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The causal effects of systemic antioxidant capacity on male infertility: A two-sample mendelian randomization analysis

Xiaolong Zhang, Zhirong Zhu, Chaodong Shen & Guiliang Tang

The present research aimed to assess the potential causal relationship between systemic antioxidant capacity and male infertility using a two-sample Mendelian randomization approach. The primary MR analysis utilized the inverse variance weighted (IVW)method, supplemented by complementary analyses including MR-Egger, weighted mode, simple mode, and weighted median methods. For male infertility, the available summarized data were gained from the open database (IEU OPEN GWAS PROJECT), which includes a total of 680 male patients with infertility and 72,799 controls of European population.10 biomarkers related to systemic antioxidant capacity were examined to investigate their potential association with male infertility, including glutathione S-transferase (GST), superoxide dismutase(SOD), glutathione peroxidase(GPX), catalase (CAT), total bilirubin, albumin, α-tocopherol, ascorbate, retinol, and uric acid. MR analyses using IVW mode revealed that genetically determined systemic antioxidant capacity biomarkers had no causal effects on male infertility risk, including GST(OR = 1.08, 95%CI: 0.91–1.29, *P* = 0.35), SOD(OR = 0.83, 95%CI: 0.66–1.04, *P* = 0.11), GPX(OR = 1.12, 95%CI: 0.92–1.36,*P* = 0.26), CAT(OR = 1.04, 95%CI: 0.83–1.29, *P* = 0.75), total bilirubin(OR = 0.98, 95%CI: 0.94–1.01, *P* = 0.18), albumin(OR = 1.14, 95%CI: 0.73–1.76, *P* = 0.57), α-tocopherol(OR = 0.56, 95%CI: 0.03–9.38, *P* = 0.69), ascorbate(OR = 1.06, 95%CI: 0.24–4.60, *P* = 0.94), retinol(OR = 1.29, 95%CI: 0.34–4.96, *P* = 0.71), and uric acid (OR = 0.88, 95% CI : 0.67–1.17, *P* = 0.39). The current study found no significantly causal link between systemic antioxidant capacity and male infertility. Further research with larger sample sizes and data from different ethnicities is needed.

Keywords Oxidative stress, Male infertility, Mendelian randomization analysis

Clinical infertility is defined as the inability of a couple to conceive after trying for a year[1]. It is reported that male issues account for 30–50% of infertility cases[2]. Testicular dysfunction, endocrinopathies, lifestyle choices, congenital anatomical issues, exposure to gonadotoxic substances, and aging are some of the factors that can lead to infertility or decreased fertility[2]. Male infertility not just results in increased psychological and social stress for the couple, but also affects the societal stability[3]. Identifying preventable causes and modifiable risk factors is crucial in reducing the societal and public health impacts of male infertility.

The role of oxidative stress is widely acknowledged in contributing to various human degenerative processes, syndromes, diseases, and aging[4]. Oxidative stress is characterized by an excess of reactive oxygen species (ROS) compared to antioxidant scavenging activities, with ROS production outweighing antioxidant defenses[5]. Environmental factors like high temperature, electromagnetic waves, air pollution, insecticides, alcohol consumption, obesity, and poor nutrition could potentially lead to an increase in ROS concentration[6]. Recent years have seen a thorough exploration of oxidative stress and the impact of ROS on the pathophysiology of human sperm function and male infertility[7–9]. Research has shown that male fertility and embryo development rely, in some measure, on the biochemical characteristics of sperm DNA, particularly the extent of DNA damage[10,11]. Oxidative stress is a significant factor in causing damage to sperm DNA, potentially leading to the modification of DNA bases[12,13].

When discussing the topic of male infertility and oxidative stress, we should distinguish between systemic oxidative stress and local oxidative stress. So far, only a small number of studies have explored the connection between systemic and local oxidative stress in sperm. In the previous study by Bergsma et al., they found that there

Department of Urology, Shaoxing People's Hospital(The First Affiliated Hospital, Shaoxing University), 568 Zhongxing North Road, 312000 Shaoxing, Zhejiang, China. email: tangguiliangsx@126.com

was no association between local(seminal plasma) and systemic oxidative stress biomarker concentrations(blood serum)[14]. Furthermore, Guz et al. discovered that there was no correlation between overall bodily oxidative stress and sperm plasma levels[15].Most studies focus on the relationship between oxidative stress in local seminal plasma and male infertility, but there is relatively little research on the relationship between systemic oxidative stress and male infertility. While certain observational research indicates a link between systemic oxidative stress and male infertility[16–18], there is no agreement on the cause-and-effect relationship between systemic oxidative stress and male infertility. Utilizing genetic variants as instrumental variables, Mendelian randomization (MR) provides a distinct chance to explore causal connections between exposures and outcomes[19]. Mendelian randomization differs from typical observational studies by utilizing genetic variants that are randomly assigned at conception, avoiding confounding and reverse causality issues[20]. By utilizing this method, researchers can address the constraints of observational studies and offer stronger evidence for causal relationships[21]. As of now, there have been no investigations into the causal relationship between systematic antioxidant capacity and the likelihood of male infertility. This research will assess the potential causal relationship between systematic antioxidant capacity and male infertility using a two-sample Mendelian randomization approach.

Materials and methods

Study design and ethics statement

A MR study was conducted to investigate the impact of 10 plasma biomarkers related to antioxidant capacity (GST, SOD, GPX, CAT, total bilirubin, albumin, α-tocopherol, ascorbate, retinol, and uric acid) on male infertility. In Fig. 1, we presented the diagram of our research plan, highlighting the three key assumptions that are fundamental to the MR study. The initial assumption claims that the instrumental variables (IVs) are strongly linked to exposure. The second assumption argues that the independent variables are not influenced by any confounding variables. The third assumption states that the independent variables impact the probability of exposure solely through their connection with the outcome, without any indirect pathways. As our data came from existing studies or public databases, we did not need to seek ethical approval from a committee.

Data sources of male infertility

For male infertility, the available summarized data were gained from the open database (IEU OPEN GWAS PROJECT: https://gwas.mrcieu.ac.uk/), which includes a total of 680 male patients with infertility and 72,799 controls of European population.

Genetic instrumental variables for plasma antioxidant capacity biomarkers

The latest GWAS provided genetic markers for 10 biomarkers related to systemic antioxidant capacity, including GST, SOD, GPX, CAT, total bilirubin, albumin, α-tocopherol, ascorbate, retinol, and uric acid. Information on GST, SOD, GPX, and CAT was obtained from the INTERVAL study[22]; while α-tocopherol and albumin data

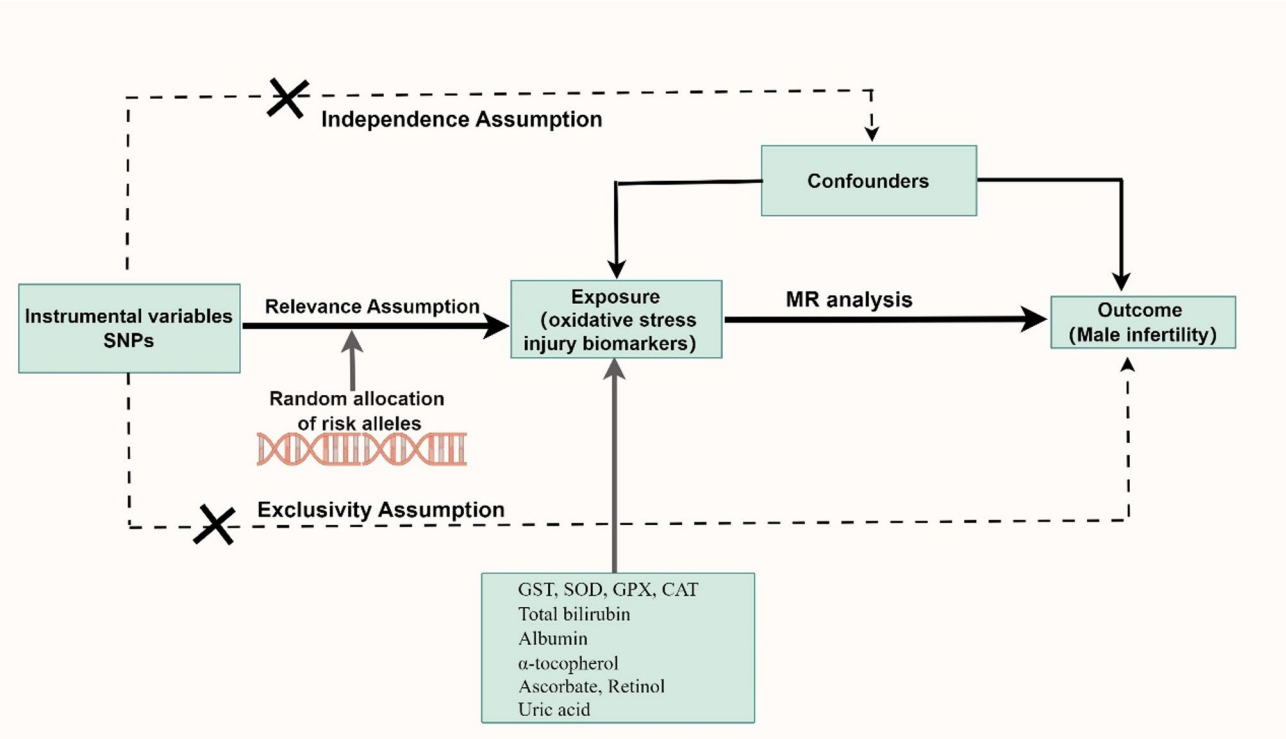

Fig. 1. An overview of the study design.

were sourced from the Twins UK cohort and KORA study[23]; the rest of the data was collected from the GWAS Catalog and UK biobank. The information about the studies and datasets utilized in the current research was presented in Table 1.

Selection of instrumental variables

The GWAS summary data was used to carefully choose suitable SNPs as instrumental variables (IVs).The selection process began with the identification of SNPs that were strongly associated with the exposure, demonstrated by a genome-wide significant P-value threshold of less than 5×10^{-8} or 5×10^{-6}. In order to avoid biased outcomes caused by linkage disequilibrium (LD), we utilized a clumping method with a strict r^2 limit of 0.001 and a window size of 10,000 kb. To further improve accuracy, the Phenoscanner database (http//www.phenoscanner.medschl.cam.ac.uk/) was utilized to exclude genetic variants linked to potential confounders. The known risk factors of male infertility by RCTs or Mendelian randomization studies are considered as potential confounders. In the present study, type 2 diabetes mellitus[24], BMI, body fat percentage, alcohol consumption[25], ulcerative colitis[26], stroke[27], COVID-19[28], and multiple sclerosis[29], are considered confounders of male infertility, and any SNPs associated with these confounders would be excluded. Afterwards, we adjusted the impact calculations for both different exposures and outcomes and removed any SNPs with alleles that were not compatible or were palindromic. Furthermore, in order to mitigate bias caused by inadequate instrumental variables, we evaluated the robustness of the instrumental variables by computing the F-statistic, where an F-statistic exceeding 10 signifies a lower likelihood of weak instrument bias[30,31].

Mendelian randomization analyses

The main analysis utilized the inverse-variance weighted (IVW) approach under a random-effects model, which accounts for heterogeneity across SNPs[32]. This study also utilized four more MR techniques: the weighted median, MR-Egger, weighted mode, and simple mode method. To assess the consistency of causal relationships across all SNPs, Cochran's Q statistic and related P-values were used in the examination of heterogeneity. Furthermore, we assessed potential horizontal pleiotropy by examining MR-Egger intercepts[33]. In order to identify and address any possible horizontal pleiotropic outliers, we employed the MR-PRESSO framework, modifying the IVW estimate by removing outliers[34]. Additionally, we performed a leave-one-out analysis to examine if the impact of any individual outlier variant on the effect estimates. The examination was performed utilizing the R software (version 4.2.3) Two-Sample MR package.

Results

Genetic instrumental variables screening

A total of 10 plasma antioxidant capacity biomarkers, namely, GST, SOD, GPX, CAT, total bilirubin, albumin, α-tocopherol, ascorbate, retinol, and uric acid were analyzed to determine their potential causality with male infertility. The study utilized a range of 5 to 249 SNPs. The F-statistics of the genetic instruments used in this research were greater than 10, indicating that the IVs were robust instruments, reducing the bias of IV estimates (shown in Supplementary Table 1).

Mendelian randomization Estimation between systematic antioxidant capacity and male infertility

Overall, in the MR analyses using IVW, all genetically determined systematic antioxidant capacity biomarkers were not associated with the risk of male infertility, including GST(OR = 1.08, 95%CI: 0.91–1.29, P = 0.35), SOD(OR = 0.83, 95%CI: 0.66–1.04, P = 0.11), GPX(OR = 1.12, 95%CI: 0.92–1.36, P = 0.26), CAT(OR = 1.04, 95%CI: 0.83–1.29, P = 0.75), total bilirubin(OR = 0.98, 95%CI: 0.94–1.01, P = 0.18), albumin(OR = 1.14, 95%CI: 0.73–1.76, P = 0.57), α-tocopherol(OR = 0.56, 95%CI: 0.03–9.38, P = 0.69), ascorbate(OR = 1.06, 95%CI: 0.24–4.60, P = 0.94), retinol(OR = 1.29, 95%CI: 0.34–4.96, P = 0.71), and uric acid (OR = 0.88, 95% CI : 0.67–1.17, P =

Phenotype	Sample size	Population ancestry	Study ID
Male infertility	73,479	European	finn-b-N14_MALEINFERT
Oxidative stress injury biomarkers			
GST	3,301	European	prot-a-1283
SOD	3,301	European	prot-a-2800
GPX	3,301	European	prot-a-1265
CAT	3,301	European	prot-a-367
Total bilirubin	342,829	European	ukb-d-30840_raw
Albumin	115,060	European	met-d-Albumin
α-tocopherol	7,725	European	met-a-340
Ascorbate	64,979	European	ukb-b-19,390
Retinol	62,991	European	ukb-b-17,406
Uric acid	343,836	European	ebi-a-GCST90018977

Table 1. Information of all GWAS summary data. Abbreviations: CAT = Catalase; GPX = glutathione peroxidase; GST = glutathione S-transferase; SOD = superoxide dismutase.

0.39, shown in Table 1). Figure 2 displayed the outcomes of IVW mode-MR analyses regarding the impact of systematic biomarkers of antioxidant capacity on male infertility. The scatter plot and forest plot of individual SNPs showing the association between systematic antioxidant capacity biomarkers and male infertility are presented in Supplementary Fig. 1 and Supplementary Fig. 2, respectively, providing a more visual representation of the results in different modes.

Sensitivity analysis

Table 2 displayed the outcomes of the MR-PRESSO global test, MR-Egger intercept test, and the Cochrane Q test. The study confirmed the absence of horizontal pleiotropy in all analyses through MR-PRESSO global test and MR-Egger intercept test results ($P > 0.05$). All Cochrane Q test results were negative, indicating no significant heterogeneity among the SNPs used as IVs in this study ($P > 0.05$). The leave-one-out analysis results (Supplementary Fig. 3) showed that none of the SNPs had a significant impact on the relationship between circulating antioxidant capacity biomarkers (such as circulating GST, SOD, GPX, CAT, total bilirubin, albumin, α-tocopherol, ascorbate, retinol, and uric acid in the blood) and male infertility, confirming the reliability of the findings.

Discussion

Male infertility is a significant public health issue that is linked to declining birth rates, population aging, and could impact social development negatively[19]. Globally, around 8–12% of couples of reproductive age are reportedly impacted by this problem[3]. Male infertility is responsible for about 50% of infertility cases and impacts roughly 5% of men in the age group capable of reproduction[35]. Male infertility is a complex condition that results from a variety of factors such as genetic, epigenetic, environmental, and lifestyle influences[36]. Factors associated with an unhealthy lifestyle, including smoking, heavy alcohol consumption, a diet high in saturated fats and proteins, lack of physical activity, stress, obesity, and older paternal age, can all increase the likelihood of male infertility[37–40].

Reactive oxygen species are extremely active agents that oxidize other substances[41,42]. Some examples of these are the superoxide anion radical, hydroxyl radical, peroxyl radical, and a group of free radicals from nitrogen like nitric oxide, peroxynitrite, nitroxyl anion, and peroxynitrous acid[43]. Sperm cell dysfunction and male infertility are often caused by oxidative stress, which damages the structural and functional integrity of spermatozoa[8,44,45]. Oxidative stress in sperm cells can result in simultaneous harm to proteins and lipids in the cellular membrane, leading to a decrease in flexibility and an elevation in permeability of the plasma membrane[46]. Decreased flexibility of the membrane leads to a reduction in movement and the capacity to merge with the oocyte, while

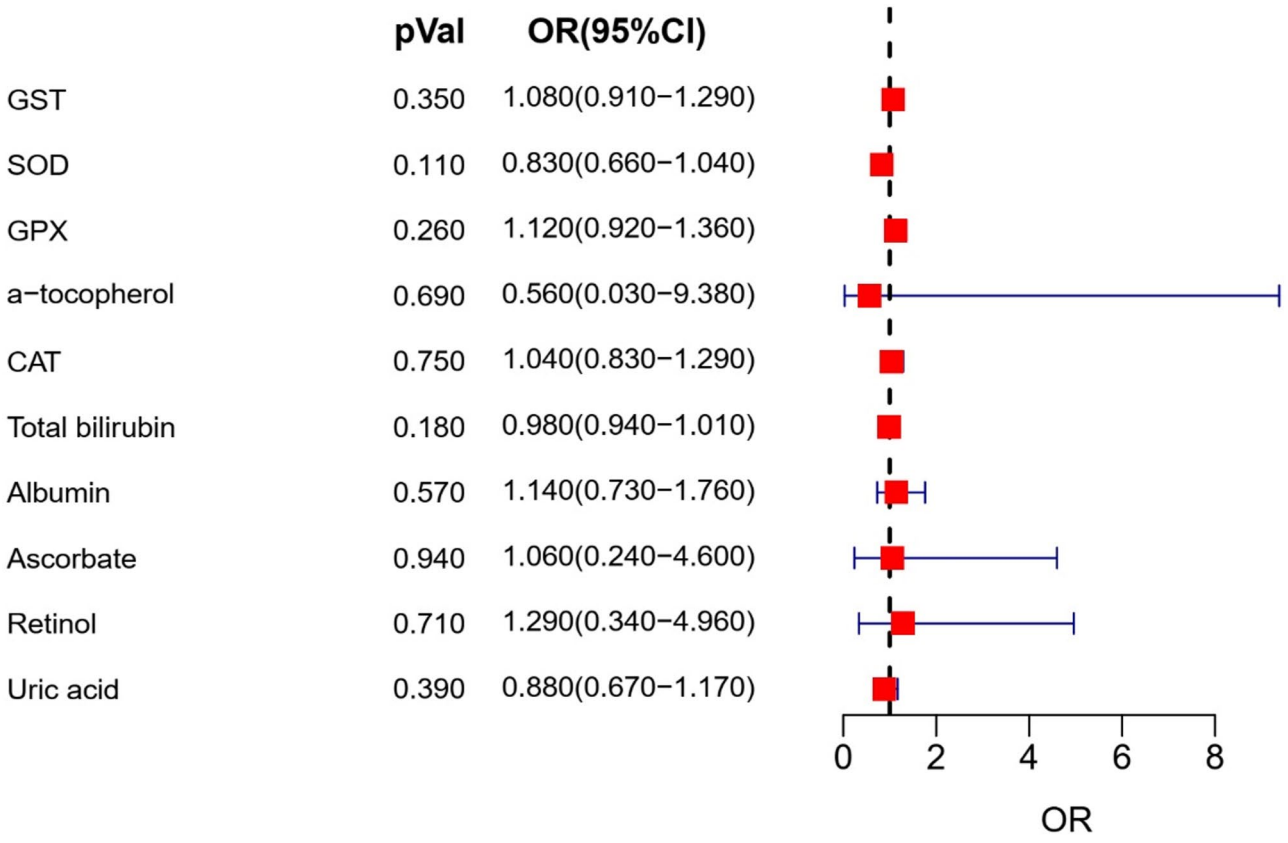

Fig. 2. The IVW mode-MR analyses results of systematic oxidative stress injury biomarkers on male infertility.

Method	nSNPs	Beta	SE	OR	95% confidence interval	*P* value	Cochran Q statistic	Heterogeneity *P*-value	MR-PRESSO global test	MR Egger intercept test
GST									0.82	0.79
MR Egger	11	0.12	0.18	1.13	0.80–1.60	0.50	6.66	0.67		
Weighted median	11	0.08	0.11	1.08	0.87–1.35	0.49				
Inverse variance weighted	11	0.08	0.09	1.08	0.91–1.29	0.35	6.73	0.75		
Simple Mode	11	0.13	0.16	1.13	0.83–1.55	0.45				
Weighted Mode	11	0.08	0.11	1.08	0.87–1.36	0.49				
SOD									0.55	0.46
MR Egger	13	−0.36	0.26	0.70	0.42–1.15	0.18	11.23	0.42		
Weighted median	13	−0.19	0.17	0.83	0.60–1.15	0.26				
Inverse variance weighted	13	−0.19	0.12	0.83	0.66–1.04	0.11	11.83	0.46		
Simple Mode	13	−0.39	0.26	0.68	0.41–1.12	0.16				
Weighted Mode	13	−0.24	0.23	0.79	0.51–1.22	0.31				
GPX									0.45	0.82
MR Egger	14	0.08	0.19	1.08	0.74–1.56	0.70	14.15	0.29		
Weighted median	14	0.12	0.13	1.13	0.87–1.45	0.36				
Inverse variance weighted	14	0.11	0.10	1.12	0.92–1.36	0.26	14.22	0.36		
Simple Mode	14	0.50	0.28	1.66	0.96–2.87	0.09				
Weighted Mode	14	0.13	0.14	1.14	0.87–1.49	0.37				
α-tocopherol									0.40	0.24
MR Egger	5	5.67	4.53	290.21	0.04–2.06e + 06	0.30	2.57	0.46		
Weighted median	5	−1.83	1.76	0.16	0.005–5.06	0.30				
Inverse variance weighted	5	−0.58	1.44	0.56	0.03–9.38	0.69	4.67	0.32		
Simple Mode	5	−2.11	2.18	0.12	0.002–8.74	0.39				
Weighted Mode	5	−1.92	2.02	0.15	0.003–7.66	0.40				
CAT									0.66	0.95
MR Egger	14	0.06	0.34	1.06	0.55–2.04	0.87	10.48	0.57		
Weighted median	14	−0.06	0.15	0.94	0.69–1.27	0.69				
Inverse variance weighted	14	0.04	0.11	1.04	0.83–1.29	0.75	10.48	0.65		
Simple Mode	14	−0.11	0.24	0.90	0.56–1.43	0.65				
Weighted Mode	14	−0.13	0.21	0.88	0.58–1.33	0.55				
Total bilirubin									0.29	0.05
MR Egger	80	−0.03	0.02	0.97	0.94–0.99	0.05	87.11	0.22		
Weighted median	80	−0.03	0.02	0.97	0.94–1.00	0.06				
Inverse variance weighted	80	−0.02	0.02	0.98	0.94–1.01	0.18	91.63	0.16		
Simple Mode	80	0.08	0.11	1.08	0.87–1.34	0.45				
Weighted Mode	80	−0.02	0.02	0.98	0.95–1.01	0.28				
Albumin							71.11	0.61	0.56	0.47
MR Egger	77	0.36	0.39	1.43	0.67–3.04	0.36				
Weighted median	77	0.26	0.39	1.29	0.59–2.78	0.51				
Inverse variance weighted	77	0.13	0.22	1.14	0.73–1.76	0.57	71.64	0.62		
Simple Mode	77	0.18	0.64	1.20	0.34–4.23	0.78				
Weighted Mode	77	0.22	0.37	1.24	0.60–2.56	0.56				
Ascorbate									0.02	0.02
MR Egger	11	2.85	1.19	17.21	1.68–176.08	0.04	10.97	0.28		
Weighted median	11	−0.99	0.80	0.37	0.08 – 1.79	0.22				
Inverse variance weighted	11	0.06	0.75	1.06	0.24 – 4.60	0.94	19.90	0.03		
Simple Mode	11	−1.21	1.28	0.30	0.02–3.65	0.37				
Weighted Mode	11	−1.32	1.16	0.27	0.03–2.61	0.28				
Retinol									0.81	0.67
MR Egger	8	0.93	1.65	2.52	0.09–64.16	0.60	3.73	0.71		
Weighted median	8	0.70	0.90	2.01	0.34–11.81	0.44				
Inverse variance weighted	8	0.25	0.69	1.29	0.34 - 4.96	0.71	3.93	0.79		
Simple Mode	8	1.12	1.29	3.08	0.25–38.35	0.41				
Weighted Mode	8	0.90	1.06	2.47	0.31–19.75	0.42				

Continued

Method	nSNPs	Beta	SE	OR	95% confidence interval	*P* value	Cochran Q statistic	Heterogeneity *P*-value	MR-PRESSO global test	MR Egger intercept test
Uric acid									0.84	0.86
MR Egger	249	−0.15	0.19	0.86	0.59–1.26	0.45	228.63	0.79		
Weighted median	249	−0.25	0.21	0.78	0.52–1.17	0.24				
Inverse variance weighted	249	−0.12	0.14	0.88	0.67–1.17	0.39	228.66	0.81		
Simple Mode	249	0.93	0.72	2.53	0.61–10.44	0.20				
Weighted Mode	249	−0.20	0.19	0.82	0.56–1.20	0.31				

Table 2. Associations between systematic oxidative stress injury biomarkers and male infertility. Abbreviations: CAT = Catalase; GPX = glutathione peroxidase; GST = glutathione S-transferase; SOD = superoxide dismutase.

heightened membrane permeability leads to a breakdown of the cells' DNA integrity[9,47]. Sperm cells with DNA damage have minimal ability to fertilize naturally, and the high levels of DNA damage in human sperm have been linked to negative clinical results such as infertility and repeated pregnancy loss[48].

When examining the impact of oxidative stress on male infertility, it is crucial to differentiate between systemic and local oxidative stress. So far, only a small number of studies have explored the connection between systemic and local oxidative stress in semen. Bergsma et al. previously examined how two frequently utilized biomarkers for oxidative stress (thiol and MDA levels) interacted in both systemic and local evaluations within the male reproductive system. No connections were discovered between the levels of oxidative stress biomarkers at the local and systemic levels[14]. Furthermore, Guz et al. discovered that there was no correlation between overall bodily oxidative stress and sperm plasma levels[15]. Many research studies have investigated the connection between male infertility and oxidative stress at a local level, as far as we know. Huang and colleagues previously performed a comprehensive analysis and meta-analysis of observational case-control studies to assess indicators of oxidative stress in the seminal fluid of individuals with male infertility. The findings showed that various indicators of oxidative stress, including catalase, GPX, GST, and GSH, were not within normal range in the seminal fluid of infertile men. The presence of oxidative stress in seminal fluid due to reduced antioxidant protection is linked to male infertility[49].

Compared to local oxidative stress, there is relatively few research on the relationship between systemic oxidative stress and male infertility. Shamsi et al.'s research revealed a correlation between sperm count and levels of blood SOD, GSH, and CAT. An association was also found between the levels of blood MDA and the percentage of abnormal morphology and deceased sperm. Therefore, by analyzing the findings, it could potentially be feasible to utilize these antioxidants present in the bloodstream as indicators in measuring the sperm characteristics[18]. Chinyere and colleagues discovered that men with normal sperm had notably elevated levels of serum GSH, nitric oxide, and overall antioxidant capacity, while also exhibiting decreased levels of total plasma peroxidase, oxidative stress index, zinc, and cadmium in comparison to men with low sperm count or no sperm at all[17]. As of now, there have been no investigations into the causal relationship between systematic antioxidant capacity and the likelihood of male infertility. This study is the first to investigate the causal link between systematic antioxidant capacity and male infertility, as far as we know. Our investigation found no significantly causal link between systemic antioxidant capacity and male infertility. The wide CIs observed for certain biomarkers (e.g., α-tocopherol: OR = 0.56, 95% CI = 0.03–9.38) reflect limited statistical power due to weak genetic instruments (fewer SNPs) or smaller exposure sample sizes (e.g., α-tocopherol: $n = 7{,}725$). Biomarkers with broader CIs (α-tocopherol, ascorbate, retinol) should be interpreted cautiously, as their null associations may stem from insufficient precision rather than a true absence of effect. In contrast, biomarkers with narrower CIs (e.g., total bilirubin: 95% CI = 0.94–1.01) provide more reliable estimates. Importantly, the consistency of null results across all biomarkers—despite varying instrument strengths—supports the conclusion that systemic antioxidant capacity is unlikely to have a major causal role in male infertility.

The present study possesses several strengths. The two sample MR analysis was initially implemented to establish a strong foundation for exploring the potential causal link between systemic antioxidant capacity and male infertility. By utilizing this methodological approach, the interference of confounding factors and reverse causation on causal inference was eliminated, ultimately improving the validity of causal inferences. Furthermore, the genetic variations associated with systemic antioxidant capacity were obtained from the largest and most comprehensive GWAS summary data accessible, guaranteeing the reliability and effectiveness of the tools used in the MR analysis. Additionally, a comprehensive investigation was carried out using leave-one-out sensitivity analysis and heterogeneity analysis. Potential confounding due to horizontal pleiotropy was detected and accounted for through the use of MRPRESSO and MR-Egger regression intercept analyses. This study did not find any evidence of horizontal pleiotropy, which is worth mentioning.

There were certain restrictions in this research. Firstly, it is worth noting that although genetically there is no evidence linking antioxidant capacity with male infertility, it is possible that elevated systemic oxidative stress caused by external stressors may play a causative role. Therefore, we need further research in the future to explore this point. Secondly, the FinnGen dataset's lack of detailed inclusion criteria for cases and controls is a recognized limitation. Male infertility cases were defined broadly, potentially encompassing heterogeneous etiologies (e.g., obstructive vs. non-obstructive), while controls included males without infertility diagnoses.

Unmeasured confounders in the control group (e.g., subfertility, undiagnosed reproductive issues) could introduce selection bias, diluting effect estimates. However, MR leverages genetic variants assigned at conception, reducing susceptibility to confounding by post-conception factors. Furthermore, sensitivity analyses showed no evidence of horizontal pleiotropy (MR-Egger intercept $P > 0.05$), suggesting minimal bias from unmeasured pathways. Future studies should prioritize datasets with granular phenotypic stratification to address this limitation. Thirdly, it is important to note a potential limitation in the study due to the limited number of cases in the GWAS data for male infertility from the FinnGen research project. In addition, substantial imbalance between the number of controls (72,799) and cases (680) presents several challenges and potential biases in the study's analysis. This significant disparity can lead to statistical imbalances that may compromise the robustness of effect estimates, making it more difficult to detect true associations or causal relationships. Furthermore, the large control group may overshadow the characteristics of the cases, potentially obscuring critical effects related to infertility. In Mendelian randomization, the primary analysis relies on genetic variants as instrumental variables, which are less susceptible to confounding and selection bias compared to traditional observational studies due to their random allocation at conception. The statistical methods employed in MR, such as IVW and MR-Egger regression, inherently account for sample size discrepancies by weighting the effect estimates of individual SNPs based on their precision. Additionally, we conducted sensitivity analyses, including leave-one-out analysis and MR-PRESSO outlier correction, to evaluate the robustness of our results. These methods mitigate potential biases caused by unbalanced sample sizes by identifying and excluding SNPs with disproportionate influence. While the case-control imbalance may reduce statistical power to detect modest associations, the MR framework prioritizes genetic instrument strength (F-statistics > 10 in our study) to minimize weak instrument bias. Future studies with more balanced cohorts are warranted to confirm these findings. Fourthly, our study focused solely on systemic antioxidant capacity and did not incorporate direct measures of oxidants (e.g., reactive oxygen species, malondialdehyde). This omission limits our ability to fully capture the oxidative stress balance, as elevated oxidant levels might counteract antioxidant effects. While we adjusted for confounders like body fat percentage, and alcohol consumption—factors linked to oxidative damage—the absence of oxidant data precludes a comprehensive assessment. Future MR studies should integrate oxidant biomarkers or utilize composite scores (e.g., oxidative stress index) to better reflect the antioxidant-oxidant equilibrium. Ultimately, this MR analysis was conducted on individuals of European descent. Further research is needed to determine if the findings of our study are applicable to different ethnic backgrounds.

Conclusion

The present investigation did not yield evidence of a substantial causal association between systemic antioxidant capacity and male infertility. Further research with larger sample sizes and data from different ethnicities is needed.

Data availability

The study contains the unique findings that were produced by the researchers. Further inquiries can be directed to the corresponding author.

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Author contributions

XLZ provided the presented idea. XLZ, CDS, ZRZ, and GLT performed the data analysis. XLZ wrote the manuscript. GLT did critical reading and editing the manuscript. All authors discussed the results and contributed to the final manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to G.T.

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