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The associations between risk factors and pituitary neuroendocrine tumors

A bidirectional Mendelian randomization study

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Abstract

The etiological basis of pituitary neuroendocrine tumors is uncertain. We used Mendelian randomization technique to investigate the potential influence of several risk factors on the likelihood of developing pituitary neuroendocrine tumors. We admitted 8 risk factors, divided into 3 lifestyle factors and 5 chronic diseases as exposure factors. We used weighted median, simple model, weighted model, inverse-variance weighted, and the MR-Egger regression method for causal effect estimations and sensitivity analyses. We observed that genetically forecasting increased moderate to vigorous physical activity levels (OR = 5.21 [1.38–19.72], *P* = .015) was linked with a higher incidence of pituitary neuroendocrine tumors. Allergic disease (asthma, hay fever, or eczema) (OR = 0.81 [0.66–0.99], *P* = .039), chronic kidney disease (OR = 0.67 [0.50–0.90], *P* = .008), increased sleep duration (OR = 0.07 [0.01–0.37], *P* = .001), and types of physical activity (e.g., swimming, cycling, keeping fit, and bowling) (OR = 0.02 [0.01–0.66], *P* = .029) were connected with lower incidence of pituitary neuroendocrine tumors. There was no evidence that the other 3 risk factors notably correlated with pituitary neuroendocrine tumors. This study provides evidence that allergic diseases, chronic kidney disease, sleep duration, and physical activity are associated with the development of pituitary neuroendocrine tumors. The findings highlight the importance of reconsidering causality in epidemiological studies to better understand risk factors and prevention strategies for pituitary neuroendocrine tumors.

Abbreviations: CKD = chronic kidney disease, FDR = false discovery rates, GWAS = genome-wide association study, IVW = inverse-variance weighted, MR = Mendelian randomization, MR-PRESSO = MR-pleiotropy residual sum and outlier, MVPA = moderate to vigorous physical activity levels, PitNETs = pituitary neuroendocrine tumors, RCT = randomized controlled trial, SNP = single nucleotide polymorphism.

Keywords: chronic diseases, lifestyle factors, Mendelian randomization, pituitary neuroendocrine tumors, risk factors

1. Introduction

Pituitary neuroendocrine tumors (PitNETs) are among the most prevalent tumors in the sellar zone.[1,2] They originate from neuroendocrine cells, constituting approximately 15% of whole intracranial neoplasms.[3] These tumors often cause patients to experience neurological, endocrine, or visual symptoms.[4] It is recommended that patients with clinical symptoms such as elevated intracranial pressure, visual impairment, or endocrine abnormalities need imaging examinations, preferably magnetic resonance imaging, for further diagnosis. Treatment includes medication, surgery, and radiotherapy.[5] Although the vast majority of PitNETs are benign tumors with high long-term survival rates, these patients often suffer from impaired neuropsychological function and quality of life. Therefore, it is necessary to clarify the risk factors of PitNETs. Early detection of risk factors and intervention in PitNET patients will help reduce the medical and economic burden of PitNET patients.

Previous observational studies have found some risk factors for PitNETs,[6–8] including lifestyle factors and chronic diseases. Multiple lifestyle factors may be linked to PitNETs, such as sleep disorders,[9] physical exercise.[10] In addition, observational studies have also revealed that patients with PitNETs have a propensity for developing metabolic disorders that are often accompanied by several chronic ailments, such as hypertension,[11] diabetes mellitus,[11] allergic diseases,[6] and chronic kidney disease (CKD).[12] Nevertheless, the roles of these chronic illnesses in the onset of PitNETs remain unclear.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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However, measuring these modifiable factors of PitNETs causality is challenging due to possible confounding and reverse causation problems that could confound the associations found in former surveys. Furthermore, conducting randomized controlled trials (RCTs) in PitNETs is challenging. Here, we conducted a Mendelian randomization (MR) study investigating the connections of 8 risk factors with PitNETs. MR is an analysis method that can infer causal relationships between exposures and outcomes.[13] In theory, this approach can avoid bias between exposures and results due to confounding factors. Because random segregation of alleles is directly related to genetic variation, it mimics random grouping in RCTs.

2. Methods

2.1. Study design

This study used MR to investigate the influence of 8 risk factors on PitNETs. In conducting the MR studies and writing the article, we followed the STROBE-MR checklist.[14] In this MR research, we made the following hypotheses: (i) Genetic variation is strongly related to risk factors. (ii) Genetic variation is not affected by confounding factors. (iii) Genetic variation affects results only through risk factors (Fig. 1).

2.2. Data sources

Genome-wide association Study (GWAS) data for PitNETs were obtained from the FinnGen European cohort study. FinnGen Research is a global research project combining genomic information and digital health data.[15] 1402 PitNETs cases and 375,875 controls were included in the FinnGen study round 9. PitNETs endpoints were determined according to the International Classification of Diseases, 10th Revision (ICD-10). The ICD-10 codes for PitNETs are D35.2. GWAS data from FinnGen had been approved by the FinnGen committee. The GWAS outcome data were publicly available through the Finngen GWAS summary statistics. Link: https://r9.finngen.fi/. We obtained GWAS data on lifestyle factors and chronic diseases. Moreover, we considered them as exposure factors. All GWAS data are from Europe. Exposure factors included sleep duration, moderate to vigorous physical activity levels (MVPA), types of physical activity (e.g., swimming, cycling, keeping fit, and bowling), type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, allergic disease (asthma, hay fever or eczema), and CKD. The GWAS exposure data were publicly available online through the IEU Open GWAS project.[16] Link: https://gwas.mrcieu.ac.uk/. Sources and information on GWAS data for all exposures and outcomes mentioned in this study were listed in Table S1, Supplemental Digital Content, http://links.lww.com/MD/N991. Additionally, all data of analysis results were also included in this document.

2.3. Selecting genetic variables

We used instrumental variables in this MR study to examine the relationships between modifiable risk factors and PitNETs. Selected single nucleotide polymorphisms (SNPs) had to fulfill the criterion for a genome-wide significant correlation of $<5 \times -10^{-8}$ with each factor. We computed the F statistic for all SNPs using F = Beta2/SE2 to verify the relevance hypothesis[17] (Table S2, Supplemental Digital Content, http://links.lww.com/MD/N992). $F > 10$ was considered weak instrument bias is small.[18] Selected SNPs were then pooled to obtain SNPs with a linkage disequilibrium threshold ($r^2 > 0.01$) and a distance of 10,000 kb. Later, we extracted SNPs for each exposure factor from outcomes. We harmonized exposed SNPs and outcome SNPs. Eventually, we excluded SNPs that left palindromic structures.

2.4. Statistical analysis

To explore the causal relationship between risk factors and PitNETs, we carried out a MR analysis. The Wald ratio (the ratio of genetic outcome associations to genetic exposure associations) was used to determine the correlation between the

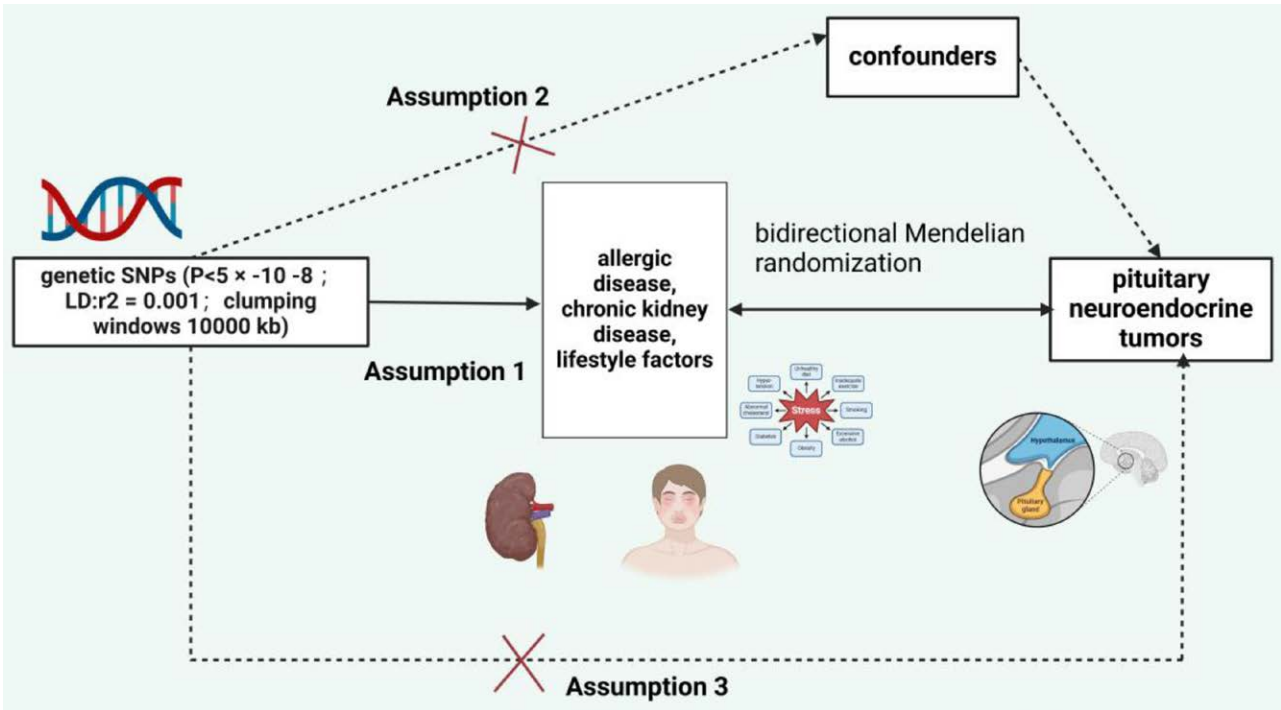

Figure 1. Overview of the design and methods used in this Mendelian randomization study.

identified variable and PitNETs for traits that contained only 1 independent variable. The primary method used inverse-variance weighted (IVW) random effects, and the secondary methods used MR-Egger, weighted median, weighted model, and simple model.[19]

In addition, several sensitivity analyses were conducted to evaluate the strength of the findings. We performed MR-IVW analysis using the I2 index and Cochran *Q* statistic and MR-Egger analysis using Rucker *Q* statistic to determine the contribution of exposure-related SNPs to outcome heterogeneity. $P > .05$ indicates no heterogeneity.[16] Horizontal pleiotropy was tested by the MR-Egger method. $P > .05$, indicating the absence of horizontal pleiotropy.[20] Subsequently, we used MR-pleiotropy residual sum and outlier (MR-PRESSO) to remove aberrant SNPs causing horizontal pleiotropy. An omission analysis was also performed to investigate whether a single SNP influenced the causal relationships between exposures and outcomes.[21] We produced funnel, scatter, leave-one-out, and forest plots to visualize our results (Figures 2 and 3, Figures S1–S3, Supplemental Digital Content, http://links.lww.com/MD/N990). Moreover, the forest plots of summary data were presented in Figure 4. To eliminate the influence of confounders, we further investigated whether the chosen SNPs with meaningful MR estimates in this research were associated with other PitNETs risk factors (http://www.phenoscanner.medschl.cam.ac.uk/). The study retested the causal effects to determine their significance after excluding the confounding SNPs. Finally, we have corrected the p-values using the false discovery rates (FDR) correction.[22,23] The FDR-adjusted $P < .05$ indicated a strong correlation between exposures and outcomes, results satisfying $P < .05$ but FDR-adjusted $P > .05$ indicate suggestive associations (Table S3, Supplemental Digital Content, http://links.lww.com/MD/N993).

All statistical analyses were performed using *R*-4.2.2 and related R packages. We used the Mendelian randomization package, MR-PRESSO package, and the TwoSampleMR package for analysis.[24] For binary exposure factor variables, the causality of the outcomes was estimated using the exposure factors' probability.[25,26] $P < .05$ was thought of as an underlying association. Beta is commonly used to estimate the causal effect of genetic variation on exposure and outcome in MR analysis. Using the formula OR = exp(beta), we convert the beta value into an odds ratio (OR). The OR is used to measure the correlation between exposure and outcome and provides a more insightful understanding of the true impact of the results. If OR = 1, it is an indication that the exposure does not affect the probability of the outcome. If OR > 1, it is an indication that the exposure is associated with a higher likelihood of the outcome. In contrast, if the OR < 1, then there is an association between the exposure and a lower

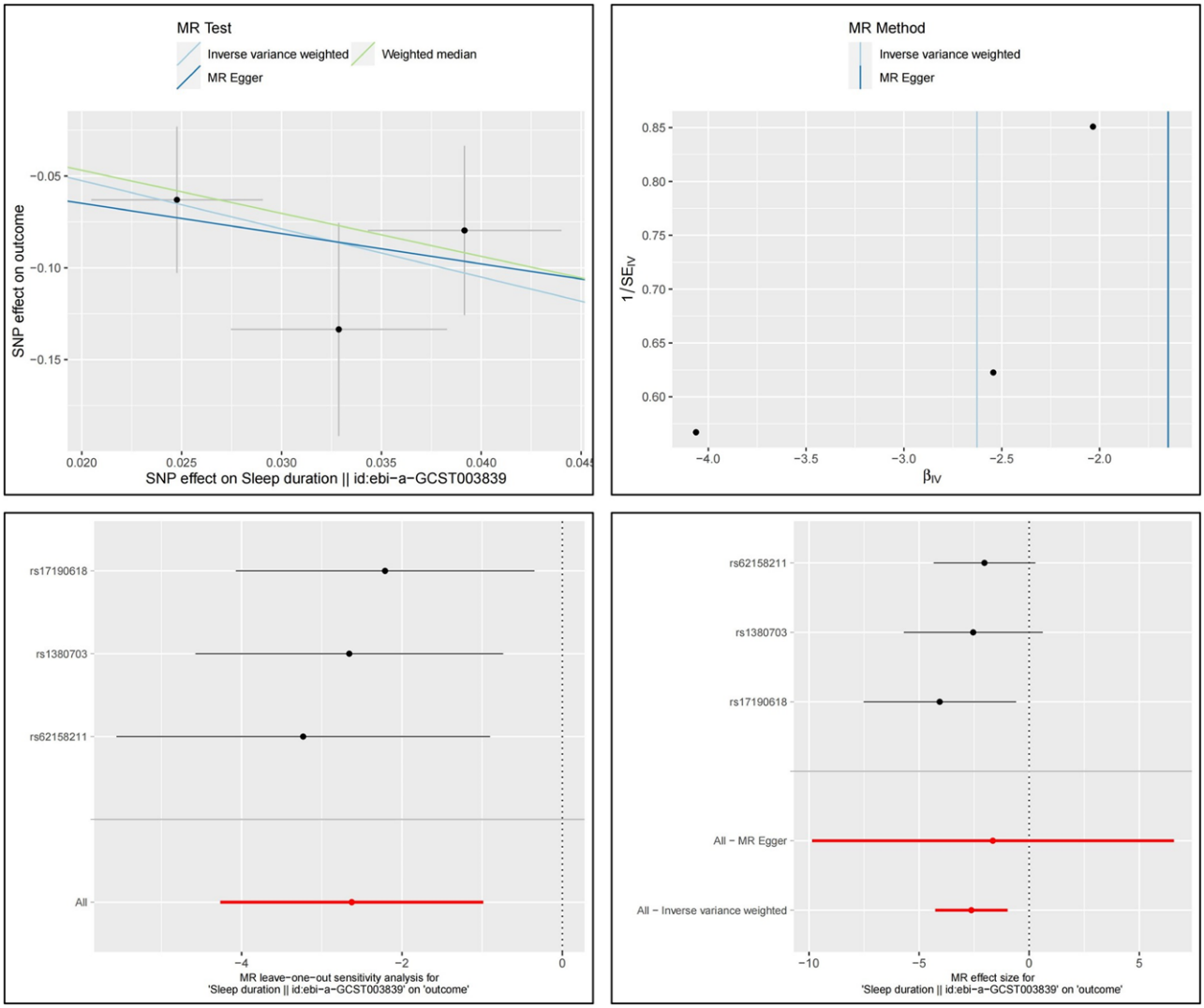

Figure 2. Scatter plot, funnel plot, forest plot, leave-one-out plot for the exposure of sleep duration.

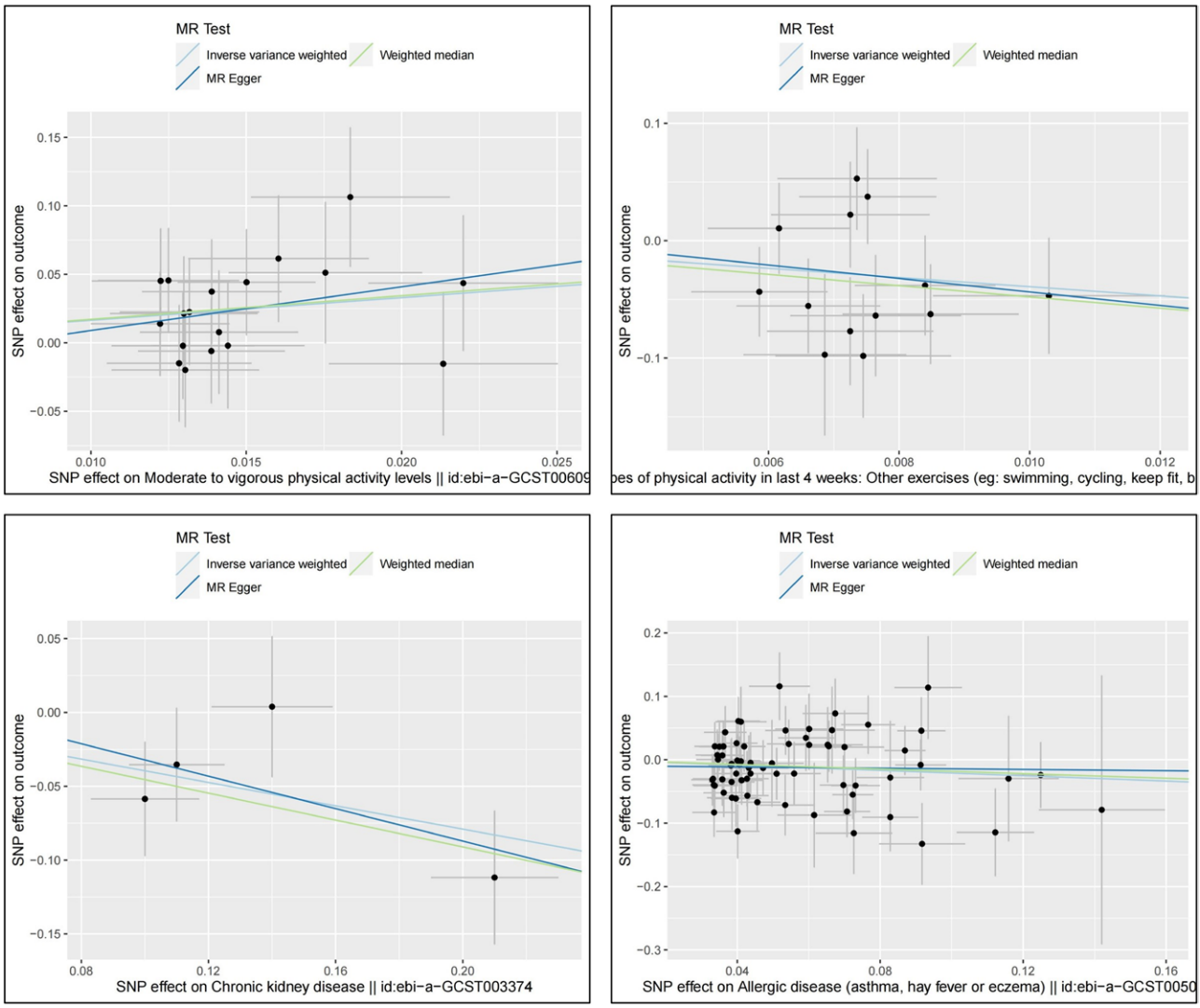

Figure 3. Scatter plot for the exposure of MVPA, types of physical activity (e.g., swimming, cycling, keeping fit, and bowling), CKD, and allergic disease. CKD = chronic kidney disease, MVPA = moderate to vigorous physical activity levels.

exposure	method	nSNP	OR(95%CI)	p-value	Het.pval	Ple.pval
Sleep duration	IVW	3	0.07(0.01 to 0.37)	0.001	0.822	0.717
MVPA	IVW	18	5.21(1.38 to 19.72)	0.015	0.959	0.689
TOPA(swimming, cycling, keep fit, bowling)	IVW	14	0.02(0.00 to 0.66)	0.029	0.300	0.888
Allergic disease (asthma, hay fever or eczema)	IVW	72	0.81(0.66 to 0.99)	0.039	0.392	0.552
Chronic kidney disease	IVW	4	0.67(0.50 to 0.90)	0.008	0.525	0.784

Figure 4. Associations between genetically predicted modifiable risk factors and pituitary neuroendocrine tumors. Het = heterogeneity, MVPA = moderate to vigorous physical activity levels, Ple = pleiotropy, SNP = single nucleotide polymorphism.

likelihood of the outcome. We performed a reverse MR analysis to check whether we were influenced by reverse causality.

3. Results

Sleep duration was related to reducing the risks of PitNETs (IVW: OR = 0.07, 95% CI: 0.01–0.37, P = .001). The causal role of physical activity was significantly associated with PitNETs. MVPA was related to the increased risks of PitNETs (IVW: OR = 5.21, 95%CI:1.38–19.72, P = .015). Nevertheless, types of physical activity (e.g., swimming, cycling, keeping fit, and bowling) were related to reducing the risks of PitNETs (IVW: OR = 0.02, 95% CI: 0.01–0.66, P = .029).

CKD was related to reducing the risks of PitNETs (IVW: OR = 0.67, 95% CI: 0.50–0.90, P = .008). Allergic diseases (asthma, hay fever, or eczema) were related to reducing the risks of PitNETs (IVW: OR = 0.81, 95% CI: 0.66–0.99, P = .039). In addition, type 1 diabetes, type 2 diabetes, and hypertension had no significant associations with PitNETs by IVW, Weighted median, MR-Egger (Table 1).

Table 1

An overview of the genetic instruments used in the MR study and the causal relationships between risk factors and pituitary neuroendocrine tumors estimated by the inverse-variance weighted method.

Risk factor	SNPs	Used SNPs*	Sample	IVW (b/se)	IVW P	IVW het P	Ple P	MPO P
Lifestyle factors								
Sleep								
Sleep duration	3	3	127,573	-3.75/1.16	**0.001**‡	0.822	0.717	NA
Physical activity								
MVPA	19	18	377,234	1.65/0.68	**0.015**†	0.959	0.689	0.958
TOPA (swimming, cycling, keep fit, bowling)	15	14	460,376	-3.92/1.79	**0.029**†	0.300	0.888	0.324
Chronic diseases								
Diabetes								
Type 1 diabetes	36	35	29,652	-0.06/0.04	0.090	0.869	0.846	0.876
Type 2 diabetes	118	118	655,666	0.04/0.06	0.554	0.099	0.757	0.109
Hypertension								
Hypertension	225	211	462,933	0.70/0.37	0.063	0.853	0.206	0.854
Allergic disease								
Allergic disease (asthma, hay fever or eczema)	74	69	360,838	-0.21/0.10	**0.039**†	0.392	0.552	0.383
Kidney disease								
CKD	4	4	117,165	-0.40/0.15	**0.008**‡	0.525	0.784	0.563

Bold values indicate IVW $P < 0.05$, which is statistically significant.

b = beta, CKD = chronic kidney disease, het = heterogeneity, IVW = inverse-variance weighted, MPO = MR-PRESSO, MVPA = moderate to vigorous physical activity levels, MR = Mendelian randomization, NA = not available, Ple = pleiotropy, SE = standard error, SNP = single nucleotide polymorphism.

*SNPs used in the present MR analysis.

†$P < .05$.

‡$P < .01$.

To avoid reverse causality, we performed a reverse MR analysis and found no causal effect of PitNETs on these risk factors. As shown in Table 1, heterogeneity was not found in lifestyle factors, chronic diseases. We used the MR-Egger method for the pleiotropy test. Furthermore, we did not find potential pleiotropy on lifestyle factors, chronic diseases. When using MR-PRESSO on all exposures, the corrected anomaly outcomes were not significantly different from the raw outcomes (Table 1).

4. Discussion

We performed a bidirectional MR analysis to investigate the relationships between PitNETs and several risk factors. For MR research on lifestyle factors and PitNETs, we discovered that sleep duration, MVPA, and types of physical activity (e.g., swimming, cycling, keeping fit, and bowling) were associated with PitNETs. Lifestyle factors may influence the development of PitNETs. MVPA increased the risks of PitNETs, whereas types of physical activity (e.g., swimming, cycling, keeping fit, and bowling) reduced the risks of PitNETs. Furthermore, most sensitivity analyses for MVPA and types of physical activity (e.g., swimming, cycling, keeping fit, and bowling) were consistent without violating the MR assumptions. Moreover, short sleep duration is likely an underlying risk factor for PitNETs.

Our study showed that reduced sleep duration is a pathogenic risk factor for PitNETs. Reduced sleep duration can affect hormone regulation, potentially leading to abnormalities in growth hormone and adrenocorticotropic hormone, which may be associated with the development of PitNETs.[27,28] In addition, chronic sleep deprivation can affect the immune system and reduce the body's ability to deal with abnormal cell growth and apoptosis.[29] Moreover, chronic sleep deprivation can cause a stress response that increases the body's inflammatory response, creating an environment conducive to developing PitNETs.[30] Finally, sleep may contribute to genetic susceptibility because PitNETs can have a familial inheritance pattern.[31,32]

This study discussed physical activity as MVPA and types of physical activity (e.g., swimming, cycling, keeping fit, and bowling). We detected that MVPA was positively related to PitNETs, whereas types of physical activity (e.g., swimming, cycling, keeping fit, and bowling) were the opposite. MVPA can activate the target glandular axis and sympathetic nervous system and alter the immune system by increasing stress,[33,34] leading to PitNETs and complications such as fatigue, decrease in aerobic capacity, and hypothalamic obesity.[35,36] By contrast, types of physical activity (e.g., swimming, cycling, keeping fit, and bowling), as low-intensity aerobic exercise, can help prevent PitNETs by relieving stress[34] and improving mood.[37] Moreover, moderate aerobic exercise is closely related to sleep and may help avoid PitNETs development by improving sleep.[38]

Our MR study on chronic diseases and PitNETs found that CKD and allergic disease (asthma, hay fever, or eczema) may affect the occurrence of PitNETs. Nevertheless, no notable evidence supported causations between type 1 diabetes mellitus, type 2 diabetes mellitus, hypertension, and PitNETs. Furthermore, there was no apparent heterogeneity or pleiotropy to support the validity of our findings.

Although multiple studies have reported an increased risk of neoplasm in patients with CKD, the effect of CKD on PitNETs risk is unclear.[39] For CKD, we found it was negatively associated with PitNETs. In previous observational studies, CKD commonly experienced derangements in the hypothalamic–pituitary–gonadal, thyroidal, and adrenal axis. Significant hormonal disturbances of the hypothalamic–pituitary axis are often associated with impaired renal function.[40] Dysfunction of these 3 glandular target axis is often associated with developing PitNETs. For our experimental results, CKD is the protective factor for PitNETs development, and we speculated that it may result from hormonal disturbances.[41] However, the specific mechanism of this is still unclear. Therefore, we still need to conduct RCTs with larger samples to verify the aforementioned finding.

The relationships between allergic diseases and tumors have long been controversial.[42] According to previous studies, allergies promoted their production in some tumors.[43] However, allergies inhibited the development of certain tumors.[44] The relationships between allergic diseases and PitNETs are unknown. In our MR study, allergic diseases (asthma, hay fever, or eczema) were negatively associated with PitNETs. It was consistent with previous research and

knowledge.[45] Allergic diseases often cause chronic inflammation, which releases various inflammatory mediators and cells. Inflammatory mediators such as IgE[46,47] and TGF-β[48] and inflammatory cells such as eosinophils[49] and basophils[50] can inhibit tumorigenesis and progression. One specific mechanism may be the improvement of the tumor microenvironment.[51] It needs RCT studies with larger samples to further clarification.

Our study has some advantages. Firstly, as in RCTs, MR analyses are less likely to be affected by reverse causality and confounding because genotypes are randomly assigned during gamete fusion. Secondly, pleiotropy and heterogeneity tests were performed as extra sensitivity analysis tools to assess the MR results' reliability. Thirdly, according to what we know, this research is the first to comprehensively explore PitNETs causality using a large-scale GWAS.

Nevertheless, several limitations of our study must be addressed. Firstly, all GWAS participants are of European descent. Therefore, whether our results can be applied to other populations and regions remains to be seen. Secondly, although we used IVW and MR-Egger methods to identify and regulate the pleiotropic effects of gene mutations, there may still be confounding factors between exposures and outcomes, such as educational level and character. They may distort the results. Thirdly, we only obtained summarized GWAS data, and the relative impact of gender, age, and other covariates on the results requires deep study. In addition, several biases presented in MR included differential survival and selection bias, and the most common one is population stratification bias.

5. Conclusion

In conclusion, our MR analysis showed that genetically predictable MVPA were related to the increased risks of PitNETs. In contrast, sleep duration, types of physical activity (e.g., swimming, cycling, keeping fit, and bowling), allergic diseases (asthma, hay fever, or eczema), and CKD were related to reducing the risks of PitNETs. Our study contributed to a better understanding of possible risk factors for developing PitNETs. Furthermore, interventions against underlying risk factors may prevent the development of PitNETs.

Author contributions

Conceptualization: Wencai Wang, Luyao Ma, Menghao Liu, Yongqiang Zhao, Wei Ye.
Data curation: Wencai Wang.
Formal analysis: Wencai Wang.
Funding acquisition: Xianfeng Li.
Investigation: Wencai Wang.
Methodology: Wencai Wang, Luyao Ma.
Project administration: Xianfeng Li.
Resources: Wencai Wang.
Software: Wencai Wang.
Supervision: Wencai Wang.
Validation: Wencai Wang.
Visualization: Wencai Wang.
Writing – original draft: Wencai Wang.
Writing – review & editing: Wencai Wang, Luyao Ma, Xianfeng Li.

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