MEDS Clinical Medicine (2024)
Clausius Scientific Press, Canada

DOI: 10.23977/medsc.2024.050405
ISSN 2616-1907 Vol. 5 Num. 4

The Causal Relationships between Hyperthyroidism, Polyomavirus Infection, and Kidney Problems: A Mendelian Randomization Study

Yuanhao Su[1,a], Yi Jin[2,b,*]

[1]*Department of General Surgery, The Second Affiliated Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, 710004, China*
[2]*Institute of Gene and Cell Therapy, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, 710061, China*
[a]*suyuanhao1232021@163.com*, [b]*2392985596@qq.com*
[*]*Corresponding author*

Keywords: Hyperthyroidism, Polyomavirus Infection, Kidney Problems, Mendelian Randomization, Causal Relationships

Abstract: Studies have suggested a correlation between hyperthyroidism, polyomavirus infection, and kidney problems, but the causal relationships remain unclear. This research seeks to investigate the causal relationships between hyperthyroidism, polyomavirus infection, and kidney problems using Mendelian randomization (MR), providing insights for clinical treatment and prevention of these conditions. Genetic data for hyperthyroidism, polyomavirus infection, and kidney issues were sourced from GWAS and analyzed using MR in separate groups. Bidirectional studies were conducted to evaluate reverse causality, followed by sensitivity analyses to determine effect stability. In the genetic evaluation, a notable positive association was observed between hyperthyroidism and polyomavirus infection, hyperthyroidism and kidney problems, and polyomavirus infection and kidney problems. This correlation was consistent across four methods: Inverse Variance Weighted (IVW), MR Egger, Weighted Median, and Weighted Mode. Additionally, reverse MR analysis indicated no reverse causality and extra sensitivity studies showed similar MR assessment results with no horizontal pleiotropy. In summary, the results indicate that hyperthyroidism is a contributing factor to a higher occurrence of polyomavirus infection and kidney problems. Additionally, polyomavirus infection is a risk factor for an increased incidence of kidney problems.

1. Introduction

Autoimmune hyperthyroidism represents a significant portion of thyroid disorders, characterized by the body's immune system erroneously attacking the thyroid gland, leading to its overactivity [1]. Among these, Graves' disease stands out as the most common manifestation, accounting for approximately 60-80% of cases of hyperthyroidism [2], occuring with an annual incidence ranging from 20 to 50 cases per 100,000 individuals [3]. The disease results from the production of

autoantibodies that stimulate the thyroid-stimulating hormone receptor (TSHR), leading to excessive thyroid hormone secretion. This condition can have a profound impact on metabolic processes, cardiovascular function, and overall health [4,5]. Graves' disease typically presents with symptoms such as weight loss, heat intolerance, increased appetite, and nervousness. It can also lead to more specific clinical signs like goiter (an enlarged thyroid gland), ophthalmopathy (eye problems), and dermopathy (skin issues). Diagnostic evaluation generally involves clinical assessment, thyroid function tests showing elevated free thyroxine (FT4) and triiodothyronine (T3) levels with suppressed thyroid-stimulating hormone (TSH), and the presence of TSH receptor antibodies (TRAb) [6]. Management of autoimmune hyperthyroidism includes antithyroid medications, radioactive iodine therapy, and surgical intervention [7].

Previous studies have shown a certain link between hyperthyroidism and viral infections [8,9]. This study focuses on the relationship between hyperthyroidism and specific virus—polyomavirus infection. Polyomaviruses are a group of small, non-enveloped DNA viruses that infect a wide range of vertebrate hosts. These viruses belong to the family polyomaviridae and are characterized by their circular, double-stranded DNA genomes of approximately 5,000 base pairs [10,11]. Polyomaviruses have been discovered in diverse species, including humans, birds, and monkeys, and they can exhibit persistent and asymptomatic infections in their natural hosts [12]. The first polyomaviruse isolated were mouse polyomavirus in 1953 [13]. Since then, several human polyomaviruses have been identified, including simian virus 40 (SV40) [14], BK virus (BKV) [15], JC virus (JCV) [16], Merkel cell polyomavirus (MCPyV) [17]. BK virus and JC virus are both ubiquitous, infecting a large portion of the human population during childhood or adolescence [18]. While primary infections are typically asymptomatic, these viruses establish latency in the kidneys and can reactivate under conditions of immunosuppression [19]. BKV reactivation can lead to nephropathy and graft loss in kidney transplant recipients [20,21]. Therefore, in this study, we further included kidney problems as a subject of investigation. We aim to explore the causal relationships between hyperthyroidism, polyomavirus infection, and kidney problems through Mendelian randomization (MR). This research seeks to provide clinical reference for the treatment of hyperthyroidism patients and the prevention of complications.

Based on the above description and the comprehensive results of MR, we observed that patients with autoimmune hyperthyroidism are more susceptible to polyomavirus infections, especially BK virus. Previous studies have found that BK virus infection may lead to renal problems, a finding which is also validated by our MR results. Thus, this study reveals the close relationship between autoimmune hyperthyroidism, polyomavirus infection, and renal pathology.

2. Methods

2.1. Study Design

Using publicly available data from the GWAS database, a Mendelian randomization analysis was conducted to assess the causal relationship between autoimmune hyperthyroidism, polyomavirus infection, and kidney problems. In our assessment, three primary assumptions were established: (1) there exists a robust association between genetic factors and exposure; (2) exposure fully explains the relationship between genetic variables and outcomes; (3) no other confounding factors, apart from the exposure, can explain the relationship between genetic variables and outcomes. All research protocols complied with the World Medical Association’s Declaration of Helsinki. Given that the data were derived from the publicly available GWAS database and all information was collected with ethical consent from the pertinent institutions, institutional ethical approval was unnecessary. The research workflow of this study is shown in Figure 1.

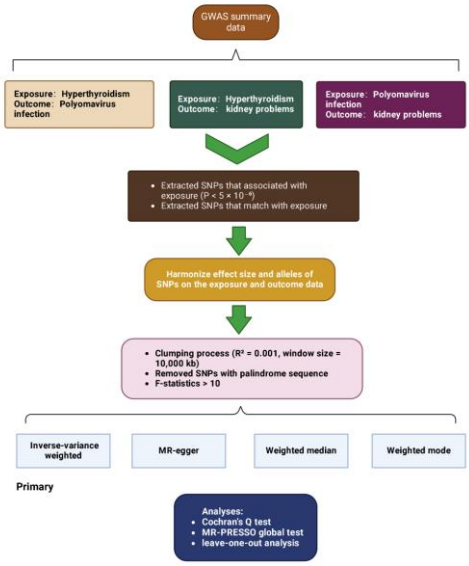

Figure 1: Study design and overview of our Mendelian randomization (MR) study.

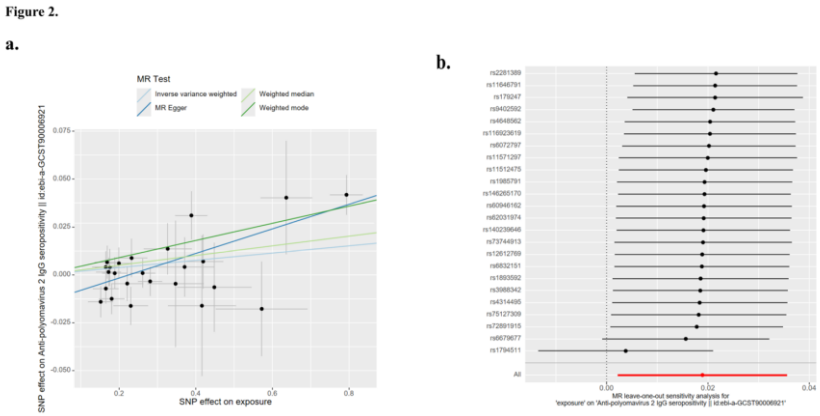

Figure 2: Causal relationship results between autoimmune hyperthyroidism (finngen_R10_AUTOIMMUNE_HYPERTHYROIDISM) and polyomavirus infection (ebi-a-GCST90006921). a. Mendelian randomization scatter plot for autoimmune hyperthyroidism and polyomavirus infection. b. Leave-one-out analysis forest plot.

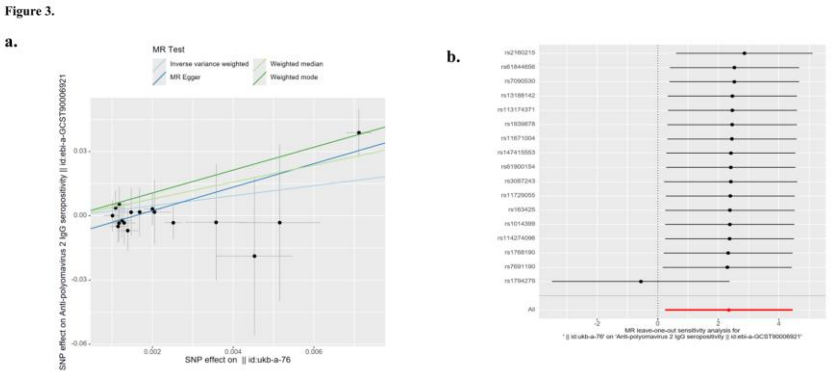

Figure 3: Causal relationship results between hyperthyroidism (ukb-a-76) and polyomavirus infection (ebi-a-GCST90006921). a. Mendelian randomization scatter plot for hyperthyroidism and polyomavirus infection. b. Leave-one-out analysis forest plot.

2.2. Data Source

The study utilized publicly available data from the Public Integrative Epidemiology Unit (IEU) GWAS database (https://gwas.mrcieu.ac.uk/), the Finnish GWAS database (https://www.finngen.fi/en), and the UK Biobank GWAS database (https://www.ukbiobank.ac.uk/).

In the IEU database, there are GWAS data on polyomavirus antibody levels involving 8,735 European subjects, and GWAS data on kidney-related issues involving 484,598 European subjects. The UK Biobank database includes GWAS data on hyperthyroidism involving 337,159 European subjects. Additionally, the Finnish database contains GWAS data on autoimmune hyperthyroidism involving 1,991 subjects. The primary goal of the study is to assess the causal relationships between hyperthyroidism, polyomavirus infection, and kidney-related issues to explore potential biological mechanisms.

2.3. Screening of Instrumental Variables (IVs)

As genetic instruments, single nucleotide polymorphisms (SNPs) associated with autoimmune hyperthyroidism that achieved genome-wide significance ($p < 5 \times 10^{-6}$) were identified. To further ensure the independence of these SNPs, stringent linkage disequilibrium pruning was performed within a 10,000 kb range, setting $R^2 < 0.001$. Additionally, to ensure the reliability and stability of the instrumental variables, all F-values for the instrumental variables were adjusted to be greater than 10.

2.4. Statistical Analysis

We conducted MR analyses using four different statistical methods: Inverse Variance Weighted (IVW), MR Egger, Weighted Median [22], and Weighted Mode for a two-sample MR analysis. These analyses were performed to statistically evaluate the causal associations between hyperthyroidism and polyomavirus infection, polyomavirus infection and kidney-related issues, and hyperthyroidism and kidney-related issues. In this analysis, we calculated the odds ratios (OR) and their 95% confidence intervals (CI) to assess causal outcomes. We also further evaluated reverse causality through reverse MR analysis. Additionally, Cochran's Q was used to evaluate SNP heterogeneity, and the Egger intercept or MR-PRESSO Global Test was used to assess SNP horizontal pleiotropy [23]. We also created scatter plots to visually present these associations and performed leave-one-out analysis to ensure the robustness of the results. All data analyses were conducted using the TwoSampleMR and MR-PRESSO packages in R software (version 4.4.1), along with related packages. Statistical significance was set at $p < 0.05$.

3. Results

3.1. The Causal Association between Autoimmune Hyperthyroidism and Polyomavirus Infection

The main prediction based on the IVW method indicates a causal relationship between autoimmune hyperthyroidism and polyomavirus infection (OR = 1.02, 95% CI = 1.002-1.036, p = 0.03). The predictions based on MR Egger, Weighted Median, and Weighted Mode methods are as follows: MR Egger (OR = 1.07, 95% CI = 1.035-1.098, p = 0.0003); Weighted Median (OR = 1.03, 95% CI = 1.003-1.049, p = 0.029); Weighted Mode (OR = 1.05, 95% CI = 1.019-1.074, p = 0.003). These results indicate a significant positive correlation between autoimmune hyperthyroidism and polyomavirus infection. These results were visualized using a scatter plot (Figure 2a). Based on

Cochran's Q statistic, this study found no significant heterogeneity (IVW, p = 0.12 > 0.05; MR Egger, p = 0.60 > 0.05), and the MR-PRESSO global pleiotropy test p-value indicated no pleiotropy-based bias (p = 0.07 > 0.05). We also performed a leave-one-out analysis to determine the stability of the results and created a forest plot (Figure 2b).

To avoid bias from a single dataset, we reanalyzed the data using hyperthyroidism-related data from the UK Biobank database. The main prediction based on the IVW method indicates a positive causal relationship between self-reported hyperthyroidism and polyomavirus infection (OR = 10.48, 95% CI = 1.272-86.298, p = 0.03). The predictions based on MR Egger, Weighted Median, and Weighted Mode methods are as follows: MR Egger (OR = 242.265, 95% CI = 7.074-8297.225, p = 0.008); Weighted Median (OR = 51.703, 95% CI = 2.505-1067.343, p = 0.011); Weighted Mode (OR = 209.155, 95% CI = 9.248-4730.115, p = 0.004). These results were visualized using a scatter plot (Figure 3a). Based on Cochran's Q statistic, this study found no significant heterogeneity (IVW, p = 0.85 > 0.05; MR Egger, p = 0.98 > 0.05), and the MR-PRESSO global pleiotropy test p-value indicated no pleiotropy-based bias (p = 0.49 > 0.05). We also performed a leave-one-out analysis to determine the stability of the results and created a forest plot (Figure 3b).

Additionally, a MR analysis was conducted specifically targeting the genetic variations related to BK polyomavirus VP1 antibody levels. This analysis also found a positive correlation between hyperthyroidism and BK polyomavirus antibody levels (Figure 4a, Figure 4b).

3.2. The Causal Association between Hyperthyroidism and Kidney Problem

The main prediction based on the IVW method indicates a causal relationship between autoimmune hyperthyroidism and kidney problems (OR = 1.0004, 95% CI = 1.0001-1.0007, p = 0.007). The predictions based on MR Egger, Weighted Median, and Weighted Mode methods are as follows: MR Egger (OR = 1.0008, 95% CI = 1.0002-1.0013, p = 0.016); Weighted Median (OR = 1.0007, 95% CI = 1.0002-1.0011, p = 0.002); Weighted Mode (OR = 1.0006, 95% CI = 1.0002-1.0011, p = 0.013). These results indicate a significant positive correlation between autoimmune hyperthyroidism and kidney problems. These results were visualized using a scatter plot (Figure 5a). Based on Cochran's Q statistic, this study found no significant heterogeneity (IVW, p = 0.56 > 0.05; MR Egger, p = 0.62 > 0.05), and the MR-PRESSO global pleiotropy test p-value indicated no pleiotropy-based bias (p = 0.56 > 0.05). We also performed a leave-one-out analysis to determine the stability of the results and created a forest plot (Figure 5b).

To avoid bias from a single dataset, we reanalyzed the data using hyperthyroidism-related data from the UK Biobank database. The main prediction based on the IVW method indicates a positive causal relationship between self-reported hyperthyroidism and kidney problems (OR = 1.046, 95% CI = 1.010-1.084, p = 0.011). The predictions based on MR Egger, Weighted Median, and Weighted Mode methods are as follows: MR Egger (OR = 1.064, 95% CI = 0.9979-1.1355, p = 0.068); Weighted Median (OR = 1.094, 95% CI = 1.039-1.152, p = 0.0006); Weighted Mode (OR = 1.094, 95% CI = 1.033-1.158, p = 0.004). These results were visualized using a scatter plot (Figure 6a). Based on Cochran's Q statistic, this study found no significant heterogeneity (IVW, p = 0.71 > 0.05; MR Egger, p = 0.68 > 0.05), and the MR-PRESSO global pleiotropy test p-value indicated no pleiotropy-based bias (p = 0.638 > 0.05). We also performed a leave-one-out analysis to determine the stability of the results and created a forest plot (Figure 6b).

3.3. The Causal Association between Polyomavirus Infection and Kidney Problems

The primary prediction using the IVW method suggests a causal relationship between polyomavirus infection and kidney problems (OR = 1.002, 95% CI = 1.0002-1.0042, p = 0.03). Predictions from the MR Egger, Weighted Median, and Weighted Mode methods are as follows:

MR Egger (OR = 1.004, 95% CI = 1.000-1.008, p = 0.103); Weighted Median (OR = 1.002, 95% CI = 1.000-1.005, p = 0.095); Weighted Mode (OR = 1.003, 95% CI = 1.0007-1.0062, p = 0.044). These findings indicate a significant positive association between polyomavirus infection and kidney problems. The results are illustrated using a scatter plot (Figure 7a). According to Cochran's Q statistic, there was no significant heterogeneity observed (IVW, p = 0.43 > 0.05; MR Egger, p =0.43 > 0.05). Furthermore, the MR-PRESSO global pleiotropy test p-value showed no evidence of pleiotropy-based bias (p = 0.40 > 0.05). A leave-one-out analysis was also conducted to assess the stability of the results, and a forest plot was created (Figure 7b).

Detailed results, including OR values, p-values, and 95% confidence intervals, along with the heterogeneity and global pleiotropy test p-values, are provided in Supplementary material.

3.4. Reverse MR Analysis to Assess the Reverse Causal Relationship

To explore reverse causal relationships, we conducted comprehensive reverse Mendelian randomization analyses. Specifically, three separate analyses were performed: one with polyomavirus infection as the exposure and hyperthyroidism as the outcome; another with kidney-related problem as the exposure and hyperthyroidism as the outcome; and a third with kidney-related problem as the exposure and polyomavirus infection as the outcome. Results from these reverse MR analyses, including IVW, MR-Egger, Weighted Median, and Weighted Mode methods, consistently showed no statistical significance, indicating no evidence supporting any reverse causal relationships.

Figure 4.

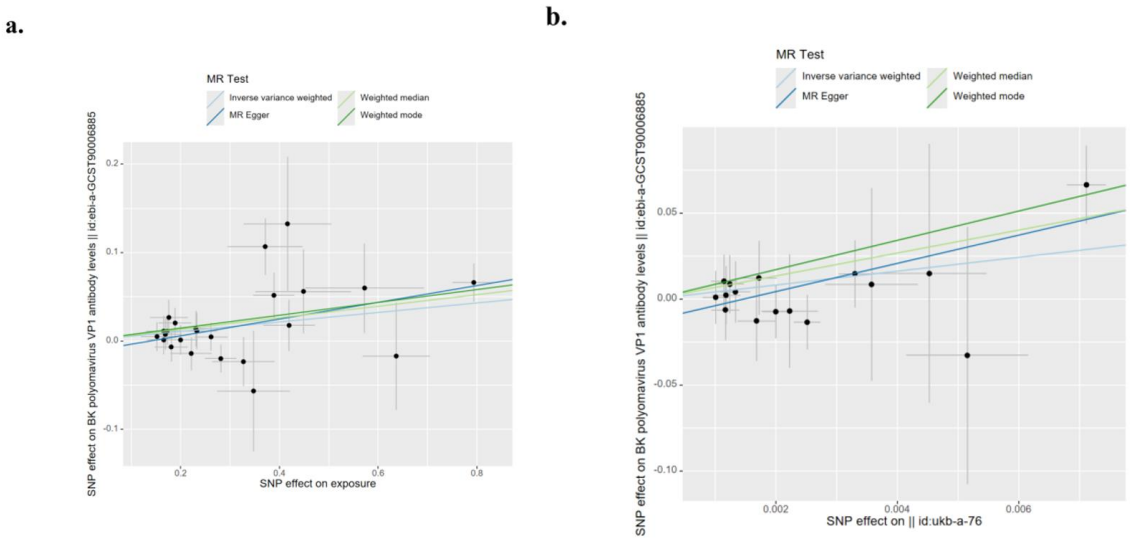

Figure 4: Causal relationship results between hyperthyroidism and BK polyomavirus antibody levels. a. Mendelian randomization scatter plot for hyperthyroidism (finngen_R10_AUTOIMMUNE_HYPERTHYROIDISM) and BK polyomavirus antibody levels (ebi-a-GCST90006885). b. Mendelian randomization scatter plot for hyperthyroidism (ukb-a-76) and BK polyomavirus antibody levels (ebi-a-GCST90006885).

Figure. 5.

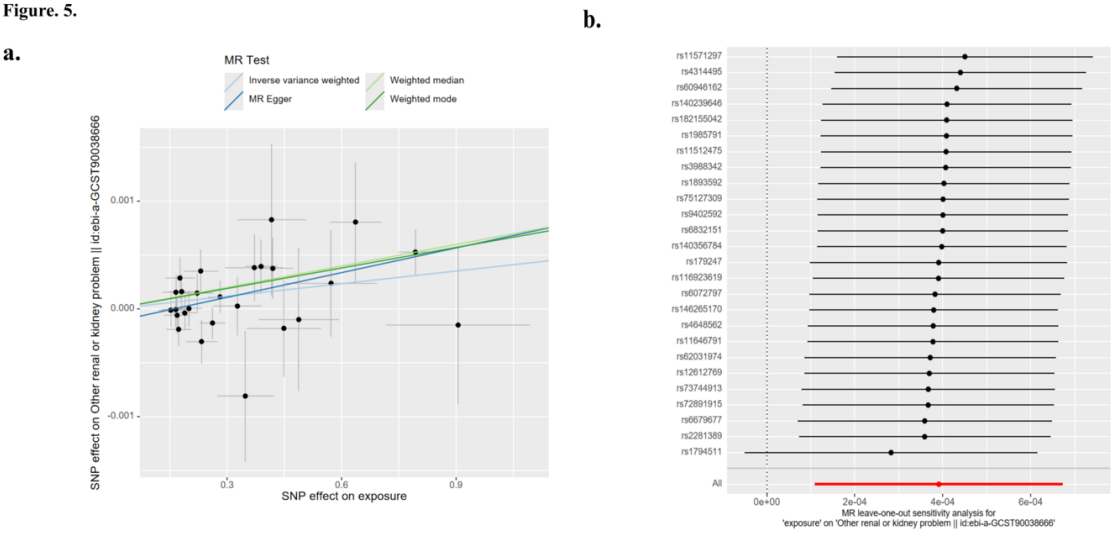

Figure 5: Causal relationship results between autoimmune hyperthyroidism (finngen_R10_AUTOIMMUNE_HYPERTHYROIDISM) and kidney problem (ebi-a-GCST90038666). a. Mendelian randomization scatter plot for autoimmune hyperthyroidism and kidney problem. b. Leave-one-out analysis forest plot.

Figure 6.

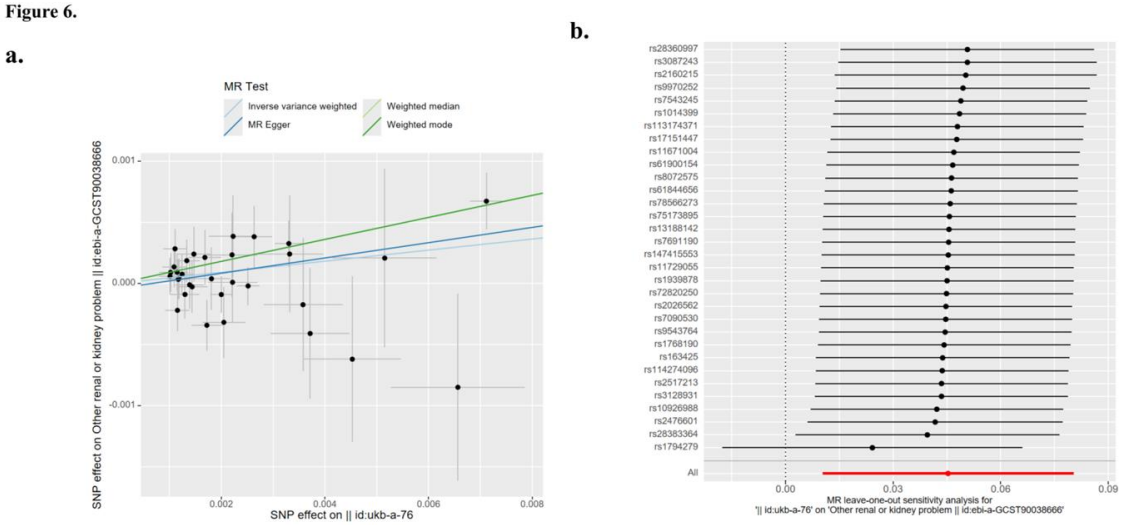

Figure 6: Causal relationship results between hyperthyroidism (ukb-a-76) and kidney problem (ebi-a-GCST90038666). a. Mendelian randomization scatter plot for hyperthyroidism and kidney problem. b. Leave-one-out analysis forest plot.

Figure. 7

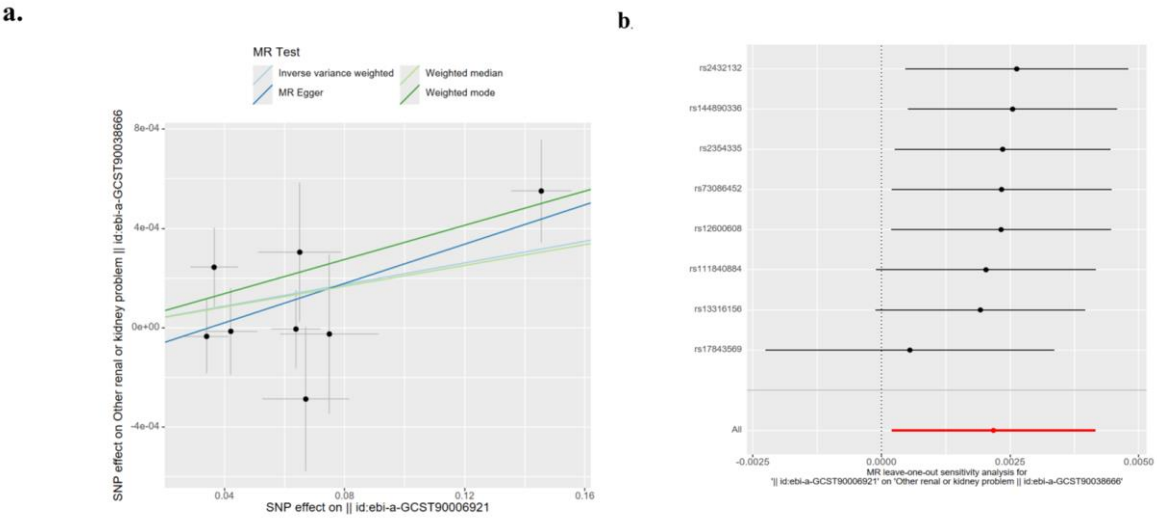

Figure 7: Causal relationship results between polyomavirus infection (ebi-a-GCST90006921) and kidney problem (ebi-a-GCST90038666). a. Mendelian randomization scatter plot for polyomavirus infection and kidney problem. b. Leave-one-out analysis forest plot.

4. Discussion

This Mendelian randomization study used large-scale publicly available genomic datasets to explore the complex relationships between hyperthyroidism, polyomavirus infection, and kidney-related problems. Our primary findings indicate positive correlations among these conditions: hyperthyroidism and polyomavirus infection, hyperthyroidism and kidney-related issues, and polyomavirus infection and kidney-related issues. The value of this analysis lies in its pioneering effort to connect hyperthyroidism, polyomavirus infection, and kidney-related problems together. Research on the relationships between these three factors is currently scarce, and this study thoroughly assessed their causal relationships. The MR method was employed to minimize bias from confounding factors and reverse causation, enabling us to infer causal relationships rather than just hypothesize.

Different viral infections are thought to be associated with autoimmune hyperthyroidism. Valtonen et al. found evidence of recent bacterial or viral infections in the serum of 36% of newly diagnosed Graves' disease (GD) patients, compared to only 10% in the control group [24]. Additionally, an elevated frequency of influenza A virus antibodies has been observed in patients with thyrotoxicosis [25]. Another study demonstrated that TRAb levels in the supernatants after reactivation were significantly higher than those from healthy subjects [26]. These findings suggest that EBV(+) cells produce TRAbs in response to reactivation, collectively suggesting a link between autoimmune hyperthyroidism and viral infections. However, the aforementioned studies merely indicate a potential association between hyperthyroidism and viral infections without establishing a causal relationship. It is widely accepted that viral infections significantly contribute to the development of autoimmune hyperthyroidism. Nevertheless, our research indicates that individuals with autoimmune hyperthyroidism have a heightened vulnerability to polyomavirus infection.

Studies have also suggested that thyroid hormones play a crucial role in renal development and physiological functions [27]. They are involved in the enhancement of activity and development of various co-transport systems within the kidney tubules, such as the Na/K ATPase, Na-H exchanger,

and Na-P co-transporter in the proximal convoluted tubule [28]. In addition to their direct effects on renal function, thyroid hormones also influence renal physiology indirectly through their impact on the cardiovascular system, the renin-angiotensin system, and renal blood flow [29]. However, there is currently a paucity of research establishing a direct causal relationship between hyperthyroidism and kidney-related pathologies. Our study further corroborates this causal link through Mendelian randomization.

Polyomaviruses are ubiquitously present in the human body, with BK virus being one of the most common [30]. Studies have found that BKV is more prevalent among transplant patients receiving immunotherapy and can lead to severe kidney and bladder diseases [31,32]. Furthermore, acute kidney injury (AKI) represents a condition of tubular cellular damage, which might make kidneys more susceptible to active infection and lead to BKV replication, suggesting a potential link between polyomavirus infection and kidney-related issues. However, the causal relationship remains unclear. Thus, our study is the first to employ Mendelian randomization to investigate this causal link, suggesting that BKV infection, as an exposure factor, contributes to the increased incidence of kidney-related diseases.

Based on the aforementioned discussions and our current Mendelian randomization results, we posit that hyperthyroidism is positively correlated with polyomavirus infection, which in turn is positively correlated with kidney problems. Moreover, hyperthyroidism is also significantly positively associated with kidney issues. Given the complex interplay among these three factors, we propose that for patients with hyperthyroidism, it is crucial to focus on protecting their immune function to prevent excessive replication of polyomaviruses, thereby mitigating the risk of developing kidney-related problems. This highlights the clinical significance of our study's findings for practical applications.

This research provides a foundational basis for further exploration in this field. While our current research demonstrates statistically significant positive correlations between hyperthyroidism, polyomavirus infection, and kidney-related issues, it is essential to acknowledge the limitations of our findings. Specifically, the positive OR values observed are relatively small, indicating that the positive effects are not particularly strong. This could be due to several reasons: our sample size might be insufficient to detect more robust correlations; alternatively, the complex interactions between genetic and environmental factors may dilute the observed associations, as these environmental factors were not accounted for in the Mendelian randomization analysis. Therefore, it is crucial to conduct more real-world studies to further validate these associations and better understand their underlying mechanisms.

In summary, this study utilized Mendelian randomization to reveal positive correlations between hyperthyroidism and both polyomavirus infection and kidney problems. Additionally, a positive correlation was found between polyomavirus infection and kidney problems. Furthermore, other substantial evidence supports the close links among these conditions. These findings provide a theoretical foundation for preventing viral infections and kidney problems in hyperthyroidism patients and offer clinical insights for their management.

References

[1] Vargas-Uricoechea H (2023) Molecular Mechanisms in Autoimmune Thyroid Disease. Cells 12.
[2] De Leo S, Lee SY, Braverman LE (2016) Hyperthyroidism. Lancet 388: 906-918.
[3] Zimmermann MB, Boelaert K (2015) Iodine deficiency and thyroid disorders. Lancet Diabetes Endocrinol 3: 286-295.
[4] Smith TJ, Hegedüs L (2016) Graves' Disease. N Engl J Med 375: 1552-1565.
[5] McIver B, Morris JC (1998) The pathogenesis of Graves' disease. Endocrinol Metab Clin North Am 27: 73-89.
[6] Bartalena L (2013) Diagnosis and management of Graves disease: a global overview. Nat Rev Endocrinol 9: 724-734.

[7] Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, et al. (2016) 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid 26: 1343-1421.
[8] Ghareebian H, Mariash C (2022) COVID-19-Induced Graves' Disease. Cureus 14: e22260.
[9] Weider T, Genoni A, Broccolo F, Paulsen TH, Dahl-Jørgensen K, et al. (2022) High Prevalence of Common Human Viruses in Thyroid Tissue. Front Endocrinol (Lausanne) 13: 938633.
[10] Calvignac-Spencer S, Feltkamp MC, Daugherty MD, Moens U, Ramqvist T, et al. (2016) A taxonomy update for the family Polyomaviridae. Arch Virol 161: 1739-1750.
[11] Moens U, Krumbholz A, Ehlers B, Zell R, Johne R, et al. (2017) Biology, evolution, and medical importance of polyomaviruses: An update. Infect Genet Evol 54: 18-38.
[12] DeCaprio JA, Garcea RL (2013) A cornucopia of human polyomaviruses. Nat Rev Microbiol 11: 264-276.
[13] Gross L (1953) A filterable agent, recovered from Ak leukemic extracts, causing salivary gland carcinomas in C3H mice. Proc Soc Exp Biol Med 83: 414-421.
[14] Eddy BE, Borman GS, Grubbs GE, Young RD (1962) Identification of the oncogenic substance in rhesus monkey kidney cell culture as simian virus 40. Virology 17: 65-75.
[15] Gardner SD, Field AM, Coleman DV, Hulme B (1971) New human papovavirus (B.K.) isolated from urine after renal transplantation. Lancet 1: 1253-1257.
[16] Padgett BL, Walker DL, ZuRhein GM, Eckroade RJ, Dessel BH (1971) Cultivation of papova-like virus from human brain with progressive multifocal leucoencephalopathy. Lancet 1: 1257-1260.
[17] Feng H, Shuda M, Chang Y, Moore PS (2008) Clonal integration of a polyomavirus in human Merkel cell carcinoma. Science 319: 1096-1100.
[18] Knowles WA, Pipkin P, Andrews N, Vyse A, Minor P, et al. (2003) Population-based study of antibody to the human polyomaviruses BKV and JCV and the simian polyomavirus SV40. J Med Virol 71: 115-123.
[19] Furmaga J, Kowalczyk M, Zapolski T, Furmaga O, Krakowski L, et al. (2021) BK Polyomavirus-Biology, Genomic Variation and Diagnosis. Viruses 13.
[20] Hirsch HH, Knowles W, Dickenmann M, Passweg J, Klimkait T, et al. (2002) Prospective study of polyomavirus type BK replication and nephropathy in renal-transplant recipients. N Engl J Med 347: 488-496.
[21] de Bruyn G, Limaye AP (2004) BK virus-associated nephropathy in kidney transplant recipients. Rev Med Virol 14: 193-205.
[22] Bowden J, Davey Smith G, Haycock PC, Burgess S (2016) Consistent Estimation in Mendelian Randomization with Some Invalid Instruments Using a Weighted Median Estimator. Genet Epidemiol 40: 304-314.
[23] Verbanck M, Chen CY, Neale B, Do R (2018) Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. Nat Genet 50: 693-698.
[24] Valtonen VV, Ruutu P, Varis K, Ranki M, Malkamäki M, et al. (1986) Serological evidence for the role of bacterial infections in the pathogenesis of thyroid diseases. Acta Med Scand 219: 105-111.
[25] Joasoo A, Robertson P, Murray IP (1975) Letter: Viral antibodies in thyrotoxicosis. Lancet 2: 125.
[26] Nagata K, Nakayama Y, Higaki K, Ochi M, Kanai K, et al. (2015) Reactivation of persistent Epstein-Barr virus (EBV) causes secretion of thyrotropin receptor antibodies (TRAbs) in EBV-infected B lymphocytes with TRAbs on their surface. Autoimmunity 48: 328-335.
[27] Bräunlich H (1984) Postnatal development of kidney function in rats receiving thyroid hormones. Exp Clin Endocrinol 83: 243-250.
[28] Basu G, Mohapatra A (2012) Interactions between thyroid disorders and kidney disease. Indian J Endocrinol Metab 16: 204-213.
[29] Kobori H, Ichihara A, Miyashita Y, Hayashi M, Saruta T (1998) Mechanism of hyperthyroidism-induced renal hypertrophy in rats. J Endocrinol 159: 9-14.
[30] Kean JM, Rao S, Wang M, Garcea RL (2009) Seroepidemiology of human polyomaviruses. PLoS Pathog 5: e1000363.
[31] Balba GP, Javaid B, Timpone JG, Jr. (2013) BK polyomavirus infection in the renal transplant recipient. Infect Dis Clin North Am 27: 271-283.
[32] Umeda K, Kato I, Kawaguchi K, Tasaka K, Kamitori T, et al. (2018) High incidence of BK virus-associated hemorrhagic cystitis in children after second or third allogeneic hematopoietic stem cell transplantation. Pediatr Transplant 22: e13183.