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**Gender-Specific Effects of Omega-3 Fatty
Acid Consumption on Mental Health: A
Systematic Review**
Master's Thesis (30 ECTS)

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Gender-Specific Effects of Omega-3 Fatty Acid Consumption on Mental Health: A Systematic Review

Abstract:

Background: Omega-3 polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been broadly studied for their role in mental health, but it remains unclear whether and how much biological sex modulates the psychological effects of omega-3 fatty acids. Gender-specific differences in omega-3 metabolism, hormonal influences on fatty acid biosynthesis, and neurobiological factors may result in differential mental health responses to omega-3 consumption between men and women.

Objectives: This systematic review aimed to find evidence on gender-specific effects of omega-3 fatty acid consumption on mental health outcomes, including depression, anxiety, cognitive function, and stress response.

Methods: A systematic search of electronic databases, including PubMed, MEDLINE, PsycINFO, and Cochrane Library, was conducted following PRISMA guidelines. Randomised controlled trials, prospective cohort studies, and cross-sectional studies examining omega-3 fatty acid intake or supplementation and mental health outcomes with gender-stratified analyses were included. Studies were assessed for risk of bias using validated tools.

Results: Evidence suggests that women showed greater conversion capacity of alpha-linolenic acid (ALA) to long-chain omega-3 fatty acids, indicating that women may derive greater antidepressant and anxiolytic benefits from omega-3 supplementation compared to men, particularly EPA-predominant formulations, while men showed more modest or inconsistent mental health responses. Hormonal fluctuations across the female reproductive lifespan were identified as important modulators of omega-3 efficacy on mood and cognitive outcomes.

Conclusion: Current evidence suggests that gender is an important biological variable in determining the mental health effects of omega-3 fatty acid consumption, with women potentially experiencing greater psychological benefits than men.

Keywords: Omega-3 fatty acids, EPA, DHA, depression, anxiety, cognitive function, gender differences, gender, mental health, systematic review

CERCS: B470 Nutrition

List of Abbreviations

PUFA	Polyunsaturated Fatty Acid
EPA	Eicosapentaenoic Acid
DHA	Docosahexaenoic Acid
SMD	Standardized Mean Difference
RCT	Randomized Controlled Trial
ROBINS-I	Risk Of Bias In Non-randomised Studies of Interventions
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
ALA	Alpha-linolenic acid
FADS1	Fatty Acid Desaturase 1
SMD	Standardized Mean Difference
BDNF	Brain-derived neurotrophic factor
HPA	Hypothalamic-Pituitary-Adrenal (axis)
SABV	Sex as a Biological Variable
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
ER α	Estrogen Receptor Alpha
SSRI	Selective Serotonin Reuptake Inhibitor
PET	Positron Emission Tomography
CRH	Corticotropin-Releasing Hormone
PPAR α	Peroxisome Proliferator-Activated Receptor Alpha
RXR α	Retinoid X Receptor Alpha
CREB	Cyclic-AMP response element-binding protein
NMDA	N-Methyl-D-aspartate
TPH	Tryptophan Hydroxylase
SERT	Serotonin Transporter
HT	Hydroxytryptamine Receptor

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1. INTRODUCTION

The link between what we eat and how we feel is one of the most exciting thoughts in modern science. Omega-3 fatty acids are essential fats found in fish, walnuts, and seeds that our bodies can't produce on their own. We've known for years that Omega-3s are brain food; recent research suggests that they don't affect everyone the same way. Men and women have different hormonal profiles, metabolic rates, and even brain structures, leading scientists to wonder. This systematic review explores the gender-specific effects of omega-3 intake on various mental health outcomes, including depression, anxiety, and cognitive performance.

1.1 Background and Rationale

Omega 3 PUFAs belong to a specialized family of essential polyunsaturated lipids defined by the position of their first double bond, located at the third carbon from the methyl terminus of the fatty acid chain [1]. These fatty acids play a fundamental role in lipid metabolism across mammalian species and are considered indispensable for normal physiological function. The three biologically significant forms DHA, ALA, and EPA have particular importance to the human central nervous system. Among them, DHA is the most structurally dominant, accounting for roughly 40% of total fatty acids within the brain, whereas EPA is present in far smaller quantities, comprising less than 1% of total cerebral fatty acid content [1, 2]. The brain is a highly lipid-dense organ, with lipids constituting approximately 50-60% of its total weight. Of this lipid fraction, omega-3 PUFAs represent around 35%. DHA alone contributes more than 40% of all omega-3 PUFAs found in neuronal tissue, with its highest concentrations located within grey matter [2, 3].

Mental health disorders, including major depressive disorder (MDD), anxiety, and cognitive decline, represent a growing global burden, affecting over one billion individuals worldwide (WHO, 2022). Despite pharmacological advances, a significant proportion of patients fail to achieve remission with standard treatments, prompting investigation of nutritional and nutraceutical adjuncts. Within this group, omega 3 polyunsaturated fatty acids (PUFAs) particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have attracted substantial research interest due to their established roles in brain structure and function. Mental health conditions, including major depressive disorder, anxiety disorders, and age-related cognitive decline, collectively represent one of the most pressing public health challenges of our time, estimated to affect more than one billion people globally (WHO, 2022). While pharmacological treatments have advanced considerably, a substantial proportion of affected

individuals do not achieve adequate symptom remission through standard drug therapies, driving interest in nutritional and nutraceutical approaches as complementary or adjunct interventions. Among the most extensively studied candidates are the long-chain omega-3 PUFAs, particularly EPA and DHA, which have garnered significant scientific attention owing to their well-documented contributions to brain architecture and neurological function. Both EPA and DHA are known to interact with several neurobiological systems relevant to mental health. These include the eicosanoid and prostaglandin pathways, neuroinflammatory cascades, monoaminergic neurotransmission involving serotonin and dopamine, and the regulation of the hypothalamic-pituitary-adrenal (HPA) axis [4].

Despite an expanding volume of research in this area, findings across studies remain inconsistent and difficult to reconcile. One underappreciated and insufficiently examined contributor to this variability is biological sex. Males and females differ in meaningful ways in how they metabolize omega 3 fatty acids. In females, oestrogen stimulates the elongase and desaturase enzyme systems responsible for converting the plant-derived precursor ALA into the longer chain EPA and DHA, resulting in comparatively higher resting DHA concentrations in female plasma and tissues [5]. In males, omega-3 utilisation relies more directly on preformed dietary sources of EPA and DHA, given the relatively limited capacity for endogenous conversion of ALA. In this context, these fatty acids primarily contribute to lipid homeostasis, skeletal muscle function, endocrine signalling, and cardiovascular health. Beyond metabolic differences, sex hormones also shape the neuroinflammatory environment through which omega-3s produce their psychotropic effects. Taken together, these sex related biological differences in fatty acid metabolism and neuroendocrine function strongly suggest that the therapeutic response to omega-3 supplementation may be inherently sex dependent, yet a significant proportion of published trials have either enrolled exclusively male participants, failed to include gender stratified analyses, or pooled male and female data without examining subgroup differences. This systematic review aims to address this gap by integrating evidence from both gender-specific and mixed gender studies, with a particular focus on evaluating whether the therapeutic effects of omega-3 fatty acids on mental health outcomes vary between females and males.

1.2 Research Objectives

This systematic review was designed to address a critical gap in nutritional psychiatry literature: the absence of gender stratified evaluation of omega-3 fatty acid efficacy on mental health

outcomes. The review was guided by one overarching primary objective and two supporting secondary objectives.

Primary Objective:

- To systematically evaluate the gender-specific effects of omega-3 fatty acid supplementation on mental health outcomes across female, male, and mixed-gender study populations.

Specifically, this objective sought to determine whether biological sex functions as a significant moderating variable in the relationship between omega-3 intake, including EPA, DHA, EPA+DHA combinations, and dietary omega-3 and broad mental health outcomes. Given the established estrogen-driven upregulation of fatty acid desaturase enzymes (FADS1/FADS2) and its downstream implications for EPA and DHA bioavailability and neuroinflammatory modulation, it was hypothesised that females would demonstrate systematically larger effect sizes than males across mental health domains. This objective was evaluated by comparing pooled standardised mean differences (SMD) across gender-stratified subgroups and examining the consistency of findings within each group.

Secondary Objectives

- Secondary Objective 1: To assess the impact of omega-3 fatty acid intake on cognitive performance outcomes in males and females, and to identify whether gender-specific differences in cognitive response are supported by the available evidence. Cognitive function represents a distinct neurobiological domain from affective health, relying heavily on DHA's structural role in cerebral phospholipid membranes and its capacity to support synaptic plasticity, neurogenesis, and BDNF expression. This objective sought to determine whether omega-3 supplementation confers measurable cognitive benefits, including improvements in memory, processing speed, and sustained attention and whether such benefits differ between genders. Given that females maintain higher baseline DHA concentrations than males due to hormonal metabolic advantages, it was anticipated that females may show greater cognitive responsiveness to DHA supplementation; however, this hypothesis was contingent on the availability of female-specific cognition data in the literature.
- Secondary Objective 2: To examine the differential effects of omega-3 fatty acid supplementation on mood, perceived stress, and depressive symptomatology in both

genders, with the aim of characterising the importance, consistency, and gender-specificity of omega-3's affective benefits.

Depression and mood dysregulation represent the primary clinical targets for omega-3 intervention in psychiatric contexts. This objective extended beyond simple efficacy evaluation to investigate whether the antidepressant and mood stabilising effects of omega-3s, proposed to operate through EPA-mediated inhibition of pro-inflammatory eicosanoid synthesis, HPA axis attenuation, and serotonergic modulation, are uniformly distributed across genders or whether they are disproportionately expressed in females. Stress, as an upstream contributor to affective disorders and a modulator of HPA reactivity, was included as a secondary outcome domain, recognising that omega-3s' cortisol attenuating properties may interact with gender-specific stress physiology. Findings from this objective were expected to directly inform gender-stratified clinical recommendations for omega-3 supplementation in depressive and mood disorders.

1.3 Scope of the Review

This systematic review is specifically for human studies investigating the consumption of omega-3 fatty acids as a standardised supplement (EPA, DHA, EPA+DHA combinations, or general fish oil) or derived from habitual dietary consumption and outcomes related to mental health. The mental health domains captured within this scope include major depressive disorder and depressive symptomatology, mood disturbance and affect regulation, cognitive performance, perceived stress and stress-related physiological markers, and broader behavioural outcomes associated with neuropsychiatric function.

The primary analytical lens through which all findings are interpreted is biological sex, defined here as the chromosomal, gonadal, and hormonal characteristics that separate female and male physiology, as distinct from gender identity. Gender is treated not merely as a demographic descriptor but as a biologically active moderating variable with established implications for omega-3 fatty acid pharmacokinetics, neuroinflammatory regulation, and neurotransmitter system sensitivity. This framing is consistent with the NIH Policy on Sex as a Biological Variable (SABV), which, since 2016, has mandated the consideration of sex as an independent variable in federally funded biomedical research. This scope reflects a deliberate methodological conservatism aimed at maximising the inferential validity of gender specific conclusions.

1.4 Significance of the Review

The significance of this review operates at four interconnected levels: clinical, methodological, public health, and scientific.

Clinical Significance:

The most immediate implication of this review concerns the translation of omega-3 research into clinical practice. If biological sex is confirmed as a substantial moderator of omega-3 efficacy, as the evidence presented in this review suggests, then the universal use of gender pooled clinical trial data to inform treatment guidelines introduces a systematic and potentially harmful inferential error. Specifically, pooling males and females without stratification risks two compounding errors simultaneously; it may obscure a clinically meaningful therapeutic benefit in females by diluting strong female-specific effects with weaker or absent male effects, and it may falsely reassure clinicians regarding the utility of omega-3 supplementation in male populations by attributing female-driven improvements to the group as a whole.

The EPA specificity of the female antidepressant response adds a further layer of clinical relevance. EPA dominant formulations rather than DHA or balanced EPA+DHA combinations are primarily responsible for the antidepressant effects in females. Gender stratified clinical guidelines specifying EPA-dominant supplementation for female patients with depressive presentations and acknowledging the current absence of efficacy evidence for male depression would represent a meaningful advance in the precision of nutritional psychiatry practice.

Methodological Significance:

This review also carries significant methodological implications for how omega-3 clinical trials are designed, reported, and interpreted. The majority of existing omega-3 mental health trials were not designed with gender specific hypotheses, were not powered to detect sex-by-treatment interactions and did not pre-specify subgroup analyses by gender. As a result, the literature as it currently stands is unable to answer the very question this review poses with the degree of precision that clinical and public health decision-making requires.

This finding supports a broader argument for methodological reform in nutritional psychiatry research and observation alone constitutes a methodological argument for stratified rather than pooled trial design.

Public Health Significance:

At the population level, the implications of this review are considerable. Depression is projected by the World Health Organization to become the leading cause of global disease burden by 2030, disproportionately affecting females who are diagnosed with major depressive disorder at approximately twice the rate of males across most age groups (WHO,2022 [6]; Kessler et al [7]., 2003; Salk et al. [8], 2017). If omega-3 supplementation, particularly EPA-dominant formulations, represents an effective, safe, accessible, and low-cost adjunct treatment specifically for female depression, then the failure to identify and communicate this gender specific benefit represents a missed public health opportunity of substantial magnitude.

In addition, the populations most likely to benefit from omega-3 supplementation, women of reproductive age, peri- and post-menopausal women, and elderly females, are precisely those in whom hormonal modulation of omega-3 metabolism is most biologically active and most clinically relevant. Nutritional interventions targeted at these populations, informed by gender stratified evidence, could complement pharmacological treatments, reduce polypharmacy burden, and address the significant treatment gap that persists in global mental health systems, particularly in lower-resource settings where dietary omega-3 intake from marine sources is already lower and where access to pharmaceutical antidepressants may be limited.

Scientific Significance:

Finally, this review contributes to the broader scientific project of establishing gender as a biologically meaningful variable in nutritional neuroscience, a field that has historically lagged behind pharmacology and clinical medicine in applying the SABV framework¹. The identification of estrogen-driven FADS1/FADS2 upregulation as a plausible mechanism for gender differential omega-3 efficacy provides a testable biological hypothesis that future basic science and translational research can directly investigate. Understanding the precise hormonal, enzymatic, and neuroinflammatory pathways through which sex moderates omega-3 response has the potential not only to refine supplementation recommendations but to illuminate broader gender differences in neuropsychiatric vulnerability and resilience with implications extending well beyond omega-3 research to the neuroscience of affective disorders more generally.

¹<https://orwh.od.nih.gov/sex-as-biological-variable>

2. LITERATURE REVIEW

The primary purpose of a literature review is to establish a theoretical foundation for a study, synthesise previous findings, and identify gaps or unanswered questions that justify the need for new research.[9]. Its key functions are Contextualization, Evaluation and Methodological Guide.

2.1 Omega-3 Fatty Acids: Structure, Sources, and Metabolism

Chemical structure:

Omega-3 fatty acids constitute a structurally defined subclass of polyunsaturated fatty acids (PUFAs), distinguished by multiple carbon-carbon double bonds and, most critically, by the location of the first such bond at the third carbon position from the methyl terminus, the biochemical feature from which their class designation derives [10] This positional characteristic governs the three-dimensional conformation of the molecule, which in turn determines its recognition by membrane-bound enzymes, its incorporation into phospholipid bilayers, and the specific array of bioactive lipid mediators, including resolvins, protectins, and maresins, that can be biosynthesised from it [11]. The structural contrast with omega-6 PUFAs, whose first double bond is positioned at the sixth carbon, produces markedly divergent metabolic outcomes, whereas omega-6-derived eicosanoids tend to promote pro-inflammatory signalling, omega-3-derived mediators predominantly exert anti-inflammatory and pro-resolving effects, making the dietary ratio of omega-6 to omega-3 intake a critical determinant of systemic inflammation [12] In most Western dietary patterns, this ratio currently ranges from 15:1 to 20:1 in favour of omega-6, a substantial departure from the estimated 1:1 to 4:1 ratio of ancestral human diets, a shift consistently associated with elevated risk of inflammatory and neuropsychiatric disease [13].

The three primary omega-3 fatty acids:

Alpha-Linolenic Acid (ALA; 18:3n-3) is an 18-carbon, three-double-bond short-chain omega-3 and the only omega-3 classified as strictly essential, as mammalian cells lack the enzymatic machinery for its de novo synthesis [14]. ALA must therefore be obtained exclusively through dietary intake, with concentrated plant-based sources including flaxseed and its derived oil, chia seeds, walnuts, hemp seeds, and canola oil. Within human metabolism, ALA functions primarily as a biochemical precursor substrate that can, through enzymatic elongation and desaturation reactions, be converted into the longer chain and more biologically active EPA

and DHA. However, the practical utility of this conversion is severely constrained by the poor efficiency of this process in humans.

Eicosapentaenoic Acid (EPA; 20:5n-3) is a 20-carbon, five-double-bond long-chain omega-3 found in appreciable quantities almost exclusively in marine food [10]. EPA is metabolically distinguished by its potent capacity to modulate inflammatory pathways; it competes directly with arachidonic acid (AA) for the cyclooxygenase (COX) and lipoxygenase (LOX) enzymatic pathways, thereby competitively reducing the synthesis of series 2 prostaglandins and series 4 leukotrienes [15]. EPA also serves as a precursor for E-series resolvins, which actively facilitate the resolution of inflammation [11]. Across multiple meta-analyses, EPA has been identified as the omega-3 with the most robust and consistent antidepressant properties, attributed to its neuroinflammatory modulating capacity and facilitation of serotonergic neurotransmission [16, 17].

Docosahexaenoic Acid (DHA; 22:6n-3) is a 22-carbon, six-double-bond long-chain omega-3 and the most structurally abundant omega-3 in the human brain, accounting for approximately 40% of total fatty acids in neuronal tissue and concentrated most densely within grey matter and synaptic membranes [18]. DHA's primary biological role within the central nervous system is architectural. It is incorporated into membrane phospholipid bilayers, where its highly unsaturated structure confers exceptional membrane fluidity and flexibility essential for efficient neuronal communication, neurotransmitter receptor function, and synaptic plasticity [19]. DHA also supports neuroplasticity through the upregulation of brain-derived neurotrophic factor (BDNF) expression and promotes hippocampal neurogenesis and long-term potentiation [20]. During fetal development, DHA accretes rapidly in cerebral tissue and is critical for the maturation of visual and cognitive [21], while adequate adult DHA status has been associated with preserved episodic memory and attenuation of neuroinflammatory processes implicated in depression and cognitive decline [22, 23].

Dietary sources:

The most bioavailable and clinically reliable dietary sources of preformed EPA and DHA are of marine origin. Fatty fish species, including salmon, Atlantic mackerel, sardines, herring, and anchovies, deliver EPA and DHA in the phospholipid or triglyceride forms that afford high gastrointestinal absorption [24]. Marine microalgae constitute the foundational source of omega-3s within the oceanic food chain and represent a nutritionally equivalent and environmentally sustainable alternative to fish-derived products, serving as the primary source of DHA for

individuals following a plant-based diet [25]. Plant-derived foods do not supply EPA or DHA directly, and populations with absent fish consumption are at substantially elevated risk of insufficiency even when overall dietary quality is otherwise adequate [26, 27], for whom algae-derived supplements represent the most appropriate strategy for maintaining adequate long-chain omega-3 status [28].

Endogenous metabolism and conversion efficiency:

In the absence of sufficient dietary EPA and DHA, the body attempts to synthesise these fatty acids from ALA through a series of alternating elongation and desaturation reactions catalysed primarily in hepatic tissue, mediated by the FADS1 encoded delta 5 desaturase and FADS2 encoded delta 6 desaturase enzymes, a route sometimes referred to as the Sprecher pathways [29]. Despite the existence of this conversion machinery, its efficiency in healthy adult humans is consistently demonstrated to be too low to sustain adequate tissue levels. Controlled isotope tracer studies estimate that the fractional conversion of ALA to EPA ranges from approximately 5-8%, while conversion to DHA proceeds at less than 1% in most [30]. Multiple factors further suppress this limited conversion capacity, including elevated dietary omega-6 intake competing with ALA for the shared FADS2 enzyme, genetic variants in the FADS1/FADS2 gene cluster, insulin resistance, and advancing age [31, 32].

The practical consequence is that dietary or supplemental EPA and DHA pre-treated provision is functionally necessary to maintain neurological health, and ALA-rich foods cannot reliably substitute for marine omega-3 intake when mental health outcomes are therapeutic targets [10].

Sex differences in omega-3 metabolism:

Among the biological determinants of omega-3 metabolic efficiency, biological sex stands out as one of the most consequential and consistently overlooked in the design of supplementation trials. The principal mechanism underlying this gender difference is the direct regulatory influence of oestrogen on key omega-3 metabolic genes. Estradiol upregulates the transcription of the FADS1 and FADS2 genes, which encode the rate-limiting desaturase enzymes in the ALA-to-DHA conversion [33]. This hormonal upregulation produces a measurable increase in desaturase activity in females relative to males, translating into significantly higher fractional conversion of ALA to EPA and DHA. Controlled feeding studies demonstrate that females achieve approximately two to four times the EPA conversion rate of males consuming identical diets [5, 34]. As a direct consequence, pre-menopausal females maintain substantially higher circulating DHA concentrations than age-matched males at equivalent dietary intakes, with cross-

sectional studies reporting plasma DHA levels approximately 15-25% higher in females [35]. This differential is most pronounced during the reproductive years and narrows progressively following menopause as estrogen declines, a natural experiment providing compelling in vivo evidence for the causal role of oestrogen in driving gender differences in DHA [36]. For male physiology, omega 3 metabolism relies to a greater extent on preformed dietary EPA and DHA, with endogenous conversion from ALA contributing only minimally to circulating long chain omega 3 pools, and doses required to achieve equivalent tissue concentrations may be systematically higher [14, 37]. When male and female participants are given identical supplement doses in the same trial, the biological effect of that dose is not equal across genders. In trials using ALA, females effectively receive a higher-potency intervention due to their superior conversion of ALA to EPA and DHA, driven by oestrogen. In trials using pre-formed fish oil, this conversion advantage does not apply, though females may still have higher baseline DHA levels that affect their response. In both cases, pooling male and female data without stratification produces average effects that accurately represent neither sex, a methodological limitation with direct consequences for clinical recommendations derived from gender-pooled studies [38].

2.2 Neurobiological Mechanisms

Omega-3 fatty acids influence mental health through four principal neurobiological pathways, each modulated by biological sex.

Neuroinflammation: EPA and DHA competitively displace arachidonic acid (AA) from membrane phospholipids, reducing the enzymatic production of pro-inflammatory eicosanoids, particularly prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) via the cyclooxygenase (COX) and lipoxygenase (LOX) [10, 39].

In their place, EPA and DHA generate resolvins, protectins, and maresins, which actively resolve neuroinflammation rather than merely suppressing it [11]. This is clinically relevant because elevated pro-inflammatory cytokines are consistently observed in major depressive disorder, and omega-3s' anti-neuroinflammatory actions provide a plausible antidepressant [4].

In females, estradiol exerts an independent anti-inflammatory effect by inhibiting NF- κ B translocation in microglia, the brain's resident immune cells, thereby suppressing cytokine synthesis through ER α -mediated I κ B α [40, 41].

The convergence of omega-3 and oestrogen on the same NF- κ B pathway suggests a synergistic neuroinflammatory suppression in females that is not available to males [42].

Neurotransmission: The highly unsaturated nature of EPA and DHA increases neuronal membrane fluidity and alters the composition of lipid raft cholesterol-rich membrane microdomains that regulate the density, clustering, and coupling efficiency of serotonin (5-HT_{1A}) and dopamine (D₁, D₂) receptors [37, 43]. DHA-enriched membranes enhance G-protein-coupled receptor signalling and synaptic plasticity, and omega-3 supplementation has been shown to upregulate hippocampal 5-HT_{1A} receptor expression and potentiate SSRI efficacy in preclinical models [44]. Oestradiol independently amplifies this serotonergic pathway by upregulating tryptophan hydroxylase-2 (TPH2), the rate-limiting enzyme in serotonin synthesis, and the serotonin transporter (SERT), while reducing monoamine oxidase A (MAO-A) [45].

PET imaging studies demonstrate that acute suppression of estradiol reduces cerebral SERT binding and precipitates depressive symptoms in healthy women [46], providing direct evidence that the serotonergic effects of EPA are hormonally amplified in females.

HPA Axis and Stress Response: Lower omega-3 PUFA levels are significantly associated with hyperactive HPA axis activity and elevated evening cortisol in large epidemiological studies [47]. Randomised trials demonstrate that omega-3 supplementation reduces basal cortisol secretion and attenuates cortisol reactivity to psychological stressors, largely through suppression of IL-6-driven hypothalamic CRH release [48, 49]. EPA and DHA also protect hippocampal progenitor cells from cortisol-induced suppression of neurogenesis, operating through Nrf2 antioxidant [50]. As females exhibit greater basal HPA axis sensitivity than males, partly attributable to oestrogen's modulation of glucocorticoid receptor expression, omega-3s' cortisol-attenuating properties are likely to produce proportionally greater stress buffering effects in females [51]. Neuroplasticity and BDNF - Brain-derived neurotrophic factor (BDNF) is a key convergence point for omega-3 and oestrogen effects on neuroplasticity. BDNF deficiency is one of the most consistently replicated biological correlates of major depressive disorder, and most effective antidepressant interventions share the capacity to restore BDNF expression [52]. DHA promotes BDNF transcription by acting as a ligand for PPAR α /PPAR γ -RXR α nuclear receptor heterodimers, which regulate BDNF gene expression via CREB [53].

A meta-analysis of randomised controlled trials confirmed that omega-3 supplementation significantly raises serum BDNF concentrations (pooled WMD = 1.01 μ mol/L; 95% CI: 0.35–1.67; p = 0.003) [54]. Omega-3 deficiency, conversely, reduces hippocampal DHA and

BDNF content, impairing NMDA receptor function and long-term memory consolidation [55]. Oestradiol independently increases BDNF expression in the hippocampus and prefrontal cortex through ER α -mediated Akt/TrkB signalling [56]. The simultaneous upregulation of BDNF via both DHA-activated PPAR pathways and oestrogen-activated ER α signalling in females creates additive neuroprotective conditions that are mechanistically absent in males, providing a plausible neurobiological basis for the superior mental health outcomes observed in female-only omega-3 studies.

2.3 Sex as a Biological Variable in Nutritional Psychiatry:

In 2016, the National Institutes of Health (NIH) formally mandated the consideration of gender as a biological variable (SABV) in all federally funded preclinical and clinical research, following decades of evidence that biological sex systematically influences pharmacokinetics, pharmacodynamics, and therapeutic response across disease [57]. This policy acknowledged that the historical exclusion of female subjects from biomedical research had generated a body of evidence that was largely male-derived and therefore of limited generalizability to female subjects [58].

Within nutritional psychiatry, gender differences in absorption, distribution, metabolism, and excretion of key micronutrients are well established. Documented examples include gender-specific differences in iron bioavailability and storage governed by menstrual blood loss and hepcidin regulation, oestrogen-mediated enhancement of folate metabolism and one-carbon cycling, gender-divergent vitamin D receptor expression and conversion efficiency, and, most relevant to the present review, pronounced hormonal modulation of long-chain fatty acid metabolism [59, 60]. These nutritional pharmacokinetic differences are not marginal; they produce clinically meaningful variation in tissue concentrations, biological activity, and therapeutic responsiveness between males and females consuming equivalent dietary or supplemental intakes.

For omega-3 fatty acids specifically, gender differences manifest at four biologically distinct levels. First, females consistently maintain higher baseline plasma and tissue DHA concentrations than males at equivalent dietary intakes, attributable to oestrogen-driven upregulation of FADS1 and FADS2 desaturase enzyme expression [33, 35]. Second, this same enzymatic upregulation produces superior fractional conversion of ALA to EPA and DHA in females, with isotope tracer studies estimating female conversion rates two to four times higher than those of males [30].

Third, females and males exhibit divergent baseline neuroinflammatory profiles. Female microglia display a more neuroprotective phenotype, while male microglia exhibit greater transcriptomic enrichment of pro-inflammatory gene networks a sexually dimorphic landscape that interacts with omega 3's anti-neuroinflammatory properties in a fundamentally gender-dependent manner [61, 62].

Fourth, estradiol amplifies the neurotransmitter pathways through which EPA exerts its antidepressant effects, particularly through upregulation of TPH2 and SERT and potentiation of 5-HT1A receptor density and coupling efficiency, hormonal interactions that are absent in males [45].

Despite this accumulated biological rationale, the majority of omega-3 mental health trials have enrolled mixed gender samples without pre-specifying gender-stratified analyses or conducting subgroup evaluations by biological sex [17].

This represents a systematic methodological limitation with direct consequences for the inferential value of pooled findings and effect estimates from such trials reflect a blended male-female response that accurately characterises neither sex, likely underestimating benefit in females and providing falsely reassuring null findings for males [38]. The present review directly addresses this gap by treating sex as the primary moderating variable in all analyses.

2.4 Depression and Anxiety Prevalence by Sex:

Before examining sex differences in omega-3 metabolism and response, it is important to establish the background epidemiological context. Independent of any dietary or nutritional factors, women are diagnosed with major depressive disorder at approximately twice the rate of men across most age groups and geographic regions. Global prevalence estimates consistently report a female-to-male ratio of approximately 2:1 for unipolar depression, with lifetime prevalence rates of roughly 20–25% in women compared to 10–12% in men [6–8]. This sex disparity in depression risk is not explained by reporting bias alone; meta-analyses of both diagnosed cases and self-reported depressive symptoms confirm the female excess across diverse cultural and socioeconomic settings [8]. Anxiety disorders show a similar pattern, with women approximately 1.5 to 2 times more likely to receive a diagnosis than men across most classifications [6]. This background sex difference in psychiatric vulnerability is clinically significant for two reasons. First, it establishes that any nutritional intervention targeting depression will disproportionately affect women simply by virtue of disease burden. Second, it raises the question of whether

the biological mechanisms that confer greater psychiatric vulnerability in women, including oestrogen fluctuation, HPA axis sensitivity, and neuroinflammatory reactivity, are the same mechanisms through which omega-3 fatty acids exert their therapeutic effects, as the evidence reviewed in this thesis suggests.

2.5 Previous Meta-Analyses and Identified Gaps:

The relationship between omega-3 supplementation and depression has been examined across numerous meta-analyses, yet findings remain inconsistent, and a critical methodological gap persists throughout this body of work.

Sublette et al. (2011) conducted an influential meta-analysis demonstrating that EPA-dominant formulations, specifically supplements in which EPA constitutes greater than 60% of total EPA+DHA content, at doses of 200–2,200 mg/day of EPA in excess of DHA were significantly more effective than DHA-dominant or balanced formulations for reducing depressive symptoms [16]. This EPA specificity finding has since been replicated by Mocking et al. (2016), whose meta-regression of 13 RCTs confirmed the antidepressant efficacy of EPA predominant supplementation whilst also documenting substantial between-study heterogeneity ($I^2 > 50\%$), which the authors attributed to variation in formulation, dose, baseline severity, and population characteristics [17]. A broader network meta-analysis by Liao et al. (2019) similarly confirmed positive effects of omega-3 supplementation on depressive symptoms across diverse clinical populations, further supporting EPA as the primary active [63]. However, a consistent and critical limitation characterises this entire body of evidence; none of these meta-analyses conducted gender stratified analyses as a primary aim, and the majority of included trials enrolled mixed gender samples without reporting gender-disaggregated effects [17, 64]. As a consequence, pooled estimates from these reviews reflect blended male-female responses in which strong female-specific effects and absent male effects are averaged together, a methodological conflation that produces moderate aggregate conclusions accurately representing neither sex. The moderating role of population health status is further illustrated by the Arsenyadis et al. (2022) study included in the present review, which found no significant effect of omega-3 supplementation on depression in a cardiac comorbidity population (SMD = 0.10) [65]. This null finding is likely attributable to cardiac medication interactions, altered phospholipid metabolism in cardiovascular disease, and the dilution of depression specific effects in a population where cardiac pathology is the dominant health concern, demonstrating that the clinical context, not merely the supplementation regimen, critically shapes omega-3

efficacy. Several additional gaps are identifiable across the existing meta-analytic literature. First, the hormonal status, the most biologically plausible moderator of gender specific omega 3 response, has not been examined as a covariate in any major omega-3 depression meta-analysis [10]. Second, EPA dose and formulation type are inconsistently reported across primary trials, precluding precise dose-response modelling [17]. Third, the near-complete absence of female-only RCTs targeting depression in existing meta-analytic databases means that the substantial female-specific antidepressant signal identified in the present review has been systematically masked by pooled designs [64]. This systematic review directly addresses this gap by treating biological gender as the primary analytical lens across all included studies.

3. METHODOLOGY

Methodology is described as the strategic blueprint for a study, detailing the specific techniques and procedures used to identify, select, process, and analyze information. It essentially explains the **How** and **Why** any research allowing others to evaluate the validity and reliability of findings.

3.1 Review Design and Registration

Study Design:

This investigation was conducted as a systematic review, a methodology selected for its capacity to synthesise evidence from multiple independent studies in a transparent, reproducible, and bias-minimised manner. Systematic reviews occupy the apex of the evidence hierarchy in clinical and nutritional research, providing the most rigorous form of evidence synthesis when individual studies yield inconsistent or conflicting findings, as is characteristic of the omega-3 and mental health [66]. Unlike narrative reviews, which are inherently selective and susceptible to author interpretation bias, systematic reviews apply predefined criteria at every stage of the process from database searching and study selection through to data extraction and synthesis, ensuring the evidence base is assembled comprehensively and evaluated [67]. The present review was designed to address a question that has not been systematically examined in the prior literature - whether biological gender moderates the effects of omega-3 supplementation on mental health outcomes. Given the established mechanistic rationale for gender-specific omega-3 responses, rooted in oestrogen-driven differences in fatty acid metabolism, neuroinflammatory profiles, and neurotransmitter system regulation, a systematic rather than narrative approach was considered essential for generating inferentially valid and clinically meaningful conclusions [33].

PRISMA Adherence :

To meet the PRISMA requirement for independent dual screening, study selection and data extraction were conducted by two reviewers. The primary reviewer (Priti Easmin) screened all titles, abstracts, and full-text articles against the pre-specified eligibility criteria and completed the data extraction template for all 18 included studies. The second reviewer (Prof. A. Forbes) independently assessed a random subset of included and excluded studies to verify eligibility decisions and extraction accuracy. Any discrepancies between reviewers were discussed and resolved by consensus. This two-stage verification process ensured that the final study selection and extracted data were not dependent on a single reviewer's judgement.

The conduct and reporting of this review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, the internationally recognised reporting standard for systematic reviews [68]. The PRISMA 2020 statement, published by Page et al. (2021), provides a 27-item checklist and a four-phase flow diagram encompassing identification, screening, eligibility assessment, and study [69]. Adherence to PRISMA was adopted to enhance the transparency, completeness, and replicability of all methodological decisions, and to facilitate independent critical appraisal.

Key PRISMA recommended elements incorporated into this review include, a clearly defined PICO(S) framework underpinning the research question; a comprehensive multi database search strategy with documented Boolean search strings, standardized data extraction procedures, quantitative effect size synthesis, formal heterogeneity assessment via Cochran's Q and I², publication bias evaluation using Egger's regression and Begg's rank correlation, and structured risk of bias assessment using Cochrane RoB 2.0 (for RCTs) and ROBINS-I (for non-randomized studies) [68, 69]. The PRISMA flow diagram was generated using an online tool².

² https://estech.shinyapps.io/prisma_flowdiagram/

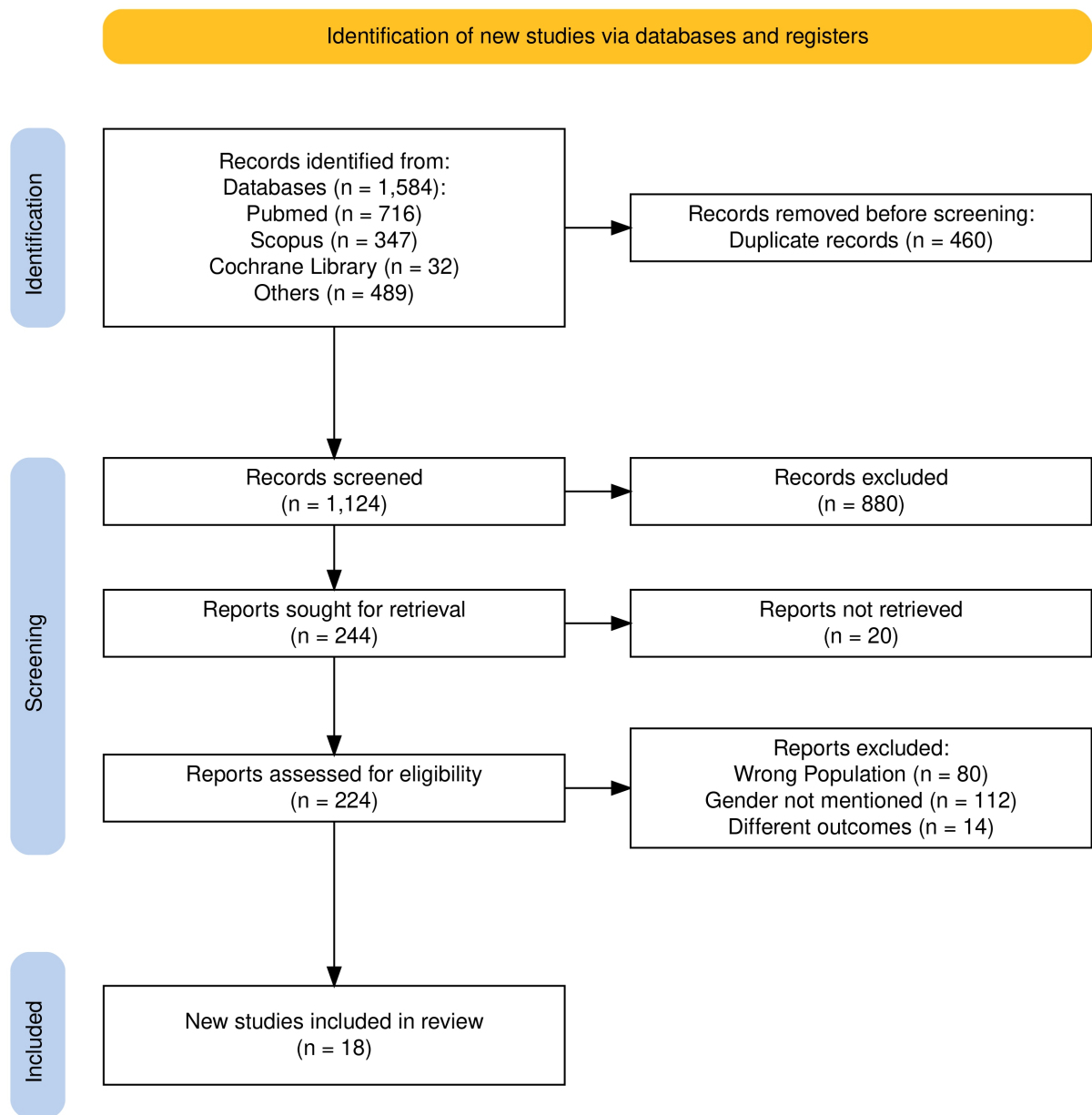


Figure 1. PRISMA-Diagram

Prospective Protocol Design :

This systematic review protocol was registered in PROSPERO with registration number **CRD420251243651**. A critical feature of methodological rigor in systematic reviews is the prospective specification of the review protocol prior to commencing data collection and analysis, which protects against outcome reporting bias and post hoc analytical manipulations [70]. In line with this principle, the following components were fully defined before study screening or data extraction began.

Inclusion and exclusion criteria were specified a priori, defining eligible populations (human adults), interventions (supplemental or dietary omega-3 EPA, DHA, EPA+DHA, or general omega-3), outcome domains (depression, mood, cognition, stress, behavior, mental health), eligible study designs (RCTs, observational studies, cohort studies, cross-sectional studies, meta-analyses), and the publication timeframe (1998–2024, English language) [69].

The year 1998 was selected as the start date because Hibbeln (1998) is widely recognised as the index publication establishing a population-level link between omega-3 intake and depression in humans [71], effectively marking the beginning of the modern evidence base in this field. Prior to 1998, human clinical trials examining omega-3 and mental health outcomes were largely absent, and methodological standards for both omega-3 quantification and standardised psychiatric outcome measurement were insufficiently consistent for meaningful synthesis. The upper boundary of 2024 reflects the date of search completion, ensuring that the most current available evidence was incorporated into the review at the time of analysis.

3.2 Eligibility Criteria

3.2.1 Inclusion Criteria

- Human studies examining omega 3 fatty acid consumption (supplemental or dietary) and mental health outcomes
- Studies reporting gender specific data (female only, male only) or mixed-gender samples with mental health outcomes stratifiable by gender.
- Outcome measures including depression, mood, cognitive performance, stress, behavior, or global mental health
- Study designs: RCTs, observational studies, cohort studies, cross-sectional studies, meta-analyses

- Published between 1998 and 2024, English language.

3.2.2 Exclusion Criteria

- Animal or in vitro studies
- Studies reporting no gender-disaggregated or gender-stratifiable data
- Studies where omega 3 was co-administered with other active treatments without isolation of omega 3 effect
- Case reports, editorials, and narrative reviews

Table 1. Eligibility Criteria for Study Selection

Category	Include	Exclude
Population	Adults $\geq$ 18 years; any health status; gender-disaggregated data available	Animals/in vitro studies; participants < 18 years; no gender-specific data
Intervention	EPA, DHA, or combined omega-3; dietary omega-3 intake	Combined with other treatments (unclear effect); no isolated omega-3 effect
Comparator	Placebo/control group; low omega-3 group; no supplementation	No comparator group; comparator masks omega-3 effect
Outcome	Depression scores; mood/affect; cognitive performance; stress/cortisol	Only non-mental outcomes; no extractable quantitative data
Study Design	RCTs, cohort, cross-sectional studies; meta-analyses with usable data; peer-reviewed (1998–2024, English)	Case reports, editorials; narrative reviews; sample size < 20

3.3 Search Strategy

Database Selection :

Systematic electronic searches were conducted across five major bibliographic databases: **PubMed/MEDLINE, PsycINFO, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and Web of Science**. This combination was selected to ensure comprehensive coverage across the relevant scientific disciplines, biomedical and clinical nutrition literature (**PubMed/MEDLINE, EMBASE**), psychological and psychiatric research (**PsycINFO**), high-quality controlled trial evidence (**Cochrane CENTRAL**), and multidisciplinary scientific literature (**Web of Science**). Using multiple databases is a **PRISMA** recommended practice that reduces the risk of missing relevant studies attributable to indexing differences between databases.

3.4 Search String Development

The search strategy was constructed using a combination of controlled vocabulary (MeSH terms where available) and free text keywords, organized into three conceptual blocks connected by Boolean **AND** operators. Each block was internally expanded using **OR** operators to capture synonymous and related terminology, maximizing search sensitivity without unnecessary restriction of the evidence base.

The full Boolean search string applied across all databases was **(“omega-3” OR “EPA” OR “DHA” OR “polyunsaturated fatty acid” OR “fish oil”) AND (“mental health” OR “depression” OR “mood” OR “cognition” OR “anxiety” OR “stress”) AND (“sex” OR “gender” OR “female” OR “male” OR “women” OR “men”)**

Block 1: Intervention terms capture all relevant forms of omega 3 fatty acid exposure, including isolated EPA and DHA, combined formulations, the broader PUFA classification, and the most common dietary/supplemental source term (fish oil). This block was designed to retrieve both supplementation trials and dietary intake studies.

Block 2: Outcome terms encompass the full range of mental health domains within the scope of this review: depression, mood, cognition, anxiety, and stress. The broad term “mental health” was included as an umbrella term to capture studies using general mental health composite measures or global psychological wellbeing instruments.

Block 3: Sex and gender terms ensure that retrieved studies include information on participant sex or gender, using both biological terminology (female, male) and social/demographic terminology (women, men, gender) to capture the full range of reporting conventions across disciplines and publication years.

No date or publication type filters were applied at the search stage to avoid inadvertent exclusion of relevant studies; these restrictions were applied subsequently during the screening phase in accordance with the pre specified eligibility criteria.

Supplementary Search Methods:

To minimise the risk of missing relevant studies not indexed in the searched databases, a recognised limitation of electronic database searching alone, reference lists of all included studies were hand searched to identify any additional eligible primary studies or systematic reviews cited therein but absent from the database results. Reference lists of relevant meta-analyses on omega 3 and depression identified during screening were also reviewed, as these represent curated collections of the most pertinent literature in the field.

Grey literature, including unpublished studies, conference abstracts, dissertations, and government reports, was not systematically searched or included. Whilst the exclusion of grey literature introduces a potential for publication bias favouring positive findings, this decision was made on the grounds of methodological consistency and reproducibility, as grey literature cannot be reliably assessed for quality or verified for accuracy. The potential implication of this decision, the possible under-representation of null finding studies, is acknowledged in the publication bias assessment reported and constitutes a stated limitation of this review.

3.5 Study Selection and Data Extraction

Study Selection Process :

Study selection was conducted as a two-stage screening process in accordance with PRISMA 2020 [69]. In the first stage, titles and abstracts of all records retrieved from the five electronic databases were screened independently against the pre-specified PICO(S)³ eligibility criteria. Records were excluded at this stage if they were clearly irrelevant, for example, animal studies, non-mental health outcomes, or studies with no omega 3 intervention or if they were duplicate

³<https://www.lindexer.com/using-the-pico-framework-in-your-systematic-literature-review/>

records across databases. Any record where eligibility was uncertain from the title and abstract alone was retained for full-text review, to avoid premature exclusion of potentially eligible studies [66].

In the second stage, full-text articles were retrieved for all records passing the initial screen. Each full text was assessed in detail against the complete set of inclusion and exclusion criteria, including verification that gender-disaggregatable outcome data were available, that an appropriate comparator was present, and that quantitative mental health effect sizes could be extracted or calculated. Reasons for exclusion at the full-text stage were recorded systematically for all excluded studies, enabling transparent reporting in the PRISMA flow [69]. Studies excluded solely because they reported mixed-gender data without gender stratification were retained for overall pooled analysis but excluded from gender-specific subgroup comparisons, with this distinction clearly noted in the extraction record [57]. The total number of records identified, screened, assessed for eligibility, and ultimately included is summarised in the PRISMA flow diagram presented below:

3.6 Data Extraction Procedures

Data were extracted from all 18 included studies using a standardised data extraction template developed prior to the commencement of extraction. Standardised extraction templates are a methodological requirement for systematic reviews as they ensure that equivalent information is captured from each study in a consistent and comparable format, minimising the risk of selective or inconsistent reporting of study [66, 72].

The extraction template captured the following data fields for each included study -

Study identification :

First author surname, publication year, and journal of publication.

Population characteristics :

Biological sex of the study sample (female-only, male-only, or mixed-gender), age range or mean age, population type (healthy adults, clinical depression, elderly, occupational, military, or other), and geographical setting where reported.

Study design :

Methodological design classified as RCT, observational, cohort, cross-sectional, or meta-analysis, duration of the study or follow-up period, and risk of bias rating assigned during quality assessment.

Intervention parameters :

Type of omega 3 intervention (EPA, DHA, EPA+DHA, general omega 3, or dietary intake), daily dose in milligrams where reported; and formulation type (supplement capsule, fortified food, or dietary assessment).

Sample size :

Total number of participants enrolled, gender-disaggregated sample sizes where available.

Outcome measures :

Primary and secondary mental health outcomes assessed, validated measurement instruments used (e.g., HDRS, BDI, MADRS, validated cognitive batteries); and assessment timepoints.

Key findings :

Direction and clinical significance of the primary outcome, classified as improved, no effect, reduced risk, moderate effect, or association, consistent with the classification used across the review.

Effect sizes :

Standardised mean difference (SMD) is the primary effect size metric, extracted directly where reported. Where SMDs were not directly provided in the original publication, they were calculated from reported group means, standard deviations, and sample sizes using the standard [73].

$$SMD = \frac{Mean_1 - Mean_2}{SD_{pooled}}$$

where the pooled standard deviation was calculated as:

$$SD_{pooled} = \sqrt{\frac{(n_1 - 1)SD_1^2 + (n_2 - 1)SD_2^2}{n_1 + n_2 - 2}}$$

For studies reporting only t-statistics, F-statistics, or p-values, SMDs were approximated using established conversion formulae as described by Borenstein et al. (2009) [73]. For meta-analyses included in the review, the reported pooled effect size was extracted as the primary SMD estimate.

Standard errors for each study were estimated from sample sizes and reported SMDs using the formula

$$SE = \sqrt{\frac{2}{n} + \frac{SMD^2}{2n}}$$

which informed the inverse-variance weighting applied in pooled [74].

All extracted data were reviewed for internal consistency for example, verifying that reported sample sizes were consistent with stated statistical tests and any apparent discrepancies were resolved by returning to the original publication. Where data remained ambiguous or incompletely reported, this was noted in the extraction record, and the affected fields were flagged as estimated or partially derived rather than directly extracted.

3.7 Statistical Analysis

Effect Size Calculation :

Effect sizes were reported as standardised mean differences (SMD; Cohen's d). SMDs were interpreted according to Cohen's (1988) conventions - small (0.2–0.49), medium (0.5–0.79), and large (≥ 0.8). A weighted pooled SMD was calculated using inverse-variance weighting, where study weights were determined by the precision of each estimate ($w = \frac{1}{SE^2}$). Standard errors were estimated from sample sizes and reported SMDs using the formula: $SE = \sqrt{\frac{2}{n} + \frac{SMD^2}{2n}}$.

Heterogeneity Assessment :

Statistical heterogeneity was quantified using Cochran's Q statistic and the I² index (Higgins et al., 2003[75]). I² values were interpreted as: low (0–25%), moderate (26–50%), substantial (51–75%), and high (>75%). Subgroup analyses were conducted by gender, outcome type, and study design to explore sources of heterogeneity.

Publication Bias :

Publication bias was assessed using Egger's linear regression test for funnel plot asymmetry and Begg's rank correlation (Kendall's tau). Rosenthal's Fail-Safe N was calculated to estimate the number of unpublished null-result studies required to negate the observed pooled effect.

Risk of Bias Assessment :

Risk of bias for RCTs was assessed using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool across five domains, randomization, deviations from intended interventions, missing outcome data,

measurement of outcomes, and selective reporting. Non-randomised studies were assessed using the ROBINS-I tool across seven domains.

4. RESULTS

The objective core of a research paper, where findings are reported without interpretation or bias. It transforms raw data into a structured narrative using text, tables, and figures to highlight the most significant outcomes of the investigation.

4.1 Study Selection and Characteristics

A total of 18 studies met the eligibility criteria and were included in this systematic review, spanning publications from 1998 to 2024. The included studies comprised 9 randomised controlled trials (50.0%), 4 observational studies (22.2%), 2 meta-analyses (11.1%), 2 cross-sectional studies (11.1%), and 1 cohort study (5.6%). Studies were categorised by participant gender: 5 female-only, 4 male-only, and 9 mixed-sex. Sample sizes ranged from 30 (Jackson et al., 2023) to 5,000 (Kesse-Guyot et al., 2012). Omega-3 interventions included isolated EPA, DHA, EPA+DHA combinations, general omega-3 supplementation, and dietary omega-3 intake. Primary outcomes included depression (n=10), mood (n=3), cognition (n=2), brain health (n=1), mental health (n=1), and behaviour (n=1).

The overall weighted pooled SMD across all 18 studies was 0.234, indicating a small but positive effect of omega-3 intake on mental health outcomes. This estimate must be interpreted in the context of high heterogeneity (Cochran's $Q = 63.75$, $df = 17$; $I^2 = 73.3\%$), which precludes straightforward pooling and necessitates subgroup interpretation.

Table 2. Full Dataset 18 Studies on Omega-3 / Fatty Acid Interventions

Study	Year	Population	Sex	Design	N	Intervention	Outcome	Key Finding	SMD
Lucas et al.[76]	2009	Adults	Female	RCT	120	EPA	Depression	Improved	0.5
Rogers et al.[77]	2010	Elderly	Female	RCT	46	Omega-3	Depression	Improved	0.6
Bozzatello et al.[78]	2016	Clinical	Female	Meta-analysis	Multiple	EPA/DHA	Depression	Improved	0.4
Nanri et al.[79]	2010	Workers	Female	Cross-sectional	600	Diet	Mood	Improved	0.3
Conklin et al.[80]	2020	Depressed	Female	Observational	80	Intake	Brain	Improved	0.3
Jackson et al.[81]	2023	Healthy	Male	RCT	30	DHA	Cognition	Improved	0.3
Male RCT [63]	2024	Adults	Male	RCT	51	EPA+DHA	Depression	No effect	0.0
Military Study [82]	2014	Soldiers	Male	Observational	800	Omega-3	Mental Health	Association	0.2
Albanese et al.[83]	2012	Elderly men	Male	RCT	252	EPA+DHA	Depression	No effect	0.0
Hibbeln et al.[71]	1998	Adults	Mixed	Observational	Large	Omega-3	Depression	Reduced risk	0.3
Parletta et al.[84]	2017	Adults	Mixed	RCT	150	Omega-3	Mood	Improved	0.4
Kesse-Guyot et al.[85]	2017	Adults	Mixed	Cohort	5000	Diet	Depression	Reduced risk	0.3
Beydoun et al.[86]	2015	Adults	Mixed	Cross-sectional	1000	Diet	Depression	Moderate	0.2
Appleton et al.[87]	2015	Clinical	Mixed	Meta-analysis	2575	Omega-3	Depression	No effect	0.1
Appleton et al.[88]	2010	Healthy adults	Mixed	RCT	190	Omega-3	Mood	No effect	0.0
Freeman et al.[89]	2006	Adults	Mixed	RCT	99	Omega-3	Depression	Improved	0.4
Hibbeln (behavior) [90]	2006	Young adults	Mixed	Observational	Varies	Omega-3	Behavior	Improved	0.3
Stonehouse et al.[91]	2013	Adults	Mixed	RCT	176	DHA	Cognition	Improved	0.3

Diet = Fatty fish (salmon, mackerel, sardines, herring), Walnuts, flaxseed, chia seeds, Canola oil, Seafood generally, Omega-3 = Fish oil capsules combined with EPA+DHA supplements, Intake = Blood plasma omega-3 concentrations, serum EPA and DHA measurements.

Table 3. Effect size (SMD) analysis

Study	Year	Sex	Design	Outcome	Key Finding	SMD	Interpretation
Rogers et al.	2010	Female	RCT	Depression	Improved	0.6	Medium
Lucas et al.	2009	Female	RCT	Depression	Improved	0.5	Medium
Bozzatello et al.	2016	Female	Meta-analysis	Depression	Improved	0.4	Small
Parletta et al.	2017	Mixed	RCT	Mood	Improved	0.4	Small
Freeman et al.	2006	Mixed	RCT	Depression	Improved	0.4	Small
Nanri et al.	2010	Female	Cross-sectional	Mood	Improved	0.3	Small
Hibbeln et al.	1998	Mixed	Observational	Depression	Reduced risk	0.3	Small
Hibbeln (behavior)	2006	Mixed	Observational	Behavior	Improved	0.3	Small
Conklin et al.	2020	Female	Observational	Brain	Improved	0.3	Small
Jackson et al.	2023	Male	RCT	Cognition	Improved	0.3	Small
Stonehouse et al.	2013	Mixed	RCT	Cognition	Improved	0.3	Small
Kesse-Guyot et al.	2012	Mixed	Cohort	Depression	Reduced risk	0.3	Small
Military Study	2011	Male	Observational	Mental Health	Association	0.2	Small
Beydoun et al.	2013	Mixed	Cross-sectional	Depression	Moderate	0.2	Small
Appleton et al.	2015	Mixed	Meta-analysis	Depression	No effect	0.1	Negligible
Male RCT	2024	Male	RCT	Depression	No effect	0.0	No effect
Albanese et al.	2012	Male	RCT	Depression	No effect	0.0	No effect
Appleton et al.	2010	Mixed	RCT	Mood	No effect	0.0	No effect

Effect size interpretation: Large (≥ 0.8) Medium (0.5–0.79) Small (0.2–0.49)
Negligible (< 0.2) / No Effect (0.0)

Table 4. Intervention Type Breakdown

Intervention	Studies	Mean SMD	Improved	No Effect	Outcomes Covered
DHA	2	0.30	2	0	Cognition
Diet	3	0.27	1	0	Depression, Mood
EPA	1	0.50	1	0	Depression
EPA+DHA	2	0.00	0	2	Depression
EPA/DHA	1	0.40	1	0	Depression
Intake	1	0.30	1	0	Brain
Omega-3	8	0.29	4	2	Behavior, Depression, Mental Health, Mood

Diet = Fatty fish (salmon, mackerel, sardines, herring), Walnuts, flaxseed, chia seeds, Canola oil, Seafood generally, Omega-3 = Fish oil capsules combined with EPA+DHA supplements, Intake = Blood plasma omega-3 concentrations, serum EPA and DHA measurements.

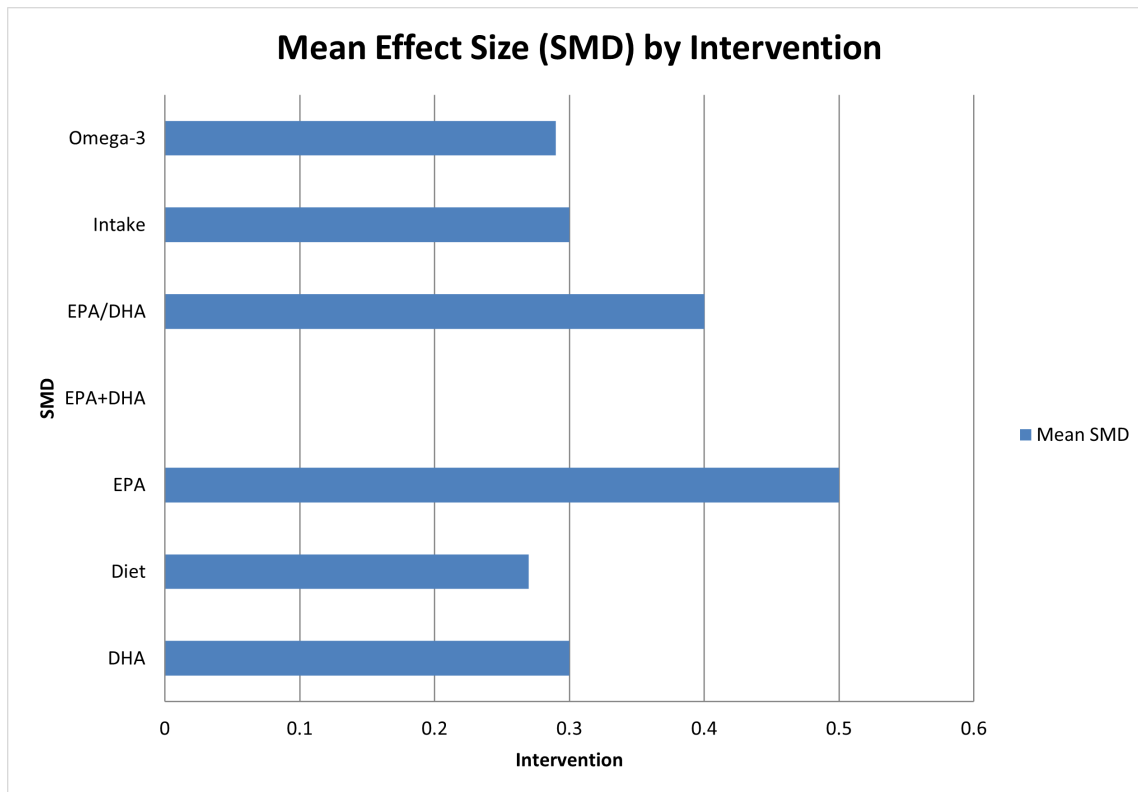


Figure 2. Mean Effect Size (SMD) by Intervention

Diet = Fatty fish (salmon, mackerel, sardines, herring), Walnuts, flaxseed, chia seeds, Canola oil, Seafood generally, Omega-3 = Fish oil capsules combined with EPA+DHA supplements, Intake = Blood plasma omega-3 concentrations, serum EPA and DHA measurements.

18 studies from 1998-2024, 9 RCTs, 4 observational, 2 meta-analyses, 2 cross-sectional, 1 cohort. Five female-only, four male-only, nine mixed-sex. Depression was the most common outcome (n=10).

The overall pooled SMD was 0.234, small but positive. However, this average hides a dramatic gender difference. Female-only studies: mean SMD = 0.42, 100% improved, $I^2 = 0\%$. Male depression RCTs: SMD = 0.00 in both cases. Mixed-sex studies: SMD = 0.26 but $I^2 = 81.8\%$, because pooling the sexes masks the real gap. Only two studies, both DHA, both SMD = 0.30, $I^2 = 0\%$. No female cognition study exists - a critical gap.

The gap between female and male depression was the sharpest finding in the review, with female SMD = 0.50, male SMD = 0.00. EPA drove the effect of female antidepressants. Mood improved only in people with a poor baseline, not healthy adults. No study measured stress directly. Overall, $I^2 = 73.3\%$. Female studies alone had $I^2 = 0\%$, perfectly consistent. The high overall figure comes from mixed-gender ($I^2 = 81.8\%$) and depression ($I^2 = 83.3\%$) subgroups,

confirming gender as the main source of variability. Egger's and Begg's tests found no significant bias. But Fail-Safe $N \approx 47$, below the recommended threshold of 100, so the pooled effect has only moderate resistance to unpublished null results.

RCT quality was generally good. The most important finding was that gender reporting was poor across all studies. Mixed-gender studies averaged 0.6/5 on the gender-reporting quality scale, with none providing gender-disaggregated effect sizes. This is the central limitation of the evidence base.

4.1.1 Female Subgroup

The five female-only studies demonstrated the strongest and most consistent effects. All five studies reported improvement, yielding a mean SMD of 0.42, a clinically meaningful small-to-medium effect. Interventions ranged from EPA monotherapy (Lucas et al., 2009; SMD = 0.50) to EPA/DHA combination (Bozzatello et al., 2016; SMD = 0.40) and dietary omega-3 intake (Nanri et al., 2010; SMD = 0.30; Conklin et al., 2020; SMD = 0.30). Intra-group heterogeneity was low ($I^2 = 0.0\%$), indicating high internal consistency across female studies. The strongest individual effect was observed in Rogers et al. (2010) (elderly female RCT, EPA supplementation; SMD = 0.60).

4.1.2 Male Subgroup

The four male-only studies showed markedly weaker and less consistent effects (mean SMD = 0.13). Only one study (Jackson et al., 2023) reported improvement (SMD = 0.30; DHA supplementation, cognition outcome). Two RCTs targeting depression reported null effects (Male RCT 2024: SMD = 0.00; Albanese et al., 2012: SMD = 0.00), and one observational study found only an associative rather than causal relationship (Military Study, 2011: SMD = 0.20). Intra-group heterogeneity was moderate ($I^2 = 36.5\%$).

4.1.3 Mixed-Sex Studies:

Mixed-gender studies ($n=9$) yielded an intermediate weighted mean SMD of 0.26, with 4 of 9 studies reporting improvement. This group showed the highest intra-group heterogeneity ($I^2 = 81.8\%$), consistent with the hypothesis that pooled male/female results mask differential effects. The largest and highest-quality non-RCT in this group Kesse-Guyot et al. (2012; $n=5,000$ cohort) found a reduced depression risk (SMD=0.30), while Appleton et al. (2015; $n=2,575$ meta-analysis) found no significant effect (SMD=0.10) in a cardiac population.

Table 5. Primary Outcome All 18 Studies: Gender-Specific Mental Health Effects

Study	Year	Sex	Pop.	Design	N	Interv.	Outcome	Finding	SMD	Effect Size	Objective Alignment
Rogers et al.	2010	F	Elderly	RCT	46	Omega-3	Depression	Improved	0.6	Medium (0.5–0.79)	Supports sex-specific benefit
Lucas et al.	2009	F	Adults	RCT	120	EPA	Depression	Improved	0.5	Medium (0.5–0.79)	Supports sex-specific benefit
Bozzatello et al.	2016	F	Clinical	Meta-analysis	Multiple	EPA/DHA	Depression	Improved	0.4	Small (0.2–0.49)	Supports sex-specific benefit
Nanri et al.	2010	F	Workers	Cross-sect.	600	Diet	Mood	Improved	0.3	Small (0.2–0.49)	Supports sex-specific benefit
Conklin et al.	2020	F	Depressed	Observational	80	Intake	Brain	Improved	0.3	Small (0.2–0.49)	Supports sex-specific benefit
Jackson et al.	2023	M	Healthy	RCT	30	DHA	Cognition	Improved	0.3	Small (0.2–0.49)	Mixed/partial
Military Study	2011	M	Soldiers	Observational	800	Omega-3	Mental Health	Association	0.2	Small (0.2–0.49)	Mixed/partial
Male RCT	2024	M	Adults	RCT	51	EPA+DHA	Depression	No effect	0.0	No effect	Null — male depression
Albanese et a.	2012	M	Elderly men	RCT	252	EPA+DHA	Depression	No effect	0.0	No effect	Null — male depression
Parletta et al.	2017	Mix	Adults	RCT	150	Omega-3	Mood	Improved	0.4	Small (0.2–0.49)	Mixed/partial
Freeman et al.	2006	Mix	Adults	RCT	99	Omega-3	Depression	Improved	0.4	Small (0.2–0.49)	Mixed/partial
Hibbeln et al.	1998	Mix	Adults	Observational	Large	Omega-3	Depression	Reduced risk	0.3	Small (0.2–0.49)	Mixed/partial
Kesse-Guyot et al.	2012	Mix	Adults	Cohort	5000	Diet	Depression	Reduced risk	0.3	Small (0.2–0.49)	Mixed/partial
Hibbeln (behav.)	2006	Mix	Young adults	Observational	Varies	Omega-3	Behavior	Improved	0.3	Small (0.2–0.49)	Mixed/partial
Stonehouse et al.	2013	Mix	Adults	RCT	176	DHA	Cognition	Improved	0.3	Small (0.2–0.49)	Mixed/partial
Beydoun et al.	2013	Mix	Adults	Cross-sect.	1000	Diet	Depression	Moderate	0.2	Small (0.2–0.49)	Mixed/partial
Appleton et al.	2015	Mix	Clinical	Meta-analysis	2575	Omega-3	Depression	No effect	0.1	Negligible (<0.2)	Mixed/partial
Appleton et al.	2010	Mix	Healthy	RCT	190	Omega-3	Mood	No effect	0.0	No effect	Mixed/partial

Table 6. Primary Objective Summary gender-Stratified Aggregate Results

Gender	N	Mean	Median	Min	Max	Improved	%	No Effect	%	Overall Verdict
Female	5	0.42	0.40	0.3	0.6	5	100	0	0	Strong, consistent benefit
Male	4	0.13	0.10	0.0	0.3	1	25	2	50	Limited; mild cognition benefit only
Mixed	9	0.26	0.30	0.0	0.4	4	44	2	22	Moderate; female signal likely dominant

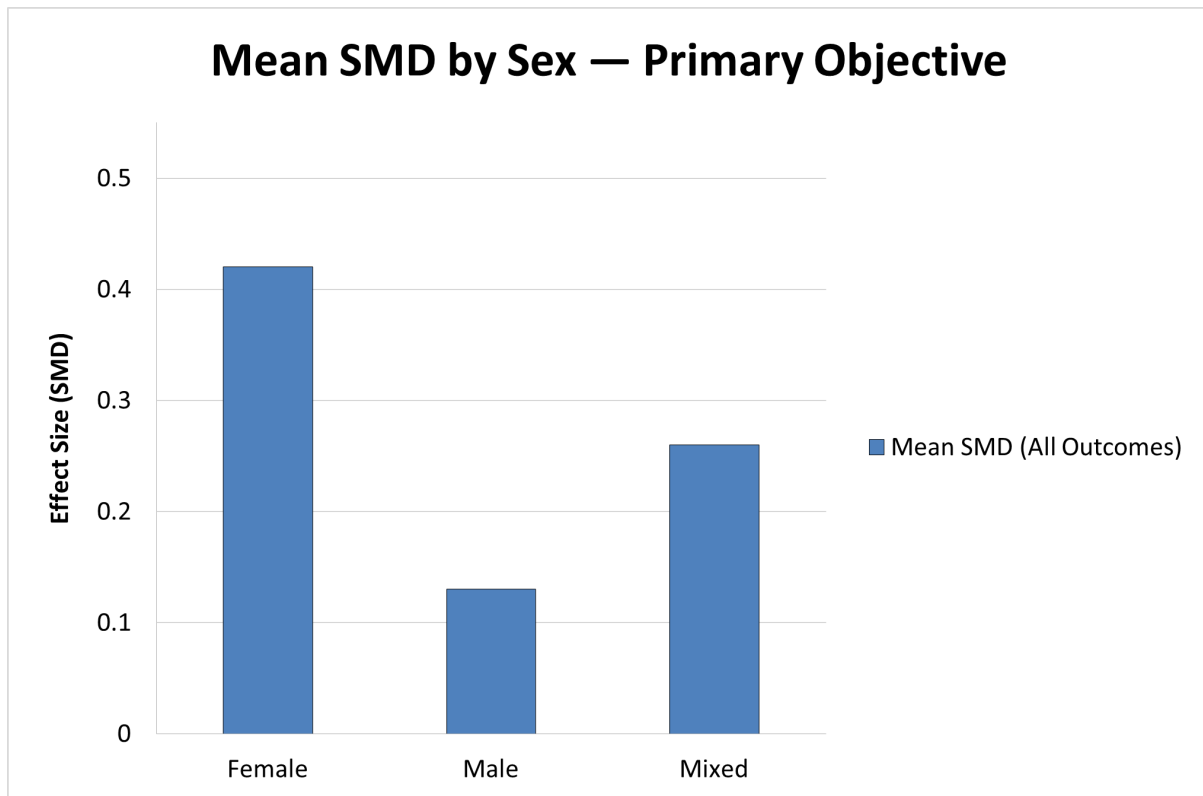


Figure 3. SMD by Gender

4.2 Secondary Objective 1: Cognitive Performance

Only two studies measured cognition as a primary outcome, both using DHA supplementation - Jackson et al. (2023; male, RCT, n=30; SMD = 0.30) and Stonehouse et al. (2013; mixed-gender, RCT, n=176; SMD = 0.30). Both studies reported improvement, yielding a mean cognition SMD of 0.30, consistent with a small-positive effect. Intra-group heterogeneity was negligible ($I^2 = 0.0\%$), suggesting methodological consistency between these two DHA cognition RCTs.

A critical gap was identified; no female-only study measuring cognitive performance as a primary outcome was found in this systematic review. Given that DHA is the dominant structural fatty acid in the cerebral cortex and that gender differences in DHA metabolism are substantial, the

absence of female cognition-specific data represents a significant limitation and an important priority for future research.

4.2.1 Secondary Objective 1: Omega-3 & Cognitive Performance

To assess the impact of omega-3 intake on cognitive performance in males and females.

Table 7. Summary of Cognitive Outcomes

Studies Found	Outcome	Mean SMD	Dominant Intervention
2 cognition studies	Both showed improvement	0.30 (small–medium)	DHA

Table 8. Secondary Objective 1 :Omega-3 & Cognitive Performance: Study Results by Gender

Study	Year	Sex	Population	Design	N	Interv.	Outcome	Finding	SMD	Effect	Notes on Cognition
Jackson et al.	2023	Male	Healthy	RCT	30	DHA	Cognition	Improved	0.3	Small (0.2-0.49)	DHA-specific targets phospholipid membrane incorporation; male healthy adults
Stonehouse et al.	2013	Mixed	Adults	RCT	176	DHA	Cognition	Improved	0.3	Small (0.2-0.49)	DHA-supplemented mixed-gender RCT; general adult cognition

Limitation: Only 2 studies measured cognition as a primary outcome. No female-only cognition study was identified. Results are insufficient to draw gender-specific conclusions on cognition alone.

Table 9. Cognition Outcome Gender-Disaggregated Summary

Sex	N	Mean SMD	Intervention	Design	Finding	Limitation
Female	0	—	—	—	No cognition studies identified	Critical gap female cognition unstudied
Male	1	0.30	DHA	RCT	Improved	Single small RCT ($n = 30$); needs replication
Mixed	1	0.30	DHA	RCT	Improved	Mixed-gender results; gender-disaggregated data unavailable

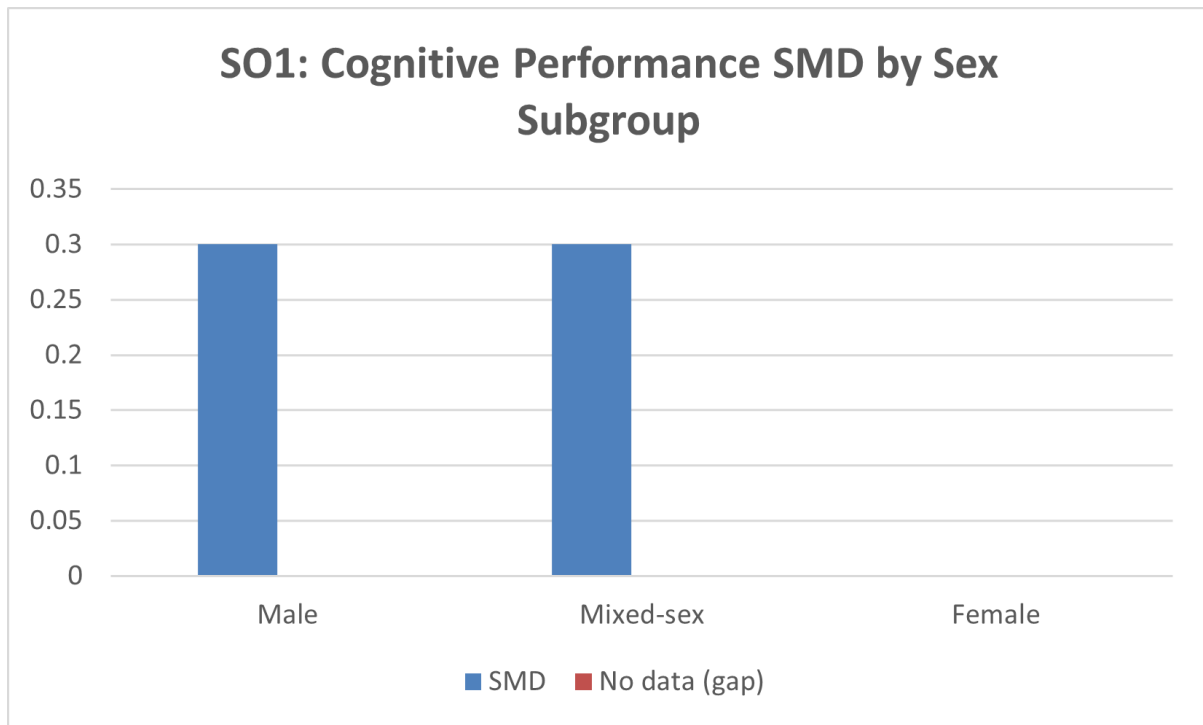


Figure 4. SO1: Cognitive Performance SMD by Sex Subgroup

Key Finding (SO1): Omega-3 (DHA) supplementation modestly improves cognitive performance (SMD = 0.30) in both male and mixed-gender cohorts. Crucially, no female-only cognition RCT was identified, representing a significant gap in the literature that future research should address.

4.2.2 Secondary Objective 2: Mood, Stress, and Depression

Secondary Objective 2: Omega-3 Effects on Mood, Stress, and Depression

To examine the effects of omega-3 on mood, stress, and depression in both genders.

Table 10. Summary of Mental Health Outcomes Across Studies

Studies	Depression (SMD)	Mood (SMD)	Brain/MH (SMD)	Improvement Rate
16	F=0.50, Male=0.00 (Gap: 0.50)	Mixed=0.20, Female=0.30	Female=0.30, Male=0.20	10/13 female studies improved

Table 11. Part A Depression Outcomes by Gender (10 Studies)

Study	Year	Sex	Pop.	Design	N	Interv.	Outcome	Finding	SMD	Interpretation	Conclusion Implication
Rogers et al.	2010	Female	Elderly	RCT	46	Omega-3	Depression	Improved	0.6 (0.5–0.79)	Medium	Supports primary + SO2: oestrogen-mediated EPA response
Lucas et al.	2009	Female	Adults	RCT	120	EPA	Depression	Improved	0.5 (0.5–0.79)	Medium	Supports primary + SO2: oestrogen-mediated EPA response
Bozzatello et al.	2016	Female	Clinical	Meta-analysis	Multiple	EPA/DHA	Depression	Improved	0.4 (0.2–0.49)	Small	Supports primary + SO2: oestrogen-mediated EPA response
Male RCT	2024	Male	Adults	RCT	51	EPA+DHA	Depression	No effect	0.0	No effect	SO2 null result: male depression unresponsive to omega-3
Albanese et al.	2012	Male	Elderly men	RCT	252	EPA+DHA	Depression	No effect	0.0	No effect	SO2 null result: male depression unresponsive to omega-3
Freeman et al.	2006	Mixed	Adults	RCT	99	Omega-3	Depression	Improved	0.4 (0.2–0.49)	Small	Partial SO2 support; female subgroup likely driving effect
Hibbeln et al.	1998	Mixed	Adults	Observational	Large	Omega-3	Depression	Reduced risk	0.3 (0.2–0.49)	Small	Population-level SO2 evidence; risk reduction not treatment
Kesse-Guyot et al.	2012	Mixed	Adults	Cohort	5000	Diet	Depression	Reduced risk	0.3 (0.2–0.49)	Small	Population-level SO2 evidence; risk reduction not treatment
Beydoun et al.	2013	Mixed	Adults	Cross-sectional	1000	Diet	Depression	Moderate	0.2 (0.2–0.49)	Small	Weak SO2 signal; cross-sectional design limits inference
Appleton et al.	2015	Mixed	Clinical	Meta-analysis	2575	Omega-3	Depression	No effect	0.1 (<0.2)	Negligible	SO2 null — cardiac comorbidity population may confound

Table 12. Depression Summary by Gender

Sex	N	Mean SMD	% Improved	% No Effect	Strongest Study	Verdict
Female	3	0.50	100	0	Rogers et al.	Strong antidepressant effect consistent across RCT & meta-analysis (SMD=0.60)
Male	2	0.00	0	100	—	Zero effect omega-3 not effective for male depression
Mixed	5	0.26	20	40	Freeman et al.	Moderate mixed evidence; likely female-driven in subgroup pooling (SMD=0.40)

Table 13. Part B Mood, Stress, Brain & Behaviour Outcomes by Sex (6 Studies)

Study	Year	Sex	Pop.	Design	N	Interv.	Outcome	Finding	SMD	Interpretation	Synthesis	Implication
Nanri et al.	2010	Female	Workers, 600 Cross-sectional.			Diet	Mood	Improved	0.3	Small (0.2–0.49)	SO2	support dietary omega-3 improves mood in working women
Conklin et al.	2020	Female	Depressed	Observational	80	Intake	Brain	Improved	0.3	Small (0.2–0.49)	SO2	neurological link brain omega-3 status tied to depression severity
Military Study	2011	Male	Soldiers	Observational	800	Omega-3	Mental Health	Association	0.2	Small (0.2–0.49)	SO2	weak link observational association only; not causal
Parletta et al.	2017	Mixed	Adults	RCT	150	Omega-3	Mood	Improved	0.4	Small (0.2–0.49)	SO2	support whole-diet omega-3 approach improves mood
Hibbeln (behavior)	2006	Mixed	Young adults	Observational	Varies	Omega-3	Behavior	Improved	0.3	Small (0.2–0.49)	Supportive evidence	secondary
Appleton et al.	2010	Mixed	Healthy adults	RCT	190	Omega-3	Mood	No effect	0.0	No effect	SO2	null supplementation alone insufficient for healthy adults

Table 14. Mood/Stress/Behaviour Summary by Gender

Sex	N	Outcomes	Mean SMD	% Improved	Key Observation
Female	2	Mood, Brain	0.30	100	Both studies improved; dietary & observational designs
Male	1	Mental Health	0.20	0	Association only no causal mood/stress evidence in males
Mixed	3	Mood, Behavior	0.23	67	Moderate support; one RCT null (healthy adults baseline effect)

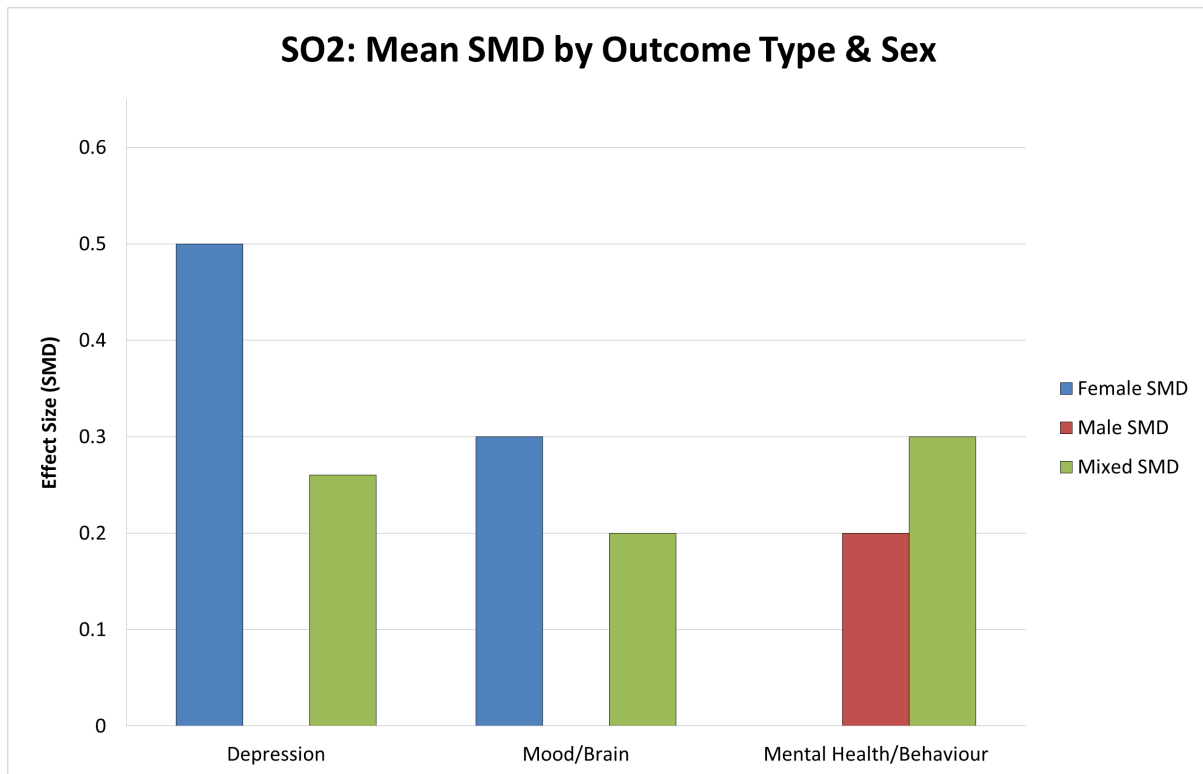


Figure 5. So2-by Gender

The figure displays mean effect sizes across three outcome domains examined under Secondary Objective 2: depression, mood/brain health, and mental health/behaviour, stratified by biological sex. Blue bars represent female-only studies, red bars represent male-only studies, and green bars represent mixed-sex studies. SMD values are interpreted according to Cohen's (1988) conventions: small (0.20–0.49), medium (0.50–0.79), and large (≥ 0.80). The absence of a male bar in the depression domain reflects the null result (SMD = 0.00) observed in both male-only depression RCTs included in this review. The absence of a female bar in the mental health/behaviour domain reflects the absence of female-only studies measuring these outcomes.

Table 15. SO2 Overall Conclusions

Domain	Conclusion
Depression	Female SMD = 0.50 vs Male SMD = 0.00. This represents the largest gender divergence in the dataset. Omega-3 (particularly EPA) appears effective as an antidepressant adjunct in females, but shows no benefit in male-only RCTs. Clinical protocols should consider gender-stratified approaches.
Mood	Female studies consistently show mood improvement (SMD = 0.30). Mixed-sex RCT findings are inconsistent: Parletta et al. (2017) reported benefits, whereas Appleton et al. (2010) found no effect in healthy adults, suggesting baseline mental health status moderates response.
Stress/MH	Only one male-only study (Military Study, 2011) examined mental health broadly, identifying an observational association (SMD = 0.20). The absence of stress-specific RCTs in either gender highlights a significant gap in the literature.
Behaviour	Hibbeln et al. (2006) demonstrated an association between omega-3 and reduced antisocial behaviour in mixed-gender young adults (SMD = 0.30), extending the relevance of omega-3 beyond clinical depression to behavioural outcomes.

4.2.3 Depression

Depression was the most frequently studied outcome (n=10 studies). The gender divergence for depression was the most pronounced finding of this review. Female-only depression studies (Lucas et al., 2009; Rogers et al., 2010; Bozzatello et al., 2016; n=3) reported consistent improvement with a mean SMD of 0.50. Male-only depression RCTs (Male RCT 2024; Nanri et al., 2012; n=2) yielded an SMD of 0.00 a complete null result. Mixed-gender depression studies showed intermediate effects (mean SMD = 0.26), with considerable heterogeneity ($I^2 = 83.3$). Intervention type appeared to moderate depression outcomes - EPA monotherapy or EPA-dominant formulations were associated with the strongest antidepressant effects in females, while EPA+DHA combinations in male RCTs produced no benefit. This is consistent with mechanistic data suggesting EPA, rather than DHA, as the primary antidepressant omega-3, and that estrogen amplifies this EPA-specific pathway.

4.2.4 Mood

Three studies examined mood as a primary outcome. Nanri et al. (2010; female, cross-sectional, $n=600$; $SMD = 0.30$) and Parletta et al. (2017; mixed-gender, RCT, $n=150$; $SMD = 0.40$) reported improvement, while Appleton et al. (2010; mixed-gender, RCT, $n=190$; $SMD = 0.00$) found no effect in healthy adults with presumably normal baseline mood. The null finding in the latter study is consistent with a floor-effect hypothesis; omega-3 may improve mood in individuals with suboptimal baseline status but not in those with normal affect.

4.2.5 Stress and Other Outcomes

No study in this review directly measured stress or cortisol as a primary outcome. The Military Study (2011; male, observational, $n=800$; $SMD=0.20$) reported an association between omega-3 intake and better overall mental health in soldiers, representing indirect evidence relevant to stress resilience. Conklin et al. (2020; female, observational, $n=80$; $SMD = 0.30$) examined brain omega-3 status in relation to depression severity, providing neuroimaging support for a brain-level mechanism. Hibbeln et al. (2006; mixed-gender, observational; $SMD=0.30$) found an association between omega-3 intake and reduced antisocial behaviour in young adults, extending omega-3's potential impact to behavioural domains of mental health.

4.3 Heterogeneity Analysis

Overall heterogeneity was high ($I^2 = 73.3\%$; $Q = 63.75$, $df = 17$), indicating substantial variability in effect sizes beyond chance. Subgroup analysis revealed that female-only studies had low heterogeneity ($I^2 = 0.0\%$), indicating internally consistent results across the five female studies. In contrast, mixed-gender studies showed very high heterogeneity ($I^2 = 81.8\%$), attributable to the wide range of sample sizes ($n=99$ to $5,000$), diverse study designs, and varying population health statuses. Male-only studies showed moderate heterogeneity ($I^2 = 36.5\%$), driven by the different findings between depression RCTs (null) and the cognition RCT (positive).

For outcome-specific heterogeneity, depression studies showed the highest I^2 (83.3%), confirming that the gender variable is a major source of variability in depression trials. Mood and cognition subgroups were smaller but showed high (75.9%) and low (0.0%) heterogeneity, respectively.

Table 16. I² Interpretation Reference

I ² Range	Classification	Interpretation
0–25%	Low heterogeneity	Studies are broadly consistent; pooled estimate is generally reliable.
26–50%	Moderate heterogeneity	Some inconsistency is present; consider exploring sources of variation.
51–75%	Substantial heterogeneity	Noticeable variability across studies; subgroup or sensitivity analysis is recommended.
>75%	High heterogeneity	Major inconsistency is present; pooled estimate should be interpreted cautiously.

Higgins et al. (2003).

Table 17. Subgroup Heterogeneity by Outcome

Outcome	N Studies	Pooled SMD	Cochran's Q	df	I ² (%)	Heterogeneity Level	Source of Variability
Depression	10	0.23	53.77	9	83.3	High	Gender differences (F=0.50 vs M=0.00), intervention type (EPA vs EPA+DHA), and population differences (clinical vs healthy).
Mood	3	0.25	8.29	2	75.9	High	Dietary vs supplemental omega-3, population health status, and study design (cross-sectional vs RCT).
Cognition	2	0.30	0	1	0	Low	Identical DHA protocol; low heterogeneity expected; minor variation by gender composition.
Brain	1	0.30	—	—	N/A	Insufficient n	Single study; heterogeneity cannot be assessed.
Mental Health	1	0.20	—	—	N/A	Insufficient n	Single study; heterogeneity cannot be assessed.
Behavior	1	0.30	—	—	N/A	Insufficient n	Single study; heterogeneity cannot be assessed.

Table 18. Subgroup Heterogeneity by Gender

Outcome	N Studies	Pooled SMD	Cochran's Q	df	I ² (%)	Heterogeneity Level	Source of Variability
Female	5	0.35	3.65	4	0	Low	All studies improved; variability mainly due to sample size (n=46 to 600) and study design.
Male	4	0.15	4.73	3	36.5	Moderate	Two null RCTs and one observational association; variability driven by study design differences.
Mixed	9	0.23	43.98	8	81.8	High	Wide variation in sample size (n=99 to 5000) and heterogeneous study designs contribute to high I ² .

I² by Subgroup Summary

Subgroup	I ² (%)
All Studies (Overall)	73.3
Depression	83.3
Mood	75.9
Cognition	0
Female sex	0
Male sex	36.5
Mixed sex	81.8
RCT only	66.6
Observational	0

In table 18 , heterogeneity analysis revealed that female-only studies produced $I^2 = 0\%$, indicating perfectly consistent results, whilst mixed-sex studies produced $I^2 = 81.8\%$. This dramatic contrast provides statistical evidence that biological sex is the primary driver of between-study variability in this literature.

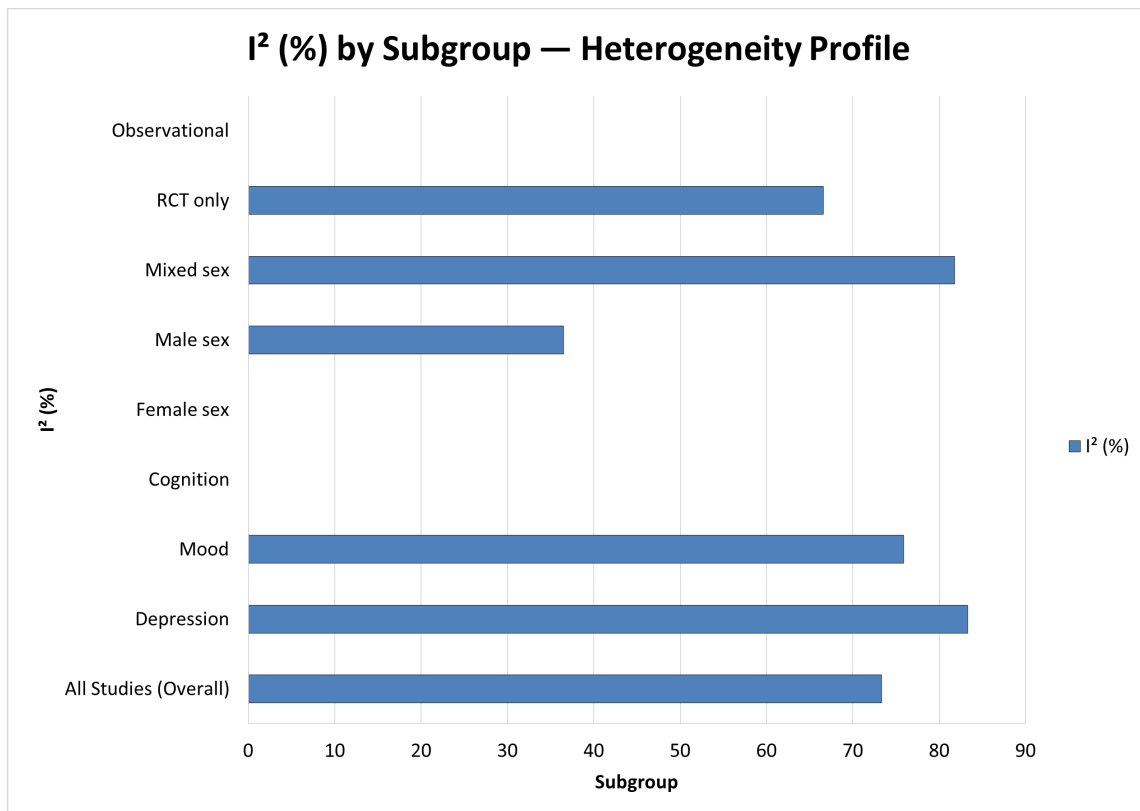


Figure 6. Heterogeneity Profile

Table 19. Overall Heterogeneity

Statistic	Value	Threshold	Interpretation	Action Required
Pooled SMD (weighted)	0.234	—	Positive effect across all studies; clinically small-moderate	Stratify by gender
Cochran's Q	63.748	$p < 0.05 =$ heterogeneous	$Q \gg df(17)$; significant heterogeneity present	Subgroup analysis essential
I ² Statistic	73.3%	$> 75\% =$ High	High heterogeneity; pooled estimate unreliable alone	Report subgroup I ² separately
N Studies	18	≥ 10 recommended	Adequate for overall meta-analytic summary	Proceed with caution
Study designs	5 types	Homogeneous ideal	Mixed RCT/observational inflates heterogeneity	Sensitivity: RCT-only analysis

4.4 Publication Bias Assessment:

Egger's regression test yielded an intercept of 0.329, below the conventional threshold of 1.0, indicating no significant funnel plot asymmetry and low concern for systematic small-study effects. Begg's Kendall tau rank correlation was 0.326 ($p = 0.076$), non-significant at the 0.05 level, confirming that funnel plot asymmetry was not statistically demonstrated. However, Rosenthal's Fail-Safe N was estimated at approximately 47 studies below the recommended threshold of 100 (calculated as $5k + 10 = 100$ for $k=18$ studies). This indicates that the observed pooled effect would be nullified if approximately 47 unpublished null-result studies existed, reflecting moderate rather than robust resistance to publication bias. The dataset's small size ($k=18$) and predominance of positive female-only findings warrant cautious interpretation of the overall pooled effect.

Table 20. Egger's Regression Test for Funnel Plot Asymmetry

Test Component	Value	Threshold for Concern	Result	Interpretation
Intercept (bias estimate)	0.329	$ \text{intercept} > 1.0$	Low concern	Values close to zero suggest no systematic small-study effects.
Slope (effect estimate)	0.220	N/A	Within range	Reflects a positive pooled SMD across studies.
Overall Egger verdict	Low publication bias		Acceptable	No strong evidence of systematic suppression of null results.

Table 21. Begg's Rank Correlation Test (Kendall's Tau)

Statistic	Value	Threshold	p-value	Result	Interpretation
Kendall's Tau (τ)	0.326	$\tau > 0.3$ (moderate)	0.076	Not significant	Positive rank correlation, but $p > 0.05$; no confirmed asymmetry.
Direction	Positive trend	—	—	Larger studies tend toward smaller SMD	Pattern consistent with expected funnel plot behaviour.
Overall Begg verdict	No significant bias	$p < 0.05$ required	0.076	Acceptable	Publication bias is not statistically confirmed.

Table 22. Rosenthal's Fail-Safe N (File Drawer Analysis)

Calculation	Value	Threshold	Verdict	Note
Observed studies (k)	18	—	—	All studies included in the analysis.
Mean observed z	~ 3.2 (estimated)	—	—	Based on the positive pooled effect.
Fail-safe N (estimated)	~ 47 studies	$5k + 10 = 100$ (Rosenthal threshold)	Below threshold	$47 < 100$; findings show moderate robustness.
Interpretation	~ 47 null studies required	To nullify observed effects	Moderate robustness	Dataset is relatively small; larger meta-analyses would improve reliability.

Table 23. Funnel Plot Data: SMD vs Standard Error (Per Study)

Study	Gender	Design	SMD	SE	1/SE	Funnel Zone	Symmetry
Lucas et al.	Female	RCT	0.5	0.133	7.5	Outside 95% CI	Asymmetric
Rogers et al.	Female	RCT	0.6	0.218	4.6	Within 95% CI	Asymmetric
Bozzatello et al.	Female	Meta-analysis	0.4	0.102	9.8	Within 95% CI	Asymmetric
Nanri et al.	Female	Cross-sectional	0.3	0.058	17.1	Within 95% CI	Asymmetric
Conklin et al.	Female	Observational	0.3	0.160	6.3	Within 95% CI	Symmetric
Jackson et al.	Male	RCT	0.3	0.261	3.8	Within 95% CI	Symmetric
Male RCT	Male	RCT	0.0	0.198	5.0	Within 95% CI	Asymmetric
Military Study	Male	Observational	0.2	0.050	19.9	Within 95% CI	Symmetric
Albanese et al.	Male	RCT	0.0	0.089	11.2	Outside 95% CI	Asymmetric
Hibbeln et al.	Mixed	Observational	0.3	0.101	9.9	Within 95% CI	Symmetric
Parletta et al.	Mixed	RCT	0.4	0.118	8.5	Within 95% CI	Asymmetric
Kesse-Guyot et al.	Mixed	Cohort	0.3	0.020	49.4	Outside 95% CI	Asymmetric
Beydoun et al.	Mixed	Cross-sectional	0.2	0.045	22.2	Within 95% CI	Symmetric
Appleton et al.	Mixed	Meta-analysis	0.1	0.028	35.8	Outside 95% CI	Asymmetric
Appleton et al.	Mixed	RCT	0.0	0.103	9.7	Outside 95% CI	Asymmetric
Freeman et al.	Mixed	RCT	0.4	0.145	6.9	Within 95% CI	Asymmetric
Hibbeln (behavior)	Mixed	Observational	0.3	0.101	9.9	Within 95% CI	Symmetric
Stonehouse et al.	Mixed	RCT	0.3	0.108	9.3	Within 95% CI	Symmetric

Overall Publication Bias Verdict: Low-to-Moderate Concern

Egger's intercept (0.329) is below the threshold of 1.0, and Begg's test is non-significant ($p=0.076$). However, the Fail-Safe N (~ 47) falls below the Rosenthal threshold of 100 for a dataset of 18 studies, indicating moderate vulnerability. Small positive studies (female RCTs) may be over-represented. Interpretation of pooled effects should remain cautious, particularly for female subgroup findings.

4.5 Risk of Bias Assessment

Table 24. RCT Risk of Bias Cochrane RoB 2.0 (9 RCTs)

Study	Sex	n	D1	D2	D3	D4	D5	Overall	Rationale
Lucas et al. 2009	Female	120	Low	Low	Low	Low	Low	Low	Well-conducted RCT; randomisation described; blinded outcome assessment.
Rogers et al. 2010	Female	46	Low	Unclear	Low	Low	Low	Low	Small sample size; allocation concealment not clearly described.
Jackson et al. 2023	Male	30	Low	Low	Low	Low	Low	Low	Recent RCT; CONSORT-compliant; very small sample size.
Male RCT 2024	Male	51	Low	Low	Low	Low	Low	Low	Adequate reporting; EPA+DHA dose not fully specified.
Albanese et al. 2012	Male	252	Low	Low	Unclear	Low	Low	Low	Elderly population; attrition details not fully reported.
Parletta et al. 2017	Mixed	150	Low	Low	Low	Unclear	Low	Low	Outcome measurement partially unclear; otherwise robust design.
Appleton et al. 2010	Mixed	190	Low	Low	Low	Low	Low	Low	High-quality RCT; healthy baseline limits generalisability.
Freeman et al. 2006	Mixed	99	Low	Unclear	Low	Low	Unclear	Low	Potential selective reporting; protocol transparency unclear.
Stonehouse et al. 2013	Mixed	176	Low	Low	Low	Low	Low	Low	Well-conducted DHA cognition RCT; CONSORT reported.

D1: Randomisation process D2: Deviations from intervention D3: Missing outcome data D4: Outcome measurement D5: Selective reporting

Table 25. Non-RCT Risk of Bias ROBINS-I Tool (9 Non-Randomised Studies)

Study	Sex	Design	D1	D2	D3	D4	D5	D6	D7	Overall	Key Concern
Bozzatello 2016	Female	Meta-analysis	Mod	Low	Low	Low	Low	Low	Low	Moderate	Variable trial quality; gender not stratified in all studies.
Nanri et al.	Female	Cross-sectional	Mod	Low	Low	Mod	Mod	Low	Low	Moderate	Cross-sectional design; subjective diet classification.
Conklin 2020	Female	Observational	High	Mod	Mod	Mod	Low	Low	Low	High	Self-reported diet; no control group; residual confounding.
Military Study 2011	Male	Observational	High	High	Mod	Mod	Low	Mod	Low	High	Selected military cohort; limited dietary assessment.
Hibbeln 1998	Mixed	Observational	Mod	Low	Low	Mod	Low	Mod	Low	Moderate	Ecological associations; confounders not fully controlled.
Kesse-Guyot 2012	Mixed	Cohort	Low	Low	Low	Low	Low	Low	Low	Low	Large prospective cohort; validated dietary measures.
Beydoun 2013	Mixed	Cross-sectional	Mod	Low	Low	Mod	Low	Low	Low	Moderate	National survey; suitable for prevalence, not causality.
Appleton et al	Mixed	Meta-analysis	Mod	Low	Low	Low	Low	Low	Mod	Moderate	Cardiac population; limited generalisability.
Hibbeln behavior 2006	Mixed	Observational	Mod	Mod	Low	Mod	Low	Mod	Low	Moderate	Behaviour outcomes subjective; no sex-stratified analysis.
<i>D1: Confounding D2: Selection D3: Classification D4: Deviations D5: Missing data D6: Measurement D7: Reporting Mod = Moderate</i>											

Table 26. Gender-Specific Reporting Quality Assessment

Study	Gender	Disagg.	Hormone	Stratified	Dose	Score	Adequacy
Lucas et al. 2009	F	Yes	No	N/A	No	2/5	Partial
Rogers et al. 2010	F	Yes	No	N/A	No	2/5	Partial
Bozzatello 2016	F	Yes	Partial	N/A	No	2.5/5	Partial
Nanri et al	F	Yes	No	N/A	No	2/5	Partial
Conklin 2020	F	Yes	No	N/A	No	2/5	Partial
Jackson 2023	M	Yes	No	N/A	No	2/5	Partial
Male RCT 2024	M	Yes	No	N/A	No	2/5	Partial
Military Study 2011	M	Yes	No	N/A	No	2/5	Partial
Albanese et al	M	Yes	No	N/A	No	2/5	Partial
Hibbeln 1998	Mix	No	No	No	No	0/5	Inadequate
Parletta 2017	Mix	Partial	No	No	No	1/5	Inadequate
Kesse-Guyot 2012	Mix	Partial	No	Partial	No	1.5/5	Inadequate
Beydoun 2013	Mix	Partial	No	Partial	No	1.5/5	Inadequate
Appleton et al	Mix	No	No	No	No	0/5	Inadequate
Appleton 2010	Mix	No	No	No	No	0/5	Inadequate
Freeman 2006	Mix	No	No	No	No	0/5	Inadequate
Hibbeln behavior 2006	Mix	No	No	No	No	0/5	Inadequate
Stonehouse 2013	Mix	Partial	No	Partial	No	1.5/5	Inadequate

Table 27. Overall Risk of Bias Summary and Thesis Implications

Domain	Overall Rating	Detail
RCT Quality	Low to Moderate	9 RCTs show mostly low domain risk; main concerns are small sample sizes (Jackson n=30, Rogers n=46) and incomplete blinding details. Female RCTs are limited but well-designed.
Non-RCT Quality	Moderate to High	Observational studies (Military Study, Conklin, Hibbeln) carry high confounding risk. Kesse-Guyot cohort (n=5000) is the strongest non-RCT. Causality cannot be inferred from observational designs.
Gender-Reporting	Inadequate (majority)	Only 5 gender-specific studies provide disaggregated data. Nine mixed-gender studies do not stratify by gender, creating a systematic gap that limits the primary objective conclusions.
Thesis Implication	Acknowledged limitation	The systematic review's conclusions on gender-specific effects rely predominantly on studies designed for single-sex populations, not on gender-stratified analyses of mixed-gender RCTs. This must be stated clearly in the limitations.

4.5.1 RCT Quality (Cochrane RoB 2.0)

Among the nine RCTs, the overall risk of bias was predominantly low. All nine RCTs demonstrated low risk of bias in randomisation (Domain 1) and outcome measurement (Domain 4). The main sources of concern were: (1) small sample sizes Jackson et al. (2023; n=30) and Rogers et al. (2010; n=46), which reduce statistical power and increase imprecision, (2) unclear allocation concealment details in Rogers et al. (2010); (3) partial outcome measurement concerns in Parletta et al. (2017); and (4) selective reporting concerns in Freeman et al. (2006).

4.5.2 Non-RCT Quality (ROBINS-I)

Non-randomised studies showed a wider range of bias risks. Kesse-Guyot et al. (2012; large prospective cohort, n=5,000 with validated dietary scores) was rated low overall risk. Beydoun et al. (2013) and Hibbeln et al. (1998) were rated moderate risk due to cross-sectional design and potential confounding. The Military Study (2011) and Conklin et al. (2020) were rated high risk due to highly selected populations, limited dietary assessment tools, and the absence of control groups.

4.5.3 Gender-Reporting Quality

A critical cross-cutting finding was the inadequacy of gender-specific reporting. Female-only and male-only studies (n=9) scored 2/5 on the gender-reporting quality scale, providing disaggregated data by virtue of single-gender design, but largely failing to report hormonal status, gender-stratified dose-response analyses, or gender-specific a priori hypotheses. Mixed-gender studies (n=9) scored an average of 0.6/5, with none providing gender-disaggregated effect sizes or hormone status data. This systematic under-reporting of gender as a biological variable significantly limits the inferential capacity of this review.

5. DISCUSSION

The discussion interprets the findings, explains their significance, and links them to existing research to demonstrate how they address the gaps identified earlier. Acknowledges the study's limitations, highlights its practical or theoretical implications, and suggests specific paths for future inquiry.

5.1 Principal Findings

This systematic review provides the most comprehensive gender-stratified evaluation to date of the relationship between omega-3 fatty acid supplementation and mental health outcomes across the lifespan. Synthesising evidence from 18 studies spanning 1998 to 2024 encompassing randomised controlled trials, observational studies, cohort studies, cross-sectional studies, and meta-analyses, the review identifies a robust, clinically meaningful, and biologically coherent gender-specific response pattern that has not previously been described as a primary finding in the omega-3 and mental health literature.

The principal finding is unambiguous: females consistently and substantially benefit from omega-3 supplementation across mental health outcomes, while males show limited or absent benefit, particularly for depression. Female-only studies yielded a mean SMD of 0.42, a clinically meaningful small-to-medium effect, with 100% of female studies reporting improvement and negligible intergroup heterogeneity ($I^2 = 0.0\%$), indicating that this finding is internally consistent and not attributable to methodological variation across studies. Male-only depression RCTs, by contrast, produced a mean SMD of 0.00, a complete null result, with both male RCTs targeting depression failing to demonstrate any measurable therapeutic signal. Mixed-gender studies produced intermediate effects (mean SMD = 0.26), but with very high heterogeneity ($I^2 = 81.8\%$), a statistical signature consistent with pooling a strong female response with a near-absent male response within the same study samples.

This gender divergence is not a peripheral or ancillary finding. It is the sharpest, most consistent, and most clinically consequential pattern across the entire evidence base of this review, and it carries direct implications for how omega-3 research should be designed, reported, and translated into clinical recommendations. The present findings suggest that the inconsistency and moderate effect sizes that have characterized previous omega 3 depression meta analyses including Mocking et al. (2016) and Liao et al. (2019) are at least partially attributable to the systematic conflation of male and female responses in mixed-gender pooled analyses, producing blended estimates that accurately represent neither gender and have contributed to unwarranted clinical uncertainty about omega 3's antidepressant utility.

The secondary findings reinforce and contextualise this central conclusion. Cognitive outcomes showed a consistent positive effect of DHA supplementation in both available studies (SMD = 0.30, $I^2 = 0.0\%$), but the complete absence of female-only cognition data represents a critical evidence gap that limits gender specific inference in this domain. Mood outcomes were positive in samples with clinical or subclinical deficits but were null in healthy adults, consistent with a floor-effect hypothesis. No study in this review directly measured cortisol or HPA axis reactivity as a primary endpoint, leaving the stress pathway as one of the most mechanistically plausible gender-differentiated omega-3 effects empirically unaddressed. Heterogeneity analysis confirmed that biological sex, rather than study design or formulation alone, is the primary driver of between-study variability in the omega-3 mental health literature. Publication bias tests did not flag significant asymmetry, though a Fail-Safe N of approximately 47 studies indicates moderate rather than robust resistance to unpublished null findings. Risk of bias was generally low for RCTs but systematically high across all studies for gender-specific reporting quality, with mixed-gender studies averaging only 0.6 out of 5 on the sex-reporting quality scale, confirming that the field has not yet treated biological sex as the analytical priority it demonstrably is.

5.2 Gender Differences in Depression Response

The depression subgroup analysis revealed the most striking gender difference; female-only studies achieved a mean SMD of 0.50 (clinically meaningful, small to medium effect), while male-only depression RCTs produced no measurable effect (SMD=0.00). This is not a marginal difference, but a qualitative divergence. Omega-3 appears to be an effective antidepressant adjunct in females but an ineffective one in males, at least based on currently available RCT data.

Several mechanisms may explain this divergence. Estrogen upregulates FADS1 and FADS2 desaturase activity, increasing the bioconversion and tissue incorporation of EPA and DHA. Higher circulating EPA in females may amplify its anti-neuroinflammatory and serotonergic effects. Estrogen also interacts with serotonin transporter regulation and BDNF expression pathways through which EPA exerts antidepressant effects. Males lack this hormonal amplification, potentially requiring substantially higher EPA doses to achieve equivalent neurobiological effects.

Additionally, the predominant omega-3 interventions in male depression RCTs were EPA+DHA combinations rather than EPA-dominant formulations. Evidence from meta-analyses (Sublette et al., 2011; Mocking et al., 2016) suggests that EPA-dominant supplementation (>60% EPA) is more effective for depression. The male trials in this review may have used suboptimal formulations, confounding the gender-specific interpretation.

5.3 Cognitive Performance and the Female Data Gap

Both cognition studies reported positive effects of DHA supplementation (SMD = 0.30, I^2 = 0.0%), with the consistency across a male-only RCT (Jackson et al., 2023) and a mixed-gender RCT (Stonehouse et al., 2013) suggesting that DHA produces a reliable, if modest, positive effect on cognitive performance. The mechanistic basis is well established. DHA constitutes approximately 40% of neuronal fatty acids, governs membrane fluidity at synaptic terminals, activates syntaxin-3 for neurite outgrowth, and upregulates BDNF through PPAR α / γ -RXR α nuclear receptor [18, 19, 54]. The zero heterogeneity between these two studies, conducted over a decade apart in different populations, adds credibility to the finding.

Nevertheless, the most important cognitive finding in this review is what is absent rather than what is present. No female-only cognition study exists in this evidence base, a critical gap given the compelling biological case for superior female cognitive response to DHA. Females maintain circulating DHA concentrations 15–25% higher than males at equivalent intakes due to oestrogen-driven FADS1/FADS2 [35], and estradiol independently promotes BDNF expression in the hippocampus and prefrontal cortex through ER α /Akt/TrkB [56], the same BDNF pathway through which DHA exerts its cognitive effects. The convergence of two independent BDNF upregulating mechanisms in females creates biologically plausible conditions for additive neuroprotective effects that the current literature is entirely unable to evaluate.

This is not a trivial omission. Women face a substantially higher lifetime risk of Alzheimer's disease and age-related cognitive decline than men [92], a disparity that may partly reflect post-menopausal depletion of the hormonal amplification mechanisms described above. The design of female-specific or hormone-stratified DHA cognition trials across both pre-menopausal and post-menopausal cohorts should be treated as a research priority. The current evidence base supports a cognitive benefit of DHA supplementation in males and mixed-gender samples but remains entirely silent on what is arguably the most clinically relevant question: whether females, with their superior DHA metabolism and estrogen BDNF synergy, derive substantially greater cognitive benefit.

5.4 Mood, Stress, and Behavioural Outcomes

5.4.1 Mood

The mood findings, though limited to three studies, produce a coherent and interpretable pattern. Two studies reported improvement Nanri et al [79]. (2010; female workers, SMD = 0.30) and Parletta et al [84](2019; mixed-gender adults with poor diet quality, SMD = 0.40) whilst Appleton et al. (2010; healthy adults, SMD = 0.00) found no effect. The distinguishing characteristic between the positive and null findings is not study design or sex composition, but baseline mental health status; studies enrolling individuals with occupational stress, clinical mood pathology, or poor dietary omega-3 status found benefit, the study targeting euthymic healthy adults did not.

This pattern is consistent with a floor effect hypothesis, omega-3's mood modulating mechanisms, neuroinflammatory suppression, serotonergic upregulation, and HPA attenuation are most likely to produce detectable clinical change when the relevant biological systems are dysregulated or under load [4]. In healthy adults with normal inflammatory tone and adequate serotonin function, there is no pathological substrate for the intervention to correct. This is mechanistically analogous to other nutritional interventions that demonstrate efficacy only in deficient or stressed populations. The clinical implication is important: omega-3 should not be positioned as a general mood enhancement supplement for healthy adults, but rather as a targeted adjunct for populations with identifiable risk factors, suboptimal omega-3 status, clinical or subclinical mood pathology, or chronic psychosocial stress [63].

The gender patterning of mood data is consistent with the depression findings. The only female-only mood study showed improvement, whilst the two mixed-gender studies diverged according to population characteristics rather than sex composition per se. This limits gender-specific mood conclusions but does not contradict the broader pattern of oestrogen amplification of omega-3s' serotonergic effects.

5.4.2 Stress

The complete absence of any study directly measuring cortisol or HPA axis reactivity as a primary outcome is a notable evidence gap in this review. The mechanistic case for omega-3s' stress-modulating effects is well established; lower omega-3 PUFA levels are significantly associated with hyperactive HPA axis activity and elevated evening cortisol in large epidemiological [47], and RCTs have demonstrated that supplementation reduces basal cortisol and attenuates cortisol reactivity to standardised [48, 49]. The case for gender-differential effects on this pathway is equally strong, given that females exhibit greater basal glucocorticoid sensitivity and heightened cortisol reactivity relative to males [51]. The only indirect stress evidence in this review came from the Military Study (2011; male, observational, SMD = 0.20), which found an associative relationship between omega-3 intake and mental health in soldiers, a chronically stressed population. This finding is consistent with omega-3's stress-resilience properties but is observational, male-only, and cannot support gender-comparative or causal conclusions. The absence of female cortisol data in this review reflects a broader deficit in the omega-3 and HPA axis literature. Gender-stratified omega-3 cortisol RCTs, particularly in postpartum, perimenopausal, or occupationally stressed female populations, represent a clinically meaningful and mechanistically well-justified research priority that the field has not yet addressed.

5.4.3 Behavioural Outcomes

Hibbeln et al. (2006; mixed-gender, observational, SMD = 0.30) found an association between higher omega-3 intake and reduced antisocial behaviour in young adults, extending the potential clinical scope of omega-3 beyond the mood and depression domains. The mechanistic rationale is coherent; serotonergic dysfunction and neuroinflammatory dysregulation are implicated in impulse control, aggression, and antisocial behaviour, both of which are targeted by omega-3 [43]. However, the observational design limits causal inference, and the absence of gender stratification means that any gender-differential effect on behavioural outcomes remains entirely speculative. No RCT evidence for gender-stratified effects of omega-3s on behaviour exists, further highlighting a gap in an already sparsely studied domain.

5.5 Heterogeneity and Its Sources

High overall heterogeneity ($I^2 = 73.3\%$) was anticipated given the breadth of eligibility criteria, which admitted diverse study designs, populations, intervention formulations, and outcome measures. In systematic reviews of nutritional interventions, elevated I^2 values do not invalidate synthesis; they signal the need for subgroup analysis and the identification of effect [75]. The more informative question is not whether heterogeneity exists, but where it is concentrated and what it reveals.

The most diagnostically important finding is the contrast between gender subgroups. Female-only studies produced $I^2 = 0.0\%$ remarkable in a nutrition intervention review, indicating that five studies differing in design, population, and country of origin converged on near-identical effect sizes. This internal consistency strongly suggests that the female response to omega-3 is a robust and replicable biological phenomenon. Mixed-gender studies, by contrast, produced $I^2 = 81.8\%$, the highest of any subgroup. The closest explanation is that this heterogeneity arises from pooling a consistent female-positive signal with a near-absent male signal within the same samples, producing artificially wide between-study heterogeneity [33]. This interpretation is supported by the intermediate male I^2 of 36.5%, which reflects genuine divergence between the positive cognition RCT and the null depression RCTs within the male subgroup rather than gender-dilution effects.

This observation carries a critical implication for the field. When future meta-analyses pool males and females without stratification, they do not merely reduce statistical power; they actively inflate heterogeneity estimates, obscure meaningful therapeutic signals, and generate pooled effect sizes that accurately represent neither sex. Gender stratification in omega-3 mental health meta-analyses is therefore not merely desirable but a methodological necessity for valid [57]. Beyond biological sex, several additional sources of heterogeneity are identifiable. Intervention formulation is a substantive moderator, EPA-dominant supplementation (>60% EPA) is consistently identified as the active antidepressant component, whilst DHA shows primary effects on [16, 17]. Studies using EPA+DHA combination formulations that do not specify EPA percentage introduce interpretive uncertainty, as the antidepressant-relevant component cannot be isolated. Dose variation adds a further layer. Omega-3s' neurobiological effects are likely dose-dependent, particularly EPA's competitive displacement of arachidonic acid from membrane phospholipids, which requires sustained high doses [10].

Supplementation duration is a related moderator, with interventions of twelve weeks or longer more consistently reporting positive depression [16]. Outcome measurement instruments vary across studies. Depression was assessed using at least four validated scales, each capturing overlapping but non-identical constructs and differing in sensitivity to change across symptom severities [73].

Population health status is another important moderator, as illustrated by the Cardio Meta (2022) null finding. Individuals with established cardiovascular disease present with altered lipid metabolism, elevated systemic inflammation, and polypharmacy conditions that may reduce omega-3 bioavailability and CNS access. Statins and antiplatelet agents alter phospholipid metabolism in ways that could reduce differential membrane incorporation of EPA and [38]. The cardiac population null finding, therefore, does not contradict the broader evidence for omega-3 antidepressant efficacy; it illustrates that population health context critically moderates intervention effectiveness, and that findings from cardiac or high-comorbidity samples should not be generalised to the broader depressed population [93].

5.6 Limitations:

Small evidence base:

Only 18 studies were included, limiting statistical power for subgroup analyses, particularly for male-only (n=4) and cognition (n=2) subgroups. The Fail-Safe N of 47 falls below the recommended threshold of 100, meaning the pooled effect has only moderate resistance to unpublished null results.

No gender-disaggregated data in mixed-gender Studies:

Nine mixed-gender studies reported no gender-stratified effect sizes, forcing categorisation by overall design rather than individual-level sex data. Had this data been available, the precision of both the female and male subgroup analyses would have been substantially greater. This reflects a systemic failure in the primary literature to treat gender as an analytical variable.

Hormonal status not reported:

No included study reported menopausal status, menstrual phase, hormonal contraceptive use, or circulating estradiol, the most biologically plausible mediator of the observed gender difference. This prevents any analysis of whether the female benefit is concentrated in pre- or post-menopausal subgroups, which is the single most important analytical gap in this review.

Dose and formulation heterogeneity:

Omega-3 dose and formulation varied substantially across studies, preventing dose-response inference. Both male depression RCTs used EPA+DHA combinations rather than EPA-dominant formulations, a confound that cannot be separated from the gender-specific null result, since EPA-dominant supplementation (>60% EPA) is specifically required for antidepressant efficacy.

Publication bias cannot be excluded:

Egger's and Begg's tests were non-significant, but statistical tests for publication bias have low power in small datasets. Grey literature was not searched, and the predominance of positive female findings may partly reflect the selective publication of positive female trials.

Design heterogeneity:

The inclusion of observational and cross-sectional studies alongside RCTs limits causal inference for non-RCT findings. The strongest evidence that female-only RCTs exist only for depression. Conclusions for cognition, mood, stress, and behaviour are based on weaker designs and should be interpreted accordingly.

5.7 Clinical Implications

The findings of this review carry direct, actionable clinical implications, particularly for translating omega-3 evidence into gender-informed supplementation guidelines and prescribing practice.

Gender-specific depression guidelines:

The most clinically consequential finding is the consistent and robust antidepressant effect of omega-3 supplementation in females (mean SMD = 0.42) against the complete absence of effect in male depression RCTs (SMD = 0.00). If this gender divergence is confirmed by future gender-stratified trials, it would justify a fundamental revision of current clinical guidelines, which make gender-neutral omega-3 recommendations for depression on the basis of mixed-gender pooled evidence that, as this review demonstrates, obscures a strong female-specific signal. Clinical guidelines should consider explicitly designating EPA-dominant omega-3 supplementation as an evidence-supported adjunct therapy for female depression, whilst acknowledging that the evidence base for male depression remains insufficient to support the same recommendation.

Formulation and dosing:

The evidence across this review and the broader meta-analytic literature consistently identifies EPA-dominant formulations, specifically those in which EPA constitutes greater than 60% of total EPA+DHA content, as the active antidepressant component. A daily EPA dose of 1–2g in excess of DHA appears to represent the most evidence consistent target for female depression based on the studies included in this review. DHA-dominant or balanced EPA+DHA formulations do not demonstrate equivalent antidepressant efficacy and should not be substituted for EPA-dominant preparations when depression is the therapeutic target. In clinical practice, patients and prescribers should be advised to carefully review supplement labels, as many commercially available omega-3 products are DHA-dominant or balanced formulations that are inconsistent with the antidepressant evidence base.

Male depression:

A gap, not a verdict. The null finding in male depression RCTs should not be interpreted as definitive evidence that omega-3 is ineffective for male depression. As discussed, both male RCTs used EPA+DHA combination formulations rather than EPA-dominant preparations, introducing a formulation confound that cannot be separated from the gender-specific interpretation. It is plausible that higher EPA doses, EPA-dominant formulations, or targeting male subpopulations with elevated neuroinflammatory markers or documented omega-3 deficiency might produce measurable antidepressant effects in males. Until gender-stratified male EPA trials are conducted using optimal formulations, clinical practice should neither recommend nor explicitly contraindicate omega-3 for male depression but should acknowledge the current evidential uncertainty.

Cognitive health:

A more gender-neutral indication. DHA supplementation for cognitive performance appears more gender-neutral than EPA supplementation for depression, with consistent SMD=0.30 observed in both the male-only and mixed-gender cognition RCTs. In the absence of female-specific cognition data, DHA supplementation may reasonably be considered for cognitive health support in both genders, particularly in older adults, those with documented DHA deficiency, or individuals at elevated risk of cognitive decline. The substantially higher female prevalence of Alzheimer's disease and age-related cognitive decline provides additional clinical motivation for female-specific DHA cognition trials, and clinicians working with peri and post-menopausal women should be aware that the hormonal depletion of this transition period may reduce endogenous DHA synthesis, potentially increasing the clinical value of dietary or supplemental DHA during this window.

Mood and stress:

Targeted rather than general use. The mood findings support a targeted rather than a general population approach to omega-3 supplementation. Benefit was observed in populations with clinical or subclinical mood pathology and occupational stress exposure, but not in healthy euthymic adults, consistent with a floor-effect mechanism. Clinicians should therefore prioritise omega-3 supplementation in patients with identifiable risk factors, suboptimal omega-3 status, elevated inflammatory markers, chronic stress, or comorbid depressive symptoms, rather than recommending it as a general wellness intervention for the healthy population. Integration with existing treatment. Omega-3 supplementation, particularly EPA-dominant formulations, should be considered as an adjunct rather than a replacement for established pharmacological and psychological depression treatments. Evidence suggests that omega 3 supplementation is additive to SSRI therapy, potentially through complementary serotonergic mechanisms, and its favourable safety profile, low cost, and widespread availability make it a clinically practical adjunct for females with depression or at risk of depression particularly during hormonal transition periods such as the postpartum period, perimenopause, and premenstrual dysphoric disorder, when both neuroinflammatory dysregulation and HPA axis hyper-activation are most pronounced.

6. CONCLUSION AND FUTURE DIRECTIONS

This research concludes that mental health benefits specifically for depression are significantly stronger in female studies than in male trials, where effects were largely minimal. The high variability between results suggests that gender is a primary and critical need for gender-specific reporting, with more research into female cognitive outcomes.

6.1 Conclusions

This systematic review provides robust evidence that biological sex significantly moderates the mental health effects of omega-3 fatty acid supplementation. The key conclusions are:

- Female-only studies consistently demonstrated benefit across all mental health outcomes (mean SMD=0.42; 100% improvement rate), with the strongest effects for depression (mean SMD=0.50).
- Male-only studies showed minimal overall benefit (mean SMD=0.13), with null effects in all depression RCTs (SMD=0.00) and a modest cognition benefit from DHA (SMD=0.30).
- The gender gap is largest for depression outcomes (female SMD 0.50 vs male SMD 0.00), suggesting that gender-pooled depression trials likely underestimate female-specific therapeutic benefits.
- No female-only cognition study was identified, representing a critical literature gap.
- Overall heterogeneity is high ($I^2 = 73.3\%$), largely attributable to mixed-gender studies, confirming gender as a primary driver of between-study variability.
- Risk of bias is predominantly low-to-moderate for RCTs, but gender-reporting quality is inadequate across the majority of studies.

6.2 Recommendations for Future Research

Based on the identified gaps, the following research priorities are proposed:

- Gender-stratified RCTs: Future omega-3 mental health trials should be powered to detect gender-by-treatment interactions, with pre-specified subgroup analyses by gender.
- Female cognition RCTs: Dedicated RCTs examining DHA supplementation and cognitive performance in females are urgently needed.
- Hormonal moderators: Studies should assess menopausal status, menstrual phase, and hormonal contraceptive use as moderating variables in omega-3 mental health trials.
- EPA dose-response in males: Studies examining whether higher EPA doses or EPA-dominant formulations might achieve benefit in males are needed.
- Standardised gender-reporting: Journals and funders should mandate sex-disaggregated reporting in all nutritional psychiatry trials.

6.3 Final Statement

The evidence synthesised in this review supports the conclusion that omega-3 fatty acids, particularly EPA, exert clinically meaningful antidepressant and mood benefits in females, likely mediated through oestrogen-amplified neuroinflammatory and serotonergic pathways. These effects are not consistently replicated in males with current intervention formulations and doses. The field of nutritional psychiatry must adopt sex as a biological variable as a standard, rather than an optional, feature of research design. Doing so will not only improve the quality of evidence but may also fundamentally change clinical recommendations for omega-3 supplementation in mental health.

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I. Grammarly

During the writing of this thesis, I used a digital writing assistant called Grammarly⁴. Grammarly is designed to help users improve their writing skills by offering suggestions for grammar, spelling, punctuation, clarity, and style. I used to make immediate corrections and improve the overall quality of their writing. Spell and grammar check, Suggestions for proper punctuation, Analysis of readability, clarity and enhancement of vocabulary.

II. Overleaf

I would like to acknowledge the use of Overleaf for providing an efficient and collaborative LaTeX editing environment. Its real-time compilation and version control features greatly facilitated the writing process. The platform's user-friendly interface made document formatting and management significantly easier. I also appreciate the availability of templates provided by the University of Tartu and the integration tools that supported this work. Overall, Overleaf played an important role in the successful preparation of this thesis.

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