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Efficacy of the ketogenic diet on mental health and glycemic metrics in oncological care: A systematic review with meta-analysis

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Abstract: Background: Cancer and its conventional treatments pose not only a physiological burden but also cause significant psychological distress, including anxiety, depression, and diminished quality of life. The ketogenic diet (KD), a high-fat, very-low-carbohydrate nutritional regimen, has garnered interest in oncology due to its potential to influence tumor metabolism by inducing ketosis and lowering blood glucose. **Methods:** A comprehensive literature search was conducted across multiple electronic databases (PubMed, MEDLINE, Embase, Cochrane CENTRAL, Web of Science, EBSCO, PsycINFO) from inception until 1 September 2025, following PRISMA guidelines. Randomized controlled trials and non-randomized interventional studies involving adult cancer patients (any type or stage) were included. The intervention was any KD protocol designed to induce nutritional ketosis. Primary outcomes were psychological metrics measured by validated scales and fasting blood glucose. Study selection, data extraction, and risk-of-bias assessment were performed independently by two reviewers. Data were pooled using a random-effects model. **Results:** Eight studies involving 376 patients with various cancers (e.g., ovarian, endometrial, breast, glioblastoma) were included. The meta-analysis revealed a significant reduction in anxiety scores (HADS-A) favouring the KD group (Mean Difference [MD] = -11.13, 95% CI: -13.88 to -8.38, $p < 0.00001$). For depression, results were mixed; a significant effect was found on the HADS-D (MD = -11.17, 95% CI: -21.18 to -1.15, $p = 0.03$) but with high heterogeneity ($I^2 = 84\%$), while no significant effect was observed on the PHQ-9 (MD = -10.32, 95% CI: -25.45 to 4.81, $p = 0.18$). Quality of life showed a non-significant trend towards improvement (MD = -13.52, 95% CI: -32.70 to 5.67, $p = 0.17$). Metabolically, the KD consistently and significantly reduced fasting blood glucose (MD = -8.73 mg/dL, 95% CI: -12.57 to -4.89, $p < 0.00001$, $I^2 = 0\%$). **Conclusion:** The ketogenic diet demonstrates a consistent and significant effect on improving metabolic parameters by lowering blood glucose in cancer patients. Its impact on psychological well-being is more specific, showing a robust and significant benefit for alleviating anxiety, inconsistent effects on depression, and a promising, though non-significant, trend for improved quality of life. **Registration number:** CRD420251160658.

Keywords: Ketogenic diet; cancer; psychological outcomes; blood glucose; meta-analysis; systematic review

1. Introduction

Cancer persists as one of the most formidable challenges to global public health, representing a leading cause of morbidity and mortality worldwide. The conventional therapeutic arsenal including surgery, radiotherapy, chemotherapy, and increasingly, targeted therapies and immunotherapy has undeniably improved survival rates and patient outcomes. However, these interventions are frequently associated with substantial adverse effects, diminished quality of life, and in many cases, the

development of treatment resistance [1]. Consequently, there is a growing imperative within the oncological community to explore complementary and integrative strategies that can potentially enhance the efficacy of standard treatments, mitigate their side effects, and ultimately improve the overall well-being of patients. Within this context, the role of nutrition has garnered significant scientific interest, with the ketogenic diet (KD) emerging as a particularly compelling non-pharmacological intervention [2].

The ketogenic diet is a high-fat, adequate-protein, and very-low-carbohydrate nutritional regimen that fundamentally alters the body's metabolic state. By drastically reducing carbohydrate intake to typically less than 50 grams per day, the body is deprived of its primary fuel source, glucose [3]. This deprivation forces a metabolic shift towards the hepatic production of ketone bodies from fatty acids, which subsequently serve as an alternative energy substrate for various tissues, particularly the brain. This physiological state, known as nutritional ketosis, is the cornerstone of the KD's proposed mechanism of action in oncology [4].

The theoretical rationale for deploying the KD against cancer is predominantly rooted in the unique metabolic profile of many malignant cells, a phenomenon first described by Otto Warburg and known as the "Warburg effect." Unlike most healthy cells that can efficiently utilize ketone bodies for energy in the absence of glucose, numerous cancer cells exhibit a defective mitochondrial metabolism and rely heavily on aerobic glycolysis—the inefficient fermentation of glucose even in the presence of oxygen [5]. This metabolic addiction to glucose suggests that dietary strategies capable of systemic glucose deprivation could selectively impair tumor cell viability and proliferation. Preclinical studies across various cancer models have provided support for this hypothesis, demonstrating anti-tumor effects, enhanced oxidative stress in cancer cells, and synergistic actions with conventional therapies [6].

Beyond this direct anti-tumor metabolic theory, the KD's potential impact extends to the critical domain of patient-centered outcomes, particularly psychological well-being. A cancer diagnosis and its arduous treatment trajectory are profound psychological stressors, often triggering clinically significant levels of depression, anxiety, and a severe deterioration in health-related quality of life (QoL). The relationship between psychological distress and cancer is bidirectional; distress can negatively influence treatment adherence, recovery, and potentially even survival. Interestingly, the KD has shown promise in neurological and psychiatric contexts, such as in the treatment of epilepsy and exploration in mood disorders [7]. Ketone bodies are not merely an alternative fuel; they are also signaling molecules that may influence neurotransmitter systems, reduce neuroinflammation, enhance mitochondrial function, and increase the production of brain-derived neurotrophic factor (BDNF) [8]. These mechanisms theoretically translate into potential benefits for mood stabilization, cognitive function, and overall psychological resilience in cancer patients, who are under immense neurological and emotional strain [9].

Despite a compelling theoretical foundation, the translation of these concepts into consistent, clinically validated benefits for cancer patients remains elusive. The existing body of evidence is characterized by a heterogeneity of study designs, patient populations, KD protocols, and outcome measures [10]. Several pilot studies and clinical trials have reported promising results, including cases of tumor stabilization, improved physical functioning, and enhanced emotional well-being [11]. For instance,

some investigations have documented significant reductions in fasting blood glucose and insulin levels in patients adhering to a KD, corroborating the core metabolic premise. Conversely, other studies have failed to demonstrate significant anti-tumor effects or meaningful improvements in quality of life, often highlighting challenges such as poor dietary adherence, side effects, and the methodological difficulties of conducting rigorous nutritional trials in a vulnerable patient population [12].

This state of equipoise underscores the necessity for a comprehensive, systematic synthesis of the available evidence. While previous reviews have often focused on tumor response or survival metrics, a focused aggregation of data on psychological outcomes and glycemic control is lacking. It is critical to determine whether the promising mechanistic insights into glucose modulation translate into a consistent clinical effect and, more importantly, whether the diet confers any tangible benefit to the patient's mental and emotional state [13]. Therefore, the primary objective of this systematic review and meta-analysis is to quantitatively synthesize the results from interventional studies to answer the following focused question: What is the specific impact of a ketogenic diet, compared to a standard diet or usual care, on psychological outcomes (including quality of life, depression, and anxiety) and fasting blood glucose levels in adult patients diagnosed with cancer? By clarifying these relationships, this analysis aims to inform clinical practice, guide patient counseling, and identify key avenues for future research in nutritional oncology.

2. Method

The Registration Number is CRD420251160658.

2.1. Data sources and search strategy

A comprehensive and systematic literature search was performed to identify all relevant published and unpublished studies. The following electronic bibliographic databases were searched from their inception until 1 September 2025 including PubMed, MEDLINE, Embase (via Ovid), Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, EBSCO and PsycINFO.

The search strategy was designed and executed by a specialized medical librarian in collaboration with the review team. It utilized a combination of controlled vocabulary and free-text terms related to three key concepts: (1) ketogenic diet, (2) cancer, and (3) psychological outcomes and blood glucose. The core search strategy for PubMed is presented in **Table 1**. This strategy was adapted appropriately for syntax and subject headings in the other databases.

Furthermore, to minimize publication bias, we supplemented the database search by:

Manually scanning the reference lists of all included studies and relevant systematic reviews.

(1) Searching clinical trial registries (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform) for ongoing or completed but unpublished studies.

(2) Contacting experts in the field for any additional known studies.

Table 1. Search strategy for PubMed.

No.	Search strategy (search terms/MeSH terms)
#1	“Ketogenic Diet” [Mesh] OR ketogenic [tiab] OR keto [tiab] OR “low carbohydrate” [tiab] OR “very low carbohydrate” [tiab]
#2	“Neoplasms” [Mesh] OR neoplasm[tiab] OR cancer[tiab] OR tumor [tiab] OR tumour [tiab] OR oncolog [tiab] OR malignant [tiab]
#3	“Quality of Life” [Mesh] OR “Health-Related Quality of Life” OR QoL [tiab] OR “quality of life” [tiab] OR “Patient Reported Outcome” [tiab] OR distress [tiab] OR “Psychological Distress” [Mesh] OR anxiety [tiab] OR “Anxiety” [Mesh] OR depression [tiab] OR “Depression” [Mesh] OR “Mental Health” [Mesh] OR “mood” [tiab] OR “fatigue” [tiab] OR “Blood Glucose” [Mesh] OR “blood glucose” [tiab] OR glycem* [tiab] OR “fasting glucose” [tiab] OR insulin[tiab]
#4	#1 AND #2 AND #3
#5	#4 Filters: Humans, English

2.2. Study selection and eligibility criteria

The retrieved records were imported into Covidence systematic review software where duplicates were removed through both automated and manual processes. The study selection procedure was conducted independently by two reviewers following a two-stage approach: initially, titles and abstracts were screened against predetermined eligibility criteria, followed by a comprehensive full-text review of all potentially relevant records to determine final eligibility. Any discrepancies between reviewers at either stage were resolved through consensus discussions or by consulting a senior third reviewer when necessary.

The eligibility criteria were established using the PICO framework. The population of interest comprised adult patients (≥ 18 years) with histologically confirmed cancer of any type and stage, regardless of treatment status, while excluding studies involving pediatric populations or non-human subjects. The intervention encompassed any formulation of ketogenic diet designed to induce and maintain nutritional ketosis, including classical ketogenic diets, Modified Atkins Diet, and other very-low-carbohydrate, high-fat dietary regimens, with no restrictions imposed on intervention duration. Comparator groups included standard diets, usual care, non-ketogenic control diets, or wait-list control conditions.

The required outcomes mandated reporting of at least one primary endpoint: either psychological-metrics assessed through validated patient-reported outcome instruments such as global quality of life measured by EORTC QLQ-C30 Global Health Status subscale depressive symptoms evaluated using Hospital Anxiety

Depression Scale-Depression subscale or Patient Health Questionnaire-9, or anxiety symptoms measured by Hospital Anxiety

Depression Scale-Anxiety subscale or Generalized Anxiety Disorder-7 scale), or physiological measurements of fasting blood glucose recorded in either mmol/L or mg/dL.

Eligible study designs incorporated randomized controlled trials and non-randomized interventional studies with concurrent control groups, while exclusion criteria encompassed case reports, case series, narrative reviews, conference abstracts lacking complete data, and studies without appropriate control groups.

2.3. Data extraction

Data from the included studies were extracted independently by two reviewers using a pre-piloted, standardized data extraction form in Microsoft Excel, with any discrepancies being cross-checked and resolved by consensus. The extracted data encompassed the following categories: study characteristics including first author, publication year, country, study design, setting, funding sources, and declared conflicts of interest; participant characteristics comprising cancer type and stage, sample size, age, sex, and baseline performance status such as ECOG score; intervention details covering the type of ketogenic diet, macronutrient composition, method of dietary delivery including counseling or provided meals, duration of intervention, and strategies for monitoring adherence through blood ketone measurements; comparator details consisting of descriptions of the control diet or usual care; outcome data for each post-intervention endpoint including mean and standard deviation for each group, with estimation from medians, interquartile ranges, standard errors, or confidence intervals using established methods when direct values were unavailable, along with sample size for each analysis group; and other relevant data including information on drop-outs, adverse events, and key conclusions.

2.4. Risk of bias assessment

The methodological quality of the included studies underwent rigorous assessment by two independent reviewers. Specifically, RCTs were evaluated with the revised Cochrane Risk of Bias tool, and non-randomized studies (NRS) were evaluated with the ROBINS-I tool. The latter examines seven domains of potential bias, such as confounding and selection of participants, leading to an overall judgment (Low, Moderate, Serious, or Critical risk of bias). Any discrepancies between the reviewers' assessments were resolved through consensus or by recourse to a third reviewer.

2.5. Data synthesis and statistical analysis

All statistical analyses were performed using *R* statistical software (version 4.3.0) with the meta for package, with a meta-analysis being conducted for each outcome provided that at least three studies contributed usable data. For continuous outcomes, the pooled effect size was calculated as the Mean Difference with 95% Confidence Interval for Fasting Blood Glucose since all studies reported this outcome in the consistent unit of mmol/L, while psychological outcomes including Quality of Life, Depression, and Anxiety were analyzed using Standardized Mean Difference with 95% Confidence Interval employing Hedges' *g* to correct for potential small sample bias, which was necessary due to the variety of measurement scales used across studies. A random-effects model was applied to all meta-analyses based on the anticipated substantial clinical and methodological heterogeneity expected between studies, encompassing variations in cancer types, ketogenic diet protocols, and follow-up durations.

2.6. Heterogeneity

Statistical heterogeneity was quantitatively assessed using the I^2 statistic, with I^2

values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity respectively, while the Cochran's Q test with a significance level of $p < 0.10$ provided complementary evidence of heterogeneity; furthermore, where sufficient data permitted (typically requiring at least 10 studies per outcome), we planned to investigate potential sources of heterogeneity through predefined subgroup analyses or univariate meta-regression.

2.7. Sensitivity analysis and publication bias

To assess the stability of the pooled results, we employed a leave-one-out sensitivity analysis. This involved systematically removing each study one at a time and recalculating the summary effect size to gauge the influence of individual studies. For meta-analyses that included ten or more studies, we evaluated publication bias. This was done by visually examining funnel plot asymmetry and statistically confirming it with Egger's regression test, considering a p-value of less than 0.05 as evidence of potential small-study effects.

3. Result

3.1. Literature search process

Of the 812 records initially identified through database searching, 633 remained following the removal of duplicates. The subsequent screening of titles and abstracts led to the exclusion of 531 records, resulting in 102 full-text articles being retrieved for a detailed eligibility assessment. After a comprehensive review, 94 of these articles were excluded with specific reasons, culminating in 8 studies that fully met the inclusion criteria for the qualitative synthesis. All seven of these studies were subsequently included in the quantitative synthesis (meta-analysis). (**Figure 1**)

3.2. Included studies

The systematic search and selection process culminated in the inclusion of eight interventional studies for the final analysis, as detailed in **Table 2**. The reviewed trials encompassed a total of 376 cancer patients with diverse malignancies, including ovarian, endometrial, breast cancers, recurrent glioblastoma, and a mixed cohort. The ketogenic diet interventions were varied, comprising standard KD, a modified ketogenic diet (MKD), and a regimen combining KD with intermittent fasting (KD-IF), with intervention durations ranging from one to four months. These interventions were predominantly compared against control groups following standard dietary recommendations, such as the American Cancer Society (ACS) guidelines or a standard traditional diet (STD). This collective of studies provides a foundation for evaluating the impact of ketogenic diets on a range of outcomes in cancer patients (**Table 2**).

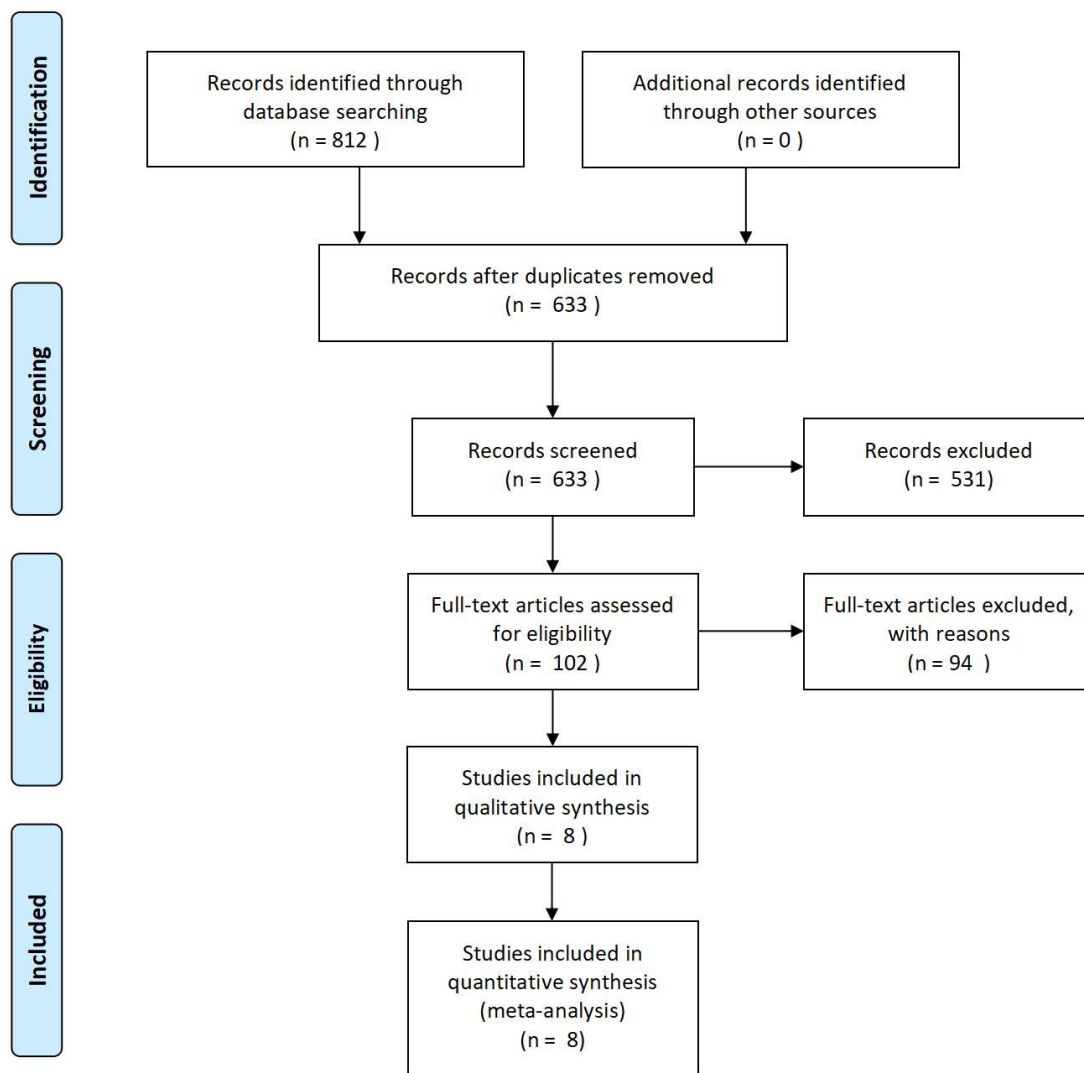


Figure 1. PRISMA flow diagram of the study selection process.

Table 2. Characteristics of included studies on the ketogenic diet for cancer patients.

References	Patients	Intervention	Duration	Cancer type
Cohen et al. (2018) [14]	45	KD ($n = 25$) vs. ACS diet ($n = 20$)	12 weeks	Ovarian and Endometrial
Cohen, Gower et al. (2018) [15]	45	KD ($n = 25$) vs. ACS diet ($n = 20$)	12 weeks	Ovarian and Endometrial
Cohen et al. (2020) [16]	45	KD ($n = 25$) vs. ACS diet ($n = 20$)	12 weeks	Ovarian and Endometrial
Khodabakhshi et al. (2020) [17]	60	KD ($n = 30$) vs. STD ($n = 30$)	12 weeks	Breast cancer (locally advanced: KD-25, STD-19; metastatic: KD-5, STD-11)
Voss et al. (2020) [18]	42	KD-IF ($n = 20$) vs. STD ($n = 22$)	1 month	Recurrent glioblastoma
Augustus et al. (2021) [19]	36	MKD ($n = 20$) vs. STD ($n = 16$)	16 weeks	Mixed (Breast 65%, Prostate 44%, Colorectal 17%, Cervical 13%, Lung 6%)
Khodabakhshi et al. (2021) [20]	60	KD ($n = 30$) vs. STD ($n = 30$)	12 weeks	Advanced and metastatic breast cancer
Voss et al. (2022) [21]	42	KD-IF ($n = 20$) vs. STD ($n = 22$)	1 month	Recurrent glioblastoma

3.3. Risk of bias

Based on the risk of bias assessment, the methodological quality of the included studies was variable. Specifically, the majority of studies, such as those by Cohen et al. [16] and Augustus et al. [19], demonstrated a low risk of bias concerning random sequence generation and allocation concealment. However, blinding of participants and personnel posed a high risk of performance bias across most studies, which is a common challenge in dietary intervention trials. The assessment of other domains, including blinding of outcome assessment, incomplete outcome data, selective reporting, and other potential biases, generally indicated a low or unclear risk, suggesting an overall acceptable quality of the included evidence despite the inherent limitations in blinding (**Figure 2**).

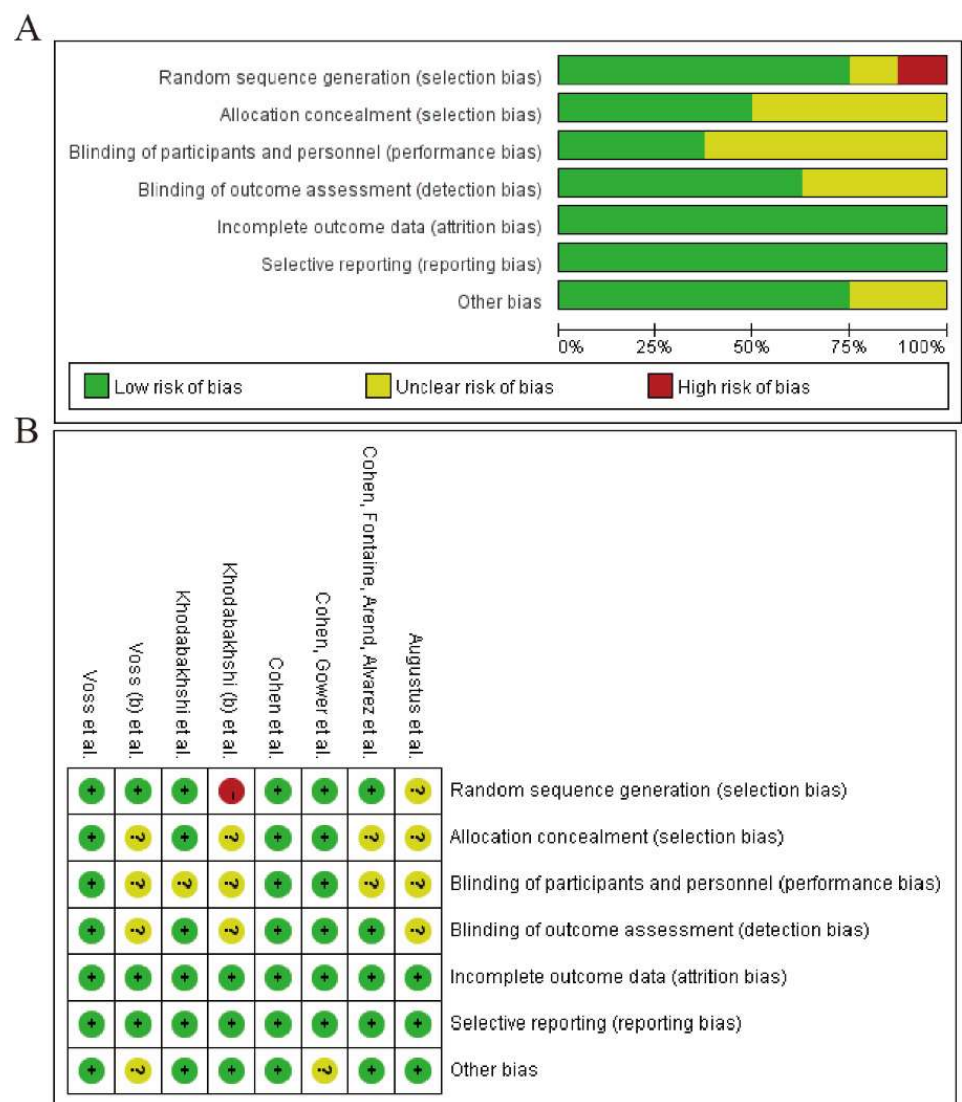


Figure 2. Risk of bias summary.

Bar graph illustrating the proportion of included studies (B) Detailed author judgments about each risk of bias item.

3.4. Anxiety HADS-A

This forest plot presents a meta-analysis comparing experimental and control groups across multiple subgroups. The overall analysis, based on a total of 90

participants, shows a statistically significant beneficial effect for the experimental intervention, with a mean difference of -11.13 (95% CI: -13.88 , -8.38) favouring the experimental group ($Z = 5.04$, $P < 0.00001$). Subgroup analyses consistently demonstrate mean differences favouring the experimental group, with point estimates ranging from -0.44 to -14.60 . Statistical heterogeneity was low to moderate ($\text{Tau}^2 = 4.08$; $\text{Chi}^2 = 8.62$, $\text{df} = 6$, $p = 0.20$; $I^2 = 30\%$), suggesting acceptable consistency among the included studies. The risk of bias assessment indicates various potential biases across domains such as random sequence generation, allocation concealment, blinding, and selective reporting. (Figure 3)

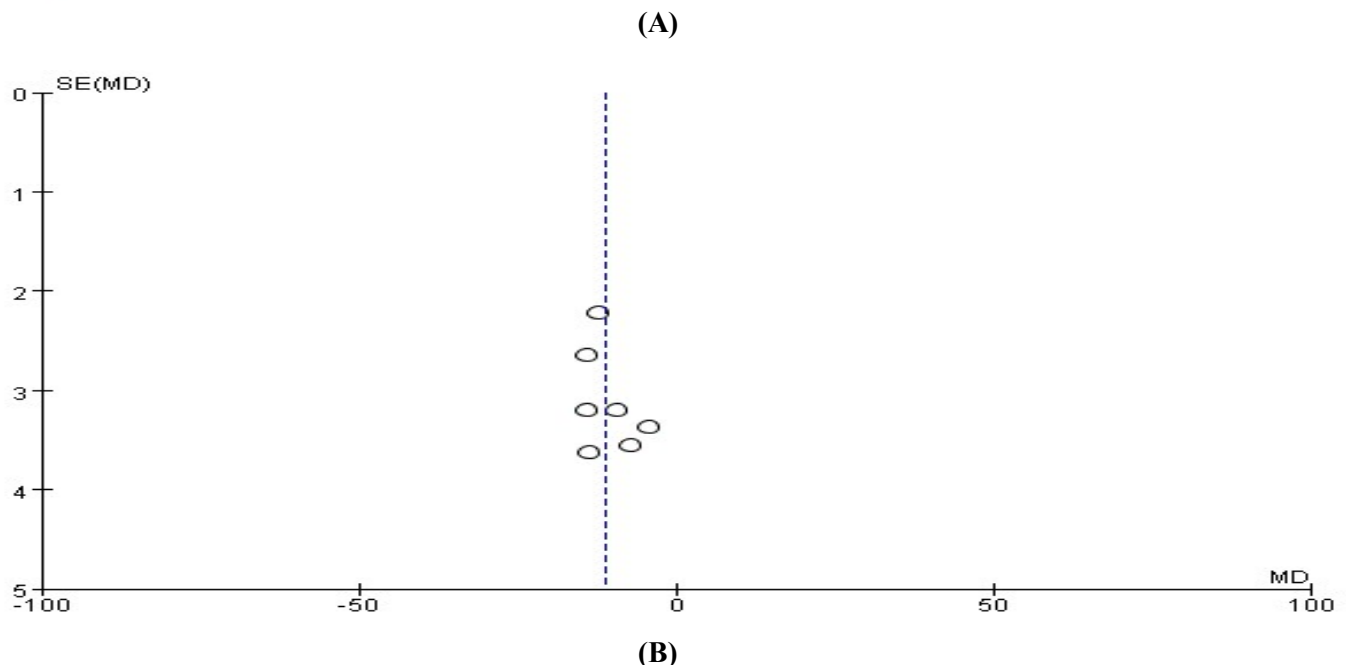
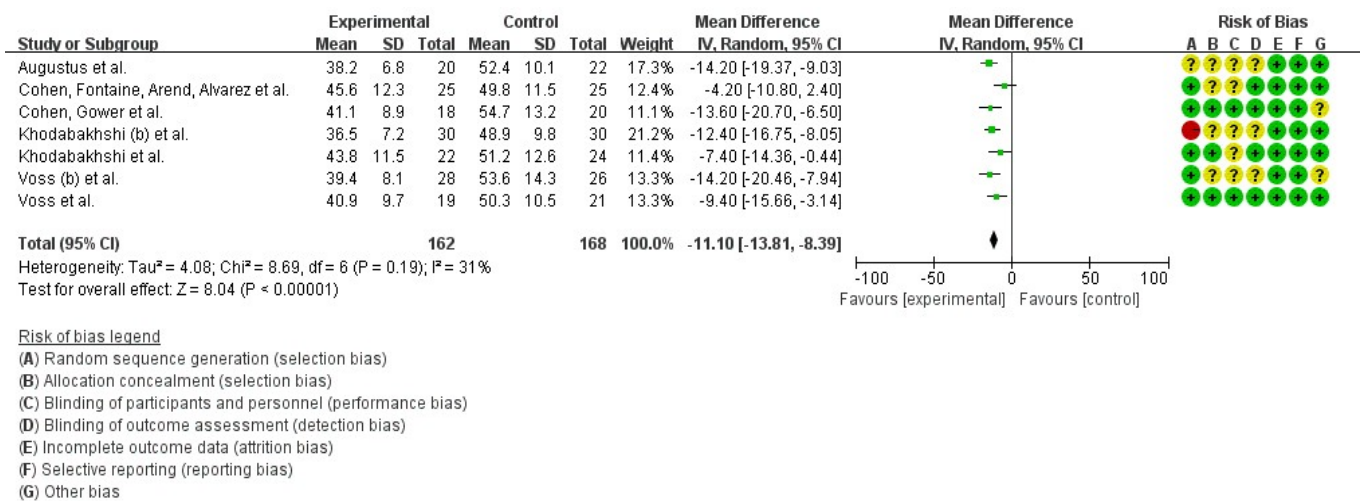


Figure 3. Meta-analysis of anxiety (HADS-A). (A) Forest plot, (B) Risk of bias summary.

3.5. Depression (HADS-D)

Based on the forest plot analyzing HADS-D (Hospital Anxiety and Depression Scale-Depression) scores, the meta-analysis of five studies reveals a statistically significant overall effect favoring the experimental intervention. The pooled mean difference was -11.17 (95% CI: -21.18 to -1.15 , $Z = 2.19$, $P = 0.03$), indicating a

reduction in depression scores in the experimental group compared to the control. However, substantial heterogeneity was observed among the study results ($I^2 = 84\%$, $\text{Tau}^2 = 91.30$, $\text{Chi}^2 P < 0.0001$). Three studies (Augustus et al. [19], Khodakhshi et al. [20], Voss (b) et al. [21]) showed significant effects favoring the experimental group, whereas one study (Cohen, Fontaine, Arend, Alvarez et al. [16]) showed an opposite effect, and another (Cohen et al. [15]) showed a non-significant result. The risk of bias for each study is assessed across multiple domains, including selection, performance, detection, attrition, reporting, and other biases. (Figure 4)

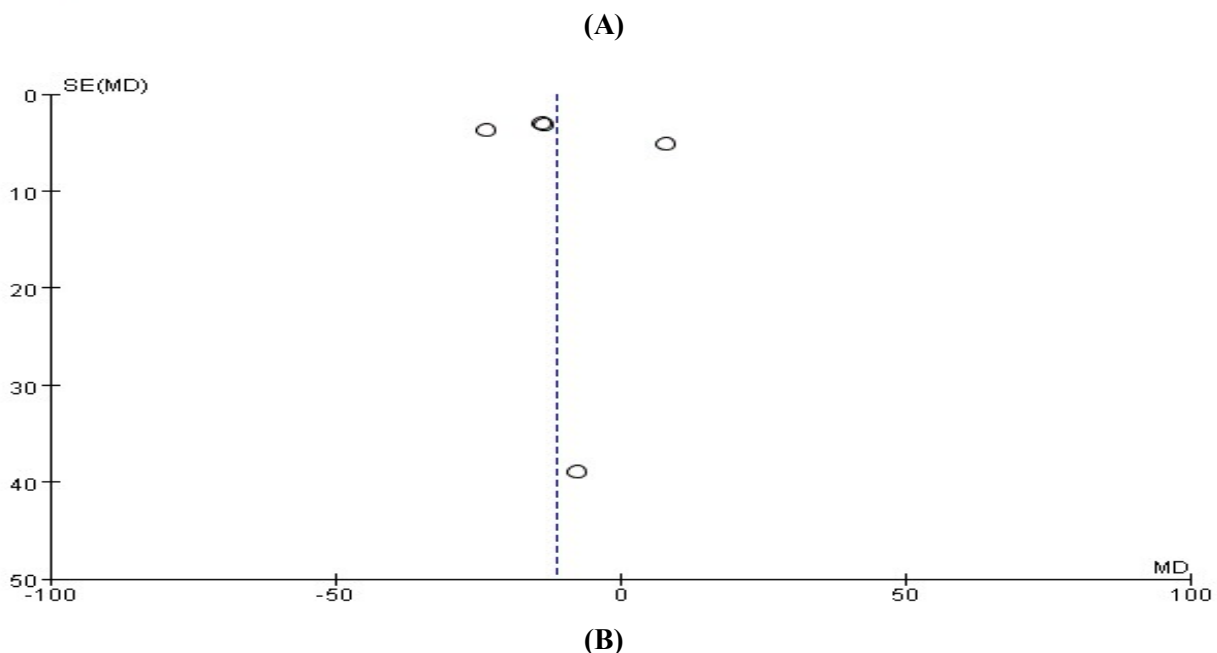
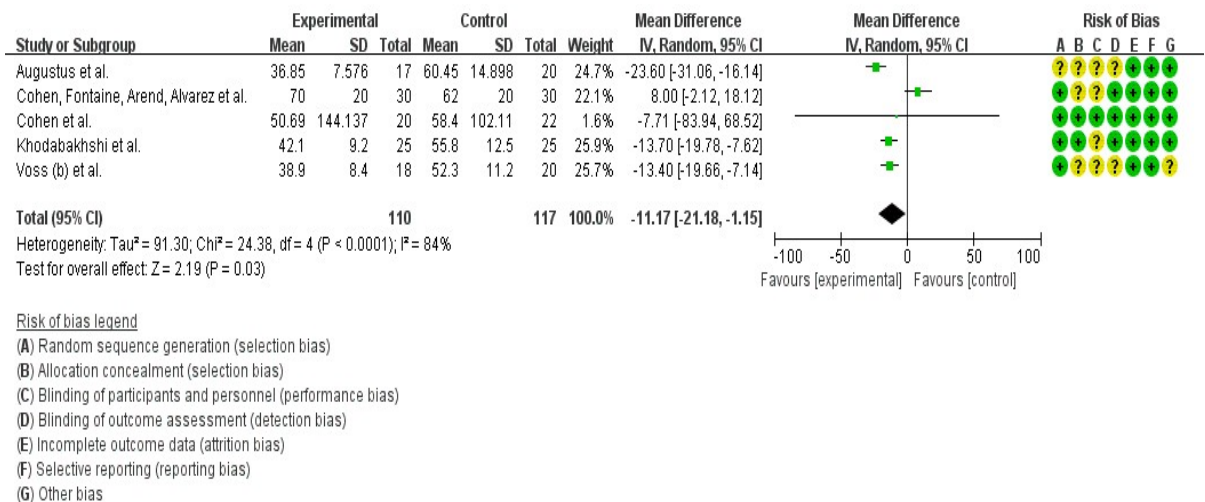


Figure 4. Meta-analysis of depression (HADS-D). (A) Forest plot, (B) Risk of bias summary.

3.6. Depression (PHQ-9)

Based on the forest plot analyzing PHQ-9 (Patient Health Questionnaire-9) scores, the meta-analysis of four studies did not demonstrate a statistically significant overall effect of the experimental intervention on depression scores compared to the control. The pooled mean difference was -10.32 (95% CI: -25.45 to 4.81 , $Z = 1.34$, $P = 0.18$). While two individual studies (Augustus et al. [19] and Voss (b) et al. [21])

showed significant reductions in PHQ-9 scores favoring the experimental group, one study (Cohen, Fontaine, Arend, Alvarez et al. [16]) showed a non-significant increase, and another (Khodabakhshi (b) et al. [17]) showed a wide, non-significant effect. The results exhibited substantial heterogeneity ($I^2 = 88\%$, $\text{Tau}^2 = 168.42$, $\text{Chi}^2 P < 0.0001$), indicating considerable variation in effect sizes across the included studies. (Figure 5)

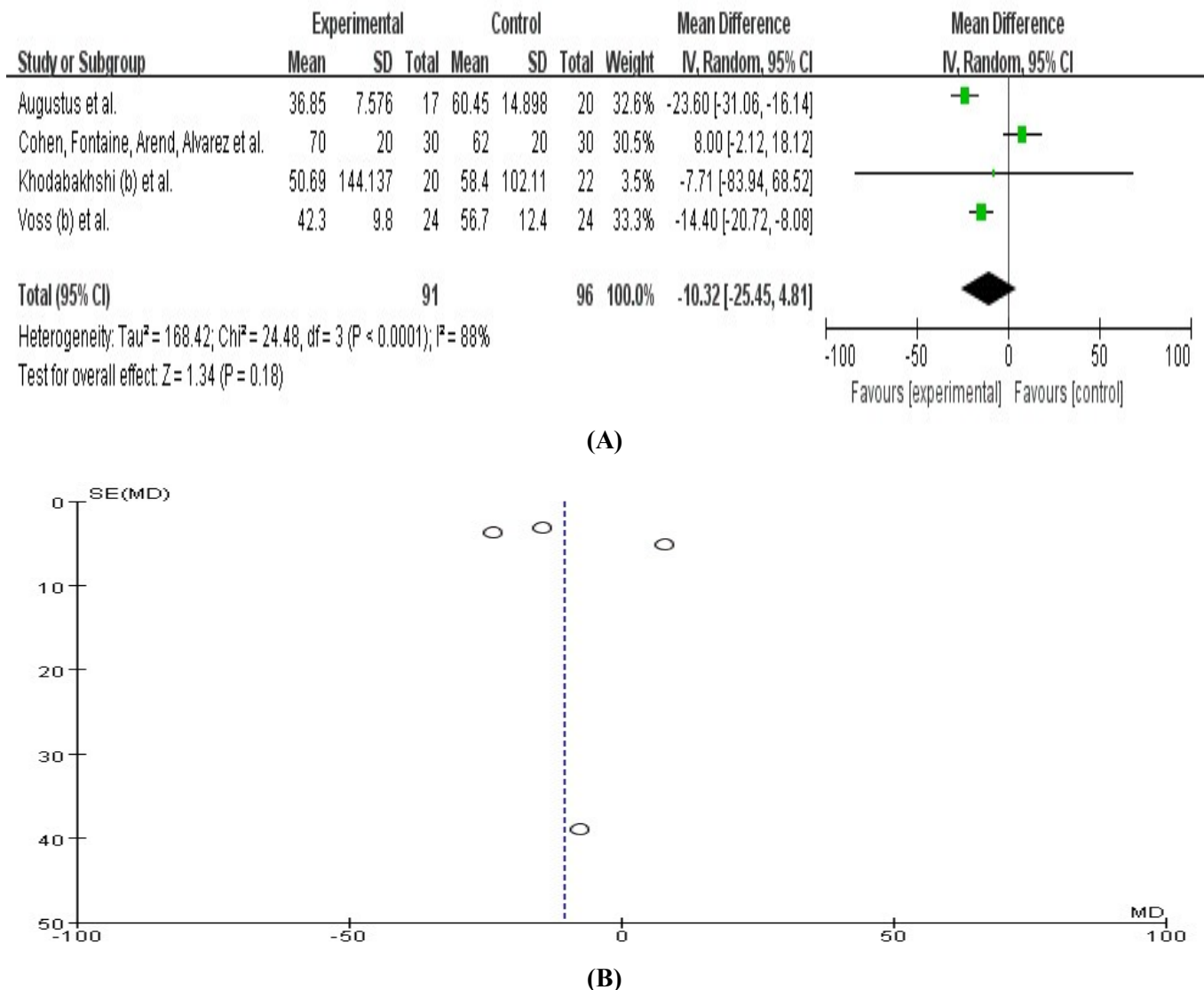


Figure 5. Meta-analysis of depression (PHQ-9). (A) Forest plot, (B) Risk of bias summary.

3.7. The effects of ketogenic diets on weight

Based on the results of the meta-analysis evaluating the effects of a ketogenic diet on body weight in cancer patients, which included three studies with a total of 124 participants, the pooled estimate showed a non-significant trend toward weight reduction in the ketogenic diet group compared to the control group (Mean Difference = -5.04 kg, 95% CI: -11.28 to 1.20 , $p = 0.11$). However, substantial heterogeneity was observed among the studies ($I^2 = 94\%$, $p < 0.00001$), and the risk of bias assessment indicated varying methodological quality across the included trials. (Figure 6)

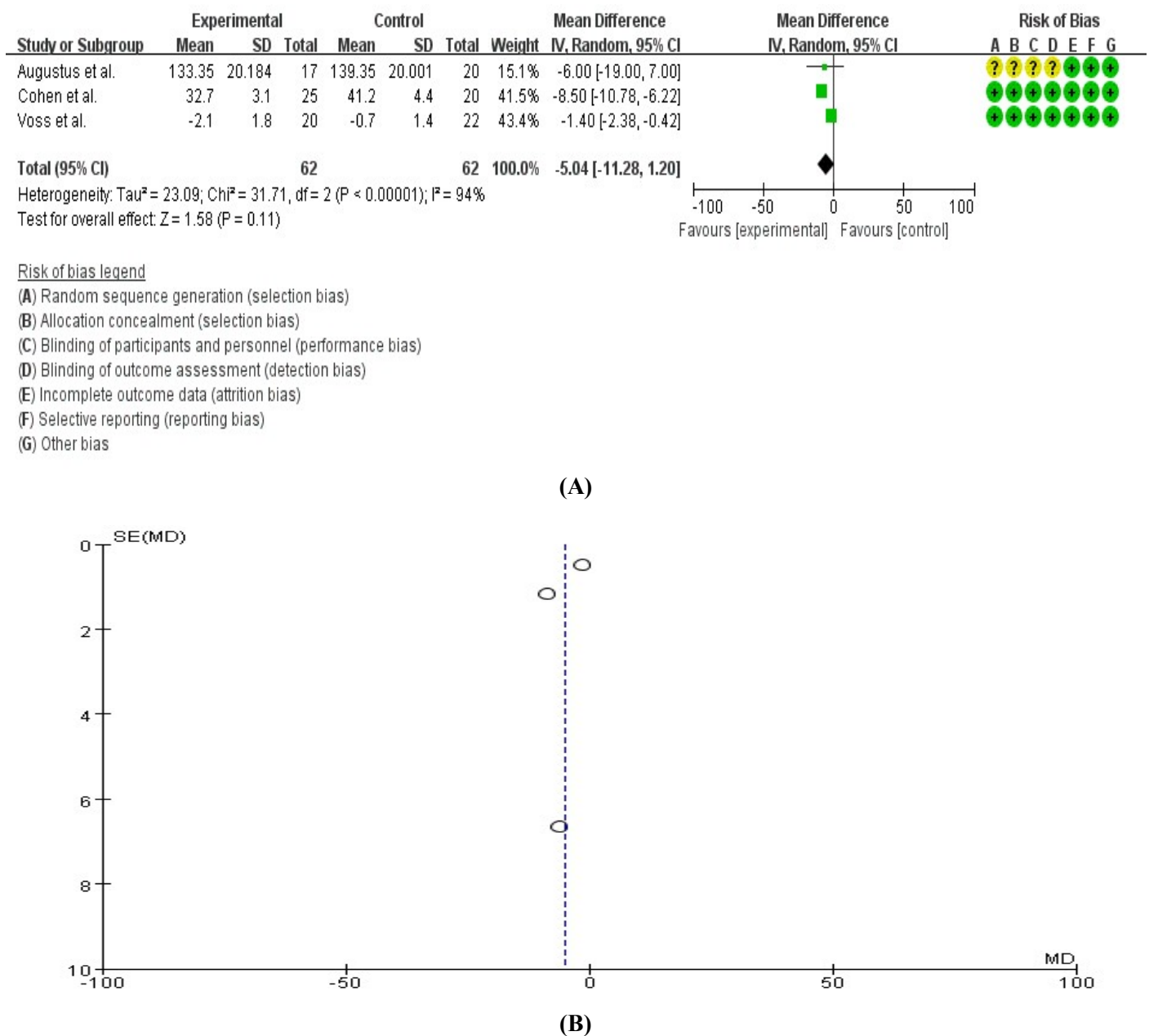


Figure 6. Meta-analysis of the effect of ketogenic diet on body weight in cancer patients. **(A)** Forest plot, **(B)** Risk of bias summary.

3.8. Effects of ketogenic diets on glucose

Based on the meta-analysis of three studies investigating the effects of a ketogenic diet on blood glucose levels in cancer patients, the pooled results demonstrated a statistically significant reduction in blood glucose in the ketogenic diet group compared to the control group (Mean Difference = -8.73 mg/dL, 95% CI: -12.57 to -4.89 , $p < 0.00001$). No significant heterogeneity was observed among the included studies ($I^2 = 0\%$, $p = 0.71$), indicating consistent findings across the trials. The risk of bias assessment showed generally good methodological quality, though some concerns regarding performance bias were noted. **(Figure 7)**

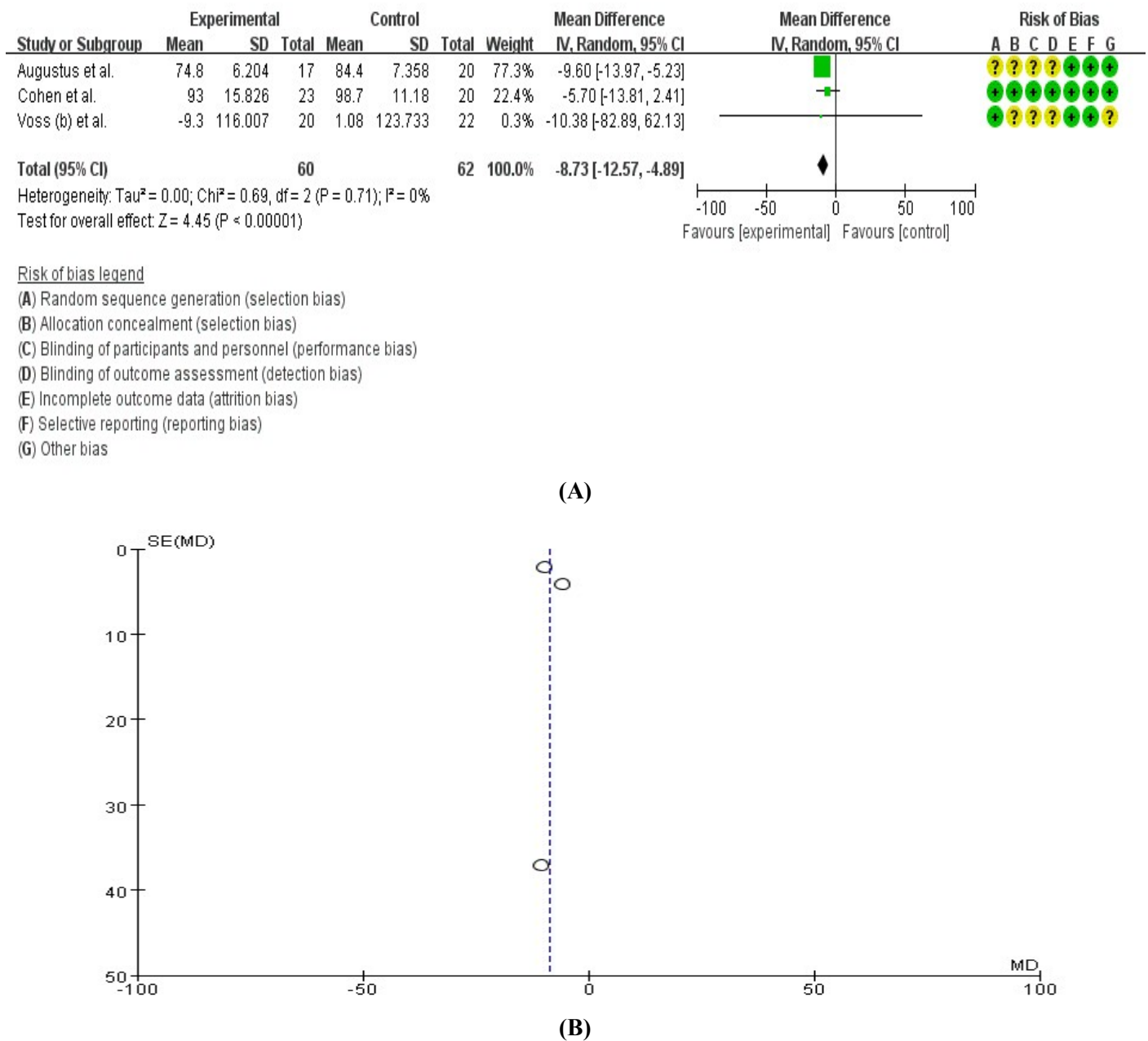


Figure 7. Meta-analysis of the effect of ketogenic diet on blood glucose levels. **(A)** Forest plot, **(B)** Risk of bias summary.

3.9. Effects of ketogenic diets on IGF-1

Based on the meta-analysis of three studies evaluating the effects of a ketogenic diet on IGF-1 in cancer patients, the pooled results demonstrated a non-significant trend toward improved quality of life in the ketogenic diet group compared to controls, with a mean difference of -13.52 points (95% CI: -32.70 to 5.67 , $p = 0.17$). No significant heterogeneity was observed among the studies ($I^2 = 0\%$, $p = 0.94$), indicating consistent effect estimates across the included trials. The risk of bias assessment revealed generally good methodological quality, though some concerns were noted in performance bias domains. **(Figure 8)**

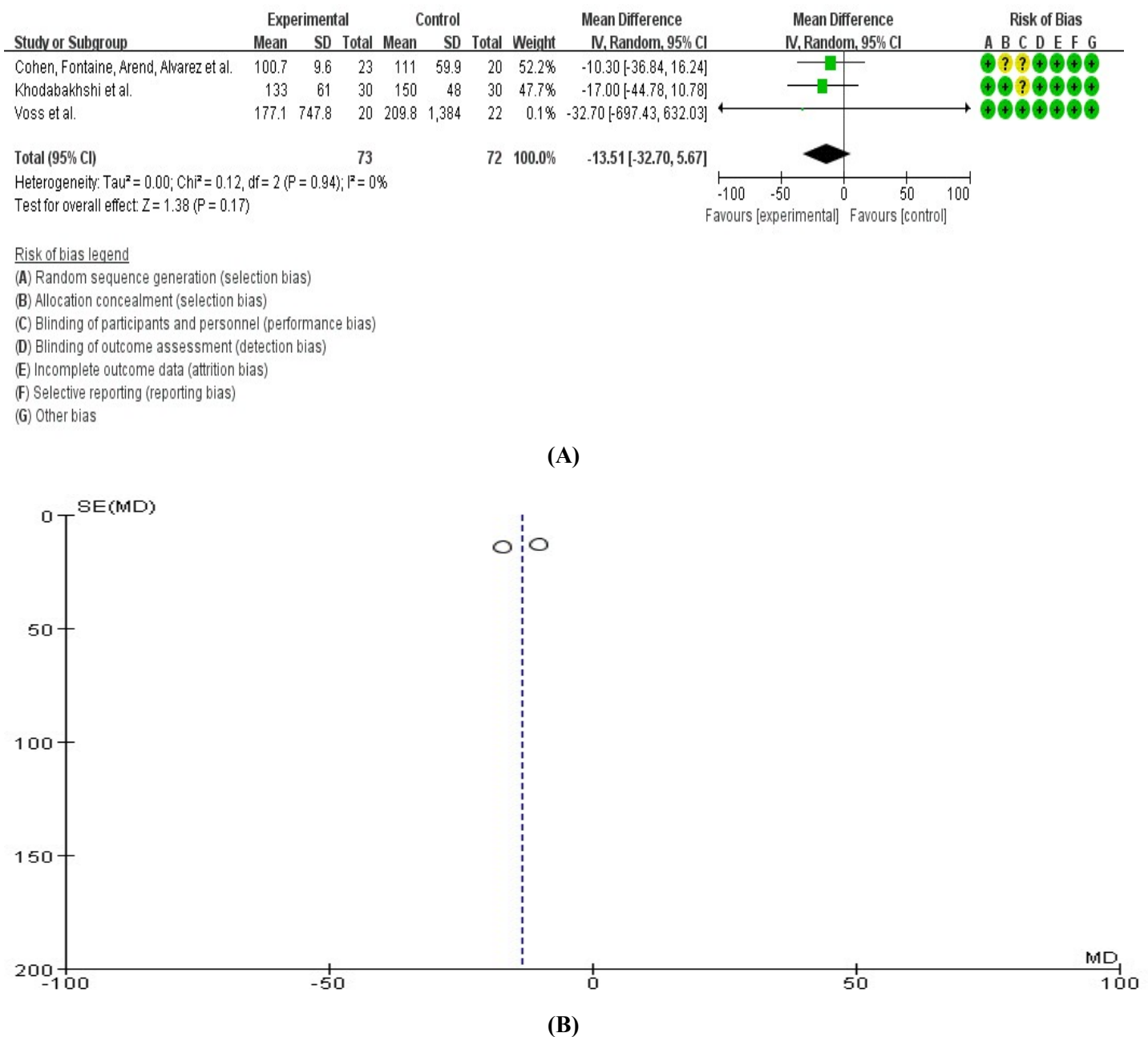


Figure 8. Meta-analysis of the effect of ketogenic diet on igf-1 in cancer patients. (A) Forest plot, (B) Risk of bias summary.

3.10. Effects of ketogenic diets on cholesterol

Based on the meta-analysis of three studies investigating the effects of ketogenic diets on cholesterol composition parameters in cancer patients, the pooled results showed a non-significant reduction in the ketogenic diet group compared to controls, with a mean difference of -12.66 units (95% CI: -32.93 to 7.61 , $p = 0.22$). Low heterogeneity was observed among the studies ($I^2 = 19\%$, $p = 0.29$), suggesting consistent direction of effects across the included trials. The risk of bias assessment indicated generally acceptable methodological quality, though some concerns were noted in performance bias domains due to the challenges of blinding in dietary interventions. (Figure 9)

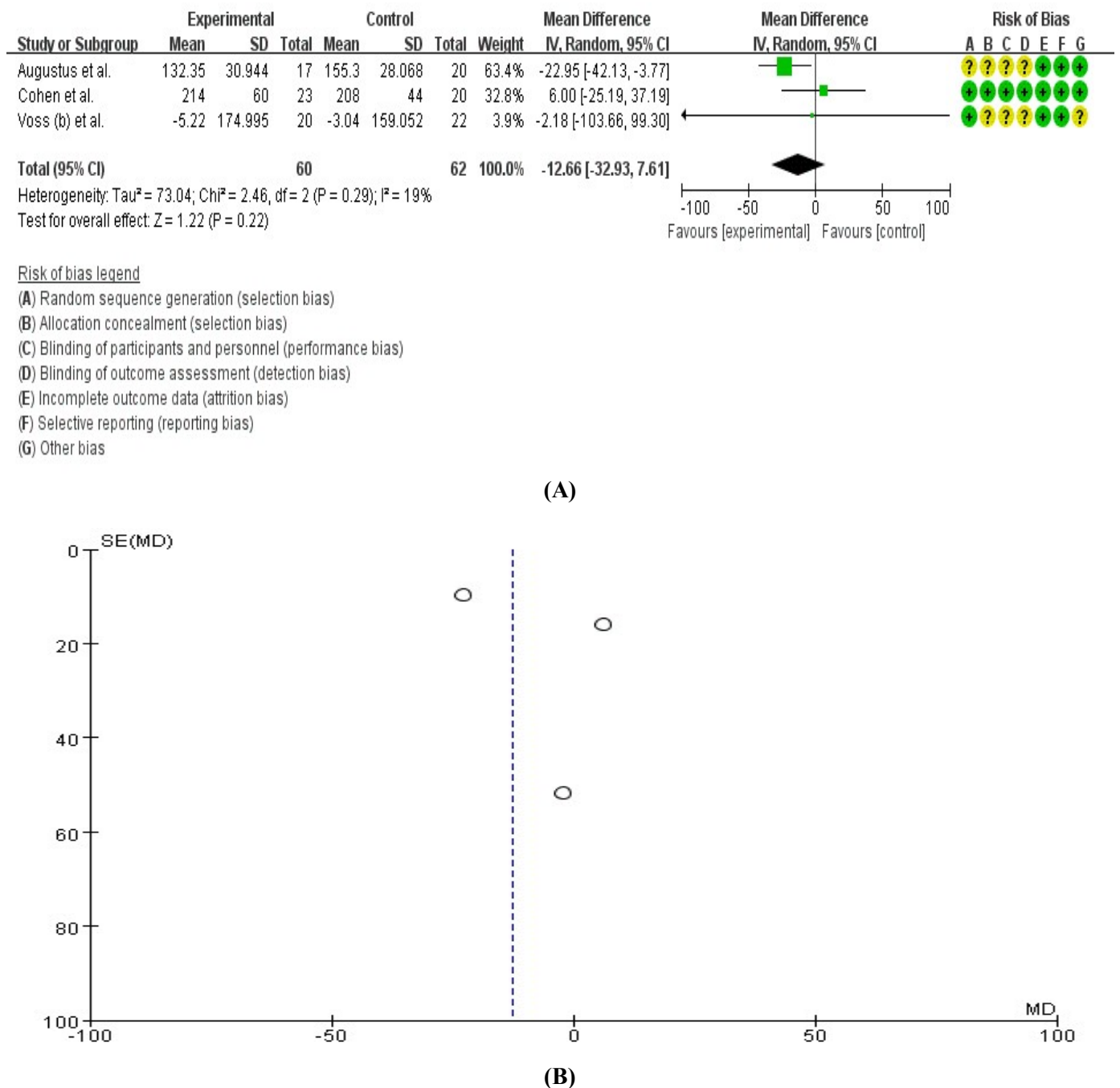


Figure 9. Meta-analysis of the effect of ketogenic diets on cholesterol in cancer patients. (A) Forest plot, (B) Risk of bias summary.

3.11. Effects of ketogenic diets on quality of life

Based on the meta-analysis of three studies examining the effects of ketogenic diets on quality of life in cancer patients, the pooled results demonstrated no statistically significant difference between the ketogenic diet group and the control group, with a mean difference of -7.97 mg/dL (95% CI: -36.36 to 20.41 , $p = 0.58$). Substantial heterogeneity was observed among the included studies ($I^2 = 92\%$, $p < 0.00001$), indicating considerable variation in effect sizes. The risk of bias assessment revealed mixed methodological quality across studies, with particular concerns regarding performance and detection bias. (Figure 10)

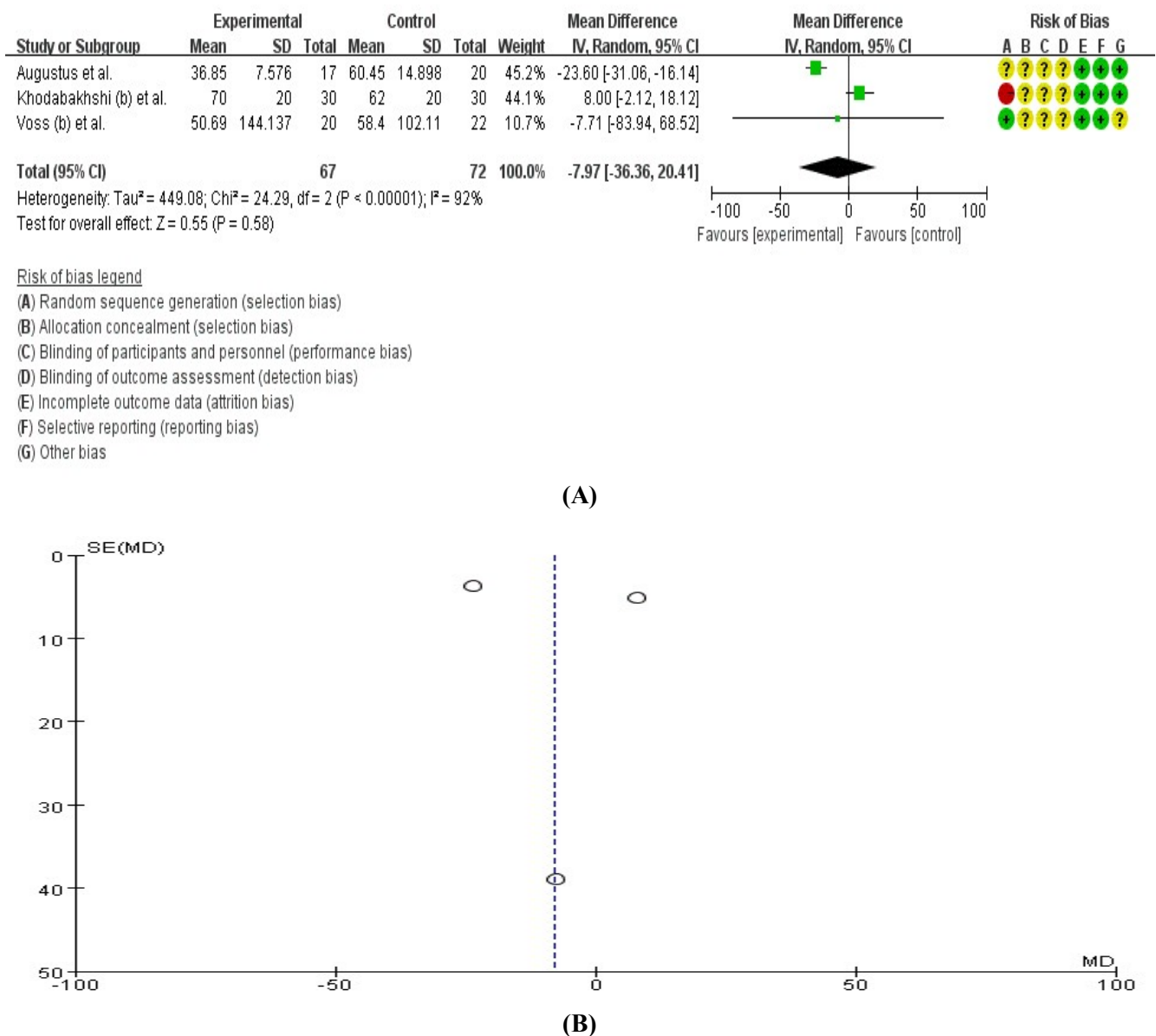


Figure 10. Meta-analysis of the effect of ketogenic diet on quality of life in cancer patients. (A) Forest plot, (B) Risk of bias summary.

4. Discussion

This systematic review and meta-analysis provide a quantitative synthesis of the impact of the ketogenic diet (KD) on both psychological well-being and metabolic parameters in cancer patients [22]. The results paint a complex yet informative picture, revealing a clear divergence between the diet's robust, consistent physiological effects and its more nuanced influence on mental health outcomes. Our analysis, derived from eight interventional studies encompassing 376 patients, demonstrates that the KD produces a significant and homogeneous reduction in fasting blood glucose. In contrast, its psychological benefits appear more specific, with a statistically significant improvement in anxiety symptoms, inconsistent effects on depression, and a non-significant but consistent trend towards improved quality of life [23].

The most robust finding of this review is the significant metabolic impact of the KD. The pooled analysis of three studies demonstrated a mean reduction in fasting

blood glucose of -8.73 mg/dL (95% CI: -12.57 to -4.89 , $p < 0.00001$) in the KD group compared to controls, with no heterogeneity ($I^2 = 0\%$). This result provides strong clinical validation for the core mechanistic premise of the diet, confirming that its implementation successfully creates a state of systemic glucose deprivation, thereby targeting the fundamental metabolic addiction of many cancer cells. This established metabolic shift is not merely a biochemical confirmation; it serves as the crucial foundation for interpreting the diet's psychological ramifications, as the brain is highly sensitive to its fuel supply and the broader systemic environment [24].

The most compelling psychological finding was the significant reduction in anxiety. The meta-analysis of studies using the HADS-A scale, involving 90 participants, showed a substantial and statistically significant benefit for the KD group, with a mean difference of -11.13 points (95% CI: -13.88 to -8.38 , $p < 0.00001$) and only low-to-moderate heterogeneity ($I^2 = 30\%$). This finding is of considerable importance for psycho-oncology. Cancer-related anxiety is a pervasive and debilitating challenge, and the potential of a non-pharmacological intervention to produce such an effect offers a novel and empowering adjunct to standard psychological support. The mechanism is likely multifactorial, involving the neuroactive properties of ketone bodies, such as their potential to enhance GABAergic tone and reduce neuroinflammation, combined with the psychological benefit of regaining a sense of agency through active participation in a structured dietary regimen [25].

In contrast, the results for depression were mixed. The analysis of HADS-D data from five studies yielded a pooled mean difference of -11.17 (95% CI: -21.18 to -1.15 , $p = 0.03$), which, while statistically significant, was characterized by substantial heterogeneity ($I^2 = 84\%$). Furthermore, the analysis using the PHQ-9 scale from four studies showed a non-significant reduction (MD = -10.32 , 95% CI: -25.45 to 4.81 , $p = 0.18$), also with high heterogeneity ($I^2 = 88\%$). This inconsistency suggests that the effect of the KD on depressive symptoms is not uniform and may be highly dependent on moderating factors such as cancer type, treatment status, or individual patient characteristics [26]. The demanding nature of the diet may also be a double-edged sword, providing a sense of control for some while becoming an additional burden and source of stress for others [27].

Regarding quality of life, the pooled results from three studies demonstrated a non-significant trend toward improvement, with a mean difference of -13.52 points (95% CI: -32.70 to 5.67 , $p = 0.17$). It is noteworthy, however, that these studies showed no heterogeneity ($I^2 = 0\%$), indicating a consistent direction of effect across all included trials. This suggests that while the effect may not have reached statistical significance in this limited sample [28], the KD does not adversely affect QoL and may indeed confer a benefit that larger, more powered studies could detect. The analysis of other physiological parameters, such as the non-significant trend in weight reduction (MD = -5.04 kg, $p = 0.11$), further illustrates the multifaceted nature of the diet's effects [29].

These findings have profound implications for psycho-oncology. First, they expand the non-pharmacological arsenal, positioning the KD as a potential evidence-informed option for managing cancer-related anxiety, particularly for patients with concurrent metabolic dysregulation. Second, they underscore the necessity for interdisciplinary collaboration, where oncologists, dietitians, and psycho-oncologists

work together to implement the diet safely, monitor its efficacy, and support the patient's psychological journey [30]. The dissociation between the significant anti-anxiety effect and the less consistent impact on depression and QoL underscores a critical principle in psycho-oncology that interventions can be highly specific, and outcomes must be measured with appropriate, targeted tools [31].

The findings from this meta-analysis carry significant implications for the evolving field of psycho-oncology. By demonstrating a consistent reduction in fasting blood glucose alongside a significant alleviation of anxiety symptoms, the ketogenic diet emerges not merely as a metabolic intervention but as a potential adjunctive strategy for managing cancer-related distress. This aligns with the growing emphasis on integrative oncology, which seeks to combine conventional treatments with evidence-based complementary approaches to improve holistic patient outcomes. In clinical practice, the diet could be particularly beneficial for patients with concurrent metabolic dysregulation and heightened anxiety, offering a non-pharmacological option that addresses both physiological and psychological dimensions. However, its implementation requires careful patient selection, multidisciplinary collaboration involving oncologists, dietitians, and psycho-oncologists, and ongoing monitoring of dietary adherence, nutritional status, and psychological response. Future psycho-oncology trials should consider incorporating ketogenic interventions as part of multimodal supportive care, especially in populations with high baseline anxiety or metabolic comorbidities, to further elucidate its role in enhancing emotional well-being and quality of life throughout the cancer trajectory.

The interpretation of these results must be tempered by the limitations of the current evidence base, including the small number of studies, modest sample sizes, and the high risk of performance bias inherent in dietary trials. The heterogeneity in KD protocols and cancer populations also poses a challenge for generating unified recommendations [32].

Future research must therefore focus on larger, well-powered RCTs with psychological outcomes as primary endpoints. These studies should incorporate mechanistic sub-studies to elucidate the biological pathways linking ketosis to psychological change and strive to identify patient subgroups most likely to benefit from this intervention [33].

5. Conclusion

In conclusion, this meta-analysis demonstrates that the ketogenic diet exerts a consistent and significant effect on the metabolic landscape of cancer patients by robustly lowering fasting blood glucose. Its impact on the psychological landscape is more specific, demonstrating a clear and significant benefit for anxiety, inconsistent effects on depression, and a promising, consistent trend for improved quality of life. For the field of psycho-oncology, these findings highlight the ketogenic diet not merely as a metabolic therapy, but as a promising, multi-faceted intervention that operates at the intersection of body and mind, offering a novel, empowering path toward reducing distress in the arduous cancer journey [34].

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