Research in Health Science
ISSN 2470-6205 (Print) ISSN 2470-6213 (Online)
Vol. 11, No. 2, 2026
www.scholink.org/ojs/index.php/rhs

*Original Paper*

# Exploring the Link between Green Spaces and Digestive System Diseases: Observational and Genetic Perspectives

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Received: March 29, 2026 Accepted: April 30, 2026 Online Published: May 9, 2026

doi:10.22158/rhs.v11n2p44 URL: http://dx.doi.org/10.22158/rhs.v11n2p44

***Abstract***

***Purpose:*** *To explore the epidemiological and genetic link between green spaces and digestive system diseases.*

***Methods:*** *The current study includes two main parts. The first part is a comprehensive meta-analysis of epidemiological findings, subsequently, two-sample epigenetic Mendelian randomization (MR) analysis is conducted to explore the genetic associations between green spaces and digestive system diseases.*

***Results:*** *The meta-analysis part included seven studies, with six cohort studies and one ecological study. After pooling up all the data, we found that green space was not significantly associated with the overall risk of digestive system diseases (OR=0.97, 95% CI=0.92 to 1.01, P=0.17, $I^2$=90.09%). Subgroup analysis showed that green space was associated with reduced risk of liver diseases (OR=0.93, 95% CI=0.88 to 0.99, P=0.02, $I^2$=79.76%). In the MR analysis, genetic evidence suggested significant causal effects between green spaces-associated DNA methylation and digestive system diseases. Specifically, the PRSS23 gene and CpG site cg10916494 were strongly associated with ulcerative colitis, indicating potential biological pathways linking green spaces and digestive system diseases.*

***Conclusion:*** *Our findings suggested that while epidemiological evidence did not strongly indicate that green spaces were associated with digestive system diseases. However, MR analysis indicated that significant causal effects between green spaces-associated DNA methylation and digestive system diseases existed.*

***Keywords***

*green space, digestive system diseases, Mendelian randomization, meta-analysis*

## 1. Introduction

In recent years, with the acceleration of global urbanization, the impact of environmental factors on human health has received increasing attention[1] Among them, green space has been recognized as a crucial environmental exposure, playing a significant role in the prevention of various chronic diseases[2-4]. Studies have shown that green spaces not only improved air quality but also had a positive impact on human health by promoting physical activity, relieving psychological stress and enhancing social interaction[5-6].

Digestive system diseases are important public health problems worldwide, including gastric cancer, colorectal cancer, liver diseases (e.g., non-alcoholic fatty liver disease, cirrhosis), inflammatory bowel disease and so on[7-9]. The occurrence of these diseases is influenced by multiple factors, such as genetic predisposition, lifestyle (e.g., dietary habits, smoking and alcohol consumption), socioeconomic status, and environmental exposures (e.g., air pollution and industrial chemicals)[10-11]. As the prevalence of digestive system diseases continues to rise globally, exploring new environmental risk factors and their underlying mechanisms is essential for the prevention and control of such diseases.

It has been shown that green spaces might affect human health by reducing chronic inflammation, modulating psychological stress, and improving the gut microbiota[12-14]. However, studies on the specific relationship between green spaces and digestive system diseases were still limited and previous findings were inconsistent[15-18]. Some studies suggested that green spaces might reduce digestive system diseases[15-16], however, other studies did not find a significant association[17-18]. In addition, most of the current studies were observational ones, making it difficult to rule out potential confounders and reverse causality. Thus, integrating epidemiologic and genetic analysis is necessary to comprehensively assess the relationship between green spaces and digestive system diseases. Therefore, the aim of this study is to explore the epidemiological and genetic link between green spaces and digestive system diseases.

## 2. Methods

Our study aimed to comprehensively assess the effect of green space on digestive system diseases by pooling up the data from epidemic studies and provided genetic evidence for a causal relationship between green space on digestive system diseases. Thus, the current study included two main parts: meta-analysis and two-sample epigenetic Mendelian randomization (MR) analysis.

### *2.1 Meta-analysis of Global Studies*

The meta-analysis part was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[19]. We predesigned the study and registered it on PROSPERO. the registration ID was CRD42024614366, and the link was https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=614366. Participants or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

*2.2 Search Strategy*

In this study, we comprehensively searched four databases including PubMed, Web of Science, Embase, and Cochrane Library according to the search strategy from inception to December 23, 2024. The search strategy mainly consisted of two keywords: “green space” and “digestive system diseases”. Detailed search strategies were provided in supplementary Table S1. In addition, we performed a citation search of all included relevant studies. The search was limited to studies published in English, and the scope was restricted to titles, abstracts, and keywords.

*2.3 Inclusion and Exclusion Criteria*

The inclusion criteria were as follows: 1, exposure to green space for participants were reported; 2, epidemiological studies assessing the association between green space and the risk of at least one type of digestive system diseases; 3, cohort, case-control, or ecologic study designs. The exclusion criteria were: 1, letters to the editor, case reports, comments, reviews, or conference abstracts; 2, studies with repeated or overlapping data; 3, studies with insufficient data; 4, pediatric studies (including individuals under 18 years of age).

*2.4 Study Selection*

Two authors independently conducted the predefined search strategy. After excluding duplicate studies, titles and abstracts were screened for relevance. Full texts of potentially eligible studies were then reviewed for quality and completeness of data. Any disagreements were resolved by discussion with a third author to reach a consensus on study inclusion.

*2.5 Data Collection*

Two authors independently collected baseline characteristics of the studies which included citation details (first author, publication year, country), study design details (sample size, study type, study population, outcome assessment methods and exposure assessment methods), and patient demographics. We also extracted all relevant estimates and 95% confidence intervals (CIs) of association relating green space with digestive system diseases. When multiple adjusted effect estimates were reported for the same outcome, the one with the most covariate control was extracted. After data collection, the two authors cross-checked the information to ensure the accuracy and completeness.

*2.6 Quality Assessment*

The Newcastle-Ottawa Scale (NOS) was to assess the quality of included studies[20]. Methodological quality was considered as follows: NOS upper 8 score was high quality, 7-8 score was medium quality, and lower than 7 was poor quality. Two authors conducted the quality assessment and had a discussion when discrepancies occurred.

*2.7 Statistical Analysis*

Odds ratios (ORs) and 95% CIs were pooled up. Beta were converted to ORs if they were not directly reported in the studies. Beta were converted using the formula: Beta=EXP(OR)[21]. The random-effect model, employing the DerSimonian-Laird method was used as the default model, and $P<0.05$ was statistically significant. To evaluate the statistical heterogeneity, I2 value and the chi-squared test were

used[22-23]. According to the Cochrane handbook, the $I^2$<30% was considered non-important, the $I^2$ range from 30% to 60% was considered moderate, and the $I^2$>60% was considered substantial. Subgroup analysis was conducted based on green places and different digestive system diseases. All statistical analysis were performed using STATA software (V18.0).

## 3. Two-sample epigenetic MR analysis

### *3.1 Data Source*

We obtained epigenetic DNA methylation (DNAm) data associated with exposure to residential surrounding green spaces from an epigenome-wide association study (EWAS)[24], which included 479 participants from the Australian Mammographic Density Twins and Sisters Study (AMDTSS). The DNAm measurements were conducted utilizing peripheral whole blood samples and the Infinium™ HumanMethylation450 BeadChip array (Illumina) platform. The relationships between residential surrounding green spaces and epigenetic alterations in blood were adjusted for a multitude of factors, such as age, educational attainment, marital status, area-level socioeconomic status, smoking behavior, cell-type proportions, and familial clustering. In total, 10 CpG sites and 15 corresponding genes were identified as being associated with surrounding green spaces (FDR<0.10).

Subsequently, we pinpointed methylation quantitative trait loci (mQTLs) associated with CpG sites and single nucleotide polymorphisms (SNPs) correlated with gene expression, which were utilized as instrumental variables. These were sourced from the Genetics of DNA Methylation Consortium (GoDMC) and the Integrative Epidemiology Unit Open Genome-Wide Association Study (IEU open GWAS) databases, respectively. The GoDMC served as a comprehensive repository encompassing both genetic and epigenetic data derived from a cohort comprising over 30,000 individuals. Meanwhile, the IEU open GWAS was a meticulously curated database that housed complete summary datasets from Genome-Wide Association Studies. It was noteworthy that all participants included in the GWAS summary data were of European descent and had provided informed consents.

For exposure, the datasets associated with gene expression was provided by a large-scale cis- and trans-eQTL analysis[25], which analyzed blood-derived expression from 31,684 individuals through the eQTLGen consortium. Detailed information could be identified by the IDs showed in Table S2. For outcomes, we obtained 311 datasets of digestive system disease from summary-level data. The data were compiled from multiple GWAS and were accessed through the IEU Open GWAS database (https://gwas.mrcieu.ac.uk/datasets). Each dataset included detailed information in Table S2 on the trait of interest, the source of the data, the consortium, the sample size, the population studied, the number of SNPs analyzed, and the associated PubMed ID for reference.

### *3.2 Instrumental Variable Selection*

The selection of these mQTLs, which functioned as genetic instrument for DNA methylation influenced by surrounding green places, applied to specific criteria. Our focus was on cis-mQTLs that exhibited a high degree of statistical significance ($P<1\times10^{-7}$), were positioned within a 1 Mb proximity to their

respective CpG sites and displayed minimal linkage disequilibrium ($r^2<0.01$). Furthermore, the filtering of SNPs associated with gene expression was conducted using a significance threshold for association with the exposure variable ($P<5 \times 10^{-8}$), and any SNPs with an F-statistic below 10 were omitted from consideration.

*3.3 Analysis of Genetic Correlation between Green Spaces and Digestive System Diseases*

We identified SNPs representing green paces linked CpG sites. Then we selected SNPs with a strong direct association with digestive system diseases, defined by a p-value threshold of less than 5×10-8 for further analysis. Subsequently, we utilized g-Profiler website (https://biit.cs.ut.ee/gprofiler/gost) to translate the SNPs into gene symbols[26]. Following this, we employed GeneMANIA (https://genemania.org) to analyze the interactions or association networks among these genes, predicting their potential functions based on publicly available biological datasets[27]. Finally, we used the igraph package in R to visualize the gene-gene interaction network.

*3.4 Statistical Analysis*

To evaluate the impact of green places on digestive system diseases, a MR analysis was undertaken employing four robust methodologies: Inverse Variance Weighted (IVW), IVW with multiplicative random effects, MR Egger, and Wald ratio. The IVW method, predicated on the assumption of no horizontal pleiotropy, served as the primary method. We conducted Cochran's Q test for heterogeneity, and MR Egger intercept test for horizontal pleiotropy. If heterogeneity was identified, the IVW analysis would employ the random effects of IVW. Should pleiotropy be detected, outliers ascertained by MR-PRESSO would be expunged; if pleiotropy persisted, the MR Egger test would be deployed for estimation. The results were presented as ORs accompanied by 95% CIs. A p-value threshold of 0.05 was established to denote a confirmed causal association. All analysis were conducted utilizing the "TwoSampleMR" package within the R software environment (version 4.4.0).

## 4. Results

*4.1 Meta-analysis*

4.1.1 Study Selection

Using the above search strategy, we retrieved a total of 5002 articles, including 553 articles from PubMed, 983 articles from Embase, 1102 articles from Web of science, and 2383 articles from the Cochrane Library with duplicate exclusion. In addition, through the citation search, we also found 12 articles. After removing 682 duplicate literatures, the remaining literatures were preliminarily screened according to the titles and abstracts, and 83 literatures were finally obtained. Four articles could not be retrieved, and a total of 79 articles were included in the full-text screening. Finally, seven studies[15-18,28-30] met the inclusion criteria and were included in the analysis (Figure 1).

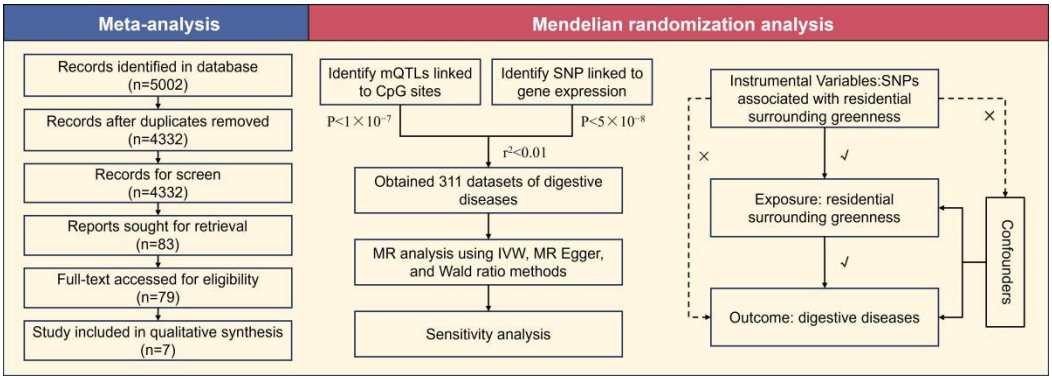



**Figure 1. Schematic Diagram of Study Design**

4.1.2 Characteristics of Included Studies

A total of seven articles were included. Four of the seven articles were from China. In terms of study design, six were cohort studies and the remaining one was ecological study. The main digestive system diseases involved in the seven studies were gastric cancer, colorectal cancer, hepatocellular carcinoma, inflammatory bowel disease, non-alcoholic fatty liver disease, liver failure, and liver fibrosis (Table1).

**Table 1. Baseline Characteristics of the Included Studies**

| Author, year | Country | Number of participants/Cases | Greenness measure | Outcomes | Conclusions | NOS |
|---|---|---|---|---|---|---|
| Liu J 2024 | China | NA/76,411 | NDVI | Gastric cancer | In summary, we observed significant positive correlations between $PM_x$ and gastric cancer incidence in high-risk areas. Conversely, NDVI exhibited a negative correlation. | 7 |
| Liu K 2024 | USA | 4,210,008/40,519 | Residential green spaces diversity for 300m buffer | Colorectal cancer | An interquartile range increase in green space cover within 300m was associated with lower incidence of total and lung cancer, but not colorectal cancer. | 9 |
| Datzmann T 2018 | Germany | 1.9 million /11,975 | NDVI | Colorectal cancer | Colorectal cancer was not affected by any of the exposures. | 8 |
| Zhang Z 2022 | China | NA/1,271 | Residential green spaces diversity for 300m buffer | Inflammatory bowel disease | Residential green space, blue space and natural environment might be protective factors against inflammatory bowel disease. | 8 |
| Agrawal M 2024 | Denmark | 1,438,487/ 3,768 | NDVI | Inflammatory bowel disease | In a nationwide cohort with long-term follow up data, early life environmental | 9 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | | | | exposures were associated with modulation of Crohn's disease risk, with a harmful effect of agriculture land use and protective effect of biodiversity and green space. | |
| Liu M 2023 | China | 411,200/5,198 | Residential green spaces diversity for 300m buffer | Nonalcoholic fatty liver disease | Residential green and blue spaces were inversely related to nonalcoholic fatty liver disease incidence. | 9 |
| Ye Z 2023 | China | 427,697/NA | Residential greenspace (per standard deviation increment) | Hepatocellular Carcinoma, liver failure, and liver fibrosis | Our findings suggest a positive association between air pollution scores and the risk of new-onset severe liver disease, while residential green spaces show an inverse association. | 8 |

Abbreviations: NDVI, Normalized Difference Vegetation Index; NA, not applicable; NOS, Newcastle-Ottawa Scale; PM, particulate matter.

4.1.3 Risk of Green Space on Digestive System Diseases

Risks of green space on digestive system diseases were conducted. The results showed that green space was not significantly associated with the risk of digestive system diseases (OR=0.97, 95% CI=0.92 to 1.01, P=0.17, $I^2$=90.09%) (Figure 2).

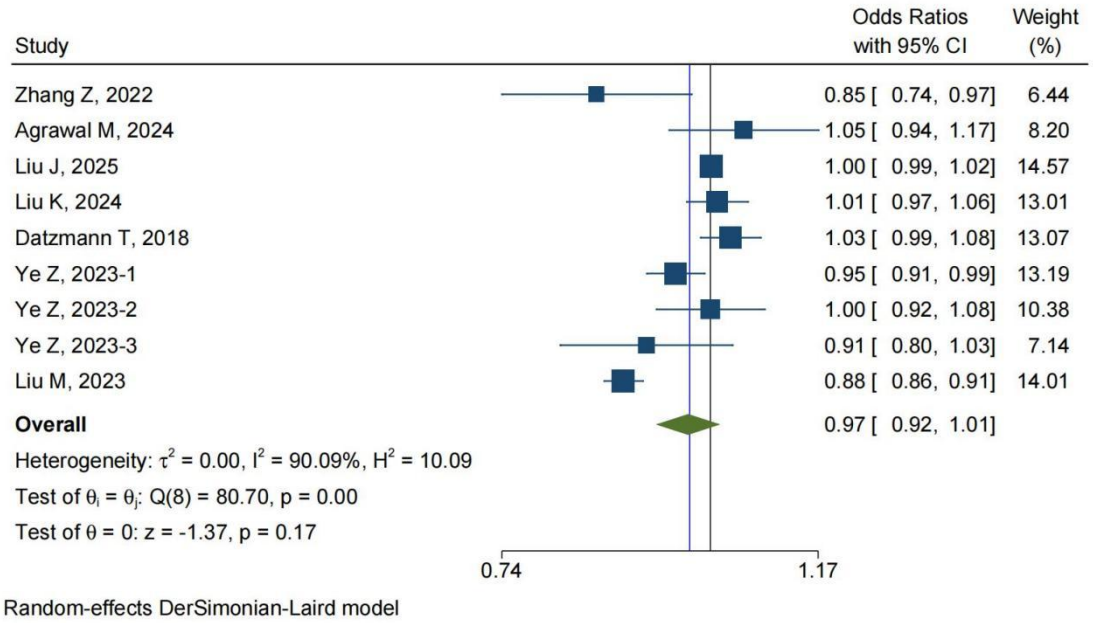



**Figure 2. Risk of Green Space on all Digestive System Diseases**

4.1.4 Subgroup of the Risk of Green Space on Different Types of Digestive System Diseases

Subgroup analysis showed that green space was associated with reduced risk of liver diseases (OR=0.93, 95% CI=0.88 to 0.99, P=0.02, $I^2$=79.76%). However, colorectal cancer (OR=1.02, 95% CI=0.99 to 1.05, P=0.21, $I^2$=0%) and inflammatory bowel disease (OR=0.95, 95% CI=0.77 to 1.11, P=0.61, $I^2$=82.53%) were not statistically associated with green space (Figure 3).

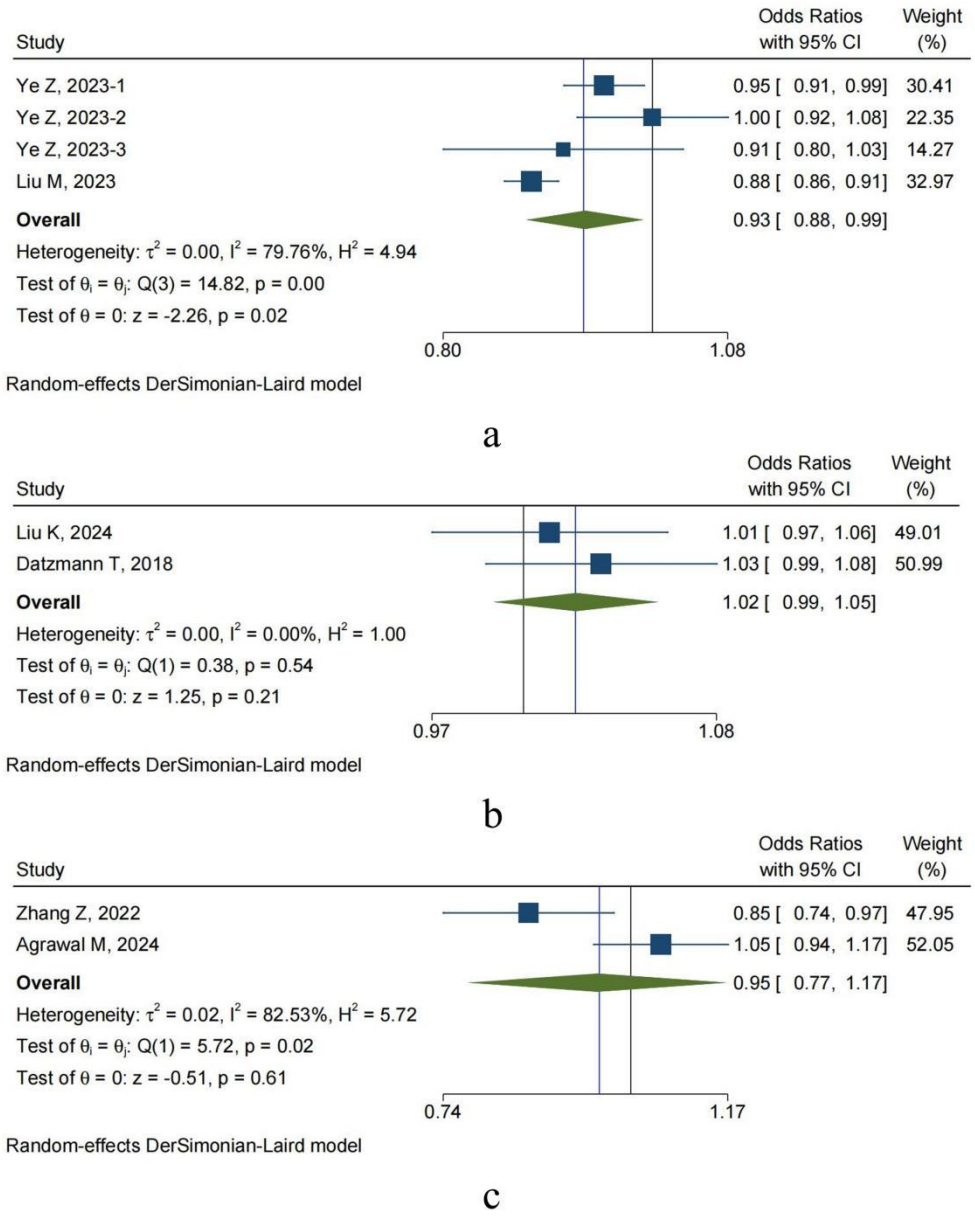



**Figure 3. Subgroup Analysis of the Risk of Green Space on Digestive System Diseases (a) Green space on liver diseases; (b) Green space on colorectal cancer; (c) Green space on inflammatory bowel disease**

## 5. MR Analysis

### *5.1 Instrumental Variable Selection*

Initially, 10 CpG sites and 15 corresponding genes were identified to be associated with residential surrounding green spaces from studies with participants of European ancestry. After applying selection criteria to ensure the reliability of our genetic instruments, we found 3 mQTLs correlated with 3 specific CpG sites, and 17 SNPs correlated with 5 genes associated with residential surrounding green spaces (Table S3).

### *5.2 Causal Associations between Green Place Linked mQTLs and Digestive System Diseases Incidence*

The MR analysis presented in this study has identified significant causal effects between green space linked gene expression or methylation and various digestive system diseases outcomes. The detailed results of the pleiotropy and heterogeneity tests were summarized in Table S4. Scatter plot presented the top ten positive associations (Figure 4). The result indicated that the gene ENSG00000150687 (PRSS23) and CpG site cg10916494 robustly linked to ulcerative colitis.

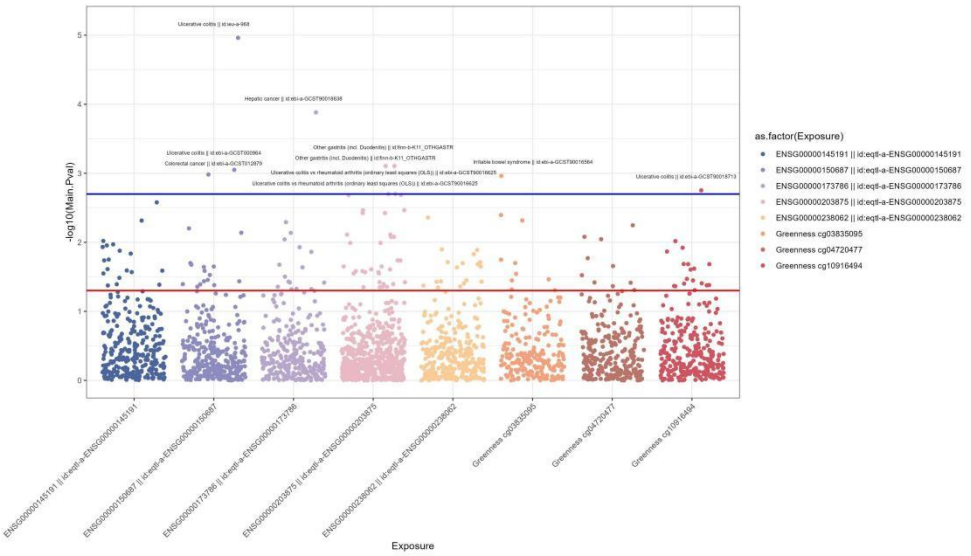
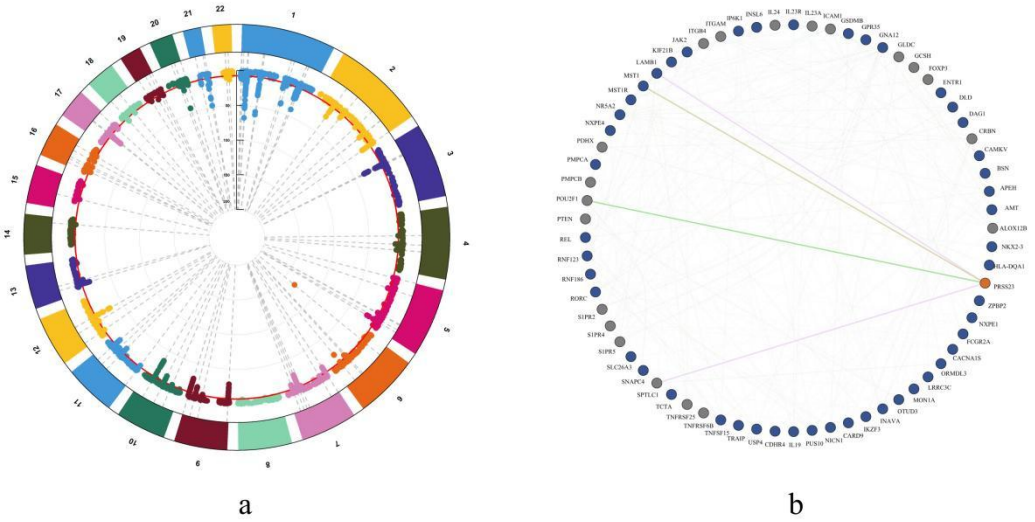



**Figure 4. Scatter Plot Presented the Top Ten Positive Associations between Green Places and Digestive System Diseases**

### *5.3 Genetic Correlation Residential Surrounding Green Places and Cancer*

The analysis in this study identified 1 gene causally associated with ulcerative colitis, and 1466 SNPs that were highly correlated ($P<5\times10-8$) with ulcerative colitis in the GWAS summary data ieu-a-968 (Figure 5a), which showed the most significant association. These SNPs were mapped to gene symbols using g:Profiler. The top 50 genes associated with ulcerative colitis and the gene PRSS23 were used for gene association network analysis using GeneMANIA, which revealed significant interactions between green places related genes and cancer-related genes, suggesting that exposure to green places might be

associated with ulcerative colitis development through specific biological pathways (Figure 5b).



a b

**Figure 5. Genetic Correlation Residential Surrounding Green Places and Digestive System Diseases**

**(a) Manhattan plot of SNPs related to digestive system diseases; (b) Gene interaction between green places and digestive system diseases**

## 6. Discussion

Our study included two main parts: meta-analysis and MR analysis. The meta-analysis part found that green space was not significantly associated with the overall risk of digestive system diseases. Subgroup analysis showed that green space was associated with reduced risk of liver diseases. In the MR analysis, genetic evidence suggested significant causal effects between green spaces-associated DNA methylation and digestive system diseases. Specifically, the PRSS23 gene and CpG site cg10916494 were strongly associated with ulcerative colitis, indicating potential biological pathways linking green spaces and digestive system diseases.

The impact of green spaces on human health has become a hot topic[1-3]. However, current epidemiologic studies presented inconsistent findings regarding whether green spaces reduced the risk of digestive system diseases[15-18]. In this study, we found no statistically significant association between green spaces and the risk of digestive system diseases from meta-analysis, but in subgroup analysis, we found that green spaces might be associated with a lower risk of liver diseases. This finding was consistent with the previous studies[16,30]. It has been shown that green spaces might improve liver function by reducing the intake of air pollutants (e.g., PM2.5 and NO2) and lowering levels of oxidative stress and chronic inflammation[31]. In addition, green spaces might promote healthy lifestyles, such as increased frequency of outdoor exercise and improved mental health, all of which were associated with a reduced risk of liver diseases[10-13]. However, for colorectal cancer and inflammatory bowel disease,

no statistically significant association was found in this study, which might be related to the study population, exposure assessment methods, and the control of confounders.

MR analysis provided novel insights into the potential causal relationship between green spaces-associated DNA methylation alterations and digestive system diseases. Our findings identified significant associations, particularly involving the PRSS23 gene and CpG locus cg10916494, which were found to be associated with ulcerative colitis. Furthermore, gene association network analysis suggested that green spaces-related genes interacted with various digestive cancer-related genes, indicating that green spaces might influence digestive health through specific biological pathways.

PRSS23 is a serine protease that is closely associated with cancer progression, inflammation regulation and tumor microenvironment[32-34]. Studies have shown that PRSS23 was highly expressed in a variety of gastrointestinal malignancies (e.g., gastric, colorectal, and hepatocellular carcinomas) and might promote tumor cell proliferation and invasion[35]. In this study, we found that the PRSS23 gene was significantly associated with ulcerative colitis, suggesting that it might be involved in the pathophysiologic process of inflammatory bowel disease. One possible mechanism was that green space might regulate PRSS23 DNA methylation levels, subsequently influencing intestinal inflammatory responses and barrier function, ultimately affecting disease susceptibility.

DNA methylation is an important epigenetic modification that regulates gene expression and is influenced by environmental factors (e.g., air pollution, diet, psychological stress)[36-38]. Our MR analysis supported the possibility that green spaces might influence the risk of developing digestive system diseases by modulating DNA methylation status. This finding provided new genetic evidence for the health effects of digestive system diseases and suggested that future studies should explore the role of DNA methylation between environmental exposure and diseases.

To the best of our knowledge, this is the first study to combine meta-analysis and MR analysis to synthesize epidemiological and genetic evidence for a more comprehensive assessment of the effects of green spaces on digestive system diseases; Furthermore, it reduces the influence of confounding factors, and MR analysis utilizes genetic variation as an instrumental variable, which can help to overcome the problem of reverse causality in traditional observational studies and improve the credibility of causal inference; Finally, gene network analysis reveals potential biological pathways and provides new insights into the molecular mechanisms by which green places affect digestive system diseases.

Although this study provided important epidemiological and genetic evidence, there were some limitations in this study. The heterogeneity of the meta-analysis was high, which might be influenced by factors such as study population, green places measurement methods, and disease diagnostic criteria. Thus, more standardized methods of exposure assessment are needed for future studies. The MR analysis was based on the genetic data mainly from European populations, which might limit its applicability to other ethnic groups, and more studies with more ethnic backgrounds are needed for validation in the future. The availability of DNA methylation data was limited, and the current analysis was based on only a small number of CpG loci, and future studies should integrate more epigenomic data to explore the

effects of environmental exposures on DNA methylation in a more comprehensive way.

In conclusion, our findings suggested that while epidemiological evidence did not strongly indicate that green spaces were associated with digestive system diseases. However, MR analysis indicated that significant causal effects between green spaces-associated DNA methylation and digestive system diseases existed. These results highlight the complexity of the relationship between environmental exposure and digestive health, further investigations on potential biological mechanisms and cohort studies are needed in the future.

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