Causal relationships between prostate cancer and six psychiatri c disorders: A two-sample Mendelian randomization study

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Research Article

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Abstract

Background

Prostate cancer (PCa) diagnosis and survival have increased significantly with the development and use of screening techniques. The PCa patient population has a higher risk of psychiatric health issues than the overall population. It has not been demonstrated that PCa and psychiatric disorders are related genetically.

Methods

The current investigation employed a two-sample bidirectional Mendelian randomization design, incorporating a genome-wide association study (GWAS) to systematically screen for genetic instrumental variables related to PCa and six psychiatric disorders, namely major depressive disorder, Alzheimer's disease, insomnia, bipolar disorder, anxiety disorders, and attention deficit hyperactivity disorder. The primary method for assessing causal associations between the two disorders was Inverse Variance Weighting (IVW), supplemented by additional analyses utilizing the MR-Egger and Weighted Median methods, as well as sensitivity analyses to confirm their dependability. In order to confirm the good outcomes of the MR study, we also chose another set of prostate cancer GWAS data from the same pedigree population. To make the results more reliable, we conducted a meta-analysis.

Results

Genetically predicted PCa was associated with higher odds of BD (OR = 1.06,95%, CI = 1.02–1.10, P_{IVW}=0.0055) and lower odds of MDD (OR = 0.97,95% CI = 0.95-1.00, PI_{VW}=0.0261) in the forward MR analysis from PCa to psychiatric disorders. Reverse MR analysis showed that genetically expected BD (OR = 1.08, 95% CI = 1.01–1.10, P_{IVW}=0.0303) was associated with higher odds of PCa. No causal association was found between the other four psychiatric disorders and PCa in the two-way analysis. Heterogeneity and horizontal pleiotropy were not observed in all results, and the robustness of the results was demonstrated by the leave-one-out results. MR analyses performed with the optional additional PCa GWAS were directionally consistent with the main analysis, confirming a causal association between MDD and PCa, but greater heterogeneity was observed in the bidirectional causal association of BD.

Conclusions

Our research suggested a potential genetic causal relationship between BD, MDD, and PCa. There was no genetically based causal relationship found between PCa, ADHD, sleeplessness, anxiety disorders, and

AD. The results of this study have significant ramifications for the future screening and management of PCa patients, particularly with regard to the inclusion of psychological therapies and support.

1. Introduction

One of the most prevalent cancers affecting the male reproductive system in the globe is prostate cancer (PCa). PCa now accounts for almost 29% of all cancers seen in men, according to cancer data for the year 2023[1]. This indicates a recent increase in the incidence of PCa. Screening techniques to detect PCa have vastly improved over recent decades. By promoting and popularising screenings such as prostate-specific antigen testing and digital rectal examinations, PCa can be detected in its early stages and treated promptly, reducing the likelihood of death for the patient[2]. Due to technical advancements, death rates have decreased, allowing us to concentrate more of our efforts on other than the patient's physical illness from PCa. When it comes to mental health illnesses, the PCa group is more vulnerable than the general population. One research revealed In PCa survivors, the risk ratio for psychiatric disorders is higher during the course of all follow-up periods. This is especially true for patients with advanced PCa, patients with abnormal body weight, and patients receiving early cancer therapy[3]. Patients' prognosis and general state of health are significantly impacted by psychiatric disorders. Males with serious psychiatric diseases usually have a 20-year lower life expectancy than the average group[4]. Additionally, psychiatric disorders dramatically raise the mortality rates of cancer patients[5, 6]. Depression prevalence is directly correlated with high-risk PCa, PCa survivors who have depression have a 61% higher risk of dying and a 2.01 times higher risk of committing suicide[3, 7, 8]. Notably, epidemiological studies on psychiatric disorders and cancer have so far produced results that are nuanced and contradictory. According to a number of studies, the chance of cancer occurrence in people with psychiatric disorders may be higher, lower, or the same as in the general population[9]. The genetics of the association between psychiatric disorders and PCa is not well studied enough. Therefore, further genetic studies are required to bridge the research gap and to furnish insights and justification for the role of psychological interventions in the standard screening and treatment of PCa.

Mendelian randomization (MR) is an epidemiological investigative tool that utilizes genetic variation as an exposure instrumental variable to establish causality between exposure and outcome, mitigating bias due to potential confounders[10]. Based on genome-wide association study (GWAS) data from a large sample, a two-way, two-sample MR investigation was conducted to look into potential causal relationships between six common psychiatric illnesses and PCa.Determining the relationship between psychiatric diseases and PCa facilitates an understanding of common pathophysiological mechanisms and risk factors. It can also provide new targets and approaches for intervention and prevention.

2. Methods

2.1. Study design

In this investigation, six psychiatric disorders (major depressive disorder (MDD), Alzheimer's disease (AD), insomnia, bipolar disorder (BD), anxiety disorders, and attention deficit hyperactivity disorder (ADHD)) were assessed in conjunction with PCa using a bidirectional MR technique. Three requirements should be met by a valid MR study:(1) Genetic variants must be strongly correlated with exposure factors. (2) Genetic variants cannot be directly correlated with the outcome. (3) No potential confounding factor can be linked to genetic variants[11]. The TwoSampleMR, MRPRESSO, and Meta software packages were used to conduct all of the MR analyses in this work using R software (4.3.0). Since all of the submitted assessments were based on publically available data, the Institutional Review Board was not required to grant authorization for the ethical conduct of this study.

2.2 GWAS data for PCa

Pooled association statistics for PCa risk were obtained from the PRACTICAL consortium (including 79,148 cases and 61,106 controls)[12], which is by far the largest sample size of studies with genetic data on PCa. See the original GWAS for further details on the study designs (case-control and cohort studies) and subject selection.

2.3 Summary statistics for psychiatric disorders

Six psychiatric IVs were selected from the GWAS, including MDD, BD, ADHD, AD, anxiety disorders, and insomnia. The data for MDD were derived from a GWAS study based on the UK Biobank, which excludes groups with other psychiatric disorders, bringing the GWAS data closer to the Composite International Diagnostic Interview- Short Form definition of MDD rather than "generalized depression" [13]. The statistics for the other five psychiatric disorders come from the Psychiatric Genomics Consortium (PGC), the largest consortium in psychiatry, which has produced a number of important results on the genetic structure of psychiatric disorders[14]. The included data are exclusively based on European ancestry to prevent racial confounding, and Table 1 lists the primary features of the included GWASs.**2.4 Selection of instrumental variables (IVs)**

IVs underwent screening according to whether or not they fulfilled the three requirements of MR. We used a p-value of less than 5×10^{-8} as a threshold to select SNPs as instrumental variables and excluded SNPs with linkage disequilibrium (LD, $R^2 < 0.001$ and within 10,000 kb), a criterion widely used in previous studies[20, 21], After that, exposure-related SNPs were extracted from the result, excluding SNPs linked to the result ($p < 1 \times 10^{-5}$) and palindromic SNPs with incompatible alleles. To mitigate the impact of unwanted genetic variations, we eliminated SNPs with $F < 10$[22]. The following is the formula for the F value: $F = R^2 \times (N - 2)/(1 - R^2)$.

Table 1
Detailed information regarding studies and datasets used in the present study.

NAME	PMID	Sample size	Study or Consortium
PCa	29892016[12]	79,148 cases, 61,106 controls	PRACTICAL consortium
MDD	30718901[13]	29,475 cases, 63,482 controls	UKB
AD	30617256[15]	71,880 cases, 383,378 controls	PGC
ADHD	36702997[16]	38,691 cases, 186,843 controls	PGC
BD	31043756[17]	20,352 cases, 31,358 controls	PGC
Anxiety disorders	26754954[18]	7016 cases, 14,745 controls	PGC
Insomnia	30804565[19]	Total sample = 1,331,010	PGC

2.5 Statistical analysis

The Inverse Variance Weighting (IVW) method, which offers the most precise assessment of causal effects in the absence of horizontal pleiotropy, served as the primary analytical tool in this work[23]. We additionally chose the weighted median (WM) and MR-Egger regression to confirm the causal relationship between psychiatric disorders and PCa to increase the reliability of the results[24]. When the IVW result was $p < 0.05$, the directionality of the results of the other two MR methods was used to check the robustness of the result to increase the strength of the causal evidence[25]. To evaluate the risk relationship between psychiatric disorders and PCa, odds ratios (OR) and their 95% confidence intervals (95%CI) were employed as markers. Four analytical techniques were used to conduct sensitivity analyses: MR-Egger intercept, MR-PRESSO, leave-one-out (LOO) method, and Cochran's Q test. Cochran's Q test was used to test for the presence of heterogeneity, which may be caused by horizontal pleiotropy and other biases. for the absence of heterogeneity, a fixed-effects IVW model was used, and vice versa, a random-effects IVW model was used. Horizontal pleiotropy was assessed using the MR-Egger intercept method[26] and the MR-PRESSO test[27], and in the presence of horizontal pleiotropy, the results of the MR-Egger regression prevailed[28]. The leave-one-out (LOO) method was used to assess whether the MR results were driven by a single SNP and was used to analyze the robustness of our results. In all of the above sensitivity analyses, $p < 0.05$ was considered to be statistically significant.

2.6 Replication and meta-analysis

We also used as a reference an additional validation analysis of the positive results using PCa genetic data from the UK European Ancestry Biobank, which includes 9,132 PCa cases and 173,493 controls[29]. We performed a meta-analysis of the results of the two analyses, which were analyzed using a random effects IVW model.

3. Results

3.1 Results of MR analysis

Details of the IVs used in the MR analyses are provided in Supplementary. All F-statistic values were more then 10, demonstrating the strength of the selected instrumental variables. The number of SNP acquired under the aforementioned screening circumstances was less than three when we used MDD with anxiety as the exposure and PCa as the result. Thus, for both analyses, we selected snp as instrumental variables using a power threshold of $p < 5 \times 10^{-6}$.

According to the IVW results, genetically predicted PCa was associated with higher odds of BD (OR = 1.06,95%, CI = 1.02–1.10, P_{IVW}=0.0054) and lower odds of MDD (OR = 0.97,95% CI = 0.95-1.00, P_{IVW}=0.0261). In the reverse MR study, genetically predicted BD (OR = 1.08, 95% CI = 1.01–1.10, P_{IVW}=0.0303) was associated with higher odds of PCa (Fig. 1). The three MR methods showed consistent directionality of positive results and the scatterplot shows these causal relationships (Fig. 2). There was no evidence of a causal relationship between PCa and the other four psychiatric diseases.

3.2 Sensitivity analysis results

The results of heterogeneity and horizontal polytropy tests are shown in Supplementary. Cochran's Q tests did not provide any significant results (P > 0.05), indicating that there was no heterogeneity. The MR-Egger intercept test and MR-PRESSO did not indicate directional pleiotropy in any of the analyses (P > 0.05), suggesting that the instrumental variables did not significantly affect the outcome through pathways other than exposure. The robustness of the results was further validated by the LOO results (see supplementary material for details).

3.3 Replication and Meta-analysis

We replicated the three positive results above using the UK Biobank PCa cohort and performed a meta-analysis of the results from both analyses. Although there was significant heterogeneity in the bidirectional causality between bipolar affective disorder and PCa due to large differences in sample size, the results from both cohorts remained consistent in directionality. In the meantime, the meta-analysis's findings confirmed that serious depression and PCa are causally related (Fig. 3)

4. Discussion

Our study used bidirectional two-sample MR analyses to examine the causal connection between PCa and six psychological disorders. To the best of our knowledge, this is the first large study using MR analysis to investigate the association between PCa and multiple psychiatric disorders, and the present study provides some actionable insights into the genetic correlation between psychiatric disorders and PCa.

According to our MR results, there is a correlation between a low risk of PCa and genetically predicted MDD. Male patients with MDD have lower levels of both total and free testosterone[30, 31] and some studies have suggested that low levels of free testosterone may reduce PCa risk after free testosterone levels have fallen to a certain threshold[32]. The MR study by Chang[34] further confirmed that bioavailable testosterone at the genetic level is a risk factor for PCa. The link between total testosterone and the incidence of PCa is still debatable, though. There is no compelling epidemiological evidence between testosterone and PCa[33, 34], despite the fact that testosterone has been demonstrated to cause PCa in rats[35, 36].

Additionally, our investigation revealed a potential genetic bidirectional link between PCa and bidirectional affective disorder. According to reports, patients with PCa have higher levels of the Dysbindin Domain-Containing 1 (DBNDD1) gene expression. Studies have looked into the downstream network of DBNDD1's co-expression pattern, and they found a significant correlation between DBNDD1 and the regulation of GSK-3β and its metabolic pathway in BD[37]. PCa patients exhibited more bipolar symptoms than the general population in a questionnaire assessment[38]. A survey in Taiwan showed an increased prevalence of bi-directional affective disorder in PCa patients[39]. Although we did not uncover large-scale statistics on the incidence of PCa in patients with BD, these findings suggest that there may be a genetic link between PCa and BD.

Although there are studies indicating a higher prevalence of depression in PCa patients[40], our study did not reveal that PCa increased the risk of major depression at a genetic level. The reciprocal causal relationships between ADHD, anxiety disorders, insomnia, and PCa were also investigated in this study. Our findings imply that there is no hereditary connection between PCa and these psychiatric disorders. However, PCa patients are more prone to depression, anxiety, and insomnia[41, 42], possibly due to the effects of physical and psychological stress caused by the diagnosis and treatment of PCa, including pain sensations, sexual dysfunction, and depressed mood. Research on the correlation between PCa and ADHD is scarcer, perhaps because the primary prevalence groups of the two diseases range in age, and studies covering such a lengthy duration are very difficult to do. Furthermore, compared to other psychiatric disorders, ADHD may seem less significant in middle-aged and older individuals since social isolation and cognitive decline are concerns that are more directly linked to health and quality of life in this age range. The mechanism of the negative association of AD with cancer is a hot topic of research, but there are conflicting reports on the riskiness between AD and PCa[43, 44], Low plasma testosterone levels are correlated with AD in older men[45], and in recent years it has been reported that androgen deprivation therapy (ADT) may promote AD. Patients with high-risk and locally advanced PCa have a better prognosis when ADT and radiotherapy (RT) are combined, however, there are numerous side effects that could arise[46, 47]. Any usage of androgen deprivation therapy is linked to an almost significant increase in the risk of anxiety, and the degree of risk is strongly correlated with the length of ADT vs RT. ADT also raises the risk of depression and the likelihood of requiring inpatient psychiatric care[48]. As a result, before beginning therapy, doctors should be aware of the possible effects of ADT on

patients' psychiatric health and should have a thorough conversation and risk assessment with patients. Our research shows that there is a genetic correlation between PCa BD and MDD, but no genetic causal relationship between PCa and other psychiatric diseases. Accordingly, in order to lessen the stress and suffering brought on by PCa and the treatment process, we should provide more psychological support and care for patients with PCa. This would raise the patients' chances of survival and quality of life overall.

Our study has a number of advantages. First off, this is the broadest and most comprehensive MR research of the genetic relationships between PCa and psychiatric diseases that we are aware of. Our study's reliability and measurement precision are enhanced by the large source volume of genetic association abstracts from the GWAS that we used. However, it is still necessary to take into account some of our study's shortcomings. First, the majority of the people in our data sources were European, which restricts the applicability of our findings to populations outside of Europe. Second, we did not perform explicit stratification analyses for variables such as sex and age, although we selected samples from male population sources whenever possible when selecting GWAS data for psychiatric disorders. Lastly, even though we minimized the possibility of going against the MR assumptions by sensitivity analyses, the impact of residual pleiotropy could not be entirely ruled out. All things considered, our study sheds light on the genetic relationships between PCa and psychiatric disorders but these shortcomings must be taken into account and resolved in subsequent research.

Declarations

Ethics approval and consent to participate

Not applicable.

Since all of the submitted assessments were based on publically available data, the Institutional Review Board was not required to grant authorization for the ethical conduct of this study.

Consent for publication

Not applicable.

Competing interests

The authors declares that there is no conflict of interest regarding the publication of this paper.

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Authors' contributions

Data curation, Huijun Chen; Supervision, Jianfei Weng; Writing – original draft, xiaojing wu; Writing – review & editing, Weiping Zhang.

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Not applicable

Availability of data and material

The data used in this study is based on publicly available data, which can be found at the URL below: GWAS pipeline output using Phesant derived variables from UKB: https://gwas.mrcieu.ac.uk/datasets/; PGC: https://pgc.unc.edu/.

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Figures

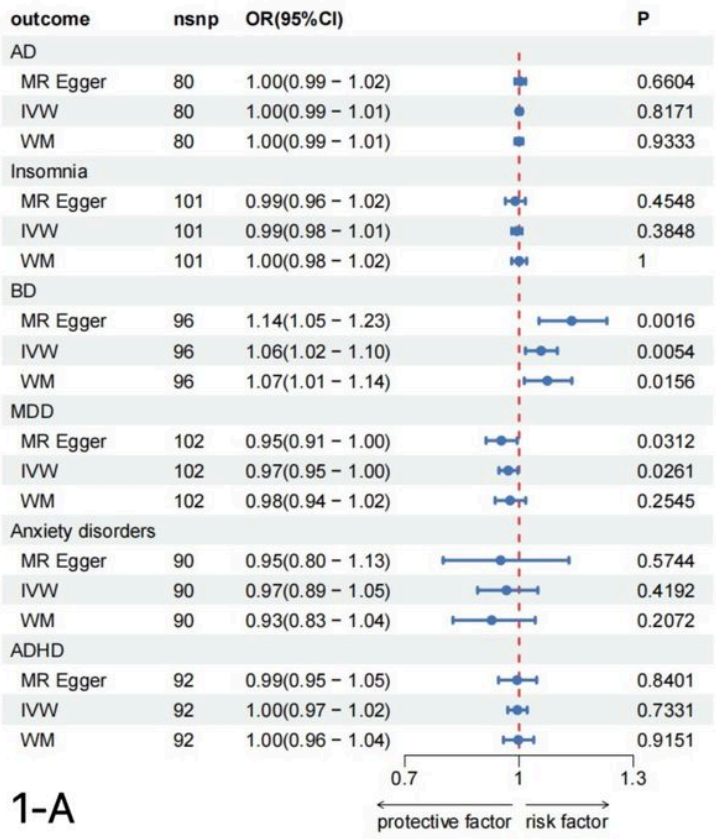

Figure 1

Forest plot of estimated bidirectional correlation between psychiatric disorders and PCa (1-A: PCa as exposure, psychiatric disorders as outcome; 1-B: psychiatric disorders as exposure, PCa as outcome.)

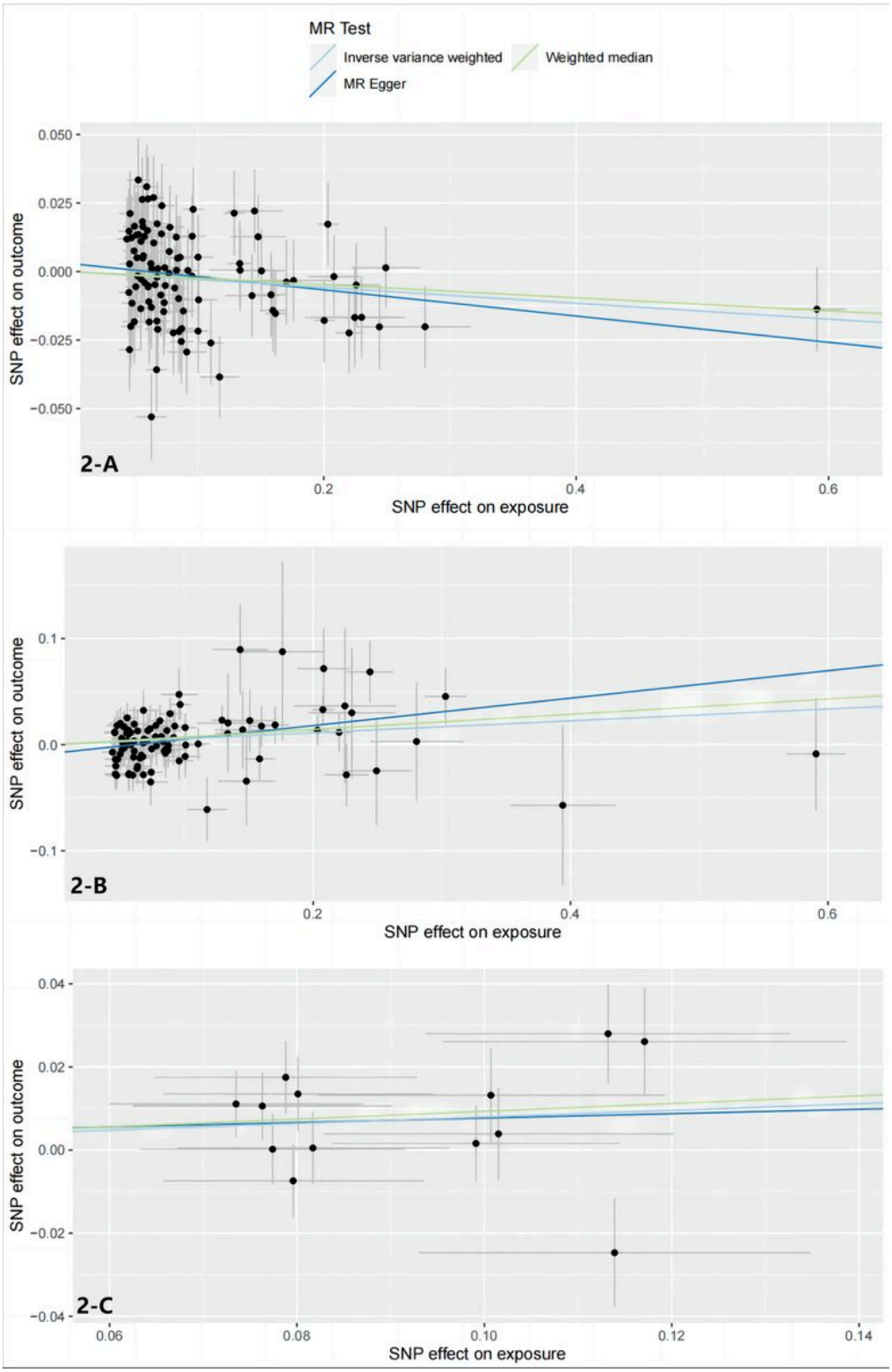

Figure 2

Scatterplot of causal effects of:2-A: PCa on risk of MDD; 2-B: PCa on risk of BD; 2-C: BD on risk of PCa.

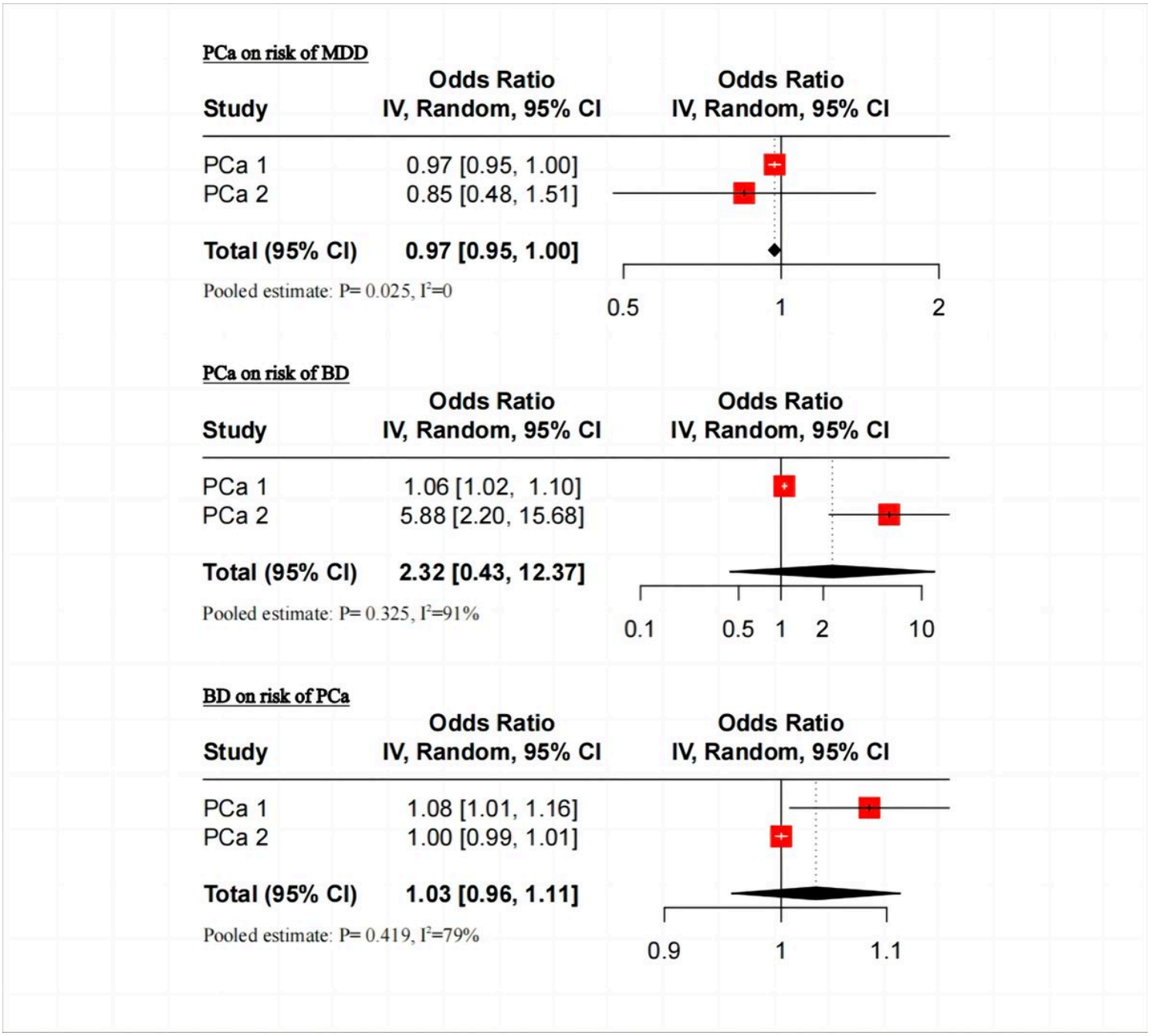

Figure 3

meta-analysis results;PCa 1:Replication of analysis results;PCa 2:Results of the first analysis.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- supplementarymaterials.xlsx