Comparison of Dropout Rates in RCTs Testing the Efficacy of Nutraceuticals and Antidepressants for Adult's Major Depressive Disorder: A Systematic Review and a Meta-Analysis

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Abstract

Major Depressive Disorder (MDD) is a significant contributor to global disability, projected to emerge as the leading cause of disability by 2030. While Antidepressants (ADTs) are a prevalent treatment option for MDD, their efficacy is constrained by low remission rates and undesirable side effects, prompting exploration of alternatives. In the last decade, the efficacy of nutraceuticals in MDD treatment has gained attention. However, there is a gap in research regarding direct comparison between the dropout rates in trials investigating the effect of ADTs and nutraceuticals on MDD. This study conducted a comprehensive comparison of efficacy and dropout rates among 17 types of ADTs and 3 types of nutraceuticals. Data were derived from RCTs included in the most recent meta-analyses on this subject. Due to a lack of previous studies on the dropout comparison of ADTs and nutraceuticals, no predictions were made in that regard. However, it was hypothesized that higher dropout rates would be associated with better treatment outcomes. The findings indicate that Nutraceuticals were more effective (Cohen's *d* = -1.96, CI: -3.40 to -.53) in MDD treatment compared to ADTs (Cohen's *d* = -.35, CI: -.39 to -.31). There were no significant differences in dropout rates between ADTs and nutraceuticals, except within control groups, where nutraceuticals demonstrated lower dropout rates (*M* =.13) compared to ADTs (*M* =.28). Furthermore, no relationship between dropout rates and treatment outcomes was observed, except within the ADTs control group where higher dropout rates corresponded to lower treatment outcomes (*t* (1,144) = -2.91, *p* = .004). This study shows the comparative efficacy and dropout dynamics of ADTs and nutraceuticals in the treatment of MDD.

Keywords: MDD, ADTs, nutraceuticals, metanalysis, RCTs, dropouts, treatment outcome

Comparison of Dropout Rates in RCTs Testing the Efficacy of Nutraceuticals and Antidepressants for Adult's Major Depressive Disorder: A Systematic Review and a Meta-Analysis

Major Depressive Disorder (MDD), also known as clinical depression is a prevalent psychiatric condition characterized by symptoms such as low mood, diminished motivation, cognitive impairments, disrupted sleep patterns, and changes in appetite. MDD ranks among the top ten contributors to global disability (Lopez & Mathers, 2006). The World Health Organization (2017) predicts that depression will become the leading cause of disability by 2030. Gender, age, genetics, and the presence of comorbid mental or physical disorders are influential determinants in both the occurrence of depression and the efficacy of the treatments (McKeever et al., 2017). Research has indicated that MDD is approximately twice as prevalent in females compared to males (Kessler et al., 1993). The relationship between age and depression is complex, with distinct patterns emerging. Hormonal changes during adolescence contribute to heightened vulnerability and increased prevalence of depression (Burt & Stein, 2002). In adulthood, depression rates vary, with younger adults facing elevated levels due to diverse stressors. Depression among older adults is concerning and often associated with health conditions, bereavement, and life changes (Kanowski, 1994). It is important to note that the public health impacts of MDD are substantial. Reduced productivity and increased absenteeism, contribute to the economic burden of MDD (Greenberg et al., 2015). Moreover, MDD also leads to heightened healthcare utilization, suicide-related costs, and reliance on social welfare programs. (Üstün et al., 2004). Early intervention and effective treatment of MDD can help mitigate these burdens and improve the overall well-being of individuals and society.

In the 1950s, the first antidepressant drugs, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) were introduced. However, concerns about their safety prompted the search for improved options (Mukherjee, 2012). In the 1980s, a safer class of antidepressants called selective serotonin reuptake inhibitors (SSRIs) emerged. SSRIs' remarkable success made prescription therapy a standard treatment for MDD of any severity (Santarsieri & Schwartz, 2015). Extensive research supports the effectiveness of ADTs and psychotherapy as treatment options for MDD (Nierenberg et al., 2008; Leichsenring et al., 2022).

ADTs are believed to regulate and normalize the level of certain neurotransmitters in the brain. SSRIs such as fluoxetine, sertraline, and escitalopram selectively inhibit the reuptake of serotonin into the presynaptic nerve terminals. This increases the concentration of serotonin available in the synapses. This heightened serotonin level is assumed to improve mood and reduce symptoms of depression (Mourilhe & Stokes,1998). Serotonin and Norepinephrine Reuptake Inhibitors (SNRIs), such as venlafaxine and duloxetine, target both serotonin and norepinephrine by blocking their reuptake (Takahashi et al., 2005). TCAs, such as amitriptyline and imipramine, are older ADTs that also affect serotonin and norepinephrine levels. However, TCAs are generally used less often nowadays due to their side effects (Arroll et al., 2005). Atypical Antidepressants include various ADTs that work through different mechanisms. Bupropion, for instance, primarily affects dopamine and norepinephrine levels (Jefferson et al., 2005). Mirtazapine increases the release of both serotonin and norepinephrine, while also blocking certain serotonin receptors (Holm & Markham,1999). MAOIs, such as phenelzine and tranylcypromine, inhibit an enzyme called monoamine oxidase, which breaks down serotonin, norepinephrine, and dopamine. By blocking this enzyme, MAOIs increase the availability of these neurotransmitters (Shulman et al., 2013). Vilazodone and vortioxetine are two of the most recently approved drugs for MDD. Both considered "SSRI Plus" agents as their core mechanism is serotonin reuptake inhibition, and manipulation of serotonin receptors (Schwartz et al., 2011).

While ADTs are believed to play a significant role in treating MDD, their mechanism of action is not without its critiques. The chemical imbalance theory, suggesting that depression is primarily caused by a deficiency of certain neurotransmitters like serotonin, has been heavily promoted by pharmaceutical companies (Leo & Lacasse, 2008). Even though a substantial amount of money and time has been dedicated to research about chemical imbalance theory, there is no actual proof to support it (Lacasse & Leo, 2005). This theory oversimplifies the complex nature of MDD and ignores the multitude of factors that contribute to its development (Leventhal & Antonuccio, 2009). Moreover, in the past years, the effectiveness of ADTs has been a subject of debate. Numerous researchers demonstrated that the differences between ADTs and placebos are minor and might not be clinically significant (Jakobsen et al., 2020; Munkholm et al., 2019). Additionally, some studies indicate that ADTs can affect mood without targeting the biological mechanism of MDD (Moncrieff & Cohen, 2005). Different studies in favor (Harmer & Cowen, 2018; Pies, 2019) and against (Eske, 2019; Pariante, 2018; Royal College of Psychiatrists, 2019) the chemical imbalance theory, show paradoxical findings. American Psychiatric Association (2021) continues the suggestion that changes in certain brain chemicals could play a role in causing depression symptoms. Nevertheless, ADTs are still promoted as a way to correct these chemical imbalances.

It is important to note that regardless of the remarkable number of prescribed ADTs, the low rate of remission and the adverse effects associated with them contribute to a significant proportion of patients (44%) discontinuing treatment within the initial three months (Bull et al., 2002). Previous research demonstrated that a significant percentage of individuals experience Nausea (Talley, 2007), sleep disturbances (Kelly et al., 2022), sexual dysfunctioning (Rothschild, 2000), and weight changes (Fava, 2000) especially during the initial weeks of treatment. Additionally, more than half of patients undergoing psychotherapy do not respond favorably, with only one-third achieving remission (Cuijpers et al., 2021). Consequently, a substantial proportion of individuals afflicted with MDD will not attain complete alleviation of their symptoms (Duval et al., 2022). Therefore, considering the increasing prevalence of MDD and the adverse effects of ADTs, establishing novel treatment approaches is essential.

There is increasing evidence supporting the link between dietary quality and mental health, as well as the potential impact of nutritional deficiencies (Sarris et al., 2015). However, it is important to consider that the initial estimation of outcomes of the studies focused on novel interventions, such as nutraceuticals, might be overly optimistic (Fanelli & Ioannidis, 2013). Therefore, incorporating RCTs and more importantly meta-analyses of RCTs is highly recommended when investigating nutraceutical treatments for MDD. These methodologies can yield high-standard evidence regarding the efficacy of novel treatments (Crowther et al, 2010). A meta-analysis conducted by (Firth et al., 2019) indicated a positive effect of diet on depression. Nutrient-based supplements are also being explored as potential treatments as standalone or additional therapies for mental health conditions (Maes et al., 2011). The exploration of nutraceuticals as a treatment avenue for MDD has been receiving significant attention over the past decades (Alvarez-Mon et al., 2021). Nutraceuticals are defined as compounds that consist of standardized nutrients or functional foods manufactured to pharmaceutical-grade standards, with the potential to treat or prevent various disorders or diseases (Travica et al., 2023). To date, the conducted meta-analyses within the realm of nutraceuticals' impact on MDD treatment exhibit certain limitations. The studies show high heterogeneity regarding their outcomes (Firth et al., 2019). In addition, the interventions primarily span short durations, often lasting 6, 8, and 12 weeks (Opie et al., 2015; Mikola et al., 2022; Zhu et al., 2022). Furthermore, issues such as statistical power, bias management, and attrition emerge as areas of concern within these studies (Thomas-Odenthal et al., 2020). Given these limitations, the utilization and generalization of the findings from these studies should be approached with caution.

The World Federation of Societies of Biological Psychiatry (WFSBP) conducted a meta-analysis of double-blind randomized controlled trials (RCTs) between 2019 and 2021, evaluating a dozen nutraceuticals. Their published guidelines highly recommended the adjunctive use of N-3 polyunsaturated fatty acids (N-3 PUFAs), also known as omega-3 fatty acids, for depression treatment (Sarris et al., 2022). Furthermore, based on comprehensive reviews of recent meta-analyses of RCTs, it seems that vitamin D (Mikola et al., 2022), probiotics (Zhu et al., 2022; Sarkar et al., 2016), and N-3 PUFAs (Sarris et al., 2022; Wolters et al., 2021) are highly effective and therefore recommended for the treatment of MDD. The following sections explain the working mechanisms of each of these nutraceuticals related to MDD.

N-3 polyunsaturated fatty acids (N-3 PUFAs)

An increasing body of evidence has endorsed the positive impacts of N-3 PUFAs on diverse neurodegenerative and neurological disorders (Dyall & Michael-Titus, 2008; Dyall et al., 2010; Denis et al., 2015). N-3 PUFAs play crucial roles in neuronal processes, encompassing monoamine neurotransmission and inflammatory responses (McNamara & Carlson, 2006). The two primary types of N-3 PUFAs with potential mental health benefits are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (Dyall, 2015). DHA, a vital constituent of cell membranes, helps maintain cell membrane integrity and influences neural communication, especially dopamine signaling (Grosso et al., 2014). Dysregulated dopamine signaling may contribute to reduced motivation and interest in rewarding activities (Brown & Gershon,1993). By increasing the sensitivity and efficacy of dopamine D2-like receptors in the Striatum, DHA helps the maintenance of optimal dopamine levels (Mocking et al., 2016). Adequate levels of DHA are vital for optimal brain function, and its deficiency has been linked to mood disorders (Song et al., 2016). EPA, on the other hand, may affect the sensitivity and efficacy of serotonin receptors in the brain. Reduced serotonin levels can lead to mood dysregulation and anhedonia (Gopaldas et al., 2019). Furthermore, EPA also impacts the synthesis of serotonin in the brain. Serotonin is derived from the amino acid tryptophan. By increasing tryptophan availability, EPA may support the production of serotonin and help the maintenance of optimal serotonin levels (Patrick & Ames, 2015). Additionally, EPA has anti-inflammatory properties. Chronic inflammation in the brain has been linked to mood disorders and disruptions in neurotransmitter systems, including serotonin. EPA with anti-inflammatory properties, can reduce inflammation and create a more favorable environment for serotonin neurotransmission (Mischoulon et al., 2022).

Vitamin D

Vitamin D receptors (VDRs) can be found on neurons and glia in different brain regions involved in mood regulation, emotional processing, and cognitive functions such as the hippocampus and cingulate cortex (Anglin et al., 2013). Humans can obtain vitamin D from various sources, such as exposure to sunlight, dietary intake, and dietary supplements (Holick, 2007). Vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) are two distinct forms of vitamin D. Previous research indicated that vitamin D3 exerts a more pronounced effect on depression compared to vitamin D2 (Parker et al., 2017). It has been proposed that vitamin D (25-hydroxyvitamin D3; 25(OH)D) plays a regulatory role as a neuroactive steroid in neuropsychological processes linked to depression (Eyles et al., 2005). Earlier cross-sectional studies have demonstrated a correlation between low levels of circulating vitamin D and depression (Anglin et al., 2013). Furthermore, Vitamin D modulates the synthesis and functioning of neurotransmitters, such as serotonin and dopamine (Berridge, 2017). Vitamin D exerts an impact on neurotrophic factors, including brain-derived neurotrophic factor (BDNF), which are essential for promoting neuron growth, survival, and maintenance. (Xu & Liang, 2021). During prolonged exposure to chronic stress, BDNF levels may decline, potentially negatively affecting neuron health. Adequate vitamin D levels can contribute to the maintenance or enhancement of BDNF expression, thereby supporting the growth and resilience of neurons in the face of stress (Koshkina et al., 2019). Stress resilience is suggested as a protective factor for MDD (Aro, 1994).

Probiotics

MDD has mostly been linked to the nervous system, encouraging numerous studies to focus on brain structures associated with its symptoms. However, recent research has indicated that the immune system and gut-brain axis also significantly influence the onset and persistence of MDD (Trzeciak & Herbet, 2021). The gut-brain axis is a bidirectional communication network between the gastrointestinal and central nervous systems (Romijn et al., 2008). Many in vivo and clinical studies have shown the substantial role of stress in the development of MDD (Nemeroff & Vale 2005). In periods of stress, the immune system negatively affects the intestinal barrier and the intestinal microbiota (the diverse community of microorganisms residing in the digestive tract) (Averina et al., 2020). It has been observed that the gut and brain work in a bi-directional manner and can affect each other's functions (Carabotti et al., 2015). Therefore, the dysfunction of the intestinal microbiota due to stress affects the processes of neurotransmitter synthesis and myelination of neurons in the prefrontal cortex (Kim & Shin, 2018). The defect in neurotransmitter synthesis such as serotonin and dopamine can result in mood disorders, sleep disturbances, and appetite change (Nautiyal et al., 2016). The development of these symptoms might be associated with the onset of MDD (Kennedy, 2022). Probiotics are live microorganisms, often referred to as "good" bacteria that affect the gut-brain axis and have shown promising effects on the improvement of MDD symptoms (Smith et al., 2021). These probiotics, also known as psychobiotics, when consumed in appropriate amounts, have a beneficial effect on mental health. Psychobiotics play a crucial role by modulating the gut microbiota, intestinal barrier function, and inflammation (Ait-Belgnaoui et al., 2012; Braniste et al., 2014). Psychobiotics positively affect the parameters of the intestinal barrier and modulate the immune response in the GALT (gut-associated lymphoid tissue) area. This helps reduce inflammation (Isolauri et al., 2002). Additionally, psychobiotics help the reductions in cortisol levels and the activity of the HPA axis, as well as the modulation of vagal nerve stimulation (Andersson et al., 2016).

The results of nutraceutical treatment for MDD seem promising with the added advantage of fewer adverse side effects. Previous studies have shown higher and/or equal effectiveness of nutraceuticals compared to ADTs in the treatment of psychological disorders (Lakhan & Vieira, 2010; Tan et al., 2007; Fink et al., 2020). However, it is essential to recognize that treatment efficacy is contingent upon treatment adherence (Jimmy & Jose, 2011). Treatment adherence refers to the extent to which an individual complies with or follows a prescribed treatment plan suggested by a healthcare professional (Nowotny et al., 2023). The previous meta-analyses demonstrated that the dropout rates of ADT treatments range between 11 and 33% (Trivedi et al., 2006; Munkholm & Paludan-Müller, 2022). Factors such as adverse side effects, lack of perceived benefits, dissatisfaction with random assignments, and challenges related to travel and distance affect the treatment adherence in RCTs of ADTs (Vergouwen et al., 2003).

Nutraceuticals come in various forms such as capsules, powders, or liquids. The taste and palatability of the product can affect patient adherence, especially if they find it unpleasant to consume (den Uijl et al., 2015; Stratton & Elia, 2007). Furthermore, although nutraceuticals tend to have fewer side effects compared to ADTs, some individuals may still experience mild adverse effects (Lester et al., 2022). Moreover, patients' belief in the effectiveness of nutraceutical treatments can significantly impact their adherence. Some patients may have a strong preference for conventional medications over natural treatments, leading to non-adherence to nutraceutical treatments (Aikens et al, 2005). Although individual studies have reported drop-out rates for specific nutraceuticals like vitamin D (Srifuengfung et al., 2023), probiotics (Theodora et al., 2019), and N-3 PUFAs (Appleton et al., 2021) separately, there is a notable gap in the literature regarding the comprehensive study of MDD treatment adherence in nutraceuticals. Therefore, to consider the utilization of nutraceuticals as a treatment option for MDD, it is imperative to learn more about the dropout rates in trials investigating the efficacy of nutraceuticals in the treatment of MDD.

While dropouts are typically viewed as unfavorable for research studies, it's important to recognize that in certain instances, increased dropout rates might be a result of symptom improvement (Pekarik,1992). In a meta-analysis assessing the effectiveness of 21 ADTs, Cipriani et al (2018) categorized dropouts into two groups: those due to adverse side effects and those due to improved symptoms. The findings revealed a notable positive link between dropout rates and symptom enhancement in numerous instances, suggesting that participants withdrew from the study due to observed symptom improvements.

Given the novelty of the subject, there is a lack of studies investigating a direct comparison between dropout rates of nutraceutical treatments, such as N-3 PUFAs, vitamin D, probiotics, and ADTs in the treatment of MDD. Moreover, one of the limitations of previous studies is that they did not focus on specific types of depression (MDD, bipolar, etc.), but rather investigated depression as a general construct without considering the distinct subtypes (Alavi et al., 2019; Kaviani et al., 2020; Tian et al., 2022). In addition, previous investigations examining the effects of nutraceuticals and ADT treatments on depression included participants with comorbid physical/psychological conditions (Patrick & Ames, 2015; Liu et al., 2013). When studying the effect of ADTs and Nutraceuticals on MDD, the presence of comorbidity with other conditions complicates the interpretation of results in several ways. Firstly, it can alter the response to the intervention, as the presence of comorbid conditions might influence how ADTs and nutraceuticals are absorbed, metabolized, or distributed in the body (Gold et al., 2020). Secondly, comorbidity might cause difficulty in determining whether observed changes are a direct result of the intervention, or they are related to the comorbid condition (Caron & Rutter, 1991). Furthermore, uncontrolled interactions between treatments addressing the comorbid condition and the primary condition of interest may result in unexpected side effects or reduced efficacy (Hermann et al., 2000).

The current study aims to conduct a systematic review and a meta-analysis in order to compare dropout rates in RCTs testing the efficacy of Nutraceutical and ADTs for Adults with MDD. To mitigate potential confounding factors, this study deliberately selects RCTs including participants diagnosed with MDD and no comorbidities. Utilizing the latest meta-analyses of RCTs about the treatment of MDD, this paper aims to address two main objectives. Firstly, whether there is a difference in dropout rates between nutraceuticals (N-3 PUFAs, Vitamin D, and Probiotics) compared to ADTs in the treatment of MDD. Secondly, whether there is an association between dropout rates and improvement of MDD symptoms.

While evaluating intervention effectiveness often hinges on effect sizes, the importance of treatment adherence is frequently overlooked. To ascertain the real-world feasibility of nutraceuticals compared to ADTs in treating MDD, a comprehensive exploration of their dropout rates becomes pivotal (Pigott et al., 2010). Notably, dropout occurrences can potentially denote both treatment ineffectiveness and/or symptom improvement (manifested by individuals discontinuing due to symptom amelioration) (Hunt & Andrews,1992; Reich & Berman, 2020).

This research aims to encourage a novel viewpoint regarding dropout rates. It goes beyond considering dropout rates solely as indicators of treatment ineffectiveness and underscores their potential significance in reflecting symptom improvement. Additionally, the study seeks to investigate and compare the efficacy of nutraceuticals and ADTs in treating MDD. In the event of discovering supportive evidence for the effects of nutraceuticals on MDD, this exploration could offer healthcare practitioners and patients an expanded array of choices when selecting treatment approaches. This pursuit is particularly relevant given the acknowledged challenges associated with traditional ADTs.

Given that the difference between the dropout rates of ADTs and nutraceuticals has not been addressed previously, it is challenging to provide any predictions. While dropout rates of ADTs and nutraceuticals have been individually studied before, no research has yet investigated a direct comparison between the two. Thus, the primary objective of this study is to explore and analyze potential differences. Regarding the second research question, it is hypothesized that higher dropout rates are associated with better treatment outcomes.

Methods

The present study entailed a systematic review and meta-analysis, utilizing data from pre-existing meta-analyses on RCTs with the primary objective of comparing the dropout rates associated with nutraceuticals and ADTs in the treatment of MDD. The requirement for approval from the Scientific and Ethical Review Board of the Faculty of Psychology and Education at Universiteit Leiden was deemed unnecessary.

Design

The initial step of the study involved selecting specific nutraceuticals to be included; N-3 PUFAs, vitamin D, and Probiotics. They were chosen based on their well-established status as extensively studied and recommended treatment options for MDD (Sarris et al., 2022). The data for this study was collected from the most recent meta-analyses of RCTs investigating the effect of ADTs and nutraceuticals in the treatment of MDD. An extensive literature review was manually conducted utilizing electronic databases (Google Scholar, PubMed, and PsycINFO), to identify the most recent metanalysis of RCTs investigating the topic. The search strategy employed a comprehensive set of keywords including meta-analyses, randomized controlled trials/RCTs, major depressive disorder/MDD, N-3 PUFAs, omega-3 fatty acids, fish oil, vitamin D, probiotics, psychobiotic, gut-brain axis, gut microbiota, intestinal microbiota, ADTs, Antidepressants, pharmaceuticals, depression, and depressive symptoms. The search strategy, selection of studies, and data synthesis followed by the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines with 2020 updates (Moher et al., 2009; Page et al., 2020).

The literature review resulted in the selection of the most recent meta-analyses of RCTs investigated the use of N-3 PUFAs (Wolters et al., 2021), Vitamin D (Mikola et al., 2022), Probiotics (Sikorska et al.,2023), and ADTs (Cipriani et al., 2018).

Inclusion and Exclusion Criteria

Only RCTs that included a placebo control group were considered for inclusion in this study. Moreover, only full-text English-written articles were included. Consequently, abstract, and unpublished literature were excluded. Furthermore, studies were required to concentrate exclusively on MDD and exclude any specific types of depression, such as perinatal, bipolar depression, or alpha-interferon-induced depression. Studies that investigated MDD in combination with psychotic or neurodegenerative diseases were also excluded from this analysis. To ensure the homogeneity of the samples, studies that included participants with (comorbid) physical or psychological conditions other than MDD were excluded. Furthermore, only studies that reported their results as mean with standard deviation (SD) or 95% confidence interval (CI) or data from which this could be calculated were included. The selected RCTs have been assessed for their quality and validity by the authors conducting the chosen meta-analyses. Participants in the included studies were restricted to adults aged 18 years and above (all genders), with a diagnosis of MDD according to standard operationalized diagnostic criteria (Feighner criteria, DSM-III, DSM-III-R, DSM-IV, DSM-5, and ICD-10) encompassing both inpatients and outpatients from the clinical population (Feighner et al., 1972).

The articles present in the aforementioned meta-analyses have undergone screening for inclusion and exclusion criteria. The RCTs meeting the predefined criteria for this research were chosen for data extraction and subsequent analysis. The study was preregistered at the Open Science Framework (OSF) to ensure transparency and minimize potential biases in data analysis (https://osf.io/254qz/).

Measures

The severity of MDD symptoms was measured using the Hamilton Rating Scale for Depression (HAM-D 17, 21, and 24), Beck Depression Inventory (BDI), Beck Depression Inventory-II (BDI-II), Hospital Anxiety and Depression Scale (HADS), and the Montgomery–Åsberg Depression Rating Scale (MADRS) (Hamilton,1960; Beck et al., 1961; Zigmond & Snaith, 1983; Montgomery & Åsberg, 1979). Dropout rates were calculated by dividing the number of participants who dropped out by the total number of participants enrolled. The result was multiplied by a hundred to get the percentage value. The effect sizes of the treatments (Cohen’s d /SMD) for the change in depression score from baseline to end of treatment were calculated. Moreover, the change from baseline to follow-up was also calculated where available.

Data extraction

The data regarding the dropout rates, baseline, and end-of-treatment depression score, treatment outcome (change from baseline until the end of treatment), effect sizes (if available), standard deviations, participants’ characteristics (Age, gender), intervention duration, and MDD assessment tools were extracted.

Data Analysis

All statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 29.0 for Windows. (IBM CORP, 2020). Inferential tests were exclusively two-tailed and used a significance level of .05. Descriptive statistics were used to report the average age, gender distribution, mean sample size, and average treatment duration (in weeks).

In order to accommodate the variability exhibited by the effect sizes, random effect meta-analyses were conducted (Dersimonian & Kacker, 2007). The effect sizes for all individual studies in both ADT and nutraceutical groups as well as a cumulative effect size for both groups were calculated. To assess the heterogeneity of the effect sizes, the Q statistic and the I^2 index were calculated. I^2 statistics were used to assess the amount if heterogeneity, categorized as low ($I^2 \leq 25\%$), moderate ($25\% < I^2 < 75\%$), or high ($I^2 \geq 75\%$) (Huedo-Medina et al., 2006). For each outcome measure, a weighted mean effect size with its 95% confidence interval was calculated. Moreover, in the context of meta-analysis, moderator analyses were conducted to compare the effect sizes of treatment outcomes and dropout rates of the ADTs and nutraceuticals. A meta-regression was conducted to evaluate the possible association between dropout rates and the treatment outcome in each group. In addition, average age and gender distribution were investigated for their association with the treatment outcome. The critical p-value threshold was established at 0.05.

Results

From the 3 chosen metanalyses related to nutraceuticals, 11 RCTs were included in the current study.4 RCTs on probiotics, 4 on vitamin D, and 3 on N-3 PUFAs. From the chosen metanalysis for ADTs, 47 unique studies (144 RCTs) were included. Some of the RCTs investigated the efficacy of multiple ADTs (Appendix 1). In total 17 ADT drugs were included in the current study. A list of the included RCTs can be found in Appendix 2.

For nutraceutical RCTs, the mean sample size was 39.36 (*SD* = 31.48) and 32.45 (*SD* =12.98) in the intervention and control groups, respectively. Of the 790 participants, 433 were randomly assigned to the intervention groups and 357 to the control group. The average age was 48.11 (*SD* = 15.28) in the intervention group and 47.07 (*SD* = 14.82) in the control group. In the intervention and placebo groups respectively 72 % and 59 % of the participants were female. The treatment duration ranged from 4 to 12 weeks with a median of 8 (IQR= 0).

For ADTs, the mean sample size was 136.44 (*SD* = 72.21) and 131.49 (*SD* = 69.57) in the intervention and control groups, respectively. Of the 38,582 participants, 19,647 were randomly assigned to the intervention groups and 18,935 to the placebo group. The mean age was 43.8 (*SD* = 7.44) in the intervention group and 44.04 (*SD*= 7.98) in the placebo group. In the intervention and placebo groups respectively 56 % and 53 % of the participants were females. The treatment duration ranged from 4 to 12 weeks with a median of 8 (IQR= 2). Descriptive statistics are shown in Table 1.

Table 1

Descriptive Statistics of studies included in the metanalysis on Nutraceuticals

	Mean	SD	Minimum	Maximum
% female intervention group	.72	.20	.32	1.00
% female control group	.59	.26	.15	1.00
Mean Age intervention group	48.11	15.28	36.15	84.90
Mean age control group	47.07	14.82	36	83
Sample size intervention groups	39.36	31.48	20	131
Sample size control group	32.45	12.98	20	65
Treatment duration (weeks)	8.00	2.53	4	12
Descriptive Statistics of studies included in the metanalysis on Antidepressants				
% female intervention group	.56	.20	.01	.78
%female Control group	.53	.20	.01	.78
Mean Age intervention group	43.80	7.44	33.90	79.90
Mean Age Control group	44.04	7.98	33.90	79.30
Sample size intervention group	136.44	72.21	19.00	371.00
Sample size control group	131.49	69.57	10.00	376.00
Treatment duration (weeks)	7.29	1.18	4.00	12.00

In the intervention group, the sample size was significantly larger in ADTs (*M* = 136.44) than in nutraceuticals (*M* = 39.36), (*F* (1,153) = 19.50, $p < .001$). Moreover, in the intervention group, the percentage of female participants was higher in nutraceuticals (*M* = .72) than in ADTs (*M* =.56), (*F* (1, 153) = 6.49 $p < .012$). In the control group, the sample size was significantly larger in ADTs (*M* = 131.49) than in nutraceuticals (*M* = 32.45), (*F* (1,153) = 22.11, $p < .001$)

Treatment Outcome ADTs vs. Nutraceuticals

A random effect meta-analysis on the treatment outcome of nutraceuticals and ADTs was conducted. Effect sizes and characteristics for each individual study included in the meta-analysis are shown in Appendix 1. The results show that nutraceuticals significantly lowered MDD symptoms compared to placebo (SMD = -1.96, 95% CI: -3.40, -.53). There was considerable heterogeneity between the studies (I^2 = 0.99). The Galbraith Plot (Appendix 1) showed that the effect sizes of the RCT conducted by Kazemi et al (2019) functioned as an outlier. Therefore, after conducting a sensitivity analysis and removing that RCT the heterogeneity decreased (I^2 = 0.78). However, since using a random-effects model accounts for the heterogeneity between studies (DerSimonian & Kacker, 2007), this RCT remained included in further analyses. ADTs also significantly lowered the MDD symptoms compared to placebo (SMD = -.35, 95% CI: -.39, -.31). The heterogeneity between the studies was high (I^2 = .73). The Galbraith plots are shown in Appendix 1. The results of a moderator analysis showed that nutraceuticals had a significantly larger effect size on the treatment outcome than the ADTs (SMD = -.98, 95% CI: -1.21 to -.75, $p < .001$, I^2 = .77).

Age, Gender, and Dropout-rates Association with Treatment Outcome

In the intervention groups of both ADTs and nutraceuticals, there was no significant relationship between the dropout rates, mean age, and percentage of female participants and the treatment outcomes (effect sizes). In the nutraceuticals control groups, there was no significant relationship between the dropout rates, mean age, and percentage of female participants and the treatment outcomes (effect sizes). However, in the ADTs control group, higher dropouts were associated with lower treatment outcomes. The results are shown in Table 2 and Appendix 1 (Bubble plots).

Table 2

Regression Coefficients Antidepressants Intervention group

	Estimate	SE	t	P-value	95% CI Lower	95% CI Upper
Dropout rate	.08	.19	.44	.661	-.29	.45
% Female	.08	.10	.76	.450	-.13	.28
Average Age	-.004	.003	-1.17	.243	-.009	.002
Regression Coefficients Antidepressant Control Group						
Dropout rate	-.44	.15	-2.91	.004	-.75	-.14
% Female	.19	.10	1.81	.073	-.02	.39
Average Age	-.002	.003	-.66	.514	-.007	.003
Regression Coefficients Nutraceuticals Intervention Group						
Dropout rate	1.87	7.16	.26	.801	-15.07	18.82
% Female	-1.86	4.93	-.37	.717	-13.54	9.81
Average Age	.04	.07	.58	.575	- .130	.21
Regression Coefficients Nutraceuticals Control Group						
Dropout rate	-8.04	10.45	-.76	.467	-32.76	16.67
% Female	-1.19	4.04	-.29	.777	-10.73	8.35
Average age	.01	.08	.16	.873	-.16	.19

Dropout-Rates ADTs vs. Nutraceuticals

To compare the dropout rates between the ADTs and nutraceuticals in the intervention and control groups, multiple moderator analyses were conducted. Within the nutraceutical group, there were no significant differences between the dropout rates of intervention and control group (SMD = -.10, 95% CI: -.21 to .02, $p = .088$, $I^2 = .76$). Similarly, for ADTs no significant differences were observed between the dropout rates of control and intervention groups (SMD = .01, 95% CI: -.02 to .04, $p = .350$, $I^2 = .92$). The difference between dropout rates of intervention and control groups was significantly higher in nutraceuticals than ADTs (SMD = 1.53, 95% CI:

0.22 to 2.83, *p* = .022, I^{2} = .99). In the intervention groups, no significant differences between the nutraceuticals and ADTs were observed (SMD = -.02, 95% CI: -.10 to .07, *p* = .670, I^2 = .90). In the control groups, nutraceuticals had significantly lower dropout rates than ADTs (SMD = -.13, 95% CI: -.22 to -.04, *p* = .008, I^2 = .93). Table 3

Table 3

Average Dropout Rates in ADTs and Nutraceuticals

	Mean	SD
Nutraceutical intervention group	.20	.16
Nutraceutical control group	.13	.10
ADT intervention group	.26	.12
ADT control group	.28	.15

Discussion

The purpose of the current systematic review and meta-analysis study was to address two main objectives. Firstly, whether there is a difference in dropout rates between nutraceuticals (N-3 PUFAs, Vitamin D, and Probiotics) compared to ADTs in the treatment of MDD. Secondly, whether there is an association between dropout rates and improvement of MDD symptoms. Due to a lack of previous investigation regarding the direct comparison of dropout rates in ADTs and nutraceuticals, no specific hypotheses were made for the first objective and the current study explored and analyzed potential differences. Regarding the second objective, it was hypothesized that higher dropout rates are associated with better treatment outcomes.

The results showed that both nutraceuticals and ADTs significantly decreased MDD symptoms. Moreover, the symptom improvement was higher in nutraceuticals than in ADTs. These results hold important implications in practical contexts for several key reasons. Given that nutraceutical treatments represent a newer approach while ADTs are widely regarded as established strategies for MDD treatment, the finding that nutraceuticals yielded better treatment outcomes introduces a paradigm shift. This shift empowers clinicians and patients with greater flexibility when evaluating different MDD treatment options. Within the context of informed treatment decision-making, healthcare providers might recommend either nutraceuticals or

ADTs, considering patient preferences, and potential side effects (van Zomeren, 2023; Cohen et al., 2021). The findings also suggest the potential for adjunctive use of nutraceuticals alongside ADTs and psychotherapy, a strategy that previous studies have supported (Fusar-Poli et al., 2019; Sarris et al., 2016; Ceskova & Silhan, 2018). Furthermore, these results align with earlier studies that explored the potential of nutraceuticals as an alternative for patients who didn't respond well to traditional ADTs (Ismail et al., 2018; Sarris et al., 2015). This adds to the range of treatment options available for MDD patients. Moreover, the potential of nutraceuticals as an alternative for treatment-resistant patients highlights the need for future studies focused on this specific subgroup. It is important to note that there was a considerable difference in the number of RCTs on nutraceuticals (11) and ADTs (144). Therefore, the interpretation of results should be approached with caution.

In the intervention groups, there was no significant difference in the dropout rate between nutraceuticals and ADTs. This result could be attributed to shared factors within both groups. Notably, the median duration of interventions was equivalent for both ADTs and nutraceuticals. Previous research has highlighted duration as a key influence on dropout rates (Demyttenaere et al., 2001). Moreover, in the intervention group, ADTs and nutraceuticals did not differ in terms of average age. Age-related cognitive factors could also contribute to the parallel treatment adherence observed between ADTs and nutraceuticals in the intervention group (Zivin & Kales, 2008). This information might enhance clinicians' confidence in offering either treatment option, as dropout rates do not appear to be a major factor influencing the choice between these interventions. Consequently, adhering to the principles of Patient-Centered Medical Management (PCMM) becomes more straightforward. Within this principle, emphasizing patient preferences, potential side effects, and individual health contexts is paramount in the decision-making process (Rush & Thase, 2018).

In the control groups, nutraceuticals exhibited lower dropout rates compared to ADTs. Despite all trials being RCTs, the extent of blindness within the trials was not comprehensively examined in all RCTs, possibly impacting participant expectations. Participants who suspect they are receiving a placebo might be more inclined to drop out (Kemmler et al., 2005). Considering that the utilization of nutraceuticals in treating MDD is relatively novel, people tend to be more familiar with the effects and side effects of ADTs compared to nutraceuticals (Nasri et al., 2014). Consequently, participants within the ADTs placebo group might have discerned the lack of anticipated outcomes, leading them to deduce their assignment to the placebo group and subsequently discontinue their involvement in the trial. Conversely, participants engaging with nutraceuticals might have had fewer specific expectations, which could have played a role in their sustained participation throughout the trial.

Certain studies view dropout as an adverse outcome, reflecting intervention ineffectiveness and poor clinical progress (Hunt & Andrews,1992; Samstag et al., 1998). Contrary, other studies propose that participants who drop out might have reached a satisfactory level of improvement, resulting in reduced motivation to continue the trial (Barkham et al., 2006; Reich & Berman, 2020). Therefore, it is crucial to interpret dropouts in relation to treatment outcomes. Few studies have directly assessed the relationship between dropout and outcome, and findings have been inconsistent (Cahill et al., 2003; Silverman & Beech, 1979).

In ADTs and nutraceutical intervention groups and nutraceuticals control group, dropout rates, average age, and percentage of female participants were not associated with the treatment outcomes. However, in the ADTs control group, higher dropouts were associated with lower treatment outcomes. This result conflicts with the hypothesis and the evidence from previous research suggesting a positive relationship between higher dropout rates and symptom improvements (Pekarik,1992; Cipriani et al., 2018). Building upon earlier discussion, it is plausible that participants realized their allocation to the ADT placebo condition due to minimal symptom improvement. This might have influenced them to withdraw from the study. Consequently, a relationship between higher dropout rates and lower treatment outcomes in the ADT control group was observed. This result's research implication highlights the need for assessment of blinding effectiveness in future studies.

While this study provides valuable insight into the efficacy of ADTs and nutraceutical treatments for MDD, it's essential to recognize its limitations. One important limitation of this study is that there were considerable differences between ADTs and nutraceuticals in terms of the number of included RCTs, sample sizes, and gender distribution. Despite the calculation of weighted effect sizes, these variations could still potentially impact the results and the study's empirical power (Alamolhoda et al., 2017. The restriction of inclusion criteria to adult patients diagnosed with MDD, without any other forms of depression or physical/psychological comorbidities, limits the applicability of the results of these specific clinical subgroups. Furthermore, the presence of comorbidities could exert a moderating influence on the effects of supplementation on MDD, possibly restricting the beneficial effects to non-comorbid patients (Schef et al., 2017). The fact that the current study did not analyze subgroups based on their comorbidity status, aligns with previous meta-analyses (Appleton et al., 2015; Bai et al., 2018). Furthermore, excluding unpublished data might affect the possibility of publication bias. There's a risk that studies with negative or non-significant results might not be represented, leading to an overestimation of the effectiveness of interventions (Thornton & Lee, 2000). Diligent attempts were undertaken to access all RCTs used in the metanalysis; however, not all RCTs were available to the public or provided sufficient statistical information for inclusion in the analysis. Consequently, certain RCTs employed in the selected metanalysis were excluded.

All in all, despite the limitation, the findings from this systematic review and meta-analysis present valuable insights into the effectiveness of ADTs and Nutraceuticals. Given the global rise in MDD cases and the ongoing pursuit of new treatment approaches (Ferrari et al., 2013), the study's revelation that nutraceuticals are more effective than ADTs in the treatment of MDD provides an important breakthrough. This enhances the range of treatment options available to healthcare professionals, offering them greater flexibility in tailoring treatments to individual patients. Moreover, the observation that dropout rates were similar between nutraceuticals and ADTs in the intervention group might suggest that nutraceuticals can be integrated into clinical practice with less concern about high attrition. Moreover, this study has prompted a shift in perspective from viewing dropout merely as a signal of treatment ineffectiveness to understanding it also as a potential indication of achieved progress.

It is recommended that future research explore a wider array of nutraceutical types beyond the most extensively studied ones. Additionally, investigating dosages of ADTs and nutraceuticals emerges as an essential consideration for forthcoming studies. According to Wolters et al (2021) The differences in dosages might contribute to the heterogeneity between studies. Collaboration among academia, industry, and study authors is essential to generate further research that delves into the analysis of individual patient data within network meta-analyses. These analyses will make it possible to predict personalized clinical outcomes, which include anticipating side effects, comparing effectiveness at various time points, and accounting for differing baseline severities (Zhou et al., 2020).

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Appendix 1

Number of investigated ADTs per study

	N	%
Alexopou	2	1.0%
Alvarez2	3	1.6%
Asnis201	3	1.6%
Bakish20	2	1.0%
Baldwin2	3	1.6%
Ban1998	1	0.5%
Bosc1997	2	1.0%
Boulenge	3	1.6%
Boyer200	2	1.0%
CL3-2009	6	3.1%
Clayton2	5	2.6%
Cohn1985	1	0.5%
Cohn1996	1	0.5%
Croft201	1	0.5%
Cunningh	4	2.1%
Davidson	1	0.5%
DeMartin	1	0.5%
Dube2010	1	0.5%
Dunbar19	4	2.1%
Dunlop20	1	0.5%
Edwards1	1	0.5%
Fabre199	3	1.6%
Feighner	11	5.8%
Fontaine	2	1.0%
Gastpar2	1	0.5%
Gommoll2	1	0.5%
Griebel2	2	1.0%
Halikas1	2	1.0%
Heiligen	1	0.5%
Henigsbe	2	1.0%
Heun2013	1	0.5%
Higuchi	2	1.0%
Iwata201	1	0.5%
Jacobsen	2	1.0%

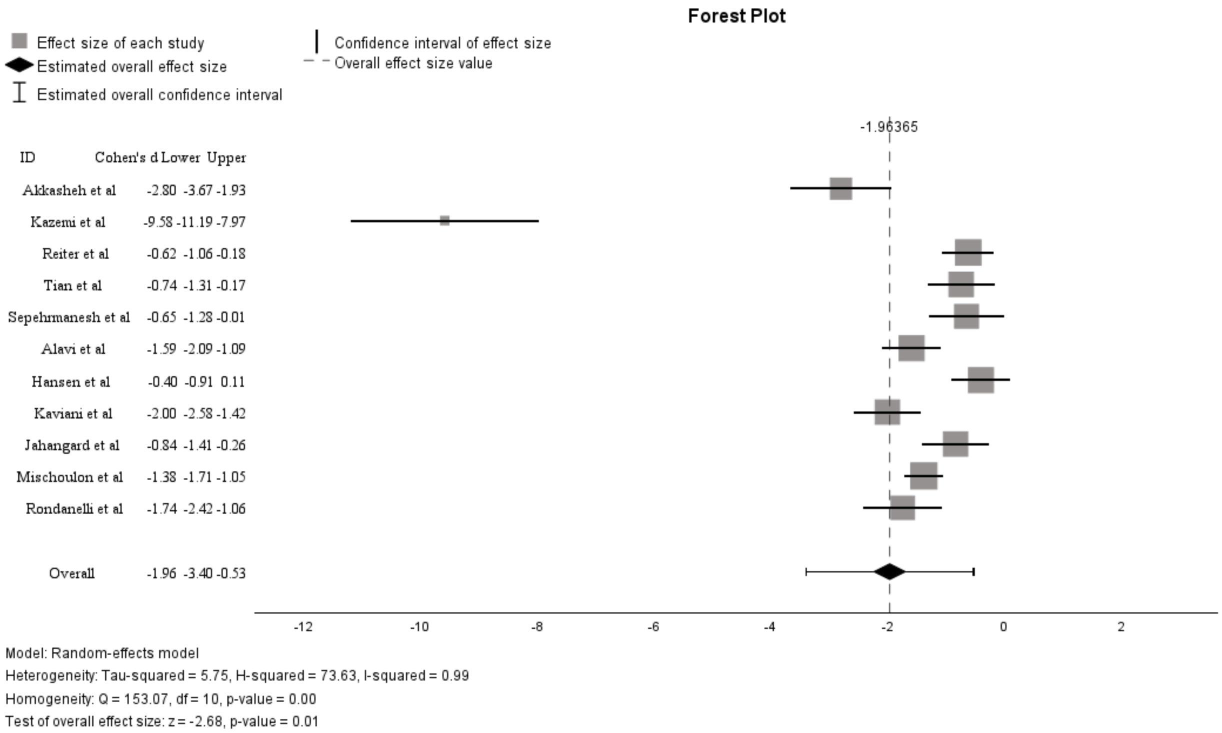
Jain2013	1	0.5%
Kasper20	1	0.5%
Katona20	2	1.0%
Keller20	1	0.5%
Kennedy2	2	1.0%
Learned2	2	1.0%
Lecrubie	1	0.5%
Lieberma	2	1.0%
Liebowit	3	1.6%
Loo2002	2	1.0%
Mahables	9	4.7%
Mao2015	1	0.5%
Mathews2	3	1.6%
McIntyre	2	1.0%
Mendels1	2	1.0%
Mischoul	1	0.5%
Montgome	1	0.5%
Olie1997	1	0.5%
Olie2007	1	0.5%
PAR 01 0	1	0.5%
Raskin20	1	0.5%
Rickels1	1	0.5%
Roose200	1	0.5%
Roth1990	1	0.5%
Rudolph1	3	1.6%
Sambunar	1	0.5%
Schneide	1	0.5%
Schweize	1	0.5%
Sheehan2	3	1.6%
Sramek19	1	0.5%
Stahl201	2	1.0%
Stark198	1	0.5%
Thase199	1	0.5%
Tollefso	1	0.5%
Vartiain	1	0.5%
Versiani	1	0.5%
Wade2002	1	0.5%
Wang 201	1	0.5%

Zajecka2	2	1.0%
Zhang201	1	0.5%

Effect Size Estimates for Individual Studies (Nutraceuticals)

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight
Akkasheh et al	-2.798	.4448	-6.290	<,001	-3.670	-1.926	.168
Kazemi et al	-9.581	.8212	-11.667	<,001	-11.191	-7.972	.156
Reiter et al	-.618	.2261	-2.735	.006	-1.062	-.175	.172
Tian et al	-.739	.2895	-2.552	.011	-1.306	-.172	.171
Sepehrmanesh et al	-.648	.3244	-1.997	.046	-1.284	-.012	.171
Alavi et al	-1.588	.2564	-6.193	<,001	-2.091	-1.085	.172
Hansen et al	-.400	.2577	-1.552	.121	-.905	.105	.172
Kaviani et al	-2.003	.2952	-6.785	<,001	-2.582	-1.424	.171
Jahangard et al	-.836	.2949	-2.833	.005	-1.414	-.258	.171
Mischoulon et al	-1.378	.1669	-8.257	<,001	-1.705	-1.051	.173
Rondanelli et al	-1.739	.3464	-5.020	<,001	-2.418	-1.060	.170

Forest plot Nutraceuticals



Effect Size Estimates for Individual Studies

ID	Effect Size	Std. Error	Z	Sig. (2-tailed)	95% Confidence Interval Lower	95% Confidence Interval Upper	Weight	Weight (%)
Alexopou u	-.236	.1219	-1.938	.053	-.475	.003	17.644	.7
Alexopou u	-.301	.1217	-2.474	.013	-.540	-.063	17.658	.7
Alvarez2	-.572	.1395	-4.098	<,001	-.845	-.298	16.320	.7
Alvarez2	-.580	.1423	-4.075	<,001	-.859	-.301	16.115	.7
Alvarez2	-.551	.1378	-3.995	<,001	-.821	-.280	16.447	.7
Asnis201	-.133	.1055	-1.263	.207	-.340	.074	18.886	.8
Asnis201	-.233	.1058	-2.201	.028	-.440	-.025	18.868	.8
Asnis201	-.262	.1056	-2.485	.013	-.469	-.055	18.883	.8
Bakish20	-.311	.1034	-3.009	.003	-.514	-.108	19.050	.8
Bakish20	-.291	.1034	-2.818	.005	-.494	-.089	19.045	.8
Baldwin 2	-.171	.1136	-1.509	.131	-.394	.051	18.272	.8

Baldwin 2	-.162	.1147	-1.416	.157	-.387	.062	18.192	.8
Baldwin 2	-.243	.1142	-2.127	.033	-.467	-.019	18.230	.8
Ban1998	-.790	.1597	-4.944	<,001	-1.103	-.477	14.853	.6
Bosc199 7	-.569	.1280	-4.447	<,001	-.820	-.318	17.183	.7
Bosc199 7	-.561	.1277	-4.393	<,001	-.811	-.311	17.207	.7
Boulenge	-.576	.1159	-4.971	<,001	-.804	-.349	18.098	.8
Boulenge	-.741	.1176	-6.301	<,001	-.972	-.511	17.969	.8
Boulenge	-1.002	.1216	-8.243	<,001	-1.240	-.764	17.671	.7
Boyer20 0	-.314	.1113	-2.820	.005	-.532	-.096	18.451	.8
Boyer20 0	-.379	.1130	-3.353	<,001	-.600	-.157	18.323	.8
CL3-2009	-.119	.1194	-.995	.320	-.353	.115	17.836	.8
CL3-2009	-.258	.1189	-2.171	.030	-.491	-.025	17.877	.8
CL3-2009	-.063	.1198	-.522	.602	-.297	.172	17.806	.8
CL3-2009	-.211	.1209	-1.746	.081	-.448	.026	17.718	.8
CL3-2009	-.024	.0982	-.246	.806	-.217	.168	19.431	.8
CL3-2009	-.063	.1144	-.551	.582	-.287	.161	18.214	.8
Clayton2	.036	.1155	.307	.759	-.191	.262	18.133	.8
Clayton2	-.237	.1159	-2.043	.041	-.464	-.010	18.103	.8
Clayton2	-.232	.0958	-2.422	.015	-.420	-.044	19.614	.8
Clayton2	-.231	.0811	-2.848	.004	-.390	-.072	20.665	.9
Clayton2	-.290	.0809	-3.582	<,001	-.448	-.131	20.681	.9
Cohn198 5	-1.358	.2097	-6.473	<,001	-1.769	-.947	11.655	.5
Cohn199 6	-.382	.2176	-1.753	.080	-.808	.045	11.215	.5
Croft201	-.468	.0891	-5.250	<,001	-.642	-.293	20.102	.9

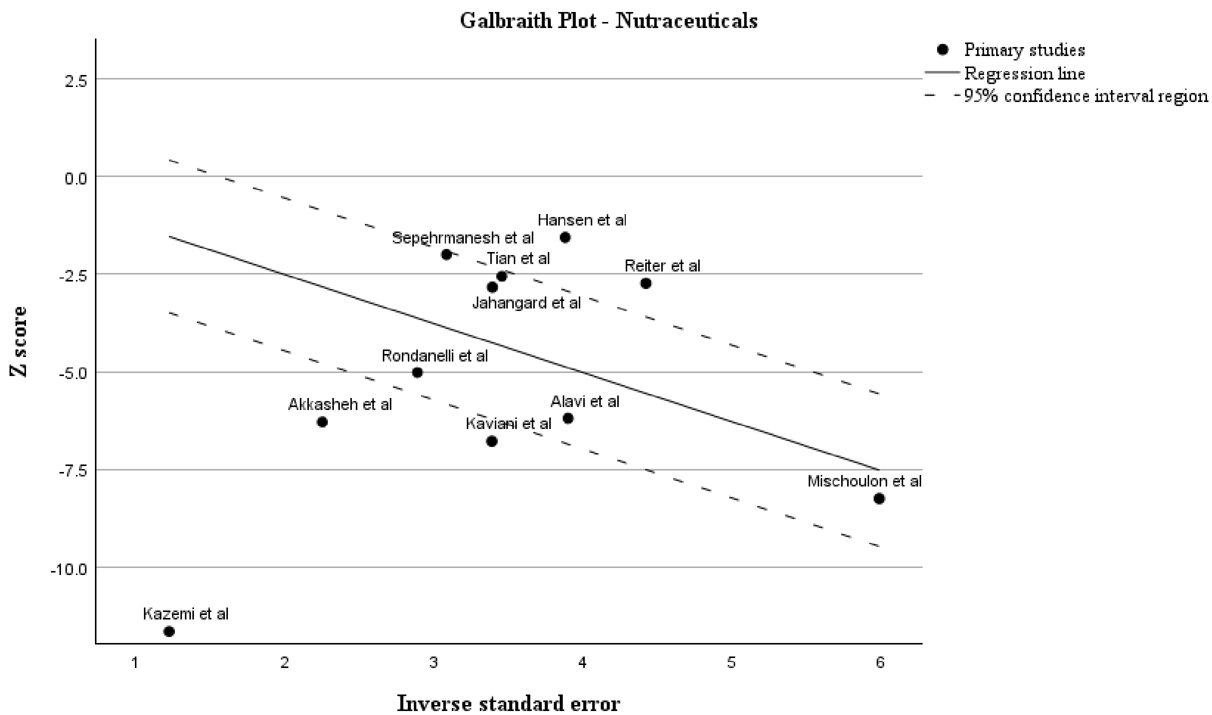
Cunningh	-.493	.1647	-2.996	.003	-.816	-.171	14.508	.6
Cunningh	-.339	.1629	-2.084	.037	-.659	-.020	14.634	.6
Cunningh	-.508	.1448	-3.506	<,001	-.791	-.224	15.930	.7
Cunningh	-.263	.1435	-1.831	.067	-.544	.019	16.024	.7
Davidson	-.181	.1330	-1.357	.175	-.441	.080	16.803	.7
DeMartin	-.403	.1310	-3.081	.002	-.660	-.147	16.960	.7
Dube2010	-.356	.1539	-2.313	.021	-.658	-.054	15.266	.6
Dunbar19	-.574	.1937	-2.962	.003	-.953	-.194	12.605	.5
Dunbar19	-.599	.2409	-2.485	.013	-1.071	-.127	10.014	.4
Dunbar19	-.206	.2285	-.903	.366	-.654	.242	10.633	.5
Dunbar19	-.703	.2290	-3.072	.002	-1.152	-.255	10.609	.4
Dunlop20	-.284	.1019	-2.785	.005	-.483	-.084	19.161	.8
Edwards1	-.444	.3124	-1.421	.155	-1.056	.168	7.174	.3
Fabre199	-.371	.1479	-2.510	.012	-.661	-.081	15.699	.7
Fabre199	-.267	.1485	-1.799	.072	-.558	.024	15.658	.7
Fabre199	-.204	.1486	-1.370	.171	-.495	.088	15.649	.7
Feighner	-1.809	.4572	-3.956	<,001	-2.705	-.912	3.987	.2
Feighner	-.877	.2341	-3.746	<,001	-1.336	-.418	10.350	.4
Feighner	-.538	.2276	-2.363	.018	-.984	-.092	10.681	.5
Feighner	.030	.2196	.135	.893	-.401	.460	11.109	.5
Feighner	-.561	.2280	-2.461	.014	-1.008	-.114	10.663	.5
Feighner	-.603	.2259	-2.671	.008	-1.046	-.161	10.771	.5
Feighner	-.759	.2315	-3.280	.001	-1.213	-.306	10.480	.4
Feighner	-.511	.1856	-2.753	.006	-.875	-.147	13.116	.6
Feighner	-.084	.1243	-.677	.498	-.328	.160	17.461	.7
Feighner	-.391	.1252	-3.119	.002	-.636	-.145	17.394	.7

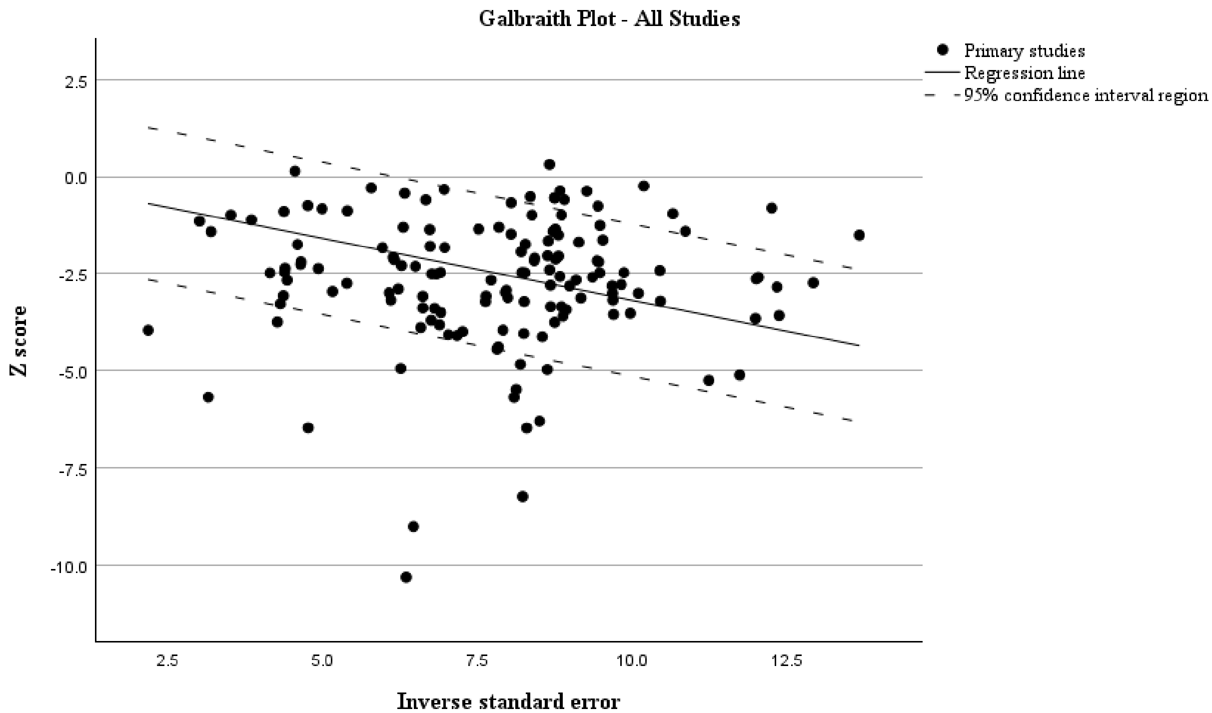
Feighner	-.368	.1256	-2.931	.003	-.614	-.122	17.368	.7
Fontaine	-.157	.2100	-.750	.453	-.569	.254	11.640	.5
Fontaine	-.472	.2149	-2.198	.028	-.894	-.051	11.362	.5
Gastpar2	-.376	.1259	-2.984	.003	-.622	-.129	17.345	.7
Gommoll 2	-.081	.1059	-.763	.445	-.288	.127	18.857	.8
Griebel2	-.208	.1587	-1.310	.190	-.519	.103	14.923	.6
Griebel2	-.466	.1608	-2.899	.004	-.781	-.151	14.781	.6
Halikas1	-.481	.2029	-2.370	.018	-.878	-.083	12.053	.5
Halikas1	-.167	.2003	-.832	.406	-.559	.226	12.202	.5
Heiligen	-.487	.2152	-2.263	.024	-.909	-.065	11.346	.5
Henigsbe	-.491	.1213	-4.046	<,001	-.729	-.253	17.690	.8
Henigsbe	-.591	.1221	-4.838	<,001	-.830	-.351	17.630	.7
Heun201 3	-.358	.1449	-2.474	.013	-.642	-.074	15.921	.7
Higuchi	-.230	.1061	-2.172	.030	-.438	-.022	18.844	.8
Higuchi	-.172	.1050	-1.637	.102	-.378	.034	18.924	.8
Iwata201	-.130	.0922	-1.413	.158	-.311	.050	19.879	.8
Jacobsen	-.233	.1136	-2.054	.040	-.456	-.011	18.275	.8
Jacobsen	-.386	.1152	-3.352	<,001	-.612	-.160	18.152	.8
Jain2013	-.066	.0817	-.812	.417	-.226	.094	20.626	.9
Kasper20	-.549	.1481	-3.703	<,001	-.839	-.258	15.686	.7
Katona2 0	-.483	.1170	-4.127	<,001	-.712	-.254	18.016	.8
Katona2 0	-.781	.1206	-6.478	<,001	-1.018	-.545	17.742	.8
Keller20	-.384	.1120	-3.429	<,001	-.603	-.164	18.400	.8
Kennedy 2	-.675	.1231	-5.483	<,001	-.916	-.434	17.554	.7
Kennedy 2	-.703	.1236	-5.689	<,001	-.946	-.461	17.515	.7
Learned2	-.185	.1244	-1.487	.137	-.429	.059	17.459	.7
Learned2	-.405	.1126	-3.597	<,001	-.626	-.184	18.348	.8
Lecrubie	-.348	.1624	-2.143	.032	-.666	-.030	14.666	.6
Lieberma	-.167	.1275	-1.310	.190	-.417	.083	17.219	.7
Lieberma	-.346	.1296	-2.668	.008	-.600	-.092	17.063	.7
Liebowit	-.277	.1154	-2.403	.016	-.504	-.051	18.136	.8
Liebowit	-.192	.1157	-1.661	.097	-.419	.035	18.113	.8

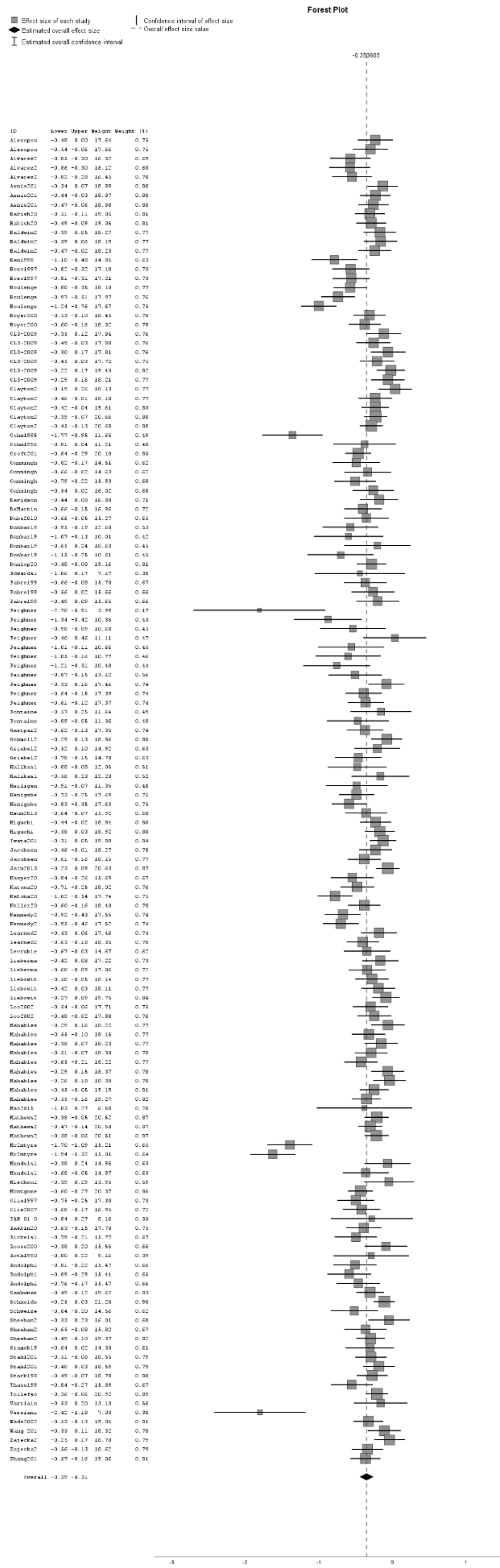
Liebowit	-.090	.0939	-.958	.338	-.274	.094	19.751	.8
Loo2002	-.300	.1211	-2.480	.013	-.538	-.063	17.709	.8
Loo2002	-.250	.1188	-2.101	.036	-.482	-.017	17.883	.8
Mahables	-.063	.1144	-.552	.581	-.287	.161	18.218	.8
Mahables	-.323	.1153	-2.802	.005	-.549	-.097	18.150	.8
Mahables	-.155	.1142	-1.359	.174	-.379	.069	18.227	.8
Mahables	-.292	.1133	-2.575	.010	-.514	-.070	18.298	.8
Mahables	-.430	.1144	-3.755	<,001	-.654	-.205	18.216	.8
Mahables	-.067	.1124	-.598	.550	-.287	.153	18.369	.8
Mahables	-.042	.1133	-.372	.710	-.264	.180	18.300	.8
Mahables	-.251	.1014	-2.477	.013	-.450	-.052	19.195	.8
Mahables	-.354	.1004	-3.527	<,001	-.551	-.157	19.274	.8
Mao2015	-.382	.3319	-1.150	.250	-1.032	.269	6.580	.3
Mathews2	-.216	.0831	-2.596	.009	-.379	-.053	20.523	.9
Mathews2	-.305	.0835	-3.657	<,001	-.469	-.142	20.502	.9
Mathews2	-.220	.0834	-2.637	.008	-.383	-.056	20.508	.9
McIntyre	-1.394	.1547	-9.015	<,001	-1.698	-1.091	15.212	.6
McIntyre	-1.627	.1576	-10.323	<,001	-1.936	-1.318	15.006	.6
Mendels1	-.069	.1582	-.434	.665	-.379	.241	14.964	.6
Mendels1	-.366	.1594	-2.294	.022	-.678	-.053	14.874	.6
Mischoul	-.051	.1729	-.296	.767	-.390	.288	13.947	.6
Montgome	-.436	.0853	-5.114	<,001	-.603	-.269	20.373	.9
Olie1997	-.500	.1264	-3.954	<,001	-.748	-.252	17.301	.7

Olie2007	-.422	.1311	-3.221	.001	-.679	-.165	16.951	.7
PAR 01 0	-.282	.2842	-.994	.320	-.840	.275	8.156	.3
Raskin20	-.390	.1212	-3.220	.001	-.628	-.153	17.698	.8
Rickels1	-.499	.1470	-3.396	<,001	-.787	-.211	15.771	.7
Roose20 0	-.090	.1500	-.602	.547	-.384	.204	15.548	.7
Roth199 0	-.290	.2596	-1.117	.264	-.799	.219	9.159	.4
Rudolph 1	-.512	.1511	-3.385	<,001	-.808	-.215	15.470	.7
Rudolph 1	-.591	.1519	-3.889	<,001	-.888	-.293	15.413	.7
Rudolph 1	-.466	.1511	-3.086	.002	-.763	-.170	15.468	.7
Sambuna r	-.307	.0957	-3.210	.001	-.495	-.120	19.620	.8
Schneide	-.111	.0732	-1.511	.131	-.254	.033	21.198	.9
Schweize	-.521	.1639	-3.181	.001	-.843	-.200	14.562	.6
Sheehan 2	-.048	.1436	-.335	.737	-.330	.233	16.014	.7
Sheehan 2	-.368	.1463	-2.515	.012	-.655	-.081	15.818	.7
Sheehan 2	-.298	.0991	-3.009	.003	-.492	-.104	19.369	.8
Sramek1 9	-.307	.1676	-1.834	.067	-.636	.021	14.302	.6
Stahl201	-.293	.1100	-2.664	.008	-.509	-.077	18.547	.8
Stahl201	-.185	.1095	-1.693	.090	-.400	.029	18.586	.8
Stark198	-.277	.1069	-2.595	.009	-.487	-.068	18.782	.8
Thase19 9	-.555	.1453	-3.819	<,001	-.840	-.270	15.892	.7
Tollefso	-.212	.0774	-2.740	.006	-.364	-.060	20.918	.9
Vartiain	-.164	.1853	-.885	.376	-.527	.199	13.134	.6
Versiani	-1.801	.3168	-5.683	<,001	-2.422	-1.180	7.033	.3
Wade200 2	-.329	.1033	-3.181	.001	-.531	-.126	19.055	.8

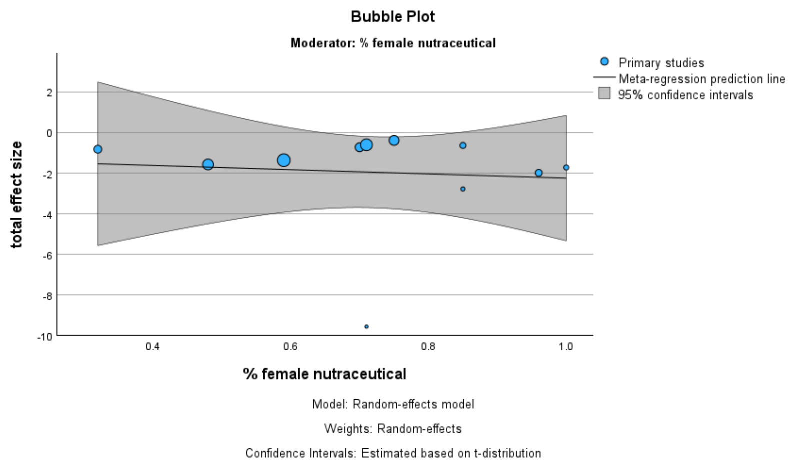
Wang 201	-.112	.1130	-.993	.321	-.334	.109	18.325	.8
Zajecka2	-.041	.1080	-.379	.705	-.253	.171	18.700	.8
Zajecka2	-.341	.1091	-3.128	.002	-.555	-.127	18.617	.8
Zhang20 1	-.367	.1032	-3.554	<,001	-.569	-.165	19.062	.8

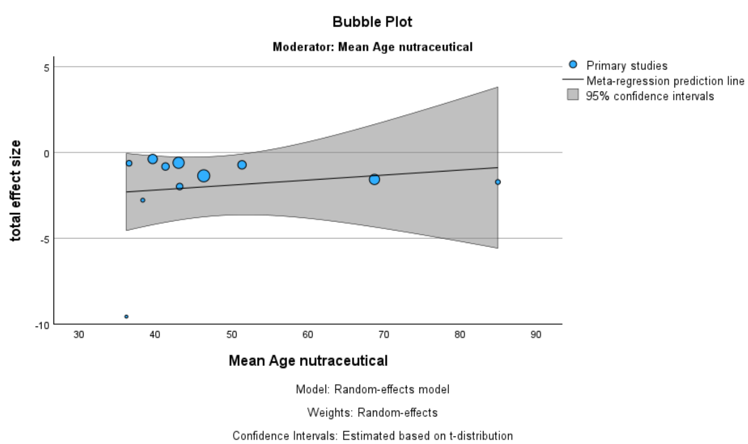


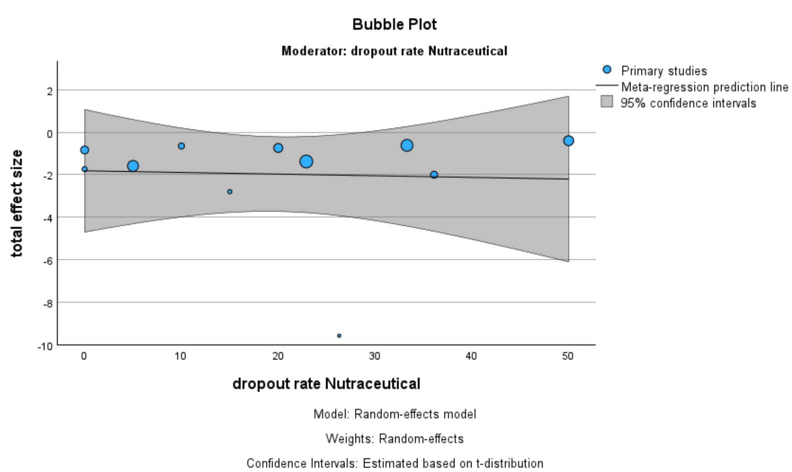

Galbraith Plot - All Studies
Primary studies
Regression line
95% confidence interval region
Z score
2.5
0.0
-2.5
-5.0
-7.5
-10.0
2.5
5.0
7.5
10.0
12.5
Inverse standard error


Forest Plot
Effect size of each study
Estimated overall effect size
Estimated overall confidence interval
Confidence interval of effect size
Overall effect size value
Model: Random-effects model

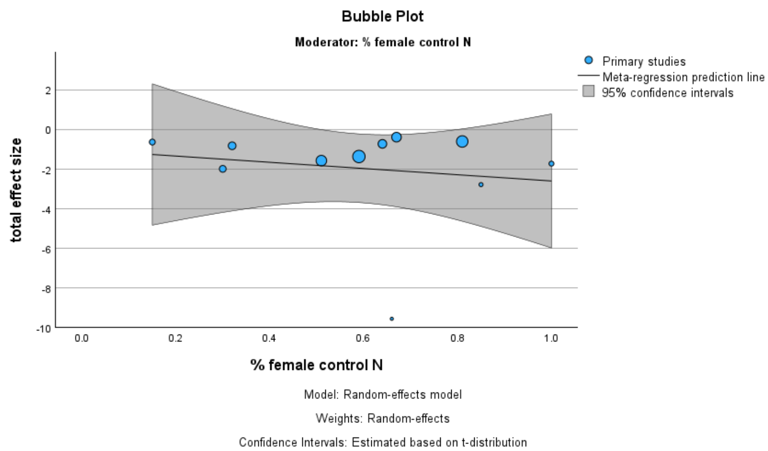
Bubble Plots Nutraceuticals Intervention Group

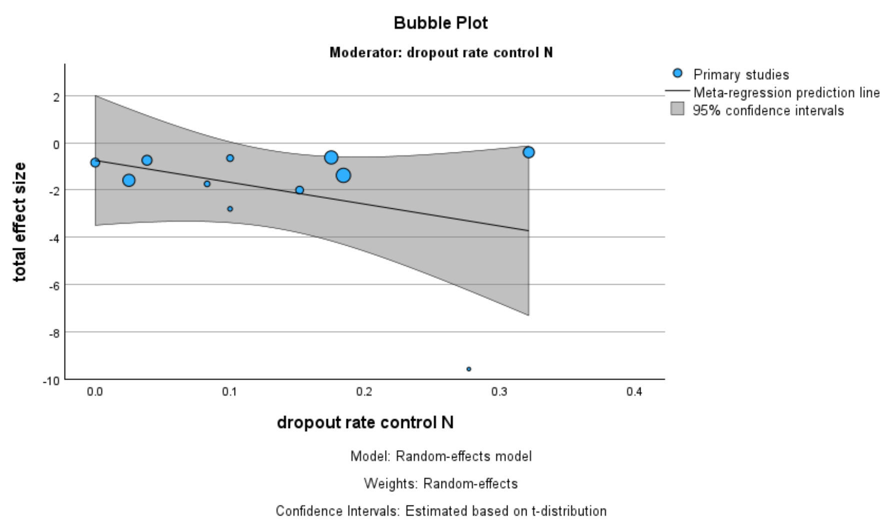


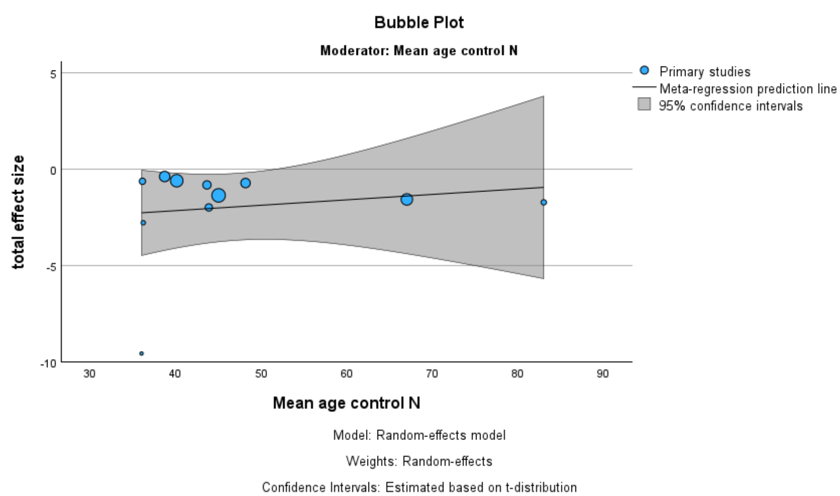




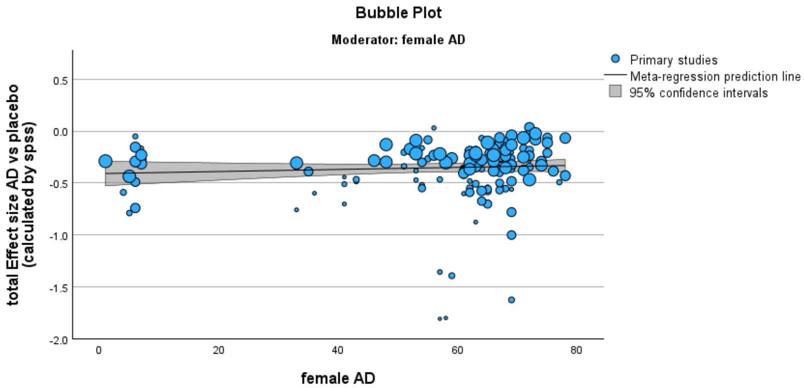
Bubble Plots Nutraceuticals Control Group







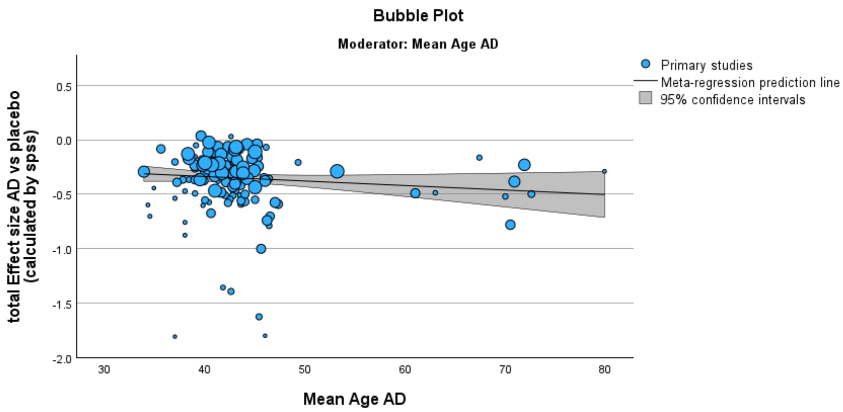
Bubble Plots ADTs Interventions



Model: Random-effects model

Weights: Random-effects

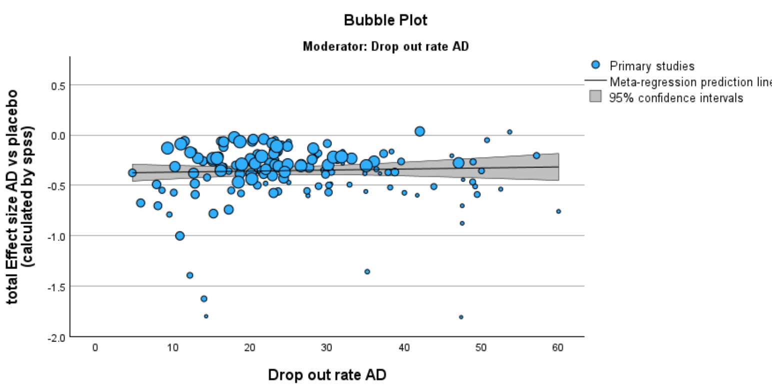
Confidence Intervals: Estimated based on t-distribution



Model: Random-effects model

Weights: Random-effects

Confidence Intervals: Estimated based on t-distribution

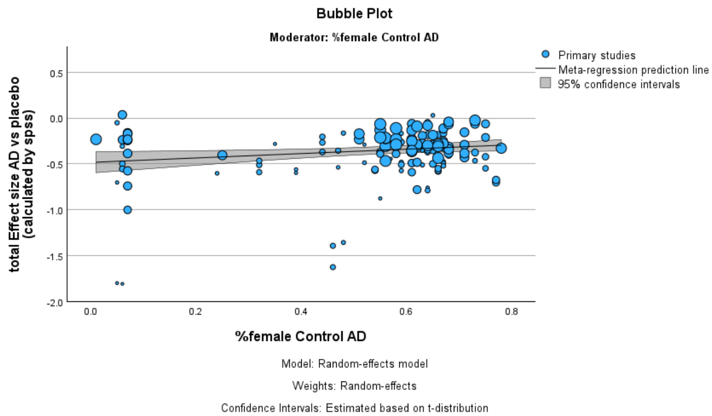


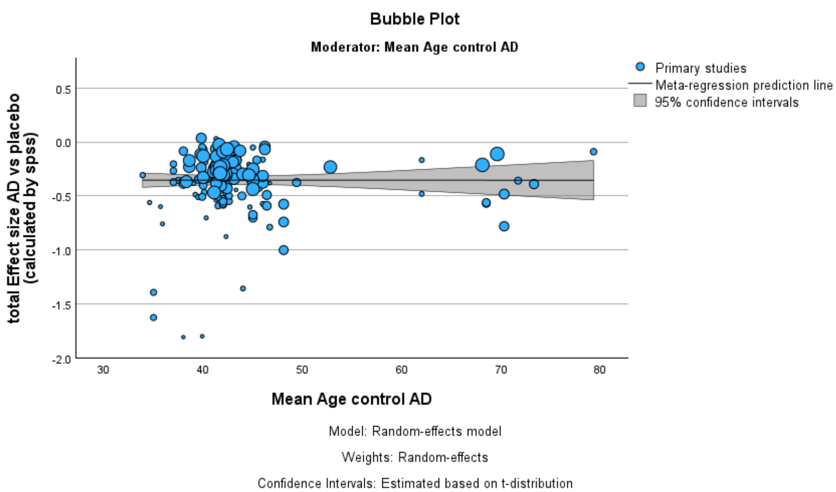
Model: Random-effects model

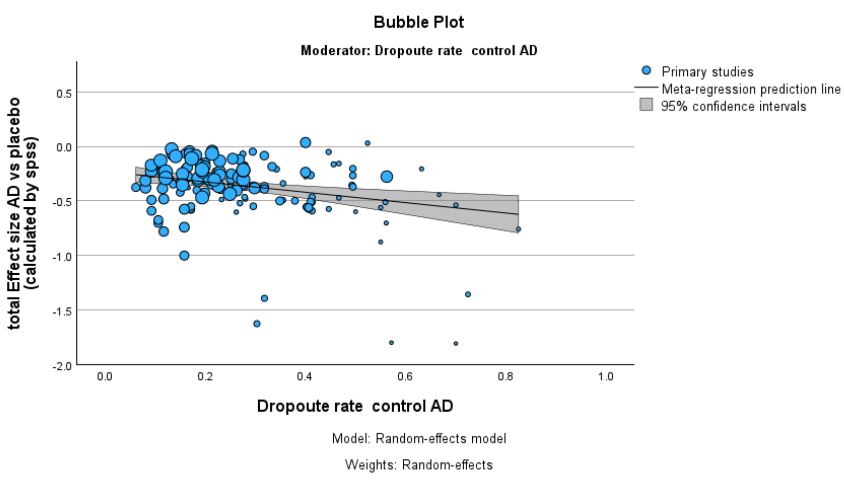
Weights: Random-effects

Confidence Intervals: Estimated based on t-distribution

Bubble Plots ADTs Control Groups







Appendix 2

(References of included RCTs)

Nutraceuticals

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CL3-20098-026. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report /human/000916/WC500038315.pdf 74. CL3-20098-036 □ Unpublished data provided from Servier upon request. 75. CL3-20098-048 https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2005-002388-95

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Appendix 3

(Abbreviations)

ADT	antidepressant treatment
MDD	major depressive disorder
MAOI	monoamine oxidase inhibitor;
TCA	tricyclic antidepressants
SSRIs	selective serotonin reuptake inhibitors
SNRIs	serotonin and norepinephrine reuptake inhibitors
RCT	randomized controlled trial
WFSBP	world federation of societies of biological psychiatry
N-3 PUFAs	N-3 polyunsaturated fatty acids
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
VDRs	vitamin D receptors
BDNF	brain-derived neurotrophic factor
GALT	gut-associated lymphoid tissue
HAM-D	Hamilton Rating Scale for Depression
BDI	Beck Depression Inventory
HADS	Hospital Anxiety and Depression Scale
MADRS	Montgomery–Åsberg Depression Rating Scale