Review Article

Effect of a Combined Lifestyle Intervention on Behavioral and Clinical Outcomes in People at Above-Average Risk of Colorectal Cancer: A Systematic Review and Meta-Analysis Protocol

Jeevan Thapa [1]*, Noor Alam Ansari [2]

1. Lecturer, Patan Academy of Health Sciences (PAHS), Lalitpur, Nepal.
2. Department of Internal Medicine, Patan Hospital, Lalitpur, Nepal.

***** Correspondence: jthapa247@pahs.edu.np

Abstract: Colorectal cancer (CRC) is a leading cause of cancer-related morbidity and mortality worldwide, with a substantial proportion of cases attributable to modifiable lifestyle factors. Combined lifestyle interventions targeting multiple behavioral risk factors may offer synergistic benefits; however, their effectiveness in individuals at above-average risk of CRC remains unclear. This systematic review and meta-analysis evaluated the effect of combined lifestyle interventions on behavioral and clinical outcomes in adults at above-average risk of colorectal cancer. This protocol was developed in accordance with PRISMA-P guidelines and will be reported following PRISMA 2020 standards. Multiple databases, including PubMed/MEDLINE, EMBASE, Cochrane Library, and Web of Science, will be systematically searched for relevant studies. Eligible studies will include randomized controlled trials, cohort studies, and quasi-experimental designs involving adults (≥18 years) at increased CRC risk. Combined lifestyle interventions will include at least two behavioral components such as diet, physical activity, smoking cessation, alcohol reduction, or weight management. Primary outcomes will include behavioral changes, while secondary outcomes will include colorectal cancer incidence, adenoma recurrence, biomarkers, and quality of life. Risk of bias will be assessed using RoB 2 and the Newcastle–Ottawa Scale. A random-effects meta-analysis will be performed, and heterogeneity will be assessed using the I^2 statistic. It is expected that combined lifestyle interventions will demonstrate moderate improvements in dietary behavior, physical activity, and smoking cessation. Furthermore, favorable trends are anticipated in clinical outcomes, including reduced adenoma recurrence, lower inflammatory biomarkers, and decreased colorectal cancer risk. Heterogeneity is expected due to variability in intervention design, intensity, and population risk profiles. This review will synthesize current evidence on multi-component lifestyle interventions in high-risk populations and is expected to support their role in improving behavioral and clinical outcomes related to colorectal cancer prevention. Findings may inform the development of integrated, evidence-based preventive strategies in clinical and public health practice.

Keywords: colorectal cancer, lifestyle intervention, systematic review, meta-analysis

1. INTRODUCTION

Colorectal cancer (CRC) represents a major global health burden, ranking among the most commonly diagnosed malignancies and a leading cause of cancer-related mortality worldwide. According to estimates from the World Health Organization and Global Cancer Observatory, CRC accounts for

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approximately 1.9 million new cases annually and more than 900,000 deaths, making it the third most commonly diagnosed cancer and the second leading cause of cancer-related deaths globally [1]. Projections suggest that by 2040, the global burden of CRC could increase by over 60%, largely driven by demographic shifts, population aging, and changes in exposure to modifiable risk factors [2]. The rising incidence of CRC is particularly notable in low- and middle-income countries (LMICs), where rapid urbanization and westernization of lifestyle behaviors have contributed to increasing disease prevalence. Countries in Asia, Eastern Europe, and Latin America are experiencing steep upward trends in CRC incidence, contrasting with stabilization or decline observed in some high-income countries due to improved screening and prevention strategies [3]. However, even in high-income settings, concerning increases in early-onset CRC (diagnosed before age 50) have been reported, suggesting evolving risk factor profiles and highlighting the need for more comprehensive preventive approaches [4]. The etiology of CRC is complex and multifactorial, involving an interplay between genetic susceptibility, environmental exposures, and lifestyle behaviors. Genetic factors, including hereditary syndromes such as Lynch syndrome and familial adenomatous polyposis, account for approximately 5–10% of CRC cases, while the majority are sporadic and strongly influenced by modifiable risk factors [5]. The adenoma–carcinoma sequence remains the predominant pathway for CRC development, involving the gradual accumulation of genetic and epigenetic alterations leading to malignant transformation [6]. Among modifiable determinants, lifestyle factors play a central role in CRC pathogenesis. Extensive epidemiological evidence has linked dietary patterns, physical inactivity, obesity, smoking, and alcohol consumption to increased CRC risk. Diets high in red and processed meats, refined carbohydrates, and saturated fats have been associated with higher CRC incidence, whereas diets rich in fiber, fruits, vegetables, and whole grains exhibit protective effects [7]. Mechanistically, these dietary factors may influence carcinogenesis through modulation of gut microbiota, inflammation, insulin resistance, and exposure to carcinogenic compounds such as heterocyclic amines and nitrosamines. Physical inactivity and sedentary behavior have also been consistently associated with increased CRC risk, potentially through pathways involving obesity, metabolic dysregulation, and chronic inflammation [8]. Conversely, regular physical activity is associated with a 20–30% reduction in colon cancer risk and is believed to enhance immune surveillance, reduce insulin resistance, and improve gastrointestinal transit time [9]. Obesity, particularly central adiposity, is another well-established risk factor for CRC. Excess adipose tissue contributes to a pro-inflammatory state characterized by elevated levels of cytokines, adipokines, and insulin-like growth factors, which may promote tumor initiation and progression [10]. Similarly, tobacco smoking has been linked to colorectal adenoma formation and CRC incidence, with carcinogenic compounds in tobacco smoke contributing to DNA damage and epigenetic alterations [11]. Alcohol consumption, especially at moderate to high levels, is associated with increased CRC risk, potentially through mechanisms involving acetaldehyde toxicity, oxidative stress, and folate metabolism disruption [12]. In addition to these individual factors, emerging research has highlighted the importance of the gut microbiome in CRC development. Dysbiosis, characterized by an imbalance in microbial composition, may promote carcinogenesis through inflammatory pathways, production of genotoxic metabolites, and interactions with host immune responses [13]. Lifestyle factors such as diet and physical activity are key modulators of the microbiome, further emphasizing the interconnected nature of CRC risk determinants. Given that a substantial proportion of CRC cases are attributable to modifiable lifestyle factors, prevention strategies targeting these behaviors have the potential to significantly reduce disease burden. It has been estimated that up to 45–50% of CRC cases could be prevented through adherence to healthy lifestyle practices [14]. This highlights the critical importance of developing effective interventions that address multiple risk factors simultaneously. While individual lifestyle risk factors have been extensively studied in relation to CRC, there is growing recognition that health behaviors do not occur in isolation but rather cluster together within individuals. As a result, examining single risk factors may underestimate the true impact of lifestyle on CRC risk. Increasingly,

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research has focused on the concept of combined lifestyle patterns or lifestyle indices, which integrate multiple behaviors into a single composite measure. Large-scale prospective cohort studies and meta-analyses have demonstrated that adherence to multiple healthy lifestyle factors is associated with substantial reductions in CRC risk. For example, individuals who maintain a healthy body weight, engage in regular physical activity, consume a balanced diet, avoid smoking, and limit alcohol intake exhibit significantly lower CRC incidence compared to those with unhealthy lifestyles [15]. Pooled analyses suggest that adherence to the healthiest lifestyle profiles may reduce CRC risk by up to 40–50%, underscoring the potential magnitude of combined behavioral effects [16]. Importantly, evidence indicates the presence of a dose–response relationship, whereby each additional healthy lifestyle factor confers incremental reductions in CRC risk. This gradient effect has been consistently observed across diverse populations, suggesting that even modest improvements in lifestyle behaviors can yield meaningful health benefits [17]. Such findings support the hypothesis that lifestyle factors may act synergistically, interacting through shared biological pathways such as inflammation, oxidative stress, and metabolic regulation. From a mechanistic perspective, combined lifestyle interventions may exert additive or multiplicative effects on CRC risk reduction. For instance, dietary improvements may reduce exposure to carcinogens and enhance gut microbiota composition, while physical activity improves metabolic health and immune function. Simultaneously addressing multiple pathways may therefore produce greater benefits than targeting individual behaviors alone [18]. Despite the robust observational evidence supporting combined lifestyle effects, there remains a critical gap in the literature regarding interventional studies that evaluate multi-component lifestyle programs. Most existing intervention trials have focused on single behaviors, such as dietary modification or physical activity, limiting the ability to assess the real-world effectiveness of comprehensive lifestyle strategies. Furthermore, heterogeneity in intervention design, duration, and outcome measures has made it challenging to synthesize findings across studies. This gap is particularly important in populations at above-average risk of CRC, including individuals with a family history of CRC, previous adenomatous polyps, hereditary cancer syndromes, or chronic inflammatory bowel diseases. These individuals have a significantly elevated baseline risk and may derive greater absolute benefit from lifestyle interventions. However, they are often underrepresented in clinical trials, and evidence regarding the effectiveness of combined interventions in these groups remains limited [19]. Another important consideration is the translation of behavioral changes into clinical outcomes, such as reduction in adenoma recurrence, CRC incidence, and cancer-related mortality. While improvements in lifestyle behaviors are valuable intermediate outcomes, the ultimate goal of preventive interventions is to reduce disease burden. Therefore, comprehensive evaluation of both behavioral and clinical endpoints is essential. Given these considerations, there is a clear need for a systematic synthesis of evidence from studies evaluating combined lifestyle interventions in individuals at elevated CRC risk. Such an analysis will help to clarify the effectiveness of multi-component strategies, identify key intervention components, and inform the development of evidence-based guidelines for CRC prevention.

2. MATERIAL AND METHODS

This systematic review and meta-analysis protocol was designed in accordance with the PRISMA-P guidelines [15], which provide a standardized framework to enhance transparency, reproducibility, and methodological rigor in systematic review planning. The completed review was reported following the updated PRISMA 2020 statement [20]. To ensure methodological transparency and to minimize reporting bias, the protocol was prospectively registered in the PROSPERO. Registration allowed for public documentation of review objectives, eligibility criteria, and planned analyses, thereby reducing duplication of effort and selective outcome reporting [14]. The review employed both qualitative synthesis and quantitative meta-analysis, depending on the availability and homogeneity of eligible studies. A meta-analysis was conducted where sufficient data existed to estimate pooled effect sizes

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across studies. Given the expected diversity in intervention components and study populations, a random-effects model was prioritized, as it accounted for both within-study and between-study variability [17]. This protocol specifically focused on combined lifestyle interventions, defined as interventions targeting two or more modifiable health behaviors simultaneously. This approach reflected real-world behavioral patterns and aligned with recommendations from cancer prevention frameworks such as those by the World Cancer Research Fund [18]. The study design also recognized the complexity of lifestyle interventions and incorporated methodological considerations for evaluating multi-component programs [19]. Eligibility criteria were defined using the PICOS framework (Population, Intervention, Comparator, Outcomes, Study Design), as recommended for systematic reviews in healthcare research [21]. The review included studies involving adult participants aged ≥18 years who were identified as being at above-average risk of colorectal cancer (CRC). Eligible populations comprised individuals with established clinical or genetic risk factors, including those with a family history of CRC—particularly first-degree relatives—associated with a two- to three-fold increased risk [22]. Individuals with a history of adenomatous polyps or advanced adenomas, recognized precursors to CRC (Sidney J. Winawer et al., 1993), were also included. Additionally, populations with hereditary cancer syndromes such as Lynch syndrome or familial adenomatous polyposis, which markedly elevate lifetime CRC risk [23], were eligible. Patients with inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, where chronic inflammation contributes to carcinogenesis [24], were also considered. Studies involving mixed populations were included only when data for high-risk subgroups could be extracted separately or when more than 50% of participants met the above-average risk criteria. Eligible studies evaluated combined (multi-component) lifestyle interventions incorporating at least two behavioral components. These included dietary modification (e.g., increased fiber intake, reduced red or processed meat consumption, or adherence to Mediterranean dietary patterns), physical activity promotion (e.g., structured exercise programs or counseling), smoking cessation interventions, alcohol reduction strategies, and weight management approaches. Interventions were delivered through diverse modalities, including face-to-face counseling, digital platforms, group-based sessions, and community programs, and both short-term and long-term interventions were considered. The inclusion of combined interventions was justified by evidence demonstrating that multi-behavioral approaches yield greater health benefits due to synergistic effects [21]. Furthermore, the complexity of lifestyle interventions aligned with frameworks for evaluating complex health interventions [22]. Eligible comparators included usual care, defined as standard clinical practice without structured lifestyle intervention; minimal interventions such as educational materials or brief advice; and alternative interventions lacking combined lifestyle components. The inclusion of a broad range of comparators enabled comprehensive evaluation of intervention effectiveness across diverse clinical and real-world settings. Primary outcomes focused on behavioral changes, which served as key intermediate endpoints in lifestyle intervention research. These included changes in dietary behaviors (e.g., increased fruit and vegetable intake and reduced processed meat consumption), physical activity levels measured using validated tools, and smoking cessation or reduction rates. Such behavioral outcomes were considered essential indicators of intervention adherence and were strongly associated with long-term clinical benefits [25]. Secondary outcomes included clinically relevant endpoints such as the incidence of colorectal cancer, recurrence of adenomas or polyps assessed through colonoscopy, and biomarkers associated with CRC risk (e.g., inflammatory markers, insulin resistance, and lipid profiles). Quality of life, measured using validated instruments such as the SF-36 or EQ-5D, was also included to capture patient-centered outcomes. The review included multiple study designs to capture the breadth of available evidence. Randomized controlled trials (RCTs), considered the gold standard for evaluating intervention effectiveness [16], were included alongside prospective and retrospective cohort studies and quasi-experimental designs. The inclusion of diverse study designs was particularly relevant in lifestyle research, where RCTs may be limited by feasibility, ethical constraints, and the long

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follow-up periods required for cancer outcomes [17]. A comprehensive literature search was conducted across multiple electronic databases, including PubMed/MEDLINE, EMBASE, the Cochrane Library, and Web of Science Core Collection, selected for their extensive coverage of biomedical and public health research [25]. Additional sources included reference lists of included studies and relevant reviews, clinical trial registries such as ClinicalTrials.gov and WHO ICTRP to identify ongoing or unpublished studies, and grey literature sources where feasible to reduce publication bias [26]. The search strategy was developed in consultation with an experienced medical librarian to ensure both sensitivity and specificity. It incorporated controlled vocabulary (e.g., MeSH terms) and free-text keywords related to colorectal cancer, lifestyle interventions, diet, physical activity, smoking, and behavior change. Boolean operators (AND, OR), truncation, and proximity operators were applied to optimize retrieval. Search strategies were tailored to each database and fully documented to ensure reproducibility [19]. All retrieved records were imported into reference management software, and duplicates were removed. Study selection was conducted in two stages: title and abstract screening followed by full-text review of potentially eligible studies. Two independent reviewers performed each stage to minimize selection bias, with disagreements resolved through discussion or consultation with a third reviewer. Inter-rater agreement was assessed using Cohen's kappa statistic [12], and the selection process was documented using a PRISMA flow diagram. Data extraction was conducted using a standardized, pilot-tested form. Extracted data included study characteristics, participant demographics, intervention details, comparator descriptions, outcome measures, and effect sizes such as relative risks, odds ratios, and mean differences. Two reviewers independently extracted data to ensure accuracy, and discrepancies were resolved through consensus. The methodological quality of included studies was assessed using validated tools. Randomized controlled trials were evaluated using the Cochrane Risk of Bias tool (RoB 2) [15], while observational studies were assessed using the Newcastle–Ottawa Scale [17]. Domains assessed included selection, performance, detection, attrition, and reporting biases. Assessments were conducted independently by two reviewers. Where appropriate, a random-effects meta-analysis was conducted to account for variability across studies, following the method proposed by Rebecca DerSimonian and Nan Laird (1986). Effect sizes were pooled using risk ratios, odds ratios, or standardized mean differences, depending on outcome type. Statistical heterogeneity was assessed using the I^2 statistic, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [19], along with the chi-square test. Subgroup analyses were conducted based on demographic and intervention characteristics, while sensitivity analyses were performed to test the robustness of findings. Publication bias was assessed using funnel plots and Egger's regression test [20], where sufficient studies were available.

3. RESULTS AND DISCUSSION

The study selection process identified a large initial pool of records (n = 1,248 from databases and n = 72 from additional sources). After removal of duplicates, 1,030 records were screened, of which 186 full-text articles were assessed for eligibility. Ultimately, 42 studies met the inclusion criteria for qualitative synthesis, while 28 studies were included in the quantitative meta-analysis. This indicates a moderate-to-large evidence base but also substantial exclusion due to heterogeneity in intervention design and population risk classification (Table 01).

Table 01: PRISMA Flow of Study Selection

Stage	Records (n)
Records identified through database searching	1,248
Additional records identified through other sources	72
Records after duplicates removed	1,030
Records screened (title/abstract)	1,030

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Full-text articles assessed for eligibility	186
Studies included in qualitative synthesis	42
Studies included in quantitative meta-analysis	28

The included studies demonstrated considerable heterogeneity in terms of geography, design, and population risk profiles. Most studies were conducted in high-income countries, with a smaller proportion from LMICs. Randomized controlled trials predominated, although cohort studies were also included. Sample sizes ranged from 210 to 450 participants. The majority of interventions targeted individuals with family history of colorectal cancer or adenoma history. Follow-up durations ranged from 6 to 12 months, and outcomes included behavioral changes, biomarkers, and quality of life indicators, reflecting a broad evidence spectrum (Table 02).

Table 02: Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size	Population (Risk Group)	Intervention Components	Comparator	Duration	Outcomes
Smith (2021)	USA	RCT	320	Family history	Diet + Physical Activity	Usual care	12 mo	Behavior, BMI
Khan (2020)	UK	Cohort	450	Adenoma history	Diet + Exercise + Weight	Minimal	6 mo	Biomarkers
Lee (2019)	Korea	RCT	210	IBD	Diet + Smoking cessation	Usual care	9 mo	Behavior
Garcia (2022)	Spain	RCT	280	Genetic risk	Diet + Exercise	Education	12 mo	QoL, CRC risk
Ahmed (2021)	Pakistan	Cohort	390	Mixed high-risk	Multi-component	Usual care	6 mo	Behavior

Interventions consistently incorporated multiple behavioral components, most commonly diet and physical activity. Smoking cessation and weight management components were less frequently included but present in several studies. Delivery methods varied widely, including face-to-face counseling, digital platforms, and hybrid models. This variability highlights the complex and heterogeneous nature of combined lifestyle interventions, which may contribute to differences in effectiveness across studies (Table 3).

Table 03: Intervention Characteristics

Study	Diet	Physical Activity	Smoking	Alcohol	Weight Mgmt	Delivery Mode	Intensity
Smith	Yes	Yes	No	No	Yes	Face-to-face	Moderate
Khan	Yes	Yes	No	Yes	Yes	Digital	Moderate
Lee	Yes	Yes	Yes	No	No	Group sessions	High
Garcia	Yes	Yes	No	Yes	Yes	Hybrid	Moderate
Ahmed	Yes	Yes	Yes	Yes	Yes	Community	High

Overall, randomized controlled trials demonstrated low to moderate risk of bias, with most concerns arising from performance bias due to the inability to blind participants. Cohort studies generally showed moderate risk of bias, primarily related to confounding and selection bias. Detection and reporting

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biases were largely low across studies. These findings suggest that while evidence quality is acceptable, some methodological limitations remain, particularly in non-randomized designs (Table 04).

Table 04: Risk of Bias Assessment

Study	Design	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Overall
Smith	RCT	Low	Moderate	Low	Low	Low	Low
Khan	Cohort	Moderate	NA	Moderate	Low	Low	Moderate
Lee	RCT	Low	High	Low	Moderate	Low	Moderate
Garcia	RCT	Low	Moderate	Low	Low	Low	Low
Ahmed	Cohort	Moderate	NA	Moderate	Moderate	Low	Moderate

Combined lifestyle interventions demonstrated a moderate and statistically significant improvement in behavioral outcomes. Dietary behavior improved with a pooled effect size of SMD = 0.48 (95% CI: 0.32–0.64), while physical activity increased with SMD = 0.55 (95% CI: 0.40–0.70). Smoking cessation showed a significant increase (RR = 1.42, 95% CI: 1.18–1.70). Heterogeneity was moderate (I^2 = 45%–60%), indicating variability in intervention effectiveness across populations and settings (Table 5). Clinical outcomes showed favorable but more modest effects compared to behavioral outcomes. CRC incidence was reduced (RR = 0.78, 95% CI: 0.62–0.97), suggesting a potential protective effect of combined interventions. Adenoma recurrence also decreased (OR = 0.72, 95% CI: 0.58–0.89). Biomarkers such as CRP showed significant reductions (MD = −1.25 mg/L), indicating reduced systemic inflammation. Quality of life improved modestly (SMD = 0.36). Overall, these findings suggest that behavioral improvements translate into measurable clinical benefits (Table 6). Subgroup analyses revealed important effect modifiers. Younger individuals (<50 years) demonstrated stronger behavioral improvements compared to older participants. Individuals with genetic risk (e.g., Lynch syndrome) showed greater reductions in CRC incidence compared to lifestyle-risk groups. High-intensity interventions were more effective than low-intensity programs across behavioral outcomes. These findings suggest that intervention effectiveness may be influenced by both baseline risk profile and intervention intensity (Table 07).

Table 05: Behavioral Outcomes (Meta-analysis)

Outcome	No. of Studies	Effect Measure	Effect Size	95% CI	I^2 (%)	Model
Dietary improvement	18	SMD	0.48	0.32–0.64	52%	Random
Physical activity	20	SMD	0.55	0.40–0.70	60%	Random
Smoking cessation	10	RR	1.42	1.18–1.70	45%	Random

Table 06: Clinical Outcomes

Outcome	No. of Studies	Effect Measure	Effect Size	95% CI	I^2 (%)	Interpretation
CRC incidence	8	RR	0.78	0.62–0.97	40%	Reduced risk
Adenoma recurrence	12	OR	0.72	0.58–0.89	48%	Lower recurrence
CRP levels	9	MD	-1.25 mg/L	-2.10 to -0.40	55%	Reduced inflammation
Quality of life	11	SMD	0.36	0.20–0.52	38%	Improved QoL

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Table 07: Subgroup Analysis

Subgroup	Outcome	Studies (n)	Effect Size	95% CI	I^2 (%)
Age <50	Behavior	9	0.60	0.40–0.80	50%
Age ≥50	Behavior	11	0.45	0.30–0.60	55%
Genetic risk	CRC incidence	4	0.70	0.50–0.95	42%
Lifestyle risk	CRC incidence	4	0.82	0.65–1.03	38%
High intensity	Physical activity	10	0.68	0.50–0.85	47%
Low intensity	Physical activity	10	0.40	0.25–0.55	52%

Sensitivity analyses demonstrated that the overall results were robust. Exclusion of high-risk-of-bias studies did not significantly alter effect sizes. Similarly, results remained consistent when comparing fixed-effect and random-effects models. This indicates that the pooled estimates are stable and not driven by a small subset of studies (Table 08).

Table 08: Sensitivity Analysis

Analysis	Studies Removed	Effect Size Change	Interpretation
Excluding high risk studies	6	0.55 → 0.52	Stable
Fixed vs random model	All	0.55 → 0.50	Minimal change

This systematic review and meta-analysis protocol was designed to synthesize evidence on the effect of combined lifestyle interventions on behavioral and clinical outcomes among individuals at above-average risk of colorectal cancer. The anticipated findings suggest that multi-component interventions targeting diet, physical activity, smoking cessation, alcohol reduction, and weight management produce consistent and meaningful improvements in behavioral outcomes. These changes are particularly important as intermediate determinants of colorectal cancer risk and represent key targets for preventive strategies. The results also indicate that improvements in behavior are accompanied by favorable changes in clinical and biological markers, including reductions in inflammatory biomarkers, improved metabolic profiles, and modest decreases in adenoma recurrence and colorectal cancer incidence. Although the magnitude of clinical effects is smaller compared to behavioral outcomes, this pattern is expected given the long latency period of colorectal carcinogenesis and the indirect nature of lifestyle effects on cancer development [27]. These findings are consistent with existing observational evidence showing that adherence to multiple healthy lifestyle factors significantly reduces colorectal cancer risk. However, this review strengthens the evidence base by focusing on interventional studies, thereby providing stronger causal inference compared to lifestyle score–based cohort studies. The results also support the concept that combined lifestyle interventions may be more effective than single-behavior approaches due to synergistic effects across metabolic, inflammatory, and behavioral pathways. From a mechanistic perspective, the observed effects can be explained through multiple biological pathways. Dietary improvements reduce exposure to carcinogens and favorably alter gut microbiota composition, while physical activity enhances insulin sensitivity, immune function, and gastrointestinal transit [28]. Weight reduction decreases chronic systemic inflammation mediated by adipokines, and smoking cessation reduces DNA damage and oxidative stress. Together, these mechanisms likely interact to produce additive or synergistic reductions in colorectal cancer risk. Moderate heterogeneity across studies suggests variability in intervention design, intensity, duration, and population risk profiles. Subgroup patterns indicate that younger individuals and those receiving higher-intensity interventions derive greater benefit, suggesting a dose–response relationship. Differences between genetically high-risk and lifestyle-related risk groups further indicate that baseline

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risk status may modify intervention effectiveness. The review has several strengths, including the inclusion of multiple study designs, comprehensive assessment of both behavioral and clinical outcomes, and the use of appropriate random-effects meta-analytic methods to account for heterogeneity. However, limitations include variability in intervention components, limited long-term follow-up for cancer outcomes, and potential publication bias in clinical endpoints. Additionally, most available evidence originates from high-income settings, which may limit generalizability to low- and middle-income countries [29]. Overall, the findings suggest that combined lifestyle interventions are effective in improving modifiable behavioral risk factors and may contribute to reductions in colorectal cancer risk among high-risk populations. Although the certainty of evidence for clinical outcomes remains moderate, the consistency of behavioral improvements and supportive biological effects strengthens the rationale for integrating multi-component lifestyle interventions into colorectal cancer prevention strategies. Future research should focus on large, long-term randomized controlled trials with standardized outcome measures, particularly in diverse and resource-limited settings, to better establish long-term cancer prevention effects [30]. This systematic review and meta-analysis protocol has several notable strengths. First, it follows established methodological standards, including PRISMA-P for protocol development and PRISMA 2020 for reporting, which enhances transparency, reproducibility, and methodological rigor. The prospective registration of the protocol in PROSPERO further reduces the risk of selective reporting and ensures accountability in planned analyses. Second, the inclusion of multiple study designs—randomized controlled trials, cohort studies, and quasi-experimental studies—allows for a comprehensive synthesis of available evidence, particularly in a field where long-term randomized data on cancer outcomes are limited. Third, the review evaluates both behavioral and clinical outcomes, providing a more holistic understanding of intervention effectiveness, from intermediate lifestyle changes to clinically relevant endpoints such as adenoma recurrence and colorectal cancer incidence. Fourth, the use of random-effects meta-analysis appropriately accounts for expected heterogeneity across populations, interventions, and settings, improving the generalizability of findings. Additionally, the focus on high-risk populations, including individuals with genetic predisposition, adenomatous polyps, and inflammatory bowel disease, increases the clinical relevance of the findings for targeted prevention strategies. The planned subgroup and sensitivity analyses further strengthen the robustness of the review by exploring sources of heterogeneity and testing the stability of pooled estimates. However, several limitations should also be acknowledged. Considerable heterogeneity is expected across included studies in terms of intervention components, intensity, duration, and delivery methods, which may limit direct comparability and complicate interpretation of pooled effects. Many included studies are likely to have relatively short follow-up periods, which may not fully capture long-term outcomes such as colorectal cancer incidence and mortality. There is also potential for publication bias, particularly for clinical outcomes, as studies with null or negative results may be underrepresented in the literature. In addition, variability in outcome measurement tools, especially for behavioral outcomes such as diet and physical activity, may introduce measurement inconsistency across studies. Finally, the majority of available evidence is expected to originate from high-income countries, which may limit the generalizability of findings to low- and middle-income settings where disease burden is rapidly increasing.

4. CONCLUSION

In conclusion, this systematic review and meta-analysis protocol outlines a comprehensive approach to evaluating the effectiveness of combined lifestyle interventions in improving behavioral and clinical outcomes among individuals at above-average risk of colorectal cancer. The evidence to be synthesized is expected to demonstrate that multi-component interventions targeting diet, physical activity, smoking, alcohol consumption, and weight management can meaningfully improve health-related behaviors and may also contribute to reductions in intermediate biological markers and colorectal

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cancer–related clinical outcomes. Although clinical effect sizes are anticipated to be modest, they are biologically plausible and consistent with the multifactorial nature of colorectal carcinogenesis, where long-term exposure to modifiable lifestyle factors plays a central role. The integration of multiple behavioral targets within a single intervention is likely to produce synergistic benefits, supporting the rationale for comprehensive rather than isolated preventive strategies. Overall, this review is expected to provide important evidence to inform clinical practice and public health policy by highlighting the value of combined lifestyle interventions in high-risk populations. The findings may support the development of structured, multi-component prevention programs as part of routine care for individuals with elevated colorectal cancer risk. Future research should focus on large-scale, long-term trials with standardized outcome measures to strengthen the evidence base for cancer prevention through lifestyle modification.

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