

# Association Between Poor Lifestyle Habits and Cutaneous Melanoma Risk: A Mendelian Randomization Study

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**Background:** There is still no consensus on the risk factors of cutaneous melanoma, and the causal relationship between poor lifestyle habits (including undersleeping, smoking, alcohol consumption and sedentary behaviour) and cutaneous melanoma remains uncertain.

**Methods:** We investigated the causal effect of poor lifestyle habits on cutaneous melanoma through the Two-sample Mendelian randomization (MR). MR analysis was performed by using the genome-wide association studies (GWAS) statistics. Single-nucleotide polymorphisms (SNPs) robustly associated with undersleeping, smoking, alcohol consumption and sedentary behaviour were used as instrumental variables, we performed five MR approaches, including inverse variance weighted (IVW), weighted median, simple mode, MR-Egger and weighted mode.

**Results:** The causal relationship between undersleeping and cutaneous melanoma was discovered in IVW (OR = 1.018, 95% CI = 1.002–1.033, P = 0.025). However, the causal association between smoking, alcohol consumption, sedentary behaviour and cutaneous melanoma have not been found in all MR approaches.

**Conclusion:** The MR analysis indicated that undersleeping is causally associated with the risk of cutaneous melanoma.

**Keywords:** cutaneous melanoma, undersleeping, Mendelian randomization, poor lifestyle habits

## Introduction

Cutaneous melanoma is a skin malignancy originating from melanocytes in the skin.<sup>1,2</sup> The mortality rate of cutaneous melanoma accounts for about 73% of the total mortality rate of skin tumors, making it the most harmful skin tumor.<sup>3,4</sup> It is reported that the global incidence of cutaneous melanoma continues to increase in recent years.<sup>5,6</sup> Although comprehensive treatment, including surgery, chemotherapy, targeted therapy and immunotherapy, is currently used for cutaneous melanoma, its prognosis is still poor, especially for patients with distant metastasis.<sup>7,8</sup> Thus, early diagnosis and treatment of cutaneous melanoma are crucial. At present, extensive research is dedicated to study the etiology of cutaneous melanoma. It has been confirmed that ultraviolet radiation, friction, dysplastic nevi, sunburns and radiation may contribute to cutaneous melanoma.<sup>9–13</sup> However, the etiology and risk factors of cutaneous melanoma are not yet fully understood.

In recent years, many studies have pointed out that bad poor lifestyle habits are associated with an increased incidence of many tumors, including cutaneous melanoma. For instance, scholars have found that people with sleep disorders are more likely to be diagnosed with cancer.<sup>14</sup> A meta-analysis article found a moderate association between alcohol consumption and increased risk of cutaneous melanoma.<sup>15</sup> Meanwhile, studies have shown that smoking is negatively related to the incidence and mortality of cutaneous melanoma.<sup>16,17</sup> There are also many studies on melanoma and dietary factors, but their results are often highly controversial.<sup>18</sup> The limitation of these studies is that they did not exclude the confounding factors, which may lead to bias. Therefore, the causal relationship between poor lifestyle habits and cutaneous melanoma remains uncertain.

Mendelian randomization (MR) is a method of inferring causal relationships using single nucleotide polymorphisms (SNPs).<sup>19,20</sup> MR has two major advantages: the allocation of genetically controlled traits follows strict randomization principles, which fundamentally reduces the influence of confounding factors; the association between alleles and diseases is invariant with the progression of disease, which minimizes the bias caused by reverse causal relationships.<sup>21,22</sup> Here, we applied the two-sample MR analysis by using the genome-wide association studies (GWAS) statistics of poor lifestyle habits (including undersleeping, smoking, alcohol consumption and sedentary behaviour) and cutaneous melanoma to investigate their genetic causality between poor lifestyle habits and cutaneous melanoma, which has significant clinical and public health implications.

## Methods

### Study Design Description

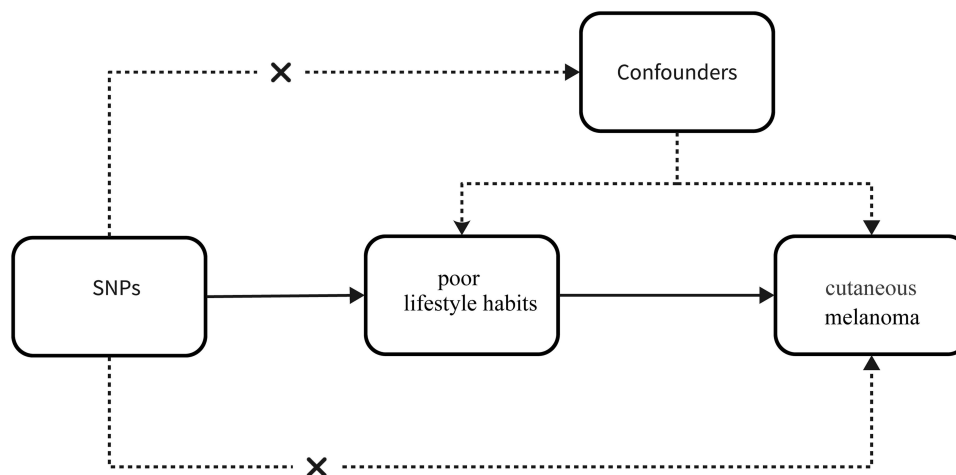
We applied the two-sample MR analysis to investigate causal association between poor lifestyle habits and cutaneous melanoma (Figure 1). The MR analysis that considered undersleeper, ever smoked, alcohol consumption, sedentary behaviour duration as the exposure and cutaneous melanoma as the outcome were conducted. This study was approved by the Ethics Committee of Shengli Oilfield Central Hospital.

### Selection of Appropriate Instrumental Variables (IVs) for MR

We picked out IVs from GWAS statistics for MR analysis. In order to include contributing SNPs, we setted appropriate the threshold ( $p < 5 \times 10^{-6}$ ) of genome-wide significance. This study is exploratory research, so we chose a relatively soft threshold. Suitable SNPs were further selected according to the linkage disequilibrium (LD,  $kb=10000$ ,  $r^2 > 0.01$ ). Subsequently, the instrument strength was evaluated through calculating F-statistics, and IVs with  $F < 10$  were considered to have weak instrument strength and excluded. LDlink websites (<https://ldlink.nih.gov/?tab=ldtrait>) could search whether variants are associated with a certain trait or disease, and was used to recognize and delete IVs related to confounding factors ( $p < 5 \times 10^{-8}$ ).

### GWAS Summary Data and Selection of IVs for Poor Lifestyle Habits

The GWAS data of poor lifestyle habits was downloaded from IEU OpenGWAS project (<https://gwas.mrcieu.ac.uk/>) and GWAS Catalog (<https://www.ebi.ac.uk/gwas/>). The details are as follows: undersleepers, study accession is ebi-a-GCST006686, sample size is 110188; ever smoked, study accession is ieu-b-4858, sample size is 99996; alcohol consumption, study accession is ieu-b-4834, sample size is 83626; sedentary behaviour duration, study accession is GCST006913, sample size is 91105 (Table 1). Based on the selection criteria for IVs mentioned earlier, 16, 70, 85, 49 SNPs that strongly associated with undersleeper, ever smoked, alcohol consumption, sedentary behaviour duration were



**Figure 1** A brief description of this study design.

**Table 1** Details of GWAS Summary Data Included in the Study

Study Name	Study Accession	Site	Population	Sample Size	Web source
Undersleepers	ebi-a-GCST006686	IEU OpenGWAS	European	110188	<a href="https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006686/">https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST006686/</a>
Ever smoked	ieu-b-4858	IEU OpenGWAS	European	99996	<a href="https://gwas.mrcieu.ac.uk/datasets/ieu-b-4858/">https://gwas.mrcieu.ac.uk/datasets/ieu-b-4858/</a>
Alcohol consumption	ieu-b-4834	IEU OpenGWAS	European	83626	<a href="https://gwas.mrcieu.ac.uk/datasets/ieu-b-4834/">https://gwas.mrcieu.ac.uk/datasets/ieu-b-4834/</a>
Sedentary behaviour duration	GCST006913	GWAS Catalog	European	91105	<a href="https://www.ebi.ac.uk/gwas/studies/GCST006913">https://www.ebi.ac.uk/gwas/studies/GCST006913</a>
Melanoma skin cancer	ieu-b-4969	IEU OpenGWAS	European	375767	<a href="https://gwas.mrcieu.ac.uk/datasets/ieu-b-4969/">https://gwas.mrcieu.ac.uk/datasets/ieu-b-4969/</a>

identified respectively. Among this SNPs, rs12731986, rs26579 and rs28732378 were found to have a strong association with confounding factors (sunburns, a risk factor for melanoma) ([Supplementary Table 1](#)), thus they have been removed. Finally, appropriate SNPs were picked out and used as IVs ([Supplementary Table 2](#)).

## GWAS Summary Data for Cutaneous Melanoma

The GWAS data of cutaneous melanoma (study accession: ieu-b-4969, sample size: 375767) were downloaded from IEU OpenGWAS project (<https://gwas.mrcieu.ac.uk/>). Details of these GWASs are showed in [Table 1](#).

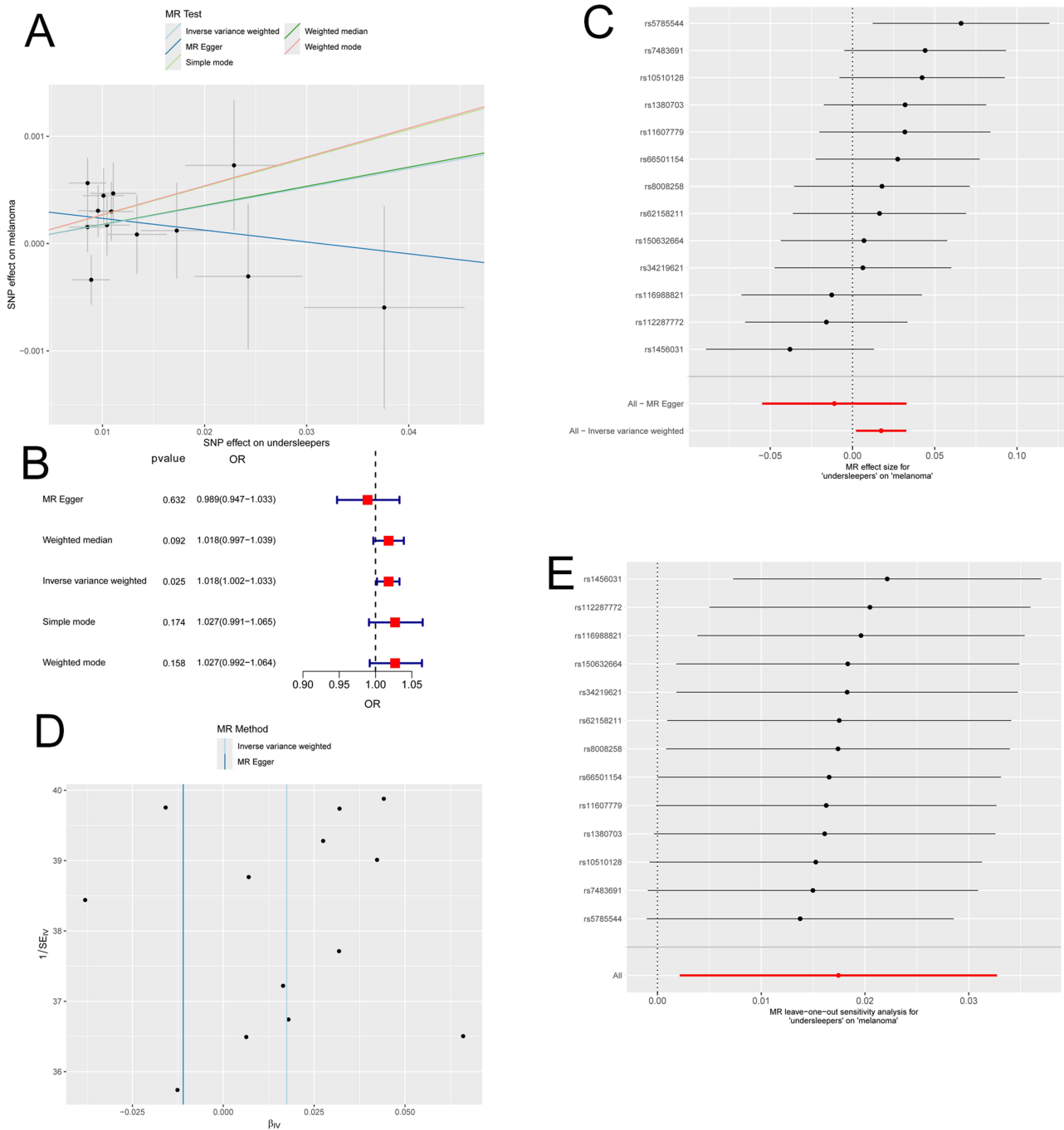
## Statistical Analysis

Five MR methods (inverse variance weighted (IVW), weighted mode, MR-Egger, simple mode and weighted median) were used to investigate the potential genetic causality between poor lifestyle habits and cutaneous melanoma. When harmonizing outcome and exposure data, SNPs that being palindromic with intermediate allele frequencies were removed.<sup>23</sup> IVW assumes that instruments can only affect the outcome through exposure rather than alternative pathway, therefore it serves as the primary method.<sup>23</sup> The disadvantage of IVW is that it may have potential horizontal pleiotropy effects, thus we performed weighted mode, MR Egger, weighted media and simple mode to complement IVW. The latter four methods can accurately evaluate causal relationships even in the presence of invalid SNPs, but their efficiency is low.<sup>24,25</sup> The existence of pleiotropy lead to the failure of independence and exclusivity assumptions, resulting in unreliable MR results. Thus, MR-Egger intercept was used as an indicator to investigate directional pleiotropy, and MR PRESSO was used to evaluate horizontal pleiotropy.<sup>26,27</sup> When the P value is less than 0.05, it is considered to have pleiotropy. Funnel plots, Cochran's Q test in MR-Egger and IVW were used to assess heterogeneity. Leave-one-out sensitivity analysis was used to detect whether a single SNP affects the overall MR result. The TwoSampleMR package in R software was used to conduct all MR analyses.

## Results

### The Casual Effect of Undersleeping on Cutaneous Melanoma

We utilized two-sample MR to reveal the causal effect of undersleeping on cutaneous melanoma. As shown in scatter plot ([Figure 2A](#)) and forest plots ([Figure 2B](#) and [C](#)), the IVW result suggested that undersleeping was causally related to cutaneous melanoma, and undersleeping is the risk factor for cutaneous melanoma (OR = 1.018, 95% CI = 1.002–1.033, P = 0.025). Except for MR Egger (OR = 0.989, 95% CI = 0.947–1.033, P = 0.632), the result of weighted median (OR = 1.018, 95% CI = 0.997–1.039, P = 0.092), simple mode (OR = 1.027, 95% CI = 0.991–1.065, P = 0.174) and weighted mode (OR = 1.027, 95% CI = 0.992–1.064, P = 0.158) were in line with IVW, but they did not reach statistical significance. MR PRESSO result ([Table 2](#), global test P = 0.318) showed that there was no potential horizontal pleiotropy, and MR-Egger intercept result ([Table 2](#),



**Figure 2** The causal effect of undersleeping on cutaneous melanoma. **(A)** Scatter plot of the association between undersleeper and cutaneous melanoma. The five methods applied in the paper were all depicted, including MR Egger, Weighted median, IVW, Simple mode and Weighted mode. **(B)** Forest plots of the association between undersleeper and cutaneous melanoma, and presented the results of five analysis methods. **(C)** Forest plot showed the MR estimate and 95% CI values for each SNP, also show the IVW and MR-Egger results at the bottom. **(D)** A funnel plot was applied to detect whether the observed association was along with obvious heterogeneity. **(E)** Leave-one-out analyses to evaluate whether any single instrumental variable was driving the causal effect.

intercept = 0.000345, P = 0.204) showed that there was no incidence of directional pleiotropy. Meanwhile, funnel plot did not find the obvious heterogeneity (Figure 2D), and no significant heterogeneity was found by using Cochran’s Q test in the IVW and MR-Egger (Table 3, Q = 13.784, P = 0.315 and Q= 11.824, P = 0.377 respectively). In addition, leave-one-out sensitivity analysis showed that there was no significant change in the association when excluding any individual SNPs (Figure 2E).

**Table 2** Pleiotropy Analyses

Exposure	Outcome	MR-Egger Intercept		MR PRESSO
		Intercept	P- intercept	Global test P
Undersleeper	Cutaneous melanoma	0.000345	0.204	0.318
Ever smoked	Cutaneous melanoma	0.000011	0.920	0.835
Alcohol consumption	Cutaneous melanoma	-0.000167	0.238	1.000
Sedentary behaviour	Cutaneous melanoma	0.000169	0.281	0.592

**Table 3** Heterogeneity Analyses

Exposure	Outcome	Cochran's Q test in IVW		Cochran's Q test in MR-Egger	
		Q	P	Q	P
Undersleeper	Cutaneous melanoma	13.784	0.315	11.824	0.377
Ever smoked	Cutaneous melanoma	48.486	0.834	48.476	0.809
Alcohol consumption	Cutaneous melanoma	35.906	1.000	34.492	1.000
Sedentary behaviour	Cutaneous melanoma	31.567	0.587	30.368	0.599

## The Casual Effect of Smoking on Cutaneous Melanoma

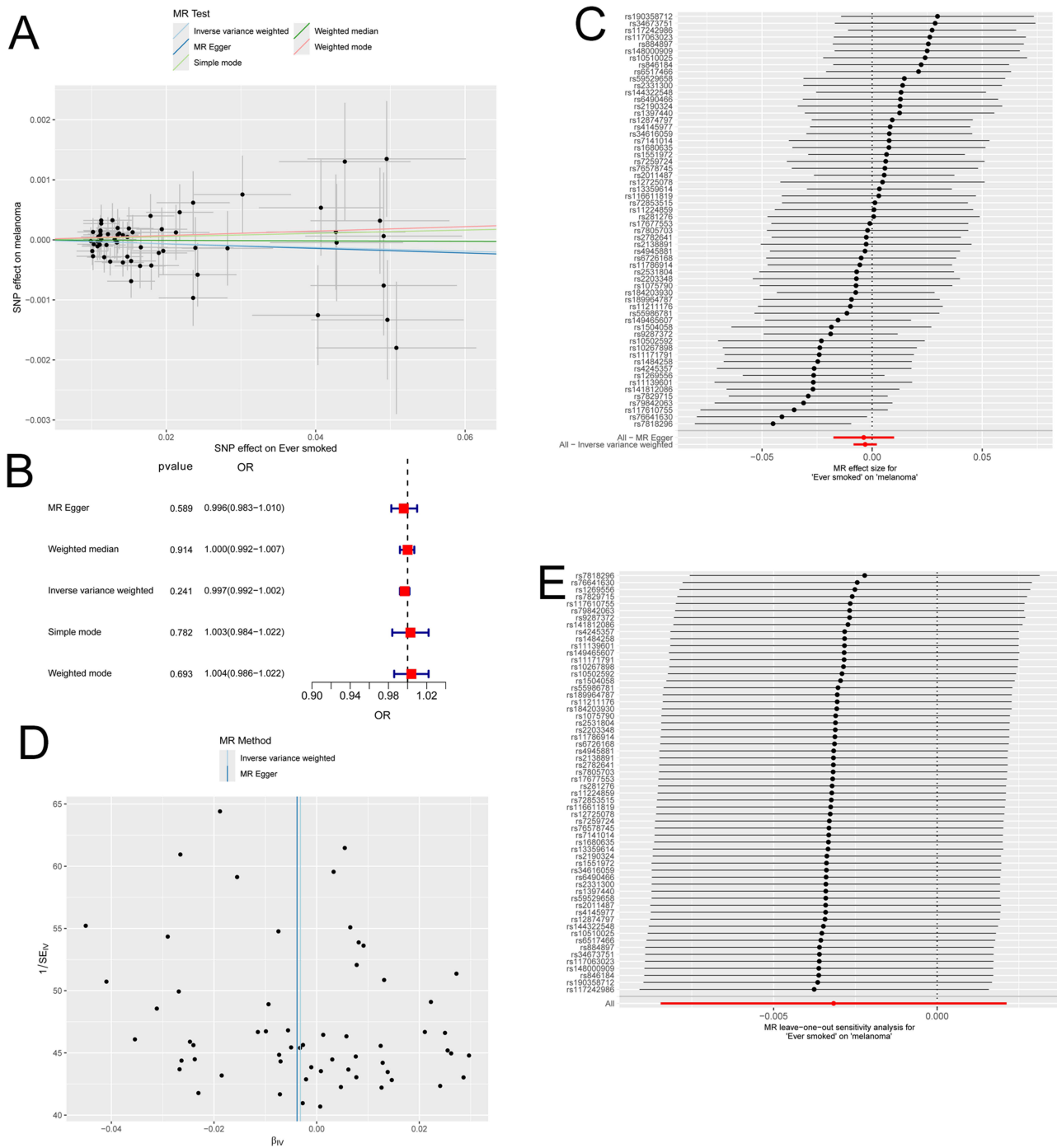
We further explored the causal effect of smoking on cutaneous melanoma. All five MR methods showed that smoking was not significantly associated with cutaneous melanoma (Figure 3A-C). The specific results are as follows: IVW (OR = 0.997, 95% CI = 0.992–1.002, P = 0.241), MR Egger (OR = 0.996, 95% CI = 0.983–1.010, P = 0.589), weighted median (OR = 1.000, 95% CI = 0.992–1.007, P = 0.914), simple mode (OR = 1.003, 95% CI = 0.984–1.022, P = 0.782) and weighted mode (OR = 1.004, 95% CI = 0.986–1.022, P = 0.693) (Figure 3A-C). In addition, the MR PRESSO (Table 2, global test P = 0.835) and MR-Egger intercept (Table 2, intercept = 0.000011, P = 0.920) did not find horizontal and directional pleiotropy. Cochran's Q test in IVW (Q = 48.486, P = 0.834) and MR-Egger (Q = 48.476, P = 0.809) (Table 3) indicated that there was no significant heterogeneity. No significant heterogeneity was found in the funnel plot (Figure 3D). Moreover, we conducted leave-one-out sensitivity analysis and did not find a significant association (Figure 3E).

## The Casual Effect of Alcohol Consumption on Cutaneous Melanoma

We next detected the causal effect of alcohol on cutaneous melanoma. No significant correlation was found between alcohol consumption and cutaneous melanoma using MR methods, including IVW (OR = 1.000, 95% CI = 0.999–1.001, P = 0.927), MR Egger (OR = 1.001, 95% CI = 0.999–1.002, P = 0.309), weighted median (OR = 1.000, 95% CI = 0.999–1.001, P = 0.675), simple mode (OR = 0.999, 95% CI = 0.997–1.002, P = 0.616) and weighted mode (OR = 0.999, 95% CI = 0.997–1.001, P = 0.457) (Figure 4A-C). No significant pleiotropy was found during the pleiotropy test (MR-Egger intercept, intercept = -0.000167, P = 0.238; MR PRESSO, global test P = 1.000) (Table 2). Funnel plot and Cochran's Q test in IVW (Q = 35.906, P = 1.000) and MR-Egger (Q = 34.492, P = 1.000) did not find significant heterogeneity (Figure 4D) (Table 3). Leave-one-out sensitivity analysis did not find a significant relation between alcohol consumption on cutaneous melanoma (Figure 4E).

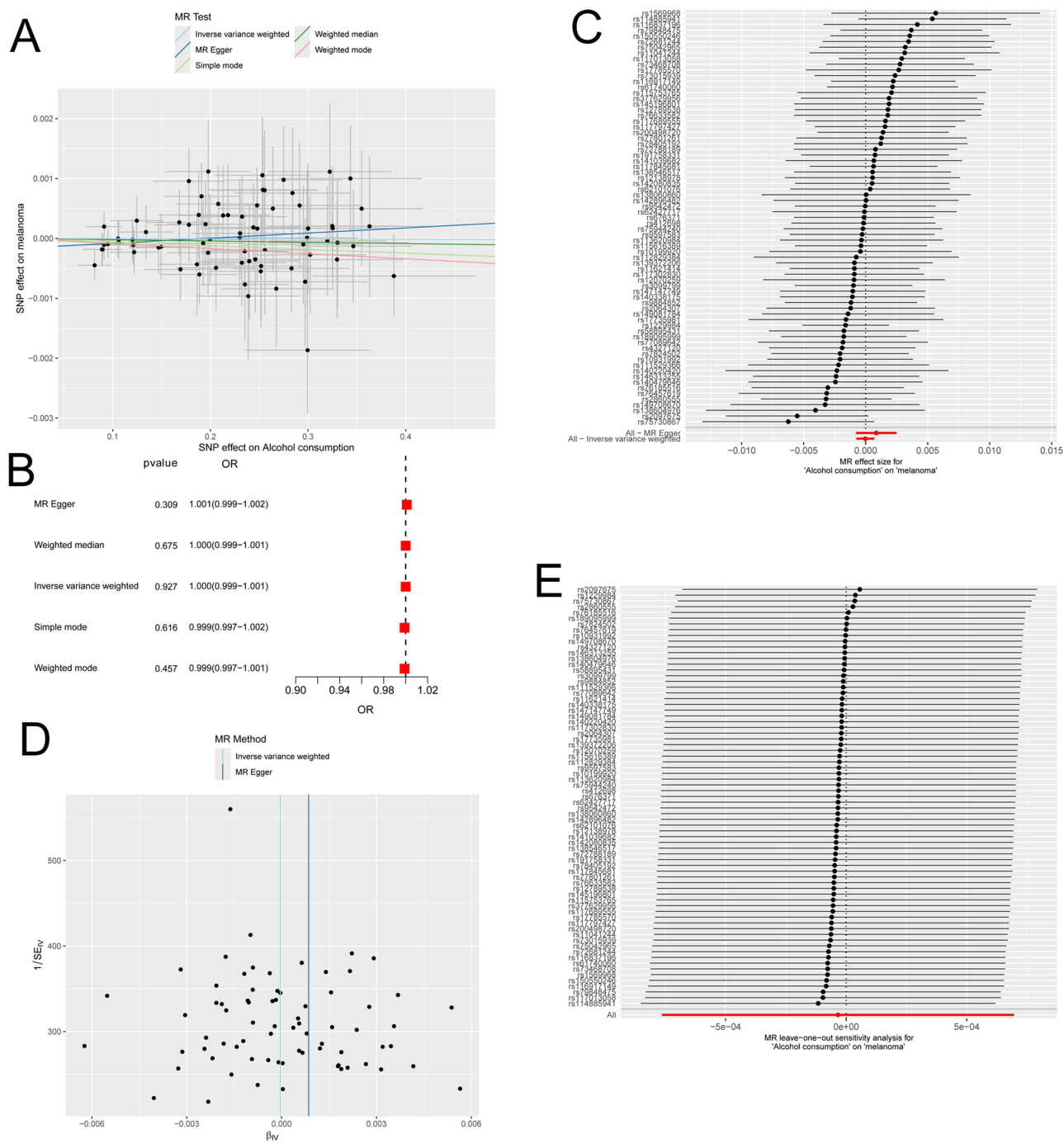
## The Casual Effect of Sedentary Behaviour on Cutaneous Melanoma

We further investigated the causal effect of sedentary behaviour on cutaneous melanoma. It was found that there is no causal relationship between sedentary behaviour and cutaneous melanoma using MR analysis, including IVW (OR =



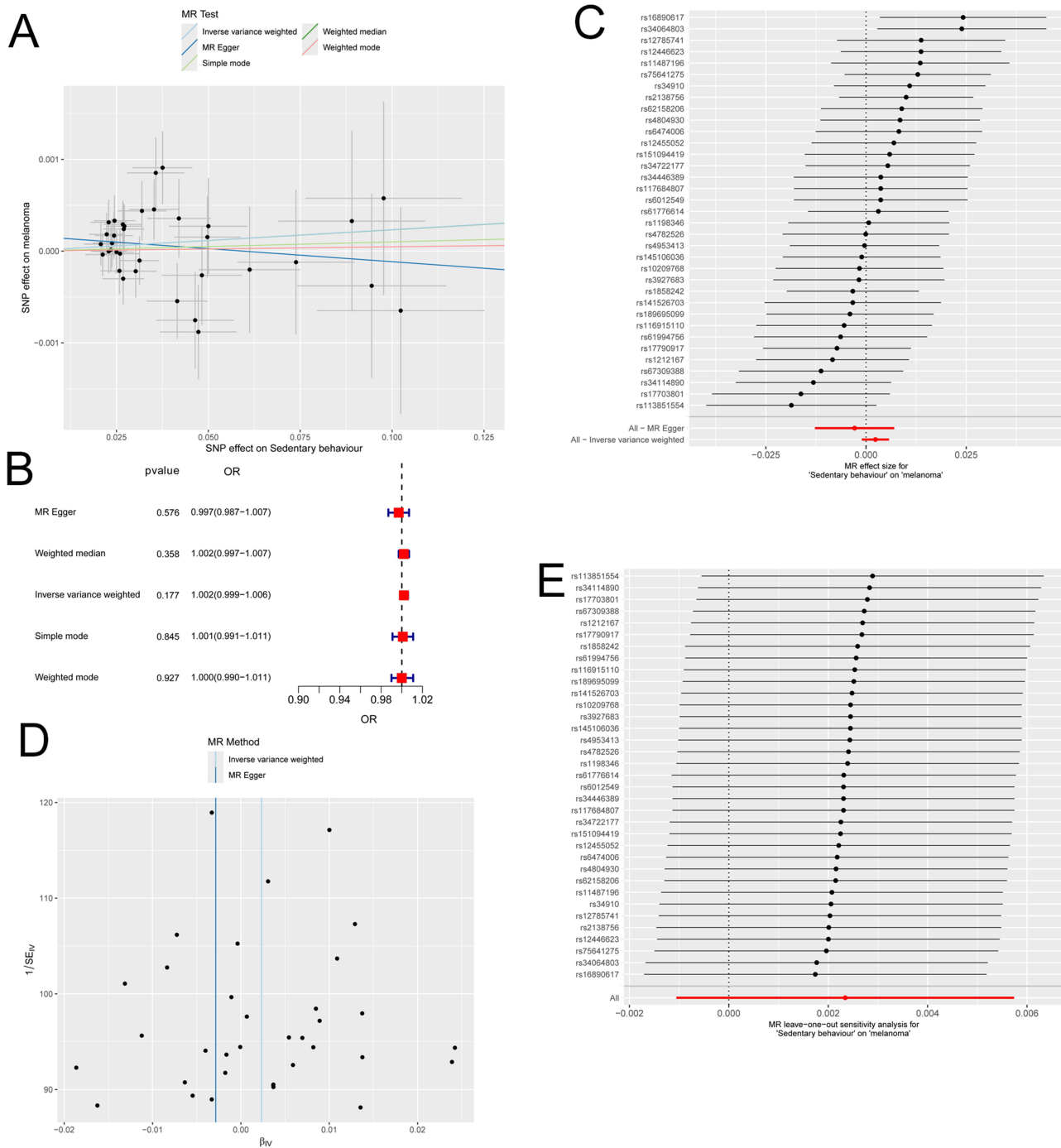
**Figure 3** The causal effect of smoking on cutaneous melanoma. **(A)** Scatter plot of the association between ever smoked and cutaneous melanoma. The five methods applied in the paper were all depicted. **(B)** Forest plots of the association between ever smoked and cutaneous melanoma, and presented the results of five analysis methods. **(C)** Forest plot showed the MR estimate and 95% CI values for each SNP, also show the IVW and MR-Egger results at the bottom. **(D)** A funnel plot was applied to detect the obvious heterogeneity. **(E)** Leave-one-out analyses to evaluate whether any single instrumental variable was driving the causal effect.

1.002, 95% CI = 0.999–1.006, P = 0.177), MR Egger (OR = 0.997, 95% CI = 0.987–1.007, P = 0.576), weighted median (OR = 1.002, 95% CI = 0.997–1.007, P = 0.358), simple mode (OR = 1.001, 95% CI = 0.991–1.011, P = 0.845) and weighted mode (OR = 1.000, 95% CI = 0.990–1.011, P = 0.927) (Figure 5A-C). We did not find any significant pleiotropy in the pleiotropy test through MR-Egger intercept (intercept = 0.000169, P = 0.281) and MR PRESSO (global test P = 0.592) (Table 2). In addition, we did not find significant heterogeneity in the data through funnel plot (Figure 5D)



**Figure 4** The causal effect of alcohol consumption on cutaneous melanoma. **(A)** Scatter plot of the association between alcohol consumption and cutaneous melanoma. The five methods applied in the paper were all depicted. **(B)** Forest plots of the association between alcohol consumption and cutaneous melanoma, and presented the results of five analysis methods. **(C)** Forest plot showed the MR estimate and 95% CI values for each SNP, also show the IVW and MR-Egger results at the bottom. **(D)** A funnel plot was applied to investigate the obvious heterogeneity. **(E)** Leave-one-out analyses to evaluate whether any single SNPs was driving the causal effect.

and Cochran’s Q test in IVW ( $Q = 31.567, P = 0.587$ ) and MR-Egger ( $Q = 30.368, P = 0.599$ ) (Table 3). As showed in Figure 5E, no causal relationship was found between sedentary behaviour and cutaneous melanoma through leave-one-out sensitivity analysis.



**Figure 5** The casual effect of sedentary behaviour on cutaneous melanoma. **(A)** Scatter plot of the association between sedentary behaviour and cutaneous melanoma. The five methods applied in the paper were all depicted. **(B)** Forest plots of the association between sedentary behaviour and cutaneous melanoma, and presented the results of five analysis methods. **(C)** Forest plot showed the MR estimate and 95% CI values for each SNP, also show the IVW and MR-Egger results at the bottom. **(D)** A funnel plot was applied to investigate the obvious heterogeneity. **(E)** Leave-one-out analyses to evaluate whether any single SNPs was driving the causal effect.

## Discussion

Extensive research has been devoted to investigate the causes and risk factors of cutaneous melanoma, and has found that ultraviolet radiation, friction, dysplastic nevi, sunburns and radiation may contribute to cutaneous melanoma.<sup>9-12</sup> In recent years, many studies have pointed out that unhealthy lifestyle habits may also associated with cutaneous melanoma, especially alcohol consumption and smoking. A prospective cohort study of the European Prospective Investigation into

Cancer and Nutrition (EPIC) found that lifetime drinking is positively associated with cutaneous melanoma and basal cell carcinoma.<sup>28</sup> A case-control study showed that patients who drank more than 1.4 drinks a week had significantly higher incidence rate of melanoma.<sup>29</sup> Some scholars found that compared with never-smokers, the incidence rate of melanoma in former smokers was significantly reduced.<sup>30</sup> However, some studies indicated that there is no significant causality between smoking and cutaneous melanoma.<sup>31</sup> These studies indicate that there is still significant controversy regarding the relationship between smoking and alcohol consumption and the development of cutaneous melanoma, which deserves further investigation. Meanwhile, scholars have found that people with sleep disorders are more likely to be diagnosed with cancer.<sup>14</sup> Insomnia has also been confirmed to be associated with a higher risk of endometrioid epithelial ovarian cancer.<sup>32</sup> Sedentary time was demonstrated to associated with higher risk of hormone-receptor-negative breast cancer.<sup>33</sup> However, the relationship between sleeping and sedentary and cutaneous melanoma has not been studied.

We used the two-sample MR analysis to investigate the causality between undersleeper, ever smoked, alcohol consumption, sedentary behaviour and cutaneous melanoma. Compared with traditional observational studies, MR has the following advantages. Randomized controlled trials are widely accepted for investigating the causality, and MR can simulate randomized controlled trials in observation environments because the allocation of SNPs during pregnancy follows strict randomization principles, thereby avoiding bias caused by confounding factors.<sup>23</sup> In addition, because the association between alleles and diseases remains unchanged, this avoids reverse causality.<sup>23</sup> In this paper, we found the genetically predicted causal role of undersleeping on the risk of cutaneous melanoma. The causal association between smoking, alcohol consumption, sedentary behaviour and cutaneous melanoma have not been proved.

In view of the increasing incidence rate and harmfulness of cutaneous melanoma, we investigated the relationship between poor lifestyle habits and the risk of cutaneous melanoma. We have found that undersleeping is a risk factor for melanoma. Moreover, undersleeping has also been identified as a potential risk factor for other cancers, including colorectal cancer, ovarian cancer and so on.<sup>32,34</sup> Therefore, the results of this study have potential significant clinical and public health implications. Undersleeping is a serious and urgent global problem that needs to be addressed. However, our research also has some limitations. Although the results of this study are reliable, small sample sizes or the potential overlap between unhealthy lifestyle habits and cutaneous melanoma may lead to bias. Our research focuses on the European population, which results in a lack of racial diversity. Therefore, we need to confirm whether our results are consistent with those of other races.

In conclusion, our study is the MR study to detect the causal relationship between poor lifestyle habits and the risk of cutaneous melanoma. MR analysis found a causal relationship between undersleeping (lack of sleep) and cutaneous melanoma, and undersleeping is its risk factor.

## Data Sharing Statement

Data is provided within the manuscript or supplementary information files.

## Ethical Approval and Consent to Participate

This study was approved by the Ethics Committee of Shengli Oilfield Central Hospital.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors declare that they have no competing interests.

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