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ORIGINAL RESEARCH

The Causal Relationship Between Physical Activity and Skin Cancer Risk: An Univariable Mendelian Randomization Study

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Background: The existing observational research on the relationship between physical activity (PA) and skin cancer (SC) is contentious, which points to the intricate nature of their association and underscores the imperative for more nuanced research to untangle the causal dynamics at play. The aim of this article is to delve deeper into this complex relationship, seeking to clarify whether PA serves as a protective factor against SC, or contributes to its risk.

Methods: We utilized data from the genome-wide association study (GWAS) of PA from GWAS Catalog (include self-reported moderate to vigorous PA (MVPA), self-reported vigorous PA (VPA), and accelerometer-based average-accelerated PA). The data of SC is from FinnGen. All of the participants are of European ancestry. We used two-sample Mendelian Randomization (TSMR) to analyze the causal relationship between PA and SC.The research was conducted using inverse variance weighted (IVW) method as the primary approach, and MR Egger regression as supplementary analytical method. To ensure the robustness of the results, Cochran's Q-test and MR pleiotropy residual sum and outlier (MR-PRESSO) global tests were used to measure sensitivity.

Results: Our analysis indicated that average-accelerated PA was associated with an increased risk of SC ($OR_{IVW} = 0.94$, 95% CI 0.93–0.96, $P < 0.001$). While neither MVPA ($OR_{IVW} = 0.99$, 95% CI 0.67–1.47, $P = 0.962$) nor VPA ($OR_{IVW} = 0.80$, 95% CI 0.29–2.18, $P = 0.656$) shows causal relationship on risk of SC.

Conclusion: Our research suggests that PA is associated with a decrease in SC, provides a new perspective for future SC prevention. Our research findings bolster the hypothesis that increased levels of PA, characterized by average acceleration, are associated with a reduced risk of developing skin cancer. This has filled the gap of research on the causal relationship between PA and SC, and could pave the way for novel preventive strategies against skin cancer.

Keywords: skin cancer, physical activity, Mendelian randomization, causal relationship

Introduction

Skin cancer (SC) has emerged as one of the most formidable cancers of the decade and currently ranks as the fifth most prevalent cancer type. Forecasts suggest that its impact will increase, potentially surpassing heart disease as the primary cause of death and the most significant obstacle to increasing life expectancy in the future.[1,2] Basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), types of SC, are prevalent types of SC, whereas melanoma represents the gravest concern.[3] The development of SC primarily results from the rapid multiplication of skin cells that have mutated or possess genetic defects, causing persistent, unrepaired DNA damage. This progression is influenced by a complex interplay of genetic, molecular, and environmental factors that facilitate the transformation of normal skin cells into cancerous ones.[4] Prominent risk factors encompass exposure to ultraviolet (UV) radiation, immune system deficiencies affecting the skin, multiple forms of DNA damage, skin pigmentation variations, and the use of tanning beds, among others.[4–7]

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Physical activity (PA) is any bodily movement produced by skeletal muscles that requires energy expenditure. This includes all movements in daily life, such as walking, running, cycling, sports, and recreational activities, as well as activities performed at work, at home, and during leisure time. Engaging in regular physical activity (PA) along with maintaining a balanced diet, managing weight, and abstaining from smoking, plays a crucial role in promoting overall health. Such practices are instrumental in reducing the incidence of various non-communicable ailments, including but not limited to cardiovascular diseases, diabetes, and cancer. Furthermore, PA is beneficial for enhancing mental well-being, sleep quality, and cognitive performance.[5] Although PA has demonstrated numerous benefits for overall health, studies examining the relationship between PA and specific diseases have shown inconsistent results, with SC being a typical example. Research by Perrier, F et al,[6] Tran, A.D et al,[7] and Patel, A.V et al[8] has indicated that PA may increase the risk of SC. However, a particular study identified that elevated levels of PA could decrease the risk of melanoma by up to 30%,[9] whereas a comprehensive meta-analysis encompassing 12 cohort studies found that 8 of these studies reported a correlation between higher levels of PA and at least a 20% increase in the risk of developing melanoma.[10] There is a viewpoint that the heightened risk of melanoma is attributed to increased accidental exposure to sunlight, given that physical activities are frequently performed outdoors in minimal attire, thereby elevating the likelihood of sunburn.[11] Yet in the previously published literature, we have not found compelling evidence to support or oppose this claim.

This highlights a limitation: traditional observational studies face challenges in eliminating confounding variables, leading to debates over their findings. Consequently, there is a call for more rigorously designed research to explore the inherent connection between PA and SC more thoroughly. It has become a consensus in academia that randomized clinical trials (RCTs) is the gold standard for studying the causal relationship between two factors. However, while RCTs offer a methodological advantage by reducing confounding factors, their application is often constrained by their scale, and they demand substantial time and financial resources.[12] In recent developments, MR has been recognized as a powerful approach for establishing causality, applicable not only to SC but also to a broad spectrum of health conditions. MR leverages genetic variants, specifically single nucleotide polymorphisms (SNPs), as instrumental variables (IVs), thereby addressing the shortcomings associated with observational studies, such as confounding and reverse causality.[13] Insights from MR studies have shed light on the causal relationships between PA and various diseases, including COVID-19, schizophrenia, breast cancer, and colorectal cancer, among others.[14–16] These advancements underscore the significance of MR in improving preventive and therapeutic strategies for SC.

In our study, we scrutinize the causal link between PA and the susceptibility to SC through the lens of MR analysis. This examination draws upon a comprehensive collection of data from GWAS. The foremost aim of this research is to furnish critical insights into the formulation of preventative measures against SC, steered by the conclusions derived from our MR analysis.

Method

Study Design

In our investigation, we implemented a two-sample MR analysis to explore the causal impact of PA on SC, drawing on summary statistics from GWAS. This approach of analysis mimics the conditions of an RCT by exploiting the natural variation in SNPs distributed among individuals, thereby reducing the influence of confounders such as gender and age. The structure and procedural diagram of this two-sample MR study are illustrated in Figure 1. The genetic instruments chosen for this analysis meet three essential criteria: (1) Relevance: The genetic instruments are closely related to the factor under investigation; (2) Independence: The genetic instruments are free from associations with any confounders that might influence both the factor and the outcome; (3) Exclusion-Restriction: The genetic instruments affect the outcome exclusively through their impact on the factor in question, without intervening through alternative routes (Figure 1). This study has been approved by the Ethics Committee of People's Hospital of Jianyang City.

Data Resource

In our investigation, the SNPs chosen to quantify exposure were derived from the groundbreaking research conducted by American scientist Yann C Klimentidis and his team in 2018.[17] This research stands as the most comprehensive GWAS

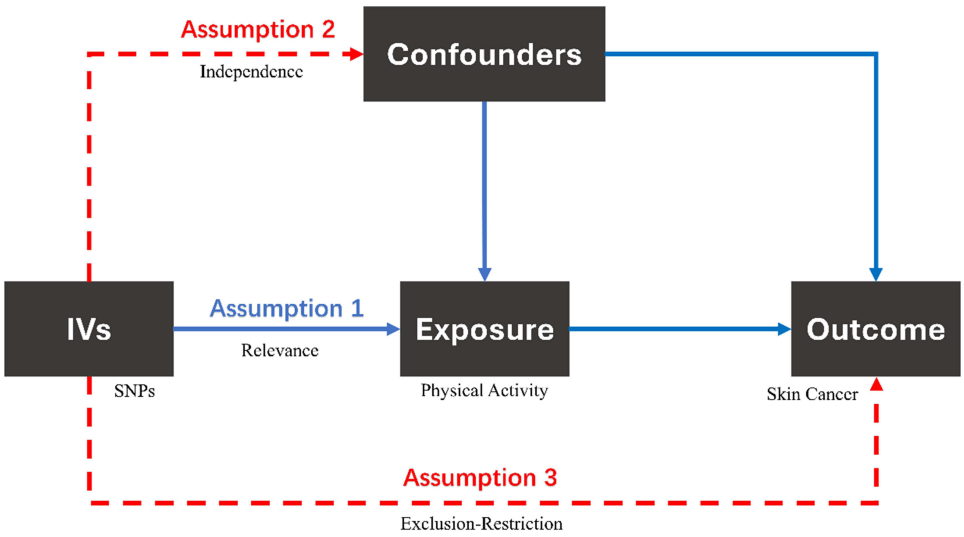

Figure 1 The flow chart of our MR study. The blue solid arrow indicates that the former has a definite impact on the latter. The red dashed arrow indicates that the former has no impact on the latter.

on PA undertaken thus far, utilizing the UK Biobank's extensive database. It incorporates three metrics based on self-reports (up to a maximum of 377,234 participants) and two metrics obtained from wrist-worn accelerometers (up to a maximum of 91,084 participants). These GWAS findings are cataloged in the GWAS Catalog at https://www.ebi.ac.uk/gwas/home, under the identifiers ebi-a-GCST006097, ebi-a-GCST006098, and ebi-a-GCST006099. The exposure in dataset GCST006097 is specified as levels of MVPA, quantified through PA metrics like frequency or intensity. In GCST006098, exposure is specifically tied to VPA, again quantified by assessing elements such as frequency or intensity of the activity. Dataset GCST006099 focuses on average-accelerated PA, which is measured through accelerometer data.

The GWAS summary statistics for the outcome variable in our analysis were sourced from the FinnGen consortium, specifically from its R10 release (https://r10.risteys.finngen.fi/). FinnGen stands as a notable collaboration between public and private sectors, focusing on genomics and personalized medicine. This consortium includes Finnish universities, healthcare organizations, the National Institute for Health and Welfare (THL), blood service providers, biobanks, the Finnish Biobank Cooperative (FINBB), and several international pharmaceutical companies. The initiative involves hundreds of thousands of Finnish individuals, with the goal of uncovering the genetic bases of various diseases through the analysis of genomic and health-related data from approximately 500,000 biobank contributors in Finland. The dataset utilized in our study is derived from the most recent FinnGen data release available at the time of our submission, referred to as R10. The specific code for the data we used is C3_SKIN_EXALLC.

The utilization of publicly accessible databases for data acquisition in our study negates the need for ethical approval, given that the information is already available in the public domain and has been collected in a manner compliant with existing ethical standards. All samples and controls were from participants of European ancestry.

Data Availability

The GWAS summary statistics for PA were acquired from the GWAS Catalog (https://www.ebi.ac.uk/gwas/home), with the foundational data originating from a study by Yann C Klimentidis et al, published in 2018.

Regarding the data on SC, it was accessed through the FinnGen project's website (https://www.finngen.fi/en). FinnGen is a significant public-private partnership dedicated to collecting and analyzing genome and health data from 500,000 Finnish biobank participants. Its dual objectives are to provide novel medically and therapeutically relevant insights and to construct a world-class resource for future research studies. These data were sourced from legitimate public repositories and have been declared to not require additional ethical oversight or consent.

Selection

To guarantee the integrity and dependability of our MR analysis, we adopted comprehensive quality control protocols for IVs selection. Initially, we pinpointed SNPs highly linked to the exposures ($p < 5\times10^{-8}$). Subsequently, any SNP with a significant association to the outcome variable was removed. Furthermore, SNP clumping was performed using an r^2 threshold of 0.001 and a 10mb window size, referencing the European 1,000 genomes project. Additionally, we filtered out SNPs suspected of pleiotropic effects. For this, Radial regression was utilized to spot outliers indicative of pleiotropy. Moreover, to mitigate the influence of weak instrumental variables, we calculated the F statistic ($F = \frac{\beta^2}{se^2}$), considering an F statistic below 10 as indicative of weak IVs.[18] Ambiguous and palindromic SNPs underwent harmonization for precision, and Steiger filtering was applied to enhance the selection process of SNPs.

Statistical and Sensitivity Analysis

In our research, we utilized the two-sample MR method to explore the causal relationship between PA and SC. The cornerstone of our analytical strategy was the Inverse Variance Weighted (IVW) method,[19] serving as the primary methodology. The IVW method employs a meta-analytical framework to aggregate the Wald ratios, representing the causal effects of individual SNPs, thereby offering the most accurate estimates possible. Additionally, the weighted median estimator is employed to derive a dependable estimate of the causal effect, assuming that a minimum of 50% of the analysis's weight is contributed by valid IVs.

To supplement our primary analysis, we incorporated several additional methods, including MR-Egger,[20] weighted median,[21] and MR-PRESSO.[22] Our MR analysis was executed within the R computing environment, utilizing the TwoSampleMR, RadialMR and MRPRESSO packages.

A comprehensive multistep sensitivity analysis was conducted to scrutinize the robustness of the findings, particularly focusing on the second and third assumptions of MR. Heterogeneity among the instrumental variables was initially assessed using Cochran's Q test.[23] The MR-Egger regression and the MR-PRESSO global test were then applied to explore the potential for horizontal pleiotropy among the instrumental variables. Furthermore, a leave-one-out analysis was carried out to evaluate whether the exclusion of any single SNP with a notable horizontal pleiotropic effect would significantly alter the MR estimates.

Result

For our examination, we selected 32 SNPs as IVs to study PA. They were distributed across three categories: 17 SNPs were associated with MVPA, 7 with VPA, and 8 with average-accelerated PA (Table 1). The F-statistics for these sets of IVs were above 29.98, 32.13, and 30.21 for each respective category (Table 1), suggesting a strong likelihood that our IV selection was not compromised by weak instrument bias. The SNPs utilized as IVs.

MR Estimate

Our analysis for the three datasets shows different results. The analysis result indicated that PA of average acceleration was associated with a decreased risk of SC ($OR_{IVW} = 0.94$, 95% CI 0.93–0.96, $P < 0.001$. $OR_{MR\ egger} = 0.91$, 95% CI 0.77–1.07, $P = 0.299$. $OR_{WM} = 0.94$, 95% CI 0.90–0.99, $P = 0.014$. $OR_{MR\ PRESSO} = 0.94$, 95% CI 0.93–0.96, $P < 0.001$) (Table 2). The MR estimates of SNPs are shown in the scatter plot (Figure 2A). In addition, the forest plot displays each SNP's causal impact on SA (Figure 2C).

However, for the analysis results MVPA ($OR_{IVW} = 0.99$, 95% CI 0.67–1.47, P=0.962. $OR_{MR\ Egger} = 1.06$, 95% CI 0.11–10.31, $P = 0.962$; $OR_{WM} = 1.13$, 95% CI 0.66–1.93, $P = 0.658$; $OR_{MR\ PRESSO}$ =0.99, 95% CI 0.67–1.47, P=0.963) and VPA ($OR_{IVW} = 0.795$, 95% CI 0.29–2.18, $P = 0.656$; $OR_{MR\ Egger} = 0.65$, 95% CI 0.00–3301.39, $P = 0.925$; OR_{WM} =0.96, 95% CI 0.27–3.38, $P = 0.954$; $OR_{MR\ PRESSO} = 0.795$, 95% CI 0.29–2.18, $P = 0.671$), which indicate there is no causal relationship between the exposures (MVPA and VPA) and SA (Table 2).

Sensitivity analyses were performed to validate the stability and reliability of our findings. The initial assessment using Cochran's Q test unveiled minimal heterogeneity among the IVs employed, with the P values for IVW and MR-Egger methods registering at 0.987 and 0.979, respectively (Table 3). This lack of heterogeneity was further supported by the

Table 1 The IVs We Employed

SNP	Effect Allele	Other Allele	Chr	Pos	Pval	Se	F	Trait
rs1186721	A	G	7	3.50E+07	4.40E-08	0.0024	29.98	MVPA
rs877483	C	T	3	5.40E+07	4.00E-08	0.0022	30.13	
rs1921981	A	G	21	4.20E+07	3.80E-08	0.0024	30.22	
rs4886868	G	T	15	7.40E+07	3.50E-08	0.0023	30.4	
rs2114286	G	A	3	4.10E+07	3.30E-08	0.0022	30.5	
rs2942127	A	G	1	2.00E+08	3.30E-08	0.0029	30.52	
rs1972763	T	C	4	1.60E+08	3.30E-08	0.0023	30.53	
rs10145335	A	G	14	9.90E+07	2.70E-08	0.0025	30.88	
rs12912808	T	C	15	9.50E+07	1.70E-08	0.0031	31.85	
rs77742115	C	T	5	1.80E+07	9.60E-09	0.0032	32.92	
rs1974771	A	G	2	5.40E+07	6.60E-09	0.0037	33.65	
rs1043595	A	G	7	1.30E+08	4.30E-09	0.0025	34.48	
rs2988004	G	T	9	3.70E+07	4.10E-09	0.0022	34.58	
rs2035562	G	A	3	8.50E+07	3.90E-09	0.0024	34.69	
rs921915	C	T	7	5.00E+07	5.70E-10	0.0022	38.44	
rs7804463	C	T	7	1.30E+08	1.20E-11	0.0022	45.99	
rs429358	C	T	19	4.50E+07	6.10E-13	0.0031	51.82	
rs9276758	A	G	6	3.30E+07	1.40E-08	0.0014	32.13	VPA
rs6667222	C	A	1	1.50E+08	8.70E-09	0.0015	33.1	
rs328902	T	C	7	3.50E+07	5.50E-10	0.0014	38.48	
rs3781411	T	C	10	1.30E+08	3.00E-10	0.002	39.67	
rs13243553	A	G	7	1.30E+08	9.00E-11	0.0013	42.02	
rs2764261	G	A	6	1.10E+08	2.00E-11	0.0014	45	
rs1248860	A	G	3	8.50E+07	1.10E-13	0.0013	55.26	
rs34517439	A	C	1	7.80E+07	4.40E-08	0.0562	29.97	Accelerometer-based PA
rs12522261	A	G	5	1.50E+08	3.90E-08	0.0383	30.21	
rs6775319	T	A	3	1.90E+07	3.50E-08	0.0408	30.43	
rs148193266	C	A	11	1.00E+08	3.10E-08	0.0922	30.67	
rs9293503	C	T	5	8.80E+07	2.10E-08	0.0587	31.42	
rs11012732	G	A	10	2.20E+07	5.40E-09	0.0386	34.04	
rs59499656	T	A	18	4.10E+07	2.40E-09	0.0383	35.6	
rs56194509	G	T	17	4.40E+07	5.00E-12	0.0439	47.68	

Notes: MVPA means moderate to vigorous physical activity. VPA means vigorous physical activity. Average acceleration PA means average acceleration physical activity.

Table 2 The Result of MR Estimate

Exposure	Method	P	OR (95% CI)
MVPA	IVW	0.962	0.991 (0.668–1.469)
	MR Egger	0.962	1.058 (0.109–10.309)
	Weighted median	0.658	1.128 (0.66–1.928)
	MR PRESSO	0.963	0.991 (0.668–1.469)
VPA	IVW	0.656	0.795 (0.29–2.18)
	MR Egger	0.925	0.649 (0.330–1.393)
	Weighted median	0.954	0.963 (0.274–3.384)
	MR PRESSO	0.671	0.795 (0.290–2.180)

(*Continued*)

Table 2 (Continued).

Exposure	Method	P	OR (95% CI)
Average acceleration PA	IVW	<0.001	0.942 (0.927–0.958)
	MR Egger	0.299	0.907 (0.768–1.073)
	Weighted median	0.014	0.944 (0.902–0.988)
	MR PRESSO	<0.001	0.942 (0.927–0.958)

Notes: MVPA means moderate to vigorous physical activity. VPA means vigorous physical activity. Average acceleration PA means average acceleration physical activity.

symmetry observed in the associated funnel plot (Figure 2B). Additionally, the MR-PRESSO global test and the MR-Egger regression analysis yielded P values of 0.995 and 0.667, respectively (Table 3), indicating an absence of horizontal pleiotropy. Such results imply that the chosen IVs are not likely to affect SC risk via mechanisms unrelated to PA. The stability of these findings was further confirmed through a leave-one-out sensitivity analysis, where the sequential exclusion of each SNP did not significantly alter the results (Figure 2D).

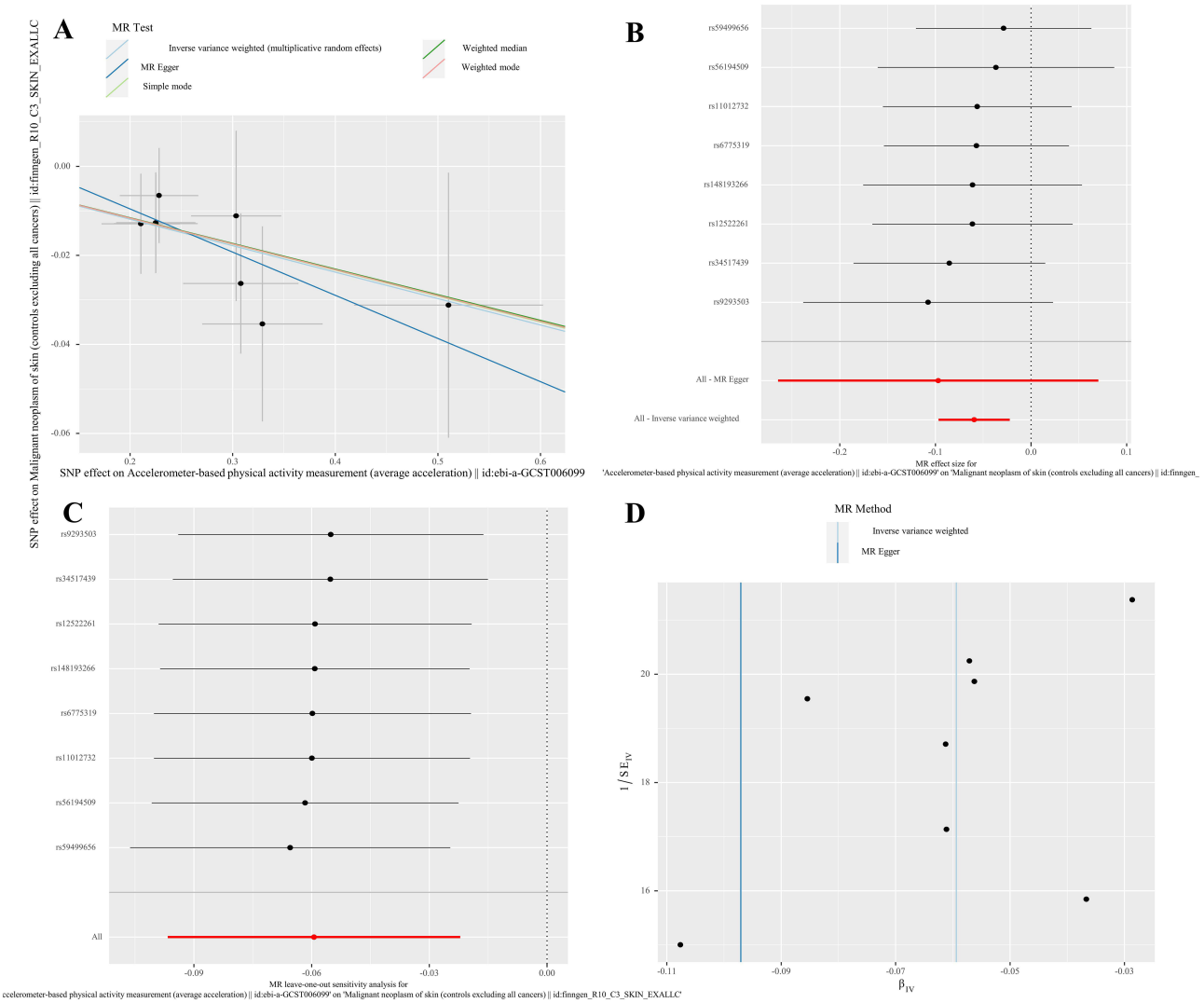

Figure 2 The estimation results of SNPs on skin cancer (SC). (**A**) the scatter plot; (**B**) the funnel plot; (**C**) the forest plot of SNPs; (**D**) the forest plot of leave-one-out analysis.

Table 3 The Result of Sensitivity Analysis

Trait	Test	Method	Effect size	*P*
MVPA	Heterogeneity	$Q_{MR\ Egger}$	17.285	0.302
		Q_{IVW}	17.289	0.367
	Pleiotropy	Egger intercept	−0.001	0.955
		Global Test	19.4462	0.371
VPA	Heterogeneity	$Q_{MR\ Egger}$	7.441	0.190
		Q_{IVW}	7.445	0.282
	Pleiotropy	Egger intercept	0.002	0.964
		Global Test	9.988	0.300
Accelerometer-based PA	Heterogeneity	$Q_{MR\ Egger}$	1.149	0.979
		Q_{IVW}	1.353	0.987
	Pleiotropy	Egger intercept	0.010	0.667
		Global Test	1.758	0.995

Notes: MVPA means moderate to vigorous physical activity. VPA means vigorous physical activity. Average acceleration PA means average acceleration physical activity.

Discussion

There is a widely acknowledged that SC is correlated with sun exposure;[24] specifically, the notion posits that increased sun exposure leads to greater UV damage, thereby elevating the risk of SC. This has led to a simplistic assumption that higher levels of PA-presumably resulting in more time spent under the sun—directly translate to a heightened risk of SC. Supporting this hypothesis, research such as the cohort study by Stenner et al[25] has been published, seemingly validating the connection between PA, sun exposure, and increased SC risk. Contrary to these assertions, our analysis introduces a revolutionary perspective, suggesting that sun exposure might act as a confounding factor in the causal relationship between PA and SC. Our study breaks new ground by providing robust genetic evidence that PA actually contributes to a reduced incidence of SC, directly challenging the prevailing narrative and offering significant insights into the complex interplay between PA, sun exposure, and SC risk.

There is no unanimous agreement on the precise mechanisms through which physical activity acts as a preventative measure against skin cancer. A prevailing hypothesis among proponents is that PA could offer protection against SC by facilitating a reduction in body mass index (BMI). Obesity is widely recognized as a significant risk factor for various cancer types. Numerous studies have corroborated the association between obesity and increased risk for cancers such as breast cancer,[26] gastric cancer,[27] endometrial cancer,[28] among others. Furthermore, PA is identified as a critical element in BMI reduction.[29,30] Leveraging this understanding, it is postulated that PA's role in diminishing SC risk might be attributed to its effectiveness in lowering BMI, thus mitigating obesity and consequently decreasing SC risk. Nonetheless, concrete evidence to substantiate this theory necessitates further comprehensive investigation.

Our study harnessed the two-sample MR approach, leveraging PA-related SNPs from three distinct datasets within the EBI database as IVs, while SC-related SNPs were sourced from the FinnGen database. The application of the MR methodology was strategically chosen to circumnavigate confounding factors, such as sun exposure, in order to directly probe the causal relationship between PA and SC. Our findings reveal a significant positive causal relationship, where PA is associated with a decreased risk of developing SC. This discovery directly contradicts the widely held belief that PA, primarily through increased sun exposure during outdoor activities, elevates SC risk. Consequently, our research offers a revolutionary perspective on SC prevention, highlighting the protective role of PA. Therefore, we advocate for healthcare professionals to recommend their patients engage in physical exercise, emphasizing indoor activities or adequately protected outdoor activities, to mitigate SC risk.

Our investigation stands out for several reasons that highlight its significant contribution to elucidating the causal connection between PA and SC risk. A key distinguishing feature of our research is its pioneering use of a two-sample

MR framework to explore this relationship. The robustness and credibility of our findings are supported by various strengths. First, broad GWAS datasets: The employment of three large-scale GWAS datasets from European populations lays a robust foundation for accurately estimating the causal relationship with considerable statistical power. Second, optimal study design: A meticulously structured study design, including thorough MR and sensitivity analyses, supports the reliability of our conclusions. Third, reliable analytical techniques: Using dependable methods to detect potential outliers enhances the trustworthiness of our results. Fourth, heterogeneity and pleiotropy evaluation: Assessing heterogeneity among instrumental variables with Cochran's Q test and evaluating potential horizontal pleiotropy with MR-Egger regression and MR-PRESSO global tests ensure our results are robust against potential biases. Fifth, strong instrumental variable association: A combined F-statistics value exceeding 29.98 across all IVs indicates a potent association with the exposure, addressing concerns of weak instrument bias. And sixth, rigorous inclusion criteria for IVs: Strict criteria for IV inclusion enhance the study's overall credibility by ensuring the robustness of findings against weak instruments. These methodological advantages underscore the reliability and validity of our results, offering insightful perspectives on the causal relationship between PA and SC.

While our study has strengths, it is non-negligible to recognize several limitations. First, our focus on populations of European ancestry limits the ability to generalize our findings to more diverse global populations. This restriction may affect the applicability of our results across different ethnicities. Second, there is a potential for residual bias arising from unexamined functions of the selected SNPs. Additionally, our reliance on summary-level data limits our ability to thoroughly control for confounders such as age and gender, which might influence the outcomes. Furthermore, of the three datasets of SNPs used as IVs for PA, only one shows a definitive relationship with SC risk. The significant variances in the F-values of these SNPs indicate that the strengths of the IVs differ, which could lead to varying conclusions. This variability underscores the need for cautious interpretation of the IV analysis results and suggests that future studies should aim for more robust genetic instruments and consider a broader range of populations to enhance the validity and generalizability of the findings. It is worth noting that we conducted a preliminary analysis of the variables included using LD Score Regression (LDSC). Contrary to the positive results demonstrated by MR, LDSC did not show significant genetic correlation between PA and SC. However, this does not affect our conclusion, as LDSC and MR are distinct analytical methods with different characteristics. The MR approach specifically targets causal inference, employing particular assumptions and methods suited for this purpose, whereas LDSC focuses more on estimating shared genetic variation, which may not directly impact causality. We are still exploring the best ways to integrate these findings.

For future research, we recommend that scholars design more comprehensive clinical trials to investigate the effects of factors such as UV radiation on SC risk. Additionally, the collection of larger-scale clinical data and the implementation of more precise SNP testing will enhance the understanding and management of this condition. These approaches will contribute to a more robust analysis of risk factors and potentially lead to more effective prevention strategies for SC.

Despite these considerations, our study's methodologically rigorous approach provides compelling evidence of a causal relationship between PA and SC risk. This encourages further investigation into PA as a potential preventative strategy against SC, highlighting the need for additional research that addresses these limitations and explores the implications of our findings across broader populations.

Conclusion

In conclusion, our study, utilizing MR to analyze comprehensive GWAS datasets, support the causal link between PA of average acceleration and SC risk. Considering the paramount importance of SC prevention, our findings highlight the necessity of adopting lifestyle modifications. Specifically, we advocate for engaging in average-accelerated physical activity outdoors with adequate sun protection or indoors as a crucial preventive strategy against SC. This approach not only promotes overall health but also significantly contributes to reducing the risk of SC, aligning with our evidence-based recommendations for public health and individual wellness.

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Disclosure

The authors report no conflicts of interest in this work.

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