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Two-samples mendelian randomization analysis of the causal relationship between depression intervention and radiotherapy sessions

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► ***Original article***

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ABSTRACT

Background: Previous research suggests that depression interventions may affect the session of radiotherapy (RT), though the causal relationship remains uncertain. This research seeks to elucidate the cause-and-effect link between treatments for depression and RT sessions through the application of two-sample Mendelian randomization (TSMR) analysis. ***Materials and Methods:*** Information on depression treatments and RT sessions was sourced from publicly available genome-wide association studies (GWAS) summary data. Genetic variations known as single nucleotide polymorphisms (SNPs) that are closely linked to depression treatments were chosen as instrumental variables (IVs). Six distinct TSMR techniques were utilized, including MR Egger, weighted median, inverse variance weighted (IVW), weighted mode, IVW with fixed effects, and MR Egger with bootstrap. The causal relationship between depression interventions and RT session was primarily assessed using the P-value from the IVW fixed effects model. Heterogeneity and pleiotropy tests were conducted to validate the findings. ***Results:*** Eight sensitive SNPs were identified for the analysis. Both the MR Egger (Q_pval=0.118>0.05) and inverse variance weighted (Q_pval=0.143>0.05) methods indicated low heterogeneity in the MR analysis. The findings remained consistent through various sensitivity tests. The IVW fixed effects analysis revealed a significant causal effect between depression intervention and RT session (P=0.016, OR=0.979, 95% CI: 0.961-0.996), indicating a negative causal relationship. ***Conclusion:*** Depression intervention appears to be a beneficial factor in reducing RT session, supporting its integration into treatment plans for RT patients to enhance their quality of life.

INTRODUCTION

Radiotherapy (RT) is a medical technique that utilizes high-energy rays or particles to treat malignant tumors. By employing individualized target delineation methods, RT precisely targets tumor cells while minimizing radiation damage to surrounding normal tissues [1]. Typical RT techniques encompass external beam radiation therapy (EBRT), brachytherapy, radioactive seed implants, and total body irradiation (TBI) [2]. Sophisticated methods like 3D conformal radiotherapy and intensity-modulated radiotherapy (IMRT) target high-dose radiation at localized tumors and are extensively employed in treating head and neck, breast, and prostate cancers [3]. Despite their effectiveness, the adverse effects of frequent treatments, including skin reactions, fatigue, and appetite loss, remain significant concerns [4]. Brachytherapy, which involves placing radioactive sources within or near cancerous tissues, reduces radiation exposure to surrounding healthy tissues [5]. It is particularly effective for certain cancers, such as prostate and cervical cancer, though the risk of infection from implanted radioactive sources poses clinical challenges [6]. Radioactive seed implants offer continuous low-dose radiation for long-term cancer treatment, but there is a risk of seed migration or expulsion [7]. TBI, while effective, is associated with severe side effects, including immunosuppression and infection, which continue to challenge medical professionals. Most patients with solid tumors require prolonged and frequent RT [8]. Some patients, such as those with brain tumors, require highly precise, staged treatments. Prolonged radiation therapy courses can increase the cumulative dose to surrounding normal tissues, elevating the risk of secondary cancers [9]. Additionally, long RT sessions can negatively impact patients' daily lives, work, and psychological well-being. Shortening RT sessions can significantly improve patients' quality of life.

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Techniques such as hypofractionated radiation therapy, stereotactic body radiotherapy (SBRT), IMRT, proton therapy, and accelerated radiotherapy can reduce RT duration while maintaining efficacy [10].

Research has shown that depression interventions, such as yoga and mindfulness, can alleviate symptoms of depression, anxiety, and stress, thereby enhancing self-control, coping abilities, treatment confidence, and patient cooperation [11]. These interventions also help mitigate RT-related side effects, such as fatigue and insomnia [12], enabling patients to better manage pain and discomfort, thus reducing the likelihood of treatment interruptions. However, definitive evidence linking depression interventions to shortened RT sessions remains elusive. Mendelian randomization (MR) uses single nucleotide polymorphisms (SNPs) as instrumental variables (IVs) to determine the causal relationship between an exposure and an outcome [13]. Because SNP alleles are distributed randomly at birth following Mendelian principles, this method lessens confounding variables and lowers the chance of reverse causation [14]. MR overcomes many limitations of randomized controlled trials, such as ethical concerns, high costs, and long durations, making it an increasingly popular analytical method [15]. Although the majority of recent research has concentrated on how depression affects patient outcomes during radiotherapy, this research adopts a novel perspective by investigating how depression treatments might alter the progression of radiotherapy. This novel perspective not only expands the research landscape for radiotherapy and psychosomatic interventions but also opens new avenues for future investigation. Our findings suggest that depression interventions may indeed shorten the course of radiotherapy, highlighting the potential for such interventions to improve patient compliance and quality of life, ultimately leading to optimized treatment outcomes.

MATERIALS AND METHODS

Study design

MR is a technique used to determine if an exposure influences disease onset, utilizing genetic variants as tools. The MR framework relies on three premises: 1) the genetic variant is closely linked to the exposure; 2) the genetic variant has no connection to the outcome; and 3) the genetic variant is independent of confounders [16].

Data sources

Data on depression intervention patients were obtained from the lEU Open GWAS Project dataset (ukb-d-20547_3), and data on Radiotherapy sessions patients were obtained from the lEU Open GWAS Project dataset (ukb-b-16024). The lEU Open GWAS Project is an open GWAS database created and maintained by the University of Bristol's Integrative Epidemiology Unit (EU). The ukb-d-20547_3 dataset, released in 2018, includes 463,010 samples, with 1,942 cases and 461,068 controls. The ukb-b-16024 dataset, also released in 2018, includes 117,763 samples, with 9,199 cases and 108,564 controls. Every dataset can be accessed through the MR base database at http://www.mrbase.org/. All research contributing data to these analyses received approval from ethics boards, and every participant gave written informed consent.

Instrumental variables (IVs) selection

Instrumental variables were chosen based on these criteria [17]: 1) an association P-value < 5.0×10^{-6}; 2) a linkage disequilibrium (LD) threshold of $r^2 < 0.001$; 3) a clumping distance of 10,000 kb; 4) in LD proxy analysis, an SNP with an LD r^2 value over 0.8 was considered a proxy for the target SNP; 5) a minimum allele frequency (MAF) threshold of 0.3, including only SNPs exceeding this threshold. SNPs that did not correlate with the outcome (P < 5.0 x 10-6) were omitted, while those with F > 10 were retained for the final analysis.

Statistical analysis

Data analysis was performed with R version 4.1.2 and the 'two sample MR' library (v0.5.5). A P-value less than 0.05 demonstrated statistical significance. Six approaches were employed to evaluate the causal link between exposure and outcome: MR Egger, weighted median, IVW, weighted mode, IVW (fixed effects), and MR Egger (bootstrap). IVW offers impartial estimates assuming all genetic variants are legitimate, whereas the weighted median technique yields accurate results if at least half of the weight is derived from valid variants [18]. MR-Egger regression was used to detect and adapt to bias caused by unbalanced pleiotropy, with the slope representing the causal effect estimate and the intercept indicating the average pleiotropic effect of all SNPs. Due to the low statistical power of MR-Egger regression, emphasis was placed on the direction and magnitude of the effect instead of its statistical significance [19]. To evaluate heterogeneity, Cochran's Q test was employed, while pleiotropy was examined through the MR-Egger intercept. Sensitivity analysis involved sequentially excluding each SNP and determining the overall effect of the remaining SNPs to assess the stability of the findings.

RESULTS

Instrumental variables

Eight critical SNPs were discovered for the randomized analysis of the causal link between depression treatment and radiotherapy sessions. The basic information for the SNPs used as IVs is shown

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in table 1. In the exposure factor dataset, a SNP located on chromosome 12 (rs10771029, chr = 12, position = 23942784) had an effect allele (EA) of A and the other allele (OA) of G. The SNP had an effect size (BETA) of 0.005 and a standard error (se) of 0.001, with a p-value indicating that the SNP was significantly associated with the exposure variable under study. The effect allele frequency (EAF) of this SNP was 0.5771 indicating that the frequency of effect allele A was 57.71% in the study population. The R^2 parameter suggests that the SNPs selected in the exposure dataset explained 95.64% of the variance in the exposure factors, which is a strong explanation for the exposure. The value of the F statistic was 21 indicating that the SNPs were of sufficient strength to make causal inferences. None of the IVs showed a significant correlation with the outcome ($P > 5.0 \times 10^{-8}$), and all IVs had F values exceeding 10, indicating a minimal risk of weak instrument bias. Figure 1B shows a forest plot of the SNPs, illustrating the causal effect estimates and their confidence intervals for each SNP, suggesting that depression intervention may reduce the duration of RT sessions.

Table 1. Detailed information on the SNPs identified in the exposure and outcome.

RS ID	chr	position	exposure						outcome						R2	F
			EA	OA	BETA	se	P	EAF	EA	OA	BETA	se	P	EAF		
rs10771029	12	23942784	A	G	0.00518675	0.00110785	2.85E-06	0.577108	A	G	-2.57E-05	0.00013614	0.85	0.575564	0.956368845	21.91940228
rs11649423	16	76018396	G	A	-0.00583487	0.00116349	5.31E-07	0.340987	G	A	-6.89E-05	0.00014273 1	0.630001	0.342782	0.961759003	25.14994612
rs13020939	2	16547675	A	G	-0.00550231	0.00111783	8.56E-07	0.580232	A	G	7.76E-05	0.00013740 2	0.57	0.578387	0.960363346	24.22917284
rs1956526	14	68799787	C	A	-0.00544739	0.00115648	2.48E-06	0.657827	C	A	0.00015293 6	0.00014149 4	0.28	0.654121	0.956872585	22.18710739
rs2397048	6	51430852	G	A	0.00585406	0.00125472	3.08E-06	0.256335	G	A	9.61E-05	0.00015459 5	0.53	0.253049	0.956078917	21.76810 87
rs3731836	2	150188932	A	C	-0.00551572	0.00110512	3.06E-06	0.473755	A	C	0.00027696 9	0.00013494 6	0.04	0.483844	0.956097127	21.77755256
rs5011439	7	12275508	C	G	0.00573982	0.00114462	5.32E-07	0.391161	C	G	-0.000425047	0.00013594 5	0.00179999	0.419013	0.961753653	25.14628806
rs6701992	1	14267706	C	A	-0.00553341	0.00117186	2.34E-06	0.671438	C	A		0.00014421 4	0.44	0.672228	0.957074865	22.29637399

Chromosome (chr), indicates the chromosome number where the SNP is located; Position (bp), indicates the exact position of the SNP on the chromosome (in base pairs); Effect Allele (EA), The effect allele of interest for Mendelian randomization analysis; Other Allele (OA), The other allele relative to the effect allele; Effect Size (BETA), The magnitude of the SNP's impact on the exposure or outcome variable; It indicates the degree of change in the exposure or outcome variable for each additional copy of the effector allele; Standard Error (se), Represents the uncertainty in the estimated effect size; Effect Allele Frequency (EAF), Denotes the proportion of the effect allele in the sample, varying between 0 and 1; R-squared (R2), Measures the percentage of variance in the exposure variable accounted for by the chosen SNP, evaluating the strength of the instrumental variable; F-statistic (F), F-test statistic used to test the significance of the instrumental variable; F > 10 indicates that the instrumental variable is strong.

Heterogeneity and pleiotropy tests

The heterogeneity test results for the exposure and outcome factors are shown in table 2. Both the MR Egger (Q_pval=0.118 > 0.05) and inverse variance weighted (IVW) (Q_pval=0.143 > 0.05) methods indicated no significant differences in the relationship between depression intervention and RT session across different SNPs, suggesting low heterogeneity in the Mendelian randomization estimates. The IVW fixed model was used for further analysis. The MR-Egger intercept pleiotropy test result indicated that the MR-Egger intercept value was -0.001 (se=0.001, P=0.530), suggesting no significant horizontal pleiotropy of the SNPs on depression intervention or RT session. In the funnel plot for visualizing heterogeneity, each point represents the effect size of one SNP, with the horizontal axis typically representing effect size and the vertical axis representing precision (e.g., standard error or confidence interval width). The funnel plot results suggested that the causal effect of depression intervention on RT session was symmetrically distributed (figure 1D), indicating that the results derived from the eight SNPs used as instrumental variables were likely not influenced by potential biases.

Table 2. Heterogeneity test results for the two-sample analysis.

exposure	outcome	method	Q	Q_df	Q_pval
ukb-d-20547_3	ukb-b-16024	MR Egger	10.153	6	0.118
ukb-d-20547_3	ukb-b-16024	IVW	10.904	7	0.143

MR, Mendelian Randomization; IVW, Inverse Variance Weighted.

Primary analysis of the two-sample study

Table 3 presents the estimates of the causal impact of exposure on outcome for each technique. The IVW fixed effects approach revealed a notable causal link between the exposure and the outcome, suggesting a cause-and-effect relationship (P=0.016, OR=0.979, 95% CI 0.961-0.996). Depression intervention was found to be a favorable factor in reducing RT session. The MR-Egger regression method indicated no significant causal effect between the exposure and outcome (P=0.582, OR=1.161, 95% CI: 0.702-1.920), but it provided supplementary information for sensitivity analysis. The weighted median method showed no significant causal effect between the exposure and outcome (P=0.215, OR=0.984, 95% CI: 0.960-1.009). The weighted mode

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method also showed no significant causal effect between the exposure and outcome (P=0.615, OR=0.990, 95% CI: 0.953-1.028). In the scatter plot of the MR analysis results (Figure 1C), each point represents one SNP. The x-axis shows the impact of the SNP on the exposure, while the y-axis illustrates the SNP's influence on the outcome. Different colored lines represent different algorithms. A slope less than 0 indicates that the exposure factor is a favorable factor for the outcome.

Table 3. MR analysis results.

method	pval	lo_ci	up_ci	OR	OR_lci95	OR_uci95
MR Egger	0.582	-0.354	0.653	1.161	0.702	1.920
Weighted median	0.215	-0.041	0.009	0.984	0.960	1.009
IVW	0.053	-0.044	0.000	0.979	0.957	1.000
Weighted mode	0.615	-0.049	0.028	0.990	0.953	1.028
IVW (fixed effects)	0.016	-0.039	-0.004	0.979	0.961	0.996
MR Egger (bootstrap)	0.324	-0.191	0.132	0.971	0.826	1.141

MR, Mendelian Randomization; IVW, Inverse Variance Weighted; OR, odds ratio; lo_ci, Lower Confidence Interval; up_ci, Upper Confidence Interval.

Sensitivity analysis

A leave-one-out approach was applied to the eight SNPs, determining the combined effect of the other SNPs (table 4). After excluding each SNP, all error bars were on the left side of zero, indicating the reliability of the MR analysis results (figure 1A). The leave-one-out analysis indicated that no individual SNP affected the link between genetically anticipated depression treatment and RT session. IVW conducts a meta-analysis of the Wald ratios for individual SNPs. Although MR Egger analyses are less statistically efficient than IVW, they are useful when horizontal pleiotropy is present (figure 1B). IVW conducted a meta-analysis of the Wald ratios for each SNP. Although MR Egger analysis has less statistical power compared to IVW, it can still be used when horizontal pleiotropy is present (figure 1B). Figure 1C, on the other hand, illustrates the role of SNPs between exposure and outcome. These lines slant upward from left to right, suggesting a positive link between depression treatment and radiotherapy sessions. These lines slope downward from left to right, suggesting that the depression intervention has a protective impact on radiotherapy sessions. Figure 1D's scatter plot illustrates the relationship between each SNP and both Exposure and Outcome, with every dot representing a specific genetic variant.

Table 4. Sensitivity analysis results.

No	Sample size	SNP	b	se	p
1	463010	rs10771029	-0.024	0.013	0.058
2	463010	rs11649423	-0.027	0.012	0.021
3	463010	rs13020939	-0.023	0.013	0.077
4	463010	rs1956526	-0.021	0.013	0.106
5	463010	rs2397048	-0.027	0.011	0.019
6	463010	rs3731836	-0.017	0.012	0.142
7	463010	rs5011439	-0.013	0.010	0.185
8	463010	rs6701992	-0.022	0.013	0.090
9	463010	All	-0.022	0.011	0.053

SNP, single nucleotide polymorphism.

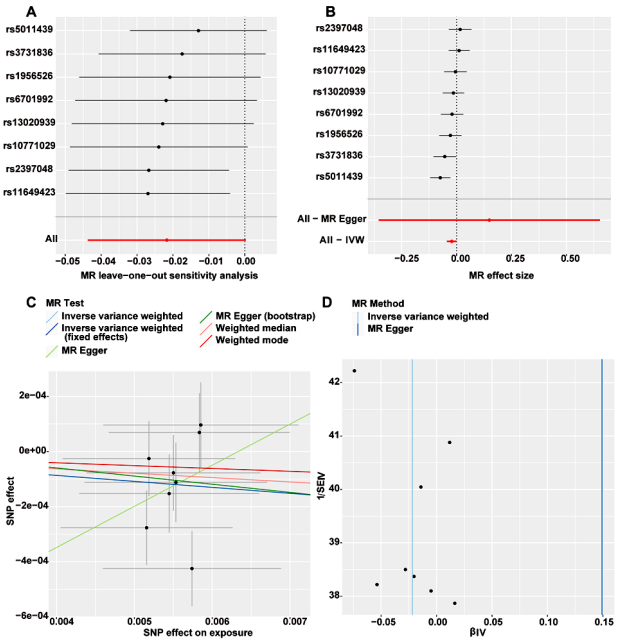

Figure 1. Main Results of the MR Analysis (**A.** Sensitivity analysis forest plot using the leave-one-out method, changes in effect estimates (β-values) for the remaining SNPs after removing each SNP individually when analyzing the causal effect of exposure factors on radiotherapy sessions; **B.** Effect Size Analysis, Show the effect size (β-value) of each SNP on radiotherapy sessions in the analysis. The vertical axis is the identifier of the SNP and the horizontal axis is the effect size; **C.** Causal relationship between SNPs and exposure factors, show the effect size of the association of each SNP on exposure factors and radiotherapy regimen. The horizontal axis is the effect size of the SNP on the exposure factor (SNP effect on exposure) and the vertical axis is the effect size of the SNP on the outcome variable (course of radiotherapy); **D.** Funnel plot evaluating heterogeneity, comparisons of effect estimates (β-values) and standard errors (SEs) from different Mendelian randomization methods (e.g. Inverse variance weighted, MR Egger) are shown.

DISCUSSION

With the rising incidence of tumors, the symptoms experienced during radiotherapy (RT) and the frequent hospital re-examinations place patients under significant stress, leading to a substantial mental burden. Previous research has also confirmed the elevated risk of psychiatric disorders, including anxiety and depression, among oncology patients undergoing RT [20]. Depression is particularly common in this population, negatively impacting their physical recovery, quality of life, and long-term survival. This study reveals a negative causal relationship between depression interventions, such as mindfulness and yoga, and the duration of RT sessions, suggesting that these interventions may help reduce the length of RT treatment.

Mindfulness-Based Stress Reduction (MBSR) is a structured training program introduced by Dr. Kabat-Zinn J in 1979. MBSR focuses on cultivating

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awareness of present experiences and fully accepting one's inner emotions, helping patients align their values with life experiences. Numerous studies have demonstrated that MBSR can alleviate discomfort during radiotherapy (RT). Liu *et al*. [21] found that MBSR effectively reduced the severity of symptoms in cervical cancer patients undergoing RT. An *et al*. [22] reported that MBSR significantly alleviated clinical symptoms in patients with advanced cervical cancer undergoing concurrent RT and chemotherapy. Pollard *et al.* [23] showed that MBSR could help patients undergoing RT for head and neck cancer achieve more positive treatment outcomes. Bagherzadeh *et al*. [24] demonstrated that MBSR improved emotional well-being and enhanced the efficacy of RT in breast cancer patients. Virginia *et al*. [25] suggested that MBSR could serve as a valuable adjunct therapy for early-stage breast cancer patients undergoing RT. Although these studies highlight the effectiveness of MBSR in the context of RT, they do not clarify the causal relationship between the two. Our research findings (figure 1) indicated a negative causal link between conducting depression treatments like MBSR and RT sessions, consistent with the pattern observed in earlier studies.

Previous studies have pointed out the need for interventions and monitoring during RT treatment in oncology patients to enhance their quality of life [26]. Yoga has shown promise in improving fatigue and immunity among cancer survivors, making it a valuable complementary therapy [27]. Numerous studies have demonstrated that yoga therapy can enhance the quality of life and physiological function of cancer patients, alleviating cancer-related fatigue during and after radiotherapy (RT). Milbury *et al.* [28] encouraged patients with high-grade gliomas (HGG) to practice yoga during RT, which led to improvements in the psychological well-being of both patients and their caregivers. Stella *et al*. [29] conducted yoga sessions for families of patients with stage III or IV cancer undergoing RT, highlighting benefits for both patients and caregivers. Jain *et al.* [30] discovered that practicing yoga notably decreased the concentrations of pro-inflammatory interleukin IL-1β and versatile interleukin IL-10 during radiation therapy, enhancing the immune function of patients and indicating yoga's potential as a valuable supplementary treatment in oncology. Kathrin *et al.* [31] demonstrated that yoga interventions helped patients undergoing chest RT maintain vitality and a positive outlook throughout follow-up. A meta-analysis suggested that yoga reduces fatigue and anxiety during RT, though it did not significantly improve depression [28]. While current research has largely focused on the symptomatic benefits of yoga during RT, the causal relationship between yoga and the duration of RT sessions remains unexplored. Further clinical data are needed to determine whether combining yoga with RT could serve as a new therapeutic approach. Our study suggests that yoga and other depression interventions may help shorten RT sessions, but more research is needed to establish specific threshold data for optimal treatment strategies. Our findings (tables 3 and 4) suggest that depressive intervention activities such as yoga can shorten RT treatment sessions, with specific threshold data to be further explored.

This study has certain limitations. First, the samples used for Mendelian randomization analysis were exclusively of European descent, so it remains uncertain whether the findings are generalizable to other populations. Secondly, the study relied on data from the GWAS database, and the number of SNPs available for analysis was constrained by the original sample size and specific screening criteria. Upcoming studies ought to increase the number of participants to strengthen the reliability of the results. Thirdly, a higher proportion of RT patients who received yoga and depression interventions were women, and due to limitations in the original data, subgroup analysis by gender was not feasible.

CONCLUSION

This study identifies a negative causal relationship between depression interventions and the duration of RT sessions, with depression interventions serving as a beneficial factor in reducing RT duration. However, further validation is required to determine whether integrating depression interventions with RT could serve as a novel combined treatment approach for optimally shortening RT sessions.

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***Conflicts of interest*:** The researchers state that the investigation was carried out without any commercial or monetary ties that might be seen as a possible conflict of interest.

***Ethical Considerations*:** This study did not require ethical review and approval, as all Mendelian

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randomization data is available to the public. All participants in the initial genome-wide association studies provided their informed consent. Written informed consent was obtained from the patients/participants for their involvement in this research.

***Author contribution*:** N.L., contributed to the conceptualization, data curation, formal analysis, and drafting of the original manuscript. Z.L., contributed to the study conception and design, supervised the project, managed the administration, reviewed and edited the manuscript, and served as the corresponding author. H.X., was responsible for methodology, validation, and investigation. X.L., handled resources and data curation. Y.Z., contributed to software development and formal analysis. S.L., managed data curation and visualization. X.W., participated in investigation and resource management. Q.W., worked on methodology and data curation. Y.L., assisted with manuscript review, editing, and validation. X.C., provided supervision and secured funding for the project.

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