjunctive incorporation of 4 g/day of creatine monohydrate alongside standard antidepressant pharmacotherapy over an 8-week period resulted in a rapid, radical reduction in depression severity scores, reaching up to approximately 56% in selected populations [20]. Currently, creatine is recognized as a highly effective, safe, and biologically justified cofactor supporting psychiatric pharmacotherapy in females, capable of tangibly improving psychological well-being across all stages of life [20, 21].

4. Musculoskeletal and Metabolic Benefits in Peri- and Postmenopausal Women

The perimenopausal and postmenopausal periods in a woman's life are characterized by a precipitous decline in estrogen secretion, which induces an array of systemic negative sequelae.

Chief among the clinical manifestations of this state are accelerated skeletal demineralization (leading to osteopenia and osteoporosis) and the progressive involution of muscle tissue, defined as sarcopenia [21, 29]. In this context, clinical investigations from the 2025–2026 cycle precisely evaluate the role of creatine supplementation as a therapeutic strategy geared toward conserving the integrity of the locomotor system in aging females. However, analysis of the latest clinical evidence calls for a clear delineation between direct effects on bone mineral density and modifications in geometric bone architecture and the functional parameters of the muscular apparatus [30, 31].

The evaluation of creatine's impact on bone mineral density (BMD), as measured by standard dual-energy X-ray absorptiometry (DXA), yields equivocal findings in the scientific literature. Isolated, long-term supplementation with this compound (at doses ranging from 1 to 3 g/day for a duration of 1–2 years) in females diagnosed with osteopenia fails to present a statistically significant advantage over placebo regarding absolute BMD values or trabecular microarchitecture [31, 32]. However, a breakthrough occurs when protocols combine creatine supplementation with regular mechanical loading through resistance training. In a rigorous 12-month clinical trial, it was demonstrated that a relative creatine dose of 0.1 g/kg/day paired with RT significantly decelerated the loss of BMD within the anatomically critical femoral neck, reducing the attrition rate to -1.2% compared to a regression of up to -3.9% in the placebo group [33]. Concurrently, a 2-year observation utilizing a dosing protocol of 0.14 g/kg/day (combining RT with walking) did not register changes in the areal bone mineral density (aBMD) of the hip or spine, yet it demonstrated a highly significant improvement in the geometric parameters of the femoral neck, such as the section modulus (a predictor of bending strength) and the buckling ratio [30]. Systematic meta-analyses confirm this trend, suggesting that although creatine rarely increases DXA-derived density *per se*, it successfully optimizes the structural and strength parameters of the skeleton, thereby directly reducing osteoporotic fracture risk among aging females [29, 34].

While the impact on bone tissue is largely indirect, the anti-sarcopenic efficacy of creatine within the postmenopausal population displays exceptional evidential consistency. Multi-center meta-analyses incorporating clinical trials dedicated exclusively to older females confirm that adding creatine to training programs extending beyond 24 weeks triggers a powerful, objective increase in both upper- and lower-body strength [35]. In larger cohort analyses, where females comprised over 69% of participants, maintenance-dose interventions (3–5 g/day) over a maximum of 32 weeks induced radical alterations in body composition, including reductions in relative adiposity and dynamic gains in LBM [36, 37].

From a clinical standpoint, the primary benefit extends far beyond only muscle hypertrophy; the enhancement of dynamic strength translates directly into improved functional capacity (e.g., timed up-and-go tests, chair-rise performance, gait speed) [29, 38]. The latest medical syntheses uniformly indicate that supplementing hormone replacement therapy or classical training with creatine exerts a complementary effect. By simultaneously activating osteoblasts and upregulating myofibrillar protein synthesis in aging females, this strategy significantly reduces the incidence of clinically dangerous falls, making it one of the most effective prophylactic tools against frailty syndrome in contemporary geriatrics [21, 29, 38].

5. Reproductive Health, Menstrual Cycle, and Premenstrual Syndrome (PMS/PMDD)

The interplay between creatine metabolism and the endocrine regulation of the hypothalamic-pituitary-ovarian axis is one of the most dynamically evolving yet under-researched domains of gynecology and reproductive medicine. Periodic fluctuations in sex steroid concentrations (principally estradiol and progesterone) throughout the menstrual cycle directly modulate the endogenous synthesis of this compound, the expression and activity of the CreaT transporter, and the kinetics of creatine kinase (CK) [6, 21]. These endocrine variations induce cyclical shifts in the bioavailability of phosphagens within high-demand target tissues, including the prefrontal cortex and uterine tissues [6, 39]. Although direct clinical interventions in females of reproductive age remain scarce, recent epidemiological and translational data from the 2024–2026 window shed new light on the metabolic significance of creatine in boosting female reproductive physiology [40].

Compelling population-level arguments have emerged from multi-center analyses of the NHANES database (evaluating a cohort of 4,522 females aged 12 years and older). It was demonstrated that a higher dietary intake of creatine in daily nutrition (at a threshold of $\geqslant$ 13 mg/kg of body weight) was strictly and independently correlated with a significant reduction in the prevalence of oligomenorrhea and irregular cycles (OR $\approx$ 0.75) [40, 41]. Concurrently, a linear decline was observed in the incidence of selected gynecological pathologies and obstetric complications, including fetal macrosomia, pelvic inflammatory disease, and the lifetime requirement for a hysterectomy or oophorectomy [40, 42]. While the authors of these reports explicitly emphasize the correlative nature of the data, which precludes direct causal inference, these findings form a firm foundation for designing future randomized controlled trials [40]. In an exercise context, it has been proven that implementing an aggressive creatine loading protocol (20 g/day for 5–7 days) in physically active females effectively offsets performance decrements in anaerobic capacity and heightened fatigue levels that physiologically manifest during the luteal phase of the menstrual cycle [43, 44].

Regarding the clinical manifestations of cycle-related affective disturbances, such as premenstrual syndrome (PMS) and premenstrual dysphoric disorder (PMDD), contemporary medical literature exhibits a considerable research lacuna. Conventional therapeutic guidelines for the management of PMS/PMDD focus on selective serotonin reuptake inhibitors (SSRIs), hormonal contraceptives, and micronutrient supplementation (calcium, magnesium, pyridoxine), largely omitting creatine as a direct clinical modality [45, 46]. Despite the hypothetical plausibility—predicated upon the optimization of prefrontal energy metabolism and documented antidepressant potency in female cohorts—no direct clinical trials verifying this hypothesis have been published to date [6, 21]. Consequently, creatine cannot currently be classified as a recommended component of standard care for PMDD [45].

Conversely, the state of science in prenatal medicine and perinatology presents a far more clearly defined trajectory. Translational research and preclinical animal models unequivocally demonstrate that maternal creatine availability determines the metabolic and energetic development of the placenta, myometrium, and developing fetal brain [39, 44]. The CK/PCr system is profoundly upregulated in uterine tissue during peak metabolic stress, most notably at parturition [39]. Crucially, *in vitro* models suggest that prophylactic maternal creatine supplementation during gestation can exert a potent neuroprotective effect, shielding the central nervous system of the fetus from the catastrophic sequelae of perinatal asphyxia and hypoxia [39]. Expert consensus from the 2025–2026 period confirms the complete absence of toxicity signals or safety issues associated with the use of high-quality chemical formulations in pregnant populations [47]. Nonetheless, owing to demanding ethical restrictions, conducting prospective clinical trials assessing tolerance and pharmacokinetics in pregnant females remains imperative before integrating creatine into widespread prenatal care standards—an objective that functions as a top priority for academic gynecology [6, 39, 44].

6. Conclusions

The contemporary state of medical science unequivocally establishes creatine as a multisystemic compound whose efficacy spectrum in women extends far beyond the historical confines of sports performance optimization. An in-depth analysis of high-level scientific evidence accumulated through the 2024–2026 research paradigm permits the formulation of the following key clinical conclusions:

1. **Kinetic Divergence and Sexual Dimorphism:** Females exhibit unique physiological traits, including a lower baseline endogenous creatine pool in the prefrontal cortex as well as a distinct vulnerability to phosphagen dysregulation secondary to hormonal fluctuations throughout the menstrual cycle. This calls for a departure from the uncritical extrapolation of male data and highlights the need for individualized supplementation protocols in female clinical medicine.
2. **Skeletal Muscle and Body Composition:** Incorporating creatine into structured resistance training plans in females stimulates dynamic strength adaptations and induces favorable, immediate modifications in body composition via cellular hyperhydration. Nonetheless, the absolute hypertrophic potential and net gains in lean body mass (LBM) are inherently more muted and less predictable than those observed in male cohorts, requiring clinicians to manage patient expectations accordingly.
3. **Evident Neuroprotective Potential:** The most consistent and clinically promising therapeutic signals relate to the preservation and optimization of the central nervous system. Creatine supplementation effectively augments cognitive processing speed in females—particularly during acute states of cellular energy crisis (e.g., sleep deprivation, mental exhaustion)—and demonstrates high efficacy as a metabolic cofactor (adjuvant therapy) when paired with standard pharmacotherapy for major depressive disorder (MDD).
4. **Geriatrics and Involutional Prophylaxis:** Within the postmenopausal female population, pairing creatine with long-term exercise interventions (exceeding 24 weeks) represents a highly effective countermeasure against sarcopenia. Although its direct impact on areal bone mineral density (aBMD via DXA) is mainly neutral, the intervention significantly optimizes the geometric strength and structural architecture of the skeleton, which, in synergy with augmented muscular power, drastically reduces the incidence of accidental falls and subsequent osteoporotic fractures.
5. **Gynecology and Prenatal Medicine:** Population-level data indicate a strong relationship between robust dietary creatine intake and the regulation of the menstrual cycle, alongside a reduced risk of major gynecological pathologies. At the preclinical tier, creatine acts as a key mediator of uterine and placental energetic homeostasis, showing a capacity to shield the fetal brain from perinatal hypoxic injury. However, this domain, much like the direct evaluation of creatine for PMS/PMDD symptomatology, continues to face a deficit of prospective human clinical trials.

To summarize, creatine is a safe, highly affordable, and versatile clinical strategy to safeguard the metabolic, skeletal, and neurological health of females throughout ontogeny. The paramount directive for modern academic gynecology and sports medicine remains the conduct

of rigorous, multicenter randomized controlled trials (RCTs) that rigorously isolate and account for female endocrine variations, thereby enabling clinical science to precisely map and fully exploit the therapeutic potential of this compound in the female population.

Disclosure

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