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Analysis

Association of modifiable risk factors and telomere length with five neuroendocrine neoplasms: a bidirectional Mendelian randomization study

Xujia Li[1,2,3,4] · **Lingli Huang**[6] · **Yue Yan**[2,3,4,5] · **Yuming Rong**[1,2,3,4] · **Xuxian Chen**[1,2,3,4] · **Mengge Gao**[7] · **Jinsheng Huang**[1,2,3,4]

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Abstract

Background The timely recognition of modifiable risk factors holds paramount importance in tumor prevention. We aimed to scrutinize the causal relationships between a spectrum of genetically modifiable risk factors and five distinct neuroendocrine neoplasms.

Methods A bidirectional two-sample Mendelian randomization (MR) analysis was employed to elucidate the causal relationships between 41 potential risk factors and five neuroendocrine neoplasms.

Results Height, obesity class 1, 2, and 3, overweight, waist-to-hip ratio, waist circumference, and serum uric acid were identified as factors associated with an augmented risk of colorectal neuroendocrine neoplasms (all $p < 0.05$). Conversely, a negative correlation was observed between fasting glucose and the risk of colorectal neuroendocrine neoplasms ($p = 0.031$). Platelet count exhibited a negative correlation with lung neuroendocrine neoplasms ($p = 0.02$). Moreover, the waist-to-hip ratio demonstrated a negative association with the risk of pancreatic neuroendocrine neoplasms. Atrial fibrillation, mean cell heamoglobin, and mean cell volume were positively associated with the risk of small intestine neuroendocrine neoplasms. In gastric neuroendocrine neoplasms, obesity class 1 and 2, overweight, and telomere length were implicated in their heightened risk. Following adjustment for multiple tests, obesity class 1 remained statistically significant to colorectal neuroendocrine neoplasms, and telomere length maintained significance in association with gastric neuroendocrine neoplasms. The outcomes of reverse MR suggested a bidirectional causal relationship between telomere length and gastric neuroendocrine neoplasms.

Xujia Li, Lingli Huang and Yue Yan have contributed equally to this work.

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✉ Mengge Gao, foc9779@126.com; ✉ Jinsheng Huang, huangjinsh@sysucc.org.cn | [1]VIP Department, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China. [2]State Key Laboratory of Oncology in South China, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China. [3]Collaborative Innovation Center for Cancer Medicine, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China. [4]Guangdong Provincial Clinical Research Center for Cancer, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China. [5]Cancer Prevention Center, Sun Yat-Sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China. [6]Department of Oncology, Zhuzhou Hospital Affiliated to Xiangya School of Medicine, Central South University, Zhuzhou 412000, Hunan, People's Republic of China. [7]Department of Clinical Nutrition, Huadu District People's Hospital, 48 Xinhua Road, Huadu, Guangzhou 510800, Guangdong, China.

Conclusion This study provided genetic evidence for the causal relationships between potentially modifiable risk factors and the risk of five neuroendocrine neoplasms. Therapeutic approaches to these factors may provide a basis for preventing neuroendocrine neoplasms.

Keywords Modifiable risk factors · Neuroendocrine neoplasms · Bidirectional · Mendelian randomization · Lifestyle factor

1 Introduction

Neuroendocrine neoplasms (NENs) manifest as heterogeneous malignant neoplasms originating from the neuroendocrine system [1]. Typically, their origin is within the gastroenteropancreatic (GEP) tract and the bronchopulmonary tree. Over recent years, there has been a discernible and consistent rise in both the incidence and prevalence of these tumors [2]. NENs exhibit heterogeneity concerning their site of origin, biological behavior, and malignant potential [3]. The survival of patients diagnosed with NENs has experienced a progressive extension, owing to an enhanced comprehension of the molecular underpinnings of the diseases and advancements in the understanding of epigenetics [4–6]. However, therapeutic alternatives for high-grade (G3, Ki-67 > 20%) NENs are constrained and are associated with an unfavorable prognosis [7]. The delineation of risk factors for NENs facilitates early identification and targeted intervention, thereby mitigating the medical and financial burdens associated with disease treatment. Recent advances in pathology classification, biomarker identification and imaging technologies may provide early detection leading to personalised treatment strategies [8].

In epidemiologic studies, several lifestyle factors, metabolic disorders, and serum biomarkers have demonstrated associations with NENs. Notable examples include exposure to ultraviolet light, circadian rhythm disruption, diabetes, obesity, smoking, alcohol consumption [9–13], whole blood serotonin, and chromogranin A [14]. Nevertheless, the findings from these observational studies have presented conflicting results. Marit et al[9] conducted a comprehensive study involving 25 investigations, with the primary objective of discerning the relationship between lifestyle factors and the developmental trajectory of GEP-NENs. Their findings indicated variations in the response of NENs in different tissues to alcohol and smoking. Notably, diabetes mellitus emerged as a significant risk factor in the onset of pancreatic NENs, demonstrating a protective role in disease progression. Conversely, BMI showed no discernible association with the development and prognosis of NENs. These results underscore the noteworthy impact of lifestyle factors on the intricate process of NET development. Lifestyle factors assume a crucial role in the pathogenesis of NENs as a disease process. However, owing to the inherent nature of observational studies, these associations are susceptible to confounding by multiple variables. This complexity poses a challenge to establishing conclusive causal inferences, hindering the accurate measurement of the causal impact of these modifiable factors on NENs [15].

Mendelian Randomization (MR) analyses, as an emerging methodology, are employed to deduce potential causality and evaluate associations between exposure factors and outcomes, utilizing genetic variants as instrumental variables (IVs) [16–18]. As Single Nucleotide Polymorphisms (SNPs) are randomly allocated at conception and remain unaffected by confounding factors, the impact of confounding and reverse causation can be mitigated. Consequently, MR analysis holds the potential to offer more robust evidence than traditional observational studies in establishing causality [16, 19]. This article aims to utilize MR analysis to investigate the causal relationships between 41 potential risk factors and five distinct neuroendocrine neoplasms. Enhancing our comprehension of the potential etiologic risk factors for NENs is imperative for more effective disease prevention strategies.

2 Materials and methods

2.1 MR design

Our study adhered to the STROBE-MR statement, which governs the reporting of MR studies. Employing a two-sample MR approach, we systematically investigated the potential causal effects of 41 potentially modifiable risk factors on five neuroendocrine neoplasms. The study is underpinned by three fundamental assumptions: (1) IVs exhibit a robust association with the exposure; (2) IVs remain unaffected by known or unknown confounders; and (3) IVs solely

influence outcomes through exposure. Ethical approval or informed consent was not required, as publicly available data were utilized. Figure 1 elucidates our study design.

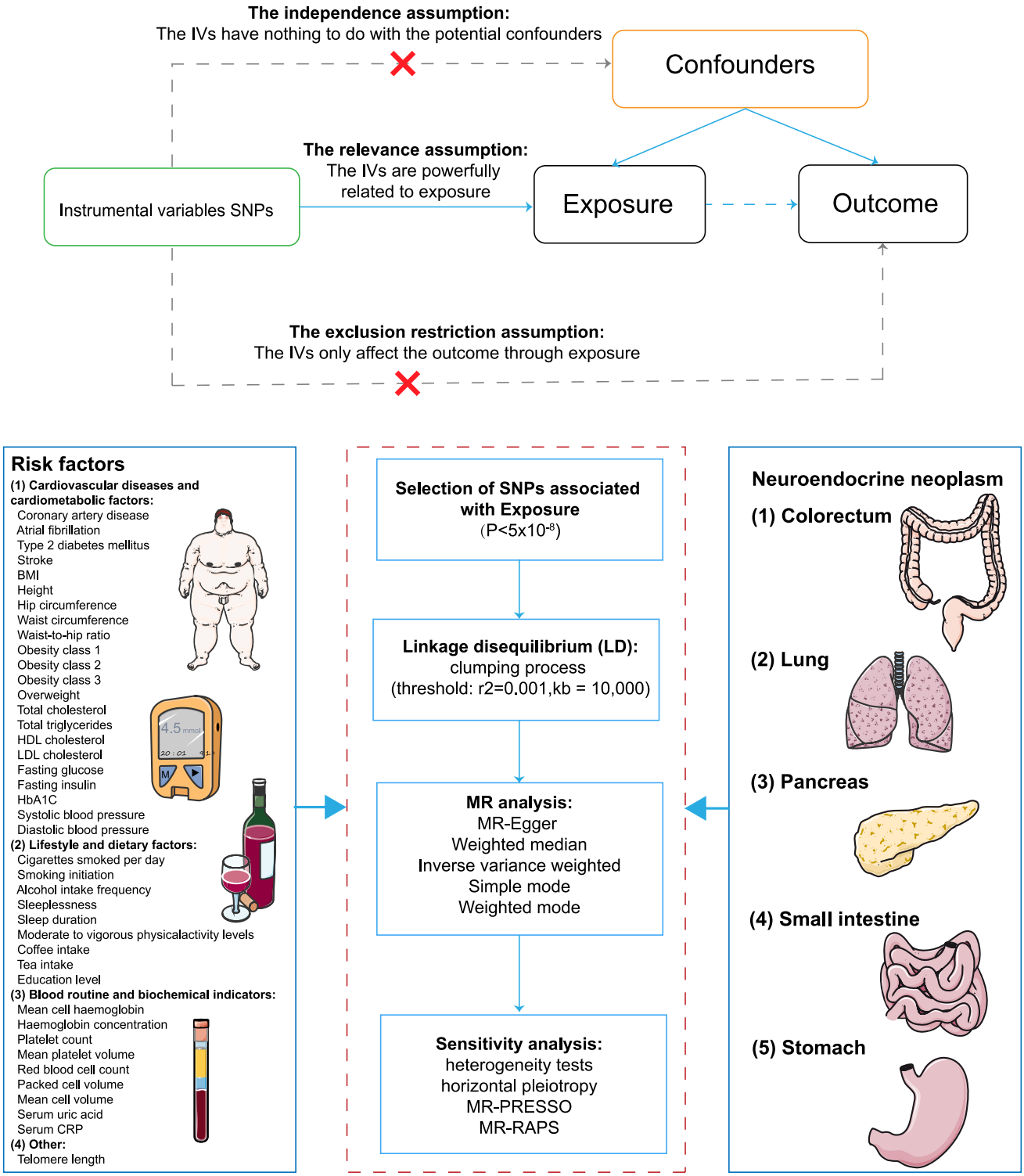

Fig. 1 Study design of bidirectional two-sample MR analysis

2.2 Data sources

Forty-one potentially modifiable risk factors were systematically categorized into four instrumental variable groups: (1) Cardiovascular diseases and cardiometabolic factors, including coronary artery disease, atrial fibrillation, type 2 diabetes mellitus, stroke, BMI, height, hip circumference, waist circumference, waist-to-hip ratio, obesity class 1, obesity class 2, obesity class 3, overweight, total cholesterol, total triglycerides, HDL cholesterol, LDL cholesterol, fasting glucose, fasting insulin, HbA1 C, systolic blood pressure, diastolic blood pressure; (2) Lifestyle and dietary factors, including cigarettes smoked per day, smoking initiation, alcohol intake frequency, sleeplessness, sleep duration, moderate to vigorous physical activity levels, coffee intake, tea intake, education level; (3) Blood routine and biochemical indicators, including mean cell haemoglobin, haemoglobin concentration, platelet count, mean platelet volume, red blood cell count, packed cell volume, mean cell volume, serum uric acid, serum CRP; (4) Other, Telomere length. Data related to the five neuroendocrine neoplasms were sourced from the FinnGen consortium (Table 1).

IVs were extracted from various databases, including (1) the most extensive publicly accessible summary-level statistics available at the time of analysis; (2) GIANT; (3) EGG; (4) UK Biobank (including MRC-IEU and Neale Lab); (5) GLGC; (6) MAGIC; (7) International Consortium of Blood Pressure; (8) GSCAN; (9) SSGAC; (10) HaemGen; and (11) GUGC. For a comprehensive understanding of the study cohort, please refer to the description of the original cohort study and Table 1.

2.3 Selection of instrumental variables

SNPs derived from genome-wide association studies (GWAS) served as IVs. A rigorous quality control program was enacted to scrutinize exposure-related single nucleotide polymorphisms (SNPs) and meticulously choose the most optimal instrumental variables (IVs). Firstly, We defined the significance threshold for SNPs as $p < 5E\text{-}08$. In the reverse MR analysis, a significance threshold of $p < 5E\text{-}06$ was established to effectively filter a significant number of available SNPs. Secondly, we assessed the linkage disequilibrium between SNPs. Among all SNPs with $R2 < 0.001$, only the SNP with the smallest P value was retained, utilizing a clumping window size of 10,000 kb. Thirdly, SNPs with allele frequencies ≤ 0.01 were excluded. Fourthly, in the presence of palindromic alleles, allele frequency information was assigned to the forward strand allele. Fifthly, the F-statistic was employed for each SNP to gauge the strength of covariance between IVs and exposure, with a threshold of $F > 10$ to exclude bias for weak IVs. In such instances, weak IVs were considered unbiased.

2.4 MR analysis

Five distinct methods were employed for MR analysis, encompassing IVW [20], MR-Egger [21], weighted median [22], simple mode [23], and weighted mode [24]. IVW, recognized as the most commonly used and validated method, served as the primary analytical approach in this study. It provides the most compelling estimates under the assumption that all SNPs act as valid IVs. In cases where the horizontal pleiotropy assumption is absent, MR-Egger emerges as a robust alternative. Each of the remaining three methods possesses its inherent strengths and limitations, with potential applicability contingent upon specific circumstances and available data. Consequently, a supplementary analysis employing all three methods concurrently was conducted to affirm the stability of the results.

2.5 Sensitivity analysis

Sensitivity analyses were conducted to evaluate the robustness of our findings. Two methods were used to assess and address horizontal pleiotropy: Robust Adjusted Profile Score-RAPS (MR-RAPS) [25] and MR pleiotropy residual sum and outlier (MR-PRESSO) [26]. The MR-RAPS method, utilizing random effects distributions to model the multidirectional effects of genetic variation, is acknowledged for its enhanced power compared to traditional MR methods [25]. Additionally, Cochran's Q test [20] was applied to detect heterogeneity among exposure-related SNPs.

Table 1 Description of the contributing GWAS studies

Traits	Consortium/Author	Year	PMID	Sample size	No of SNPs	Units	F statistics	Ancestry
Cardiovascular diseases and cardiometabolic factors								
Coronary artery disease	Nikpay M et al	2015	26,343,387	141,217	42	logOR	30 to 443	European
Atrial fibrillation	Nielsen JB et al	2018	30,061,737	1,030,836	111	logOR	30 to 2,039	European
Type 2 diabetes mellitus	Mahajan A et al	2018	29,632,382	298,957	58	logOR	24 to 1,220	European
Stroke	Malik R et al	2018	29,531,354	446,696	8	logOR	31 to 56	European
BMI	GIANT	2015	25,673,413	339,224	79	SD (kg/m^2)	30 to 716	Mixed
Height	EGG	2013	23,449,627	13,960	4	SD	34 to 41	European
Hip circumference	GIANT	2015	25,673,412	213,038	52	SD (cm)	28 to 378	European
Waist circumference	GIANT	2015	25,673,412	245,746	65	SD (cm)	28 to 126	Mixed
Waist-to-hip ratio	GIANT	2015	25,673,412	224,459	31	SD	29 to 170	Mixed
Obesity class 1	GIANT	2013	23,563,607	98,697	17	logOR	28 to 306	European
Obesity class 2	GIANT	2013	23,563,607	72,546	11	logOR	30 to 233	European
Obesity class 3	GIANT	2013	23,563,607	50,364	2	logOR	31 to 112	European
Overweight	GIANT	2013	23,563,607	158,855	14	logOR	33 to 232	European
Total cholesterol	GLGC	2013	24,097,068	187,365	88	SD (mg/dL)	29 to 1,515	Mixed
Total triglycerides	GLGC	2013	24,097,068	177,861	55	SD (mg/dL)	30 to 1,166	Mixed
HDL cholesterol	GLGC	2013	24,097,068	187,167	89	SD (mg/dL)	30 to 1,674	Mixed
LDL cholesterol	GLGC	2013	24,097,068	173,082	81	SD (mg/dL)	28 to 1,663	Mixed
Fasting glucose	MAGIC	2012	22,581,228	58,074	22	SD	30 to 456	European
Fasting insulin	MAGIC	2012	22,885,924	108,557	14	SD	30 to 100	European
HbA1 C	MAGIC	2010	20,858,683	46,368	11	SD	33 to 244	European
Systolic blood pressure	International Consortium of Blood Pressure	2018	30,224,653	757,601	461	SD	30 to 628	European
Diastolic blood pressure	International Consortium of Blood Pressure	2018	30,224,653	757,601	460	SD	30 to 816	European
Lifestyle and dietary factors								
Cigarettes smoked per day	GSCAN	2019	30,643,251	249,752	23	SD	30 to 961	European
Smoking initiation	GSCAN	2019	30,643,251	607,291	93	logOR	30 to 145	European
Alcohol intake frequency	Neale Lab	2017	NA	336,965	44	SD	30 to 553	European
Sleeplessness	MRC-IEU	2018	NA	462,341	42	SD	30 to 199	European
Sleep duration	MRC-IEU	2018	NA	460,099	71	SD	30 to 224	European
Moderate to vigorous physical activity levels	Klimentidis YC et al	2018	29,899,525	377,234	19	SD	30 to 52	European
Coffee intake	MRC-IEU	2018	NA	428,860	40	SD	30 to 647	European
Tea intake	MRC-IEU	2018	NA	447,485	41	SD	30 to 494	European
Education level	SSGAC	2018	30,038,396	766,345	317	SD (years)	30 to 240	European
Blood routine and biochemical indicators								
Mean cell haemoglobin	HaemGen	2012	23,222,517	64,731	32	SD (pg)	25 to 493	Mixed
Haemoglobin concentration	HaemGen	2012	23,222,517	71,861	20	SD (g/dL)	26 to 158	Mixed

Table 1 (continued)

Traits	Consortium/Author	Year	PMID	Sample size	No of SNPs	Units	F statistics	Ancestry
Platelet count	HaemGen	2011	22,139,419	66,867	38	SD (10^9/L)	30 to 226	European
Mean platelet volume	HaemGen	2011	22,139,419	66,867	30	SD (log fl)	30 to 447	European
Red blood cell count	HaemGen	2012	23,222,517	66,214	30	SD (10^{12}/L)	23 to 407	Mixed
Packed cell volume	HaemGen	2012	23,222,517	63,511	14	SD (%)	30 to 84	Mixed
Mean cell volume	HaemGen	2012	23,222,517	69,335	45	SD (fl)	27 to 477	Mixed
Serum uric acid	GUGC	2013	23,263,486	110,347	27	SD (mg/dL)	35 to 1,406	European
Serum CRP	Howe LJ et al	2021	NA	61,308	38	SD	30 to 495	European
Other								
Telomere length	Codd et al	2021	NA	472,174	154	SD	30 to 1,629	European
Neuroendocrine neoplasm								
Colorectum	FinnGen (R10)	2023	36,653,562	314,544	NA	logOR	NA	European
Lung	FinnGen (R10)	2023	36,653,562	314,370	NA	logOR	NA	European
Pancreas	FinnGen (R10)	2023	36,653,562	314,322	NA	logOR	NA	European
Small intestine	FinnGen (R10)	2023	36,653,562	314,516	NA	logOR	NA	European
Stomach	FinnGen (R10)	2023	36,653,562	314,311	NA	logOR	NA	European

PMID, PubMed Unique identifier; SNP, single nucleotide polymorphism; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; CRP, C-reactive protein; SD, standard deviation; OR, odds ratio; NA, not applicable

2.6 Statistical analysis

All analyses were performed using R software (version 4.3.1). MR analysis was conducted using the TwoSampleMR (version 0.5.8) package, and P < 0.05 was considered statistically significant. In addition, we used a multiple testing adjustment threshold with 41 modifiable risk factors adjusted for P < 0.05/41. Adjusted *p*-values were considered to be statistically significantly significant or otherwise considered potentially relevant.

3 Results

3.1 Genetic instruments

Forty-one potentially modifiable risk factors were evaluated. Participants involved in the GWAS study were predominantly of European origin. After a quality control step, the IVs of the 41 modifiable risk factors are detailed in Table S1. All F-statistics exceeded the threshold of 10, indicating an absence of weak instrumental variable bias(Table S1).

3.2 Cardiovascular diseases and cardiometabolic factors for the risk of neuroendocrine neoplasms

Using the IVW method, we observed significant associations between certain modifiable risk factors and the risk of NENs. Height exhibited a noteworthy association with an increased risk of colorectal neuroendocrine neoplasms (Odds Ratio [OR] = 5.294, $p = 0.002$). Additionally, Obesity class 1 was linked to an elevated risk of colorectal (OR = 1.908, $p = 0.001$) and gastric (OR = 2.252, $p = 0.012$) neuroendocrine neoplasms. Obesity class 2 showed associations with an increased risk of colorectal (OR = 1.53, $p = 0.043$) and gastric (OR = 2.272, $p = 0.002$) neuroendocrine neoplasms. Overweight was also associated with an increased risk of colorectal (OR = 2.375, $p = 0.006$) and gastric (OR = 3.574, $p = 0.012$) neuroendocrine neoplasms. Furthermore, Obesity class 3, waist circumference, and waist-to-hip ratio demonstrated associations with an increased risk of colorectal neuroendocrine neoplasms. For colorectal neuroendocrine tumor risk, ORs from the IVW approach were 1.496 ($p = 0.028$), 2.782 ($p = 0.019$), and 5.846 ($p = 0.006$). In addition, there was a negative correlation between Fasting glucose and the risk of colorectal neuroendocrine neoplasms (OR = 0.263, $p = 0.031$). Waist-to-hip ratio was negatively correlated with pancreatic neuroendocrine neoplasms (OR = 0.105, $p = 0.031$). There was a positive correlation between Atrial fibrillation and the risk of small bowel neuroendocrine neoplasms (OR = 1.321, $p = 0.016$). Obesity class 1 exhibited a significant association with colorectal neuroendocrine neoplasms following adjustment for multiple testing (Table 2, S2). Except for potential heterogeneity noted between obesity class 2 and colorectal neuroendocrine neoplasms, neither heterogeneity nor horizontal pleiotropy was observed in any of the aforementioned results. Sensitivity analyses consistently yielded causality results, affirming the robustness of the findings (Table 3, S3).

3.3 Lifestyle and dietary factors for the risk of neuroendocrine neoplasms

In the primary analysis, there was no causal relationship between any of the nine lifestyle and dietary factors, including cigarettes smoked per day, smoking initiation, alcohol intake frequency, sleeplessness, sleep duration, moderate to vigorous physical activity levels, coffee intake, tea intake, education level, and any of the five neuroendocrine neoplasms (Table 2, S2). None of the above results observed the presence of heterogeneity and horizontal pleiotropy (Table S3).

3.4 Blood routine and biochemical indicators for the risk of neuroendocrine neoplasms

Regarding the blood routine and biochemical indicators, serum uric acid demonstrated an association with an increased risk of colorectal neuroendocrine neoplasms (OR = 1.602, $p = 0.042$). Platelet count exhibited a negative correlation with lung neuroendocrine neoplasms (OR = 0.986, $p = 0.02$). Additionally, There was a positive correlation between mean cell haemoglobin (OR = 1.422, $p = 0.017$) and mean cell volume (OR = 1.151, $p = 0.014$) and the risk of small bowel

Table 2 IVW-MR results for the associations between the risk factors with 5 neuroendocrine neoplasms

Trait	Colorectum		P value adjust	Lung		P value adjust	Pancreas		P value adjust	Small intestine		P value adjust	Stomach		P value adjust
	OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value	
Cardiovascular diseases and cardiometabolic factors															
Coronary artery disease	0.994 (0.724, 1.364)	0.97	1.000	0.635 (0.399, 1.011)	0.055	1.000	0.884 (0.525, 1.489)	0.643	1.000	0.86 (0.605, 1.222)	0.399	1.000	1.209 (0.658, 2.22)	0.54	1.000
Atrial fibrillation	1.126 (0.901, 1.407)	0.297	1.000	1.064 (0.784, 1.445)	0.69	1.000	1.062 (0.724, 1.557)	0.759	1.000	1.321 (1.053, 1.657)	**0.016**	0.656	0.754 (0.519, 1.095)	0.138	1.000
Type 2 diabetes mellitus	0.748 (0.496, 1.127)	0.165	1.000	0.821 (0.485, 1.39)	0.463	1.000	0.669 (0.373, 1.198)	0.177	1.000	0.833 (0.49, 1.413)	0.497	1.000	1.233 (0.662, 2.296)	0.509	1.000
Stroke	1.38 (0.514, 3.707)	0.522	1.000	1.079 (0.324, 3.595)	0.901	1.000	1.078 (0.266, 4.365)	0.916	1.000	1.306 (0.523, 3.265)	0.568	1.000	1.31 (0.245, 7.019)	0.752	1.000
BMI	1.792 (0.893, 3.595)	0.1	1.000	1.112 (0.397, 3.115)	0.84	1.000	0.824 (0.262, 2.592)	0.741	1.000	0.975 (0.452, 2.1)	0.948	1.000	2.853 (0.861, 9.455)	0.086	1.000
Height	5.294 (1.884, 14.876)	**0.002**	**0.042***	0.478 (0.112, 2.044)	0.32	1.000	2.367 (0.434, 12.924)	0.32	1.000	1.281 (0.435, 3.768)	0.653	1.000	1.467 (0.248, 8.678)	0.672	1.000
Hip circumference	2.037 (0.803, 5.164)	0.134	1.000	0.632 (0.21, 1.905)	0.415	1.000	1.448 (0.398, 5.263)	0.574	1.000	0.915 (0.392, 2.14)	0.838	1.000	1.92 (0.498, 7.411)	0.344	1.000
Waist circumference	2.782 (1.18, 6.561)	**0.019**	0.399	1.719 (0.542, 5.453)	0.358	1.000	1.013 (0.263, 3.911)	0.985	1.000	1.188 (0.505, 2.792)	0.693	1.000	3.963 (0.967, 16.244)	0.056	1.000
Waist-to-hip ratio	5.846 (1.648, 20.743)	**0.006**	0.126	0.46 (0.083, 2.531)	0.372	1.000	0.105 (0.014, 0.819)	**0.031**	1.000	1.117 (0.282, 4.432)	0.875	1.000	7.471 (0.926, 60.267)	0.059	1.000
Obesity class 1	1.908 (1.283, 2.836)	**0.001***	**0.041***	1.192 (0.711, 1.998)	0.505	1.000	1.15 (0.581, 2.277)	0.689	1.000	1.037 (0.652, 1.651)	0.878	1.000	2.252 (1.198, 4.233)	**0.012**	0.480
Obesity class 2	1.53 (1.012, 2.313)	**0.043**	0.903	0.981 (0.644, 1.495)	0.93	1.000	1.408 (0.861, 2.304)	0.173	1.000	0.92 (0.648, 1.307)	0.643	1.000	2.272 (1.358, 3.802)	**0.002**	0.080
Obesity class 3	1.496 (1.044, 2.145)	**0.028**	0.588	1.075 (0.648, 1.785)	0.779	1.000	1.089 (0.603, 1.969)	0.777	1.000	1.22 (0.838, 1.775)	0.3	1.000	1.679 (0.904, 3.117)	0.101	1.000
Overweight	2.375 (1.278, 4.413)	**0.006**	0.126	1.081 (0.489, 2.387)	0.848	1.000	1.193 (0.367, 3.882)	0.769	1.000	1.22 (0.58, 2.568)	0.6	1.000	3.574 (1.358, 9.405)	**0.01**	0.400

Table 2 (continued)

Trait	Colorectum		P value adjust	Lung		P value adjust	Pancreas		P value adjust	Small intestine		P value adjust	Stomach		P value adjust
	OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value	
Total cholesterol	1.183 (0.83, 1.686)	0.354	1.000	0.765 (0.442, 1.322)	0.337	1.000	0.694 (0.387, 1.243)	0.219	1.000	0.96 (0.664, 1.39)	0.83	1.000	0.672 (0.342, 1.32)	0.248	1.000
Total triglycerides	1.366 (0.813, 2.295)	0.239	1.000	0.587 (0.301, 1.144)	0.118	1.000	1.043 (0.483, 2.256)	0.914	1.000	1.127 (0.683, 1.861)	0.639	1.000	0.643 (0.285, 1.446)	0.285	1.000
HDL cholesterol	0.832 (0.546, 1.269)	0.394	1.000	0.91 (0.465, 1.781)	0.782	1.000	0.757 (0.383, 1.498)	0.425	1.000	0.849 (0.535, 1.348)	0.487	1.000	1.004 (0.493, 2.048)	0.991	1.000
LDL cholesterol	1.193 (0.852, 1.669)	0.304	1.000	0.738 (0.442, 1.231)	0.244	1.000	0.942 (0.55, 1.613)	0.827	1.000	0.924 (0.644, 1.325)	0.666	1.000	0.776 (0.398, 1.511)	0.455	1.000
Fasting glucose	0.263 (0.078, 0.885)	**0.031**	0.651	4.723 (0.576, 38.726)	0.148	1.000	0.744 (0.058, 9.568)	0.821	1.000	2.502 (0.525, 11.925)	0.25	1.000	0.49 (0.061, 3.917)	0.501	1.000
Fasting insulin	0.944 (0.017, 53.983)	0.978	1.000	31.511 (0.605, 1640.108)	0.087	1.000	14.703 (0.083, 2600.153)	0.309	1.000	3.318 (0.202, 54.553)	0.401	1.000	1.356 (0.013, 139.179)	0.897	1.000
HbA1 C	0.412 (0.073, 2.336)	0.316	1.000	1.435 (0.067, 30.734)	0.817	1.000	7.59 (0.48, 120.027)	0.15	1.000	0.501 (0.049, 5.159)	0.561	1.000	2.297 (0.129, 40.755)	0.571	1.000
Systolic blood pressure	1.008 (0.98, 1.036)	0.587	1.000	1.017 (0.978, 1.058)	0.388	1.000	1.018 (0.972, 1.066)	0.448	1.000	1.017 (0.986, 1.049)	0.291	1.000	0.977 (0.932, 1.024)	0.326	1.000
Diastolic blood pressure	0.998 (0.95, 1.048)	0.928	1.000	1.044 (0.977, 1.115)	0.203	1.000	1.056 (0.979, 1.14)	0.158	1.000	1.019 (0.969, 1.072)	0.456	1.000	1.013 (0.934, 1.098)	0.759	1.000
Lifestyle and dietary factors															
Cigarettes smoked per day	1.02 (0.579, 1.797)	0.945	1.000	1.666 (0.75, 3.697)	0.21	1.000	1.244 (0.488, 3.171)	0.648	1.000	0.824 (0.456, 1.488)	0.52	1.000	1.097 (0.414, 2.906)	0.853	1.000
Smoking initiation	1.465 (0.698, 3.073)	0.313	1.000	1.452 (0.543, 3.885)	0.457	1.000	0.826 (0.261, 2.61)	0.745	1.000	0.827 (0.399, 1.714)	0.61	1.000	1.06 (0.318, 3.53)	0.925	1.000
Alcohol intake frequency	1.236 (0.449, 3.403)	0.681	1.000	1.075 (0.252, 4.597)	0.922	1.000	3.516 (0.663, 18.651)	0.14	1.000	0.688 (0.256, 1.85)	0.459	1.000	0.353 (0.069, 1.802)	0.211	1.000

Table 2 (continued)

Trait	Colorectum		P value adjust	Lung		P value adjust	Pancreas		P value adjust	Small intestine		P value adjust	Stomach		P value adjust
	OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value	
Sleeplessness	7.919 (0.768, 81.663)	0.082	0.738	0.668 (0.025, 17.853)	0.81	1.000	1.678 (0.036, 78.974)	0.792	1.000	2.52 (0.207, 30.657)	0.468	1.000	1.946 (0.034, 110.516)	0.747	1.000
Sleep duration	0.334 (0.058, 1.939)	0.222	1.000	0.573 (0.048, 6.796)	0.659	1.000	0.24 (0.013, 4.329)	0.333	1.000	4.334 (0.693, 27.107)	0.117	1.000	0.157 (0.008, 3.237)	0.23	1.000
Moderate to vigorous physicalactivity levels	0.718 (0.05, 10.223)	0.807	1.000	7.858 (0.185, 334.173)	0.281	1.000	7.998 (0.102, 628.688)	0.35	1.000	1.024 (0.064, 16.435)	0.987	1.000	0.118 (0.001, 13.626)	0.378	1.000
Coffee intake	0.534 (0.092, 3.097)	0.485	1.000	0.568 (0.043, 7.474)	0.667	1.000	2.777 (0.154, 50.174)	0.489	1.000	0.724 (0.116, 4.517)	0.729	1.000	2.058 (0.1, 42.25)	0.64	1.000
Tea intake	0.598 (0.142, 2.512)	0.483	1.000	0.238 (0.028, 2.04)	0.19	1.000	2.534 (0.228, 28.103)	0.449	1.000	0.714 (0.16, 3.183)	0.659	1.000	1.36 (0.115, 16.008)	0.807	1.000
Education level	0.866 (0.418, 1.793)	0.699	1.000	0.847 (0.304, 2.359)	0.751	1.000	1.819 (0.548, 6.035)	0.328	1.000	0.534 (0.25, 1.142)	0.106	1.000	0.825 (0.228, 2.985)	0.769	1.000
Blood routine and biochemical indicators															
Mean cell haemoglobin	0.815 (0.617, 1.076)	0.149	1.000	0.983 (0.61, 1.583)	0.943	1.000	0.924 (0.542, 1.576)	0.772	1.000	1.422 (1.064, 1.9)	**0.017**	0.697	1.389 (0.86, 2.243)	0.179	1.000
Haemoglobin concentration	1.12 (0.459, 2.732)	0.803	1.000	0.759 (0.147, 3.913)	0.741	1.000	0.404 (0.093, 1.75)	0.225	1.000	2.437 (0.656, 9.061)	0.184	1.000	2.869 (0.476, 17.291)	0.25	1.000
Platelet count	0.998 (0.99, 1.006)	0.617	1.000	0.986 (0.974, 0.998)	**0.021**	0.861	1.011 (0.997, 1.026)	0.117	1.000	1.002 (0.993, 1.011)	0.687	1.000	0.994 (0.979, 1.009)	0.414	1.000
Mean platelet volume	11.92 (0.514, 276.551)	0.122	1.000	1.449 (0.012, 171.812)	0.879	1.000	0.14 (0.001, 25.071)	0.458	1.000	3.242 (0.121, 86.897)	0.483	1.000	15.591 (0.069, 3513.046)	0.32	1.000
Red blood cell count	1.426 (0.25, 8.142)	0.69	1.000	0.244 (0.011, 5.517)	0.376	1.000	1.307 (0.033, 51.047)	0.886	1.000	0.501 (0.05, 4.985)	0.556	1.000	0.99 (0.031, 31.667)	0.996	1.000
Packed cell volume	1.155 (0.826, 1.615)	0.4	1.000	0.922 (0.488, 1.741)	0.801	1.000	0.807 (0.464, 1.403)	0.448	1.000	1.304 (0.775, 2.192)	0.317	1.000	1.336 (0.653, 2.735)	0.428	1.000

Table 2 (continued)

Trait	Colorectum		P value adjust	Lung		P value adjust	Pancreas		P value adjust	Small intestine		P value adjust	Stomach		P value adjust
	OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value		OR (95%CI)	*P* value	
Mean cell volume	0.933 (0.839, 1.039)	0.206	1.000	0.994 (0.835, 1.183)	0.946	1.000	1.023 (0.83, 1.261)	0.83	1.000	1.151 (1.028, 1.289)	**0.014**	0.574	1.048 (0.872, 1.26)	0.615	1.000
Serum uric acid	1.602 (1.017, 2.524)	**0.042**	0.378	0.886 (0.467, 1.682)	0.711	1.000	1.415 (0.668, 2.995)	0.365	1.000	1.024 (0.636, 1.648)	0.922	1.000	0.733 (0.293, 1.831)	0.506	1.000
Serum CRP	1.232 (0.703, 2.158)	0.466	1.000	2.034 (0.927, 4.464)	0.077	1.000	1.565 (0.593, 4.126)	0.365	1.000	0.999 (0.556, 1.795)	0.997	1.000	1.133 (0.431, 2.98)	0.8	1.000
Other															
Telomere length	0.984 (0.549, 1.763)	0.956	0.956	1.684 (0.743, 3.817)	0.212	1.000	2.03 (0.789, 5.224)	0.142	1.000	1.681 (0.893, 3.163)	0.107	1.000	5.546 (2.07, 14.86)	**0.001***	**0.041***

Bold fonts represent statistically significant *p*-values

BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; CRP, C-reactive protein; OR, odds ratio; CI, confidence interval; MR, Mendelian randomization; IVW, inverse variance weighted

*Multiple tests were carried out to correct the P value, and P value less than 0.05/41 indicated significant difference in the results

Table 3 Sensitivity analyses of statistically significant MR results for the associations between the risk factors with 5 neuroendocrine neoplasms

Trait	Q	$P_{heterogeneity}$	Egger Intercept	$P_{pleiotropy}$	OR_{PRESSO} (95% CI)	P_{PRESSO}	OR_{RAPS} (95% CI)	P_{RAPS}
Colorectum								
Fasting glucose	14.963	0.598	− 0.030	0.538	0.263 (0.086, 0.807)	**0.031**	0.391 (0.141, 1.085)	0.071
Height	0.039	0.981	0.569	0.631	NA	NA	NA	NA
Obesity class 1	18.636	0.231	− 0.002	0.976	1.908 (1.283, 2.836)	**0.006**	1.930 (1.326, 2.807)	**0.001***
Obesity class 2	18.977	0.025	0.013	0.913	1.530 (1.012, 2.313)	0.071	1.550 (1.143, 2.102)	**0.005**
Obesity class 3	0.070	0.792	NA	NA	NA	NA	NA	NA
Overweight	15.669	0.207	0.023	0.807	2.375 (1.278, 4.413)	**0.017**	2.413 (1.359, 4.287)	**0.003**
Serum uric acid	14.717	0.874	0.046	0.169	1.602 (1.087, 2.361)	**0.026**	1.451 (0.923, 2.281)	0.107
Waist-to-hip ratio	31.556	0.293	0.019	0.788	5.846 (1.648, 20.743)	**0.011**	3.375 (1.034, 11.021)	**0.044**
Waist circumference	69.154	0.249	−0.007	0.893	2.782 (1.180, 6.561)	**0.023**	2.877 (1.267, 6.533)	**0.012**
Lung								
Platelet count	32.069	0.317	−0.051	0.45	0.986 (0.974, 0.998)	**0.029**	0.989 (0.978, 1.001)	0.057
Pancreas								
Waist-to-hip ratio	30.407	0.344	−0.054	0.643	0.105 (0.014, 0.819)	**0.040**	0.157 (0.022, 1.106)	0.063
Small intestine								
Atrial fibrillation	96.031	0.746	−0.012	0.486	1.321 (1.065, 1.639)	**0.013**	1.316 (1.047, 1.654)	**0.019**
Mean cell haemoglobin	23.383	0.714	0.048	0.179	1.422 (1.084, 1.864)	**0.016**	1.284 (0.968, 1.703)	0.083
Mean cell volume	36.872	0.428	0.034	0.313	1.151 (1.028, 1.289)	**0.019**	1.112 (1.000, 1.236)	0.051
Stomach								
Obesity class 1	11.077	0.747	−0.117	0.260	2.252 (1.290, 3.929)	**0.011**	2.272 (1.193, 4.327)	**0.013**
Obesity class 2	5.105	0.825	−0.039	0.784	2.272 (1.568, 3.292)	**0.001***	2.287 (1.347, 3.883)	**0.002**
Overweight	9.619	0.649	−0.128	0.366	3.574 (1.498, 8.527)	**0.013**	3.628 (1.350, 9.750)	**0.011**
Telomere length	119.63	0.772	−0.020	0.431	5.546 (2.172, 14.158)	**0.000***	5.635 (2.104, 15.09)	**0.001***

Bold fonts represent statistically significant *p*-values

MR, Mendelian randomization; OR, odds ratio; CI, confidence interval; NA, not applicable; PRESSO, Pleiotropy RESidual Sum and Outlier; RAPS, robust adjusted profile score

*Multiple tests were carried out to correct the P value, and P value less than 0.05/41 indicated significant difference in the results

neuroendocrine neoplasms (Table 2 TableS2). The presence of heterogeneity and horizontal pleiotropy was not observed in any of the above results (Table 3, S3).

3.5 Telomere length for the risk of neuroendocrine neoplasms

In gastric neuroendocrine neoplasms, Telomere length was considered to be associated with its increased risk (OR = 5.546,$p = 0.001$). This association retained statistical significance even after adjustment for multiple tests, underscoring a significant correlation between telomere length and the elevated risk of gastric neuroendocrine neoplasms (Table 2, S2). No heterogeneity and horizontal pleiotropy existed between the two. The results of the sensitivity analysis indicated the robustness of the causal relationship (Table 3, S3).

3.6 Bidirectional MR analysis

To demonstrate the directionality of causality, reverse MR analysis was undertaken. To screen for a sufficient number of available SNPs, the significance threshold was set to $p < 5E\text{-}6$. However, no SNPs meeting this threshold were available for these specific tumor types, and as a result, these exposures were exempted from the screening process. Inverse MR results revealed a causal relationship between gastric neuroendocrine neoplasms and telomere length (OR = 1.014, $p = 0.002$). There was no significant relationship between colorectal neuroendocrine neoplasms and height, serum uric acid, waist circumference, waist-to-hip ratio, obesity class 1, obesity class 2, obesity class 3, overweight, and fasting glucose

Exposure (Neuroendocrine neoplasm)	Outcome (Risk factor)	Nsnp	OR_{ivw} (95%CI)	P_{ivw}
Colorectum	Height	3	0.965 (0.927, 1.004)	0.080
Colorectum	Serum uric acid	3	1.006 (0.972, 1.041)	0.744
Colorectum	Waist circumference	3	0.988 (0.974, 1.003)	0.111
Colorectum	Waist-to-hip ratio	3	0.993 (0.978, 1.009)	0.386
Colorectum	Obesity class 1	3	1.000 (0.957, 1.044)	0.983
Colorectum	Obesity class 2	3	1.027 (0.959, 1.099)	0.443
Colorectum	Obesity class 3	3	1.060 (0.931, 1.206)	0.378
Colorectum	Overweight	3	1.000 (0.949, 1.054)	0.992
Colorectum	Fasting glucose	3	0.999 (0.989, 1.009)	0.858
Small intestine	Atrial fibrillation	10	0.996 (0.982, 1.009)	0.539
Small intestine	Mean cell haemoglobin	6	1.020 (0.995, 1.046)	0.122
Small intestine	Mean cell volume	6	1.002 (0.940, 1.068)	0.953
Stomach	Telomere length	2	1.014 (1.005, 1.024)	0.002

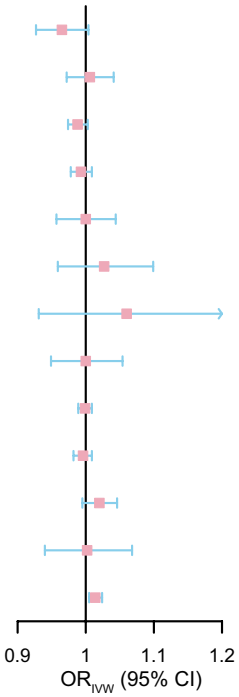

Fig. 2 Reverse Mendelian randomization analysis of neuroendocrine tumors and modifiable risk factors

($p > 0.05$). Likewise, no causal relationships were detected between small intestinal neuroendocrine neoplasms and atrial fibrillation, mean cell haemoglobin, and mean cell volume ($p > 0.05$) ($p > 0.05$) (Fig. 2, Table S4).

4 Discussion

This MR study marks the inaugural analysis of the causal relationship between modifiable risk factors and neuroendocrine neoplasms. The findings revealed that height, obesity, overweight, waist-to-hip ratio, waist circumference, and serum uric acid are associated with an elevated risk of colorectal neuroendocrine neoplasms. Conversely, fasting glucose demonstrated a negative association with the risk of colorectal neuroendocrine neoplasms. Platelet count exhibited a negative association with lung neuroendocrine neoplasms, while waist-to-hip ratio showed a negative association with pancreatic neuroendocrine neoplasms. There was a positive correlation between atrial fibrillation, mean cell haemoglobin, mean cell volume, and the risk of small intestinal neuroendocrine neoplasms. Additionally, a bidirectional causal relationship was observed between telomere length and gastric neuroendocrine neoplasms. However, there was insufficient evidence to infer causal relationships between lifestyle and dietary factors and neuroendocrine neoplasms. These findings hold critical implications for the advancement of neuroendocrine tumor prevention and treatment strategies, emphasizing the importance of early identification and intervention in modifiable risk factors.

Our findings provide possible genetic evidence supporting causal relationships between cardiometabolic factors and the susceptibility to gastrointestinal neuroendocrine neoplasms. Previous studies have indicated associations between height, weight gain, and the risk of gastric neuroendocrine neoplasms [27]. Furthermore, highly differentiated GEP-NENs have been linked with visceral obesity and metabolic syndromes, exemplified by factors such as waist circumference [28]. Lipid metabolism is involved in the development and progression of many common cancer types by altering lipid synthesis, storage, and catabolism. A study by Modica R et al. found lipid alterations to be a risk factor for NENs [29]. Another observational study has proposed that cardiometabolic markers and metabolic syndrome may serve as predictors of clinical severity in GEP-NENs [30]. The obesity carcinogenesis hypothesis, implicating genetic susceptibility to adipose stromal cell migration and excessive hypoxia in adipose tissue [31], has been previously postulated. Despite an incomplete understanding of its mechanisms on neuroendocrine tumorigenesis

[32], the metabolic effects associated with obesity are believed to contribute to an increased prevalence of GEP-NENs [33]. A retrospective study by Feola T et al. [34] analysed data on clinical characteristics, family history of cancer and other potential risk factors and showed that obesity is an independent risk factor for pancreatic NENs and intestinal NENs. Our novel MR analysis, for the first time, demonstrated a causal relationship between obesity and gastrointestinal neuroendocrine neoplasms, emphasizing the non-negligible role of obesity control in preventing the occurrence of neuroendocrine neoplasms.

Lifestyle and dietary factors are thought to be associated with the development of a variety of tumors. Prior observational studies have presented conflicting evidence regarding the association of smoking and alcohol intake with an elevated risk of neuroendocrine neoplasms [35, 36], with observed heterogeneity in risk across anatomical locations. Additionally, Barrea et al. demonstrated that physical labor was not associated with GEP-NENs tumorigenesis, aligning with our MR results. In this MR study, we found insufficient evidence to support a causal relationship between lifestyle and dietary factors, including cigarettes smoked per day, smoking initiation, alcohol intake frequency, sleeplessness, sleep duration, moderate to vigorous physical activity levels, coffee intake, tea intake, education level, and neuroendocrine neoplasms. Hence, a more nuanced exploration may be required to understand the role of lifestyle habits as risk factors for neuroendocrine neoplasms.

Telomeres play a pivotal role in mediating crucial regulatory processes in the carcinogenesis of GEP-NENs [37]. In primary pancreatic neuroendocrine neoplasms, the selective lengthening of telomeres, coupled with DAXX/ATRX deletion, has been associated with metastasis and poor survival [38, 39]. Nishio et al. demonstrated a potential association between telomere length and the development of lung neuroendocrine neoplasms [40]. Wang et al. indicated that shorter telomeres might be linked to a higher risk of Von Hippel-Lindau-related neuroendocrine neoplasms [41]. Wang et al. [42] reported that the incidence of pancreatic neuroendocrine tumours increases with age and Lu et al. [43] suggested that age is an independent risk factor for pancreatic neuroendocrine tumours. Interestingly, our study did not reveal a causal relationship between telomere length and pancreatic and lung neuroendocrine neoplasms. Contrarily, a bidirectional causal relationship was identified between telomere length and the development of gastric neuroendocrine neoplasms, suggesting a dynamic interplay between the two variables.

Our study offers valuable insights into understanding the causal relationships among 41 potentially modifiable risk factors and five neuroendocrine neoplasms, as discerned through epidemiological observations. However, there are still limitations to our study. Our reliance on available GWAS data may be limited by the quality and representativeness of these datasets. Although our MR analysis took into account known confounders, there may still be unmeasured factors affecting the relationship between cirrhosis and hepatocellular carcinoma. Our study may be limited by sample size and statistical power as well as the heterogeneity of different datasets. Firstly, in the reverse MR study, the *p*-value threshold for screening available SNPs was set at 5E-06, potentially introducing a slight instrumental bias to the reverse causality estimation. Secondly, the study's conclusions primarily rely on GWAS summary statistics of European ancestry, and their applicability to other populations remains to be evaluated. In addition, there is a lack of suitable genetic variants with strong and specific associations for tumour progression and aggressiveness (e.g., grade, stage, metastatic status). There was no way to study the relationship between age and tumour as there was no age data in the MR database. This limitation stems from the fact that these clinical and pathological features are the result of a complex set of factors, including environmental and somatic genetic variations, that cannot be captured by germline genetic variants used in MR. Therefore, our study was unable to directly assess their causal role using MR methods. Prospective clinical studies of a larger scale are indispensable in the future to unravel the nuanced causal relationships between lifestyle habits, metabolism-related diseases, telomere length, and the risk of developing neuroendocrine neoplasms.

5 Conclusion

Collectively, our MR study stands as the initial and encompassing evaluation of the causal connections among 41 potentially modifiable risk factors and the susceptibility to five neuroendocrine neoplasms. Notably, obesity and overweight emerged as pivotal contributors to neuroendocrine tumor development. Furthermore, our investigation unveiled a bidirectional causal relationship between telomere length and the occurrence of gastric neuroendocrine neoplasms. These findings contribute to the foundation of knowledge surrounding the etiology of neuroendocrine

neoplasms and provide a comprehensive understanding of the intricate causal landscape involving modifiable risk factors.

6 Limitations

The datasets used in this study, mainly from the UK Biobank and FinnGen databases, are wide-ranging but may introduce selection bias due to their population-specific origins. This may limit the generalizability and external validity of the findings.

The stringent criteria used to identify robust associations in this study may have limited the identification of some of the risk factors, thereby increasing the likelihood of false-negative results.

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Data availability Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate The data utilized in this study were sourced from publicly accessible databases and were managed under approved ethical exemptions.

Consent for publication The authors agreed to publication in the journal.

Competing interests The authors declare no competing interests.

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