Title: Conscientiousness and Opioid Use Disorder: A Two-Sample Mendelian Randomization Study

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Abstract

Background: Opioid use disorder (OUD) is a major global health problem. Personality traits, particularly conscientiousness, have been linked to lower substance use in observational studies, but causal evidence is lacking. This study aimed to investigate whether genetically predicted conscientiousness has a causal link with OUD.

Methods: The study employed a two-sample Mendelian randomization (MR) framework using summary statistics from the largest available GWAS of conscientiousness (N = 234,880; Million Veteran Program) and OUD (20,686 cases, 77,026 controls; MVP and Psychiatric Genomics Consortium) in European ancestry participants. Thirteen independent single-nucleotide polymorphisms (SNPs) ($P < 5 \times 10^{-7}$, $r^2 < 0.001$, $F > 10$) were selected as instrumental variables. The primary causal estimate used is inverse-variance weighted (IVW) MR. Sensitivity analyses included weighted median, MR-Egger regression, weighted mode, simple mode, Cochran's Q test, and leave-one-out analyses to assess pleiotropy and heterogeneity.

Results: IVW MR revealed a significant protective effect of genetically predicted conscientiousness on OUD risk ($\beta = -0.493$; 95% CI: −0.597 to −0.389; $P = 7.8 \times 10^{-21}$). Consistent effect sizes were observed across sensitivity analyses: weighted median ($\beta = -0.468$; 95% CI: −0.607 to −0.329; $P = 5.3 \times 10^{-11}$), weighted mode ($\beta = -0.467$; 95% CI: −0.683 to −0.251; $P = 1.2 \times 10^{-3}$), and simple mode ($\beta = -0.467$; 95% CI: −0.692 to −0.242; $P = 1.6 \times 10^{-3}$). MR-Egger regression direction was consistent ($\beta = -2.487$; P = 0.526), with intercept P = 0.609 indicating no horizontal pleiotropy. Cochran's Q tests indicated no heterogeneity (IVW Q = 1.22, P = 0.999; MR-Egger Q = 0.94, P = 0.999). Leave-one-out analysis confirmed the stability of causal estimates.

Conclusion: The current study provides robust evidence that higher genetically predicted conscientiousness causally reduces OUD risk. These findings suggest that self-regulatory personality traits act as protective factors and highlight potential behavioral targets for prevention strategies. These findings are not directly generalizable to non-European groups without replication. Future research should focus on cross-ancestry replication and trait subcomponents.

Keywords: Conscientiousness, Opioid Use Disorder, Mendelian Randomization, Personality Traits

Introducation

OUD continues to be a major global public health challenge, contributing substantially to morbidity and mortality worldwide (1). Although genetic factors contribute to OUD susceptibility, behavioral and psychological traits also shape individual risk trajectories(1, 2). Among these, personality dimensions may influence initiation, maintenance, and escalation of substance use, yet causal inference regarding personality and OUD remains limited.

Personality traits conceptualized through major models such as the Five-Factor Model capture enduring behavioral tendencies (3). Traits like conscientiousness, characterized by self-discipline, planning, and impulse control, are consistently linked with healthier lifestyles and reduced engagement in risky behaviors (4). For example, conscientiousness-related traits show inverse associations with a broad range of risky health behaviors, including substance use, in large meta-analytic syntheses of behavior-related outcomes (5). Longitudinal evidence further supports that conscientiousness measured earlier in life predicts lower substance use behaviors later in life (6). Moreover, systematic work demonstrates that inverse associations between conscientiousness and substance use disorder (SUD) constructs hold across multiple addiction domains, reinforcing the generalizability of this relationship (7).

In contrast, impulsivity the tendency to act rashly without adequate planning has been implicated as a core vulnerability factor in addictive behaviors (8). Trait impulsivity and its neurocognitive mechanisms (e.g., impaired response inhibition and elevated reward sensitivity) have been shown to predict SUD vulnerability across clinical and general populations(9, 10). Reviews have identified consistent roles for aspects of impulsivity such as non-planning and affect-based impulsivity in increasing risk for SUDs (8, 11). Neurobiological models also map impulsivity onto fronto-striatal and orbitofrontal circuits that regulate inhibitory control and reward valuation, processes disrupted in addiction (12).

Although the correlational associations between personality traits and substance use are robust, observational designs cannot fully disentangle causal mechanisms due to confounding, reverse causation, and measurement limitations (13). MR leverages genetic variants as instrumental variables to strengthen causal inference in cases where randomized trials are infeasible (13). By using genetic proxies for traits like conscientiousness, MR can address key biases inherent in observational research and assess whether variation in personality dispositions causally influences addiction outcomes (13).

In this context, the present study utilizes a two-sample MR design to investigate whether genetically determined variation in conscientiousness causally linked with risk of OUD. By integrating the largest available GWAS summary statistics for conscientiousness and OUD, we aim to clarify the causal contributions of personality dispositions to OUD susceptibility and inform integrative models of addiction risk.

Methods

Study Design

This study employed a two-sample MR design to investigate the potential causal effect of conscientiousness on the risk of OUD. MR leverages the random allocation of alleles at conception to strengthen causal inference and minimize confounding and reverse causation.

The validity of MR analysis relies on three core instrumental variable assumptions (Figure 1):

Relevance–Genetic variants must be robustly associated with the exposure (conscientiousness).

Independence–Genetic variants must be independent of measured and unmeasured confounders of the exposure–outcome relationship.

Exclusion Restriction–Genetic variants must influence the outcome (OUD) solely through the exposure, without horizontal pleiotropic pathways.

These assumptions were explicitly evaluated through instrument selection procedures and multiple sensitivity analyses, including tests for heterogeneity and horizontal pleiotropy.

To minimize bias due to population stratification, analyses were restricted to individuals of European ancestry in both exposure and outcome GWAS datasets. Causal estimates are not generalizable to non-European populations without independent replication. A summary of the included GWAS sources is presented in Table 1.

Table 1. Summary statistics of the GWAS included in this 2 sample Mendelian randomization study

GWAS_ID	Trait	Consortium / Author	Year	Cases (N)	Controls (N)	Total (N)	Ancestry	SNPs (N)
N	Conscientiousness	(Million Veteran Program; MVP) / Gupta et al. (14)	2024	N	N	234,880	European	~10M
N	OUD	(MVP + PGC)/ Deak et al. (15).	2022	20,686	77,026	639,063	European	~12M

Note: N indicates sample size, and M denotes million SNPs. Analyses were restricted to individuals of European ancestry to minimize population stratification bias.

Data Sources

Summary-level genetic association statistics were obtained from the largest and most recent publicly available genome-wide association studies (GWAS) for each phenotype to maximize statistical power and minimize bias from weak instruments.

- **Exposure: Conscientiousness**

Genetic instruments for conscientiousness were derived from the large-scale GWAS conducted by Gupta et al. (2024), published in *Nature Human Behaviour* (14). This GWAS primarily included participants from the MVP and represents one of the most comprehensive investigations of the genetic architecture of personality traits (14).

Genome-wide significant SNPs were selected using a significance threshold of $P < 5 \times 10^{-7}$. To ensure independence of instruments and reduce bias from linkage disequilibrium (LD), SNPs were clumped using stringent criteria ($r^2 < 0.001$ within a 10,000 kb window).

SNP harmonization was performed to align effect alleles between exposure and outcome datasets. Palindromic SNPs with intermediate allele frequencies were excluded to prevent strand ambiguity.

- **Outcome: Opioid Use Disorder**

Summary statistics for OUD were obtained from the large meta-analysis conducted by Deak et al. (2022), published in *Molecular Psychiatry*. This GWAS included 114,759 individuals of European ancestry (20,686 cases and 77,026 controls) from the MVP and the Psychiatric Genomics Consortium (PGC) (15).

The substantial sample size enhances statistical precision and reduces bias in MR estimates.

- **Instrument Strength Assessment**

To evaluate instrument strength and minimize weak instrument bias, F-statistics were calculated for each SNP using:

$$F = \frac{R^2(N-2)}{1-R^2}$$

where:

R^2 represents the proportion of variance in conscientiousness explained by the SNP,

N denotes the exposure GWAS sample size.

The proportion of explained variance (R^2) was calculated as:

$$R^2 = \frac{2 \cdot MAF \cdot (1-MAF) \cdot \beta^2}{2 \cdot MAF \cdot (1-MAF) \cdot \beta^2 + 2 \cdot MAF \cdot (1-MAF) \cdot N \cdot SE(\beta)^2}$$

An F-statistic > 10 was considered indicative of sufficiently strong instruments. All retained SNPs exceeded this threshold, indicating low risk of weak instrument bias.

- **Instrument Selection**

Genetic variants were selected according to standard MR criteria:

Genome-wide significance ($P < 5 \times 10^{-7}$)

LD independence ($r^2 < 0.001$)

Instrument strength ($F > 10$)

After harmonization and quality control procedures, 13 independent SNPs were retained as valid instruments for conscientiousness.

Mendelian Randomization Analysis

MR analyses were performed using the *TwoSampleMR* package in R (version 4.5.2). The overall study framework, including the three core instrumental variable assumptions relevance, independence, and exclusion restriction is illustrated in Figure 1.

A two-sample MR design was implemented to estimate the causal effect of conscientiousness on the risk of OUD. The primary causal estimate was derived using the IVW method, which provides the most statistically efficient estimator under the assumption that all genetic variants are valid instrumental variables or that horizontal pleiotropy is balanced (16).

To evaluate the robustness of the IVW findings and account for potential violations of MR assumptions, several complementary sensitivity methods were applied. These included the weighted median, MR-Egger regression, weighted mode, and simple mode approaches (17). The weighted median estimator provides consistent causal estimates when at least 50% of the total weight is contributed by valid instruments (18). MR-Egger regression was used to assess and correct for directional (unbalanced) horizontal pleiotropy, with the intercept term serving as a formal test for pleiotropic bias (19). The weighted and simple mode estimators further strengthen inference by identifying the most common causal effect estimate across instruments (17).

Additionally, leave-one-out analysis was conducted to determine whether the observed association was disproportionately influenced by any single SNP. The MR-Egger intercept and its 95% confidence interval were examined to detect evidence of horizontal pleiotropy.

Collectively, these complementary analyses were implemented to ensure the robustness, consistency, and validity of the causal inference. Causal estimates are not transportable to non-European populations without independent replication.

Ethical approval and data availability

The study was reviewed and approved by the Ethics Committee of Iran University of Medical Sciences (approval code: IR.IUMS.REC.1402.888), All the data used in this study were obtained from publicly accessible databases, and the original studies received ethical approval and informed consent from the participants. All methods have been carried out in accordance with the relevant guidelines and regulations.

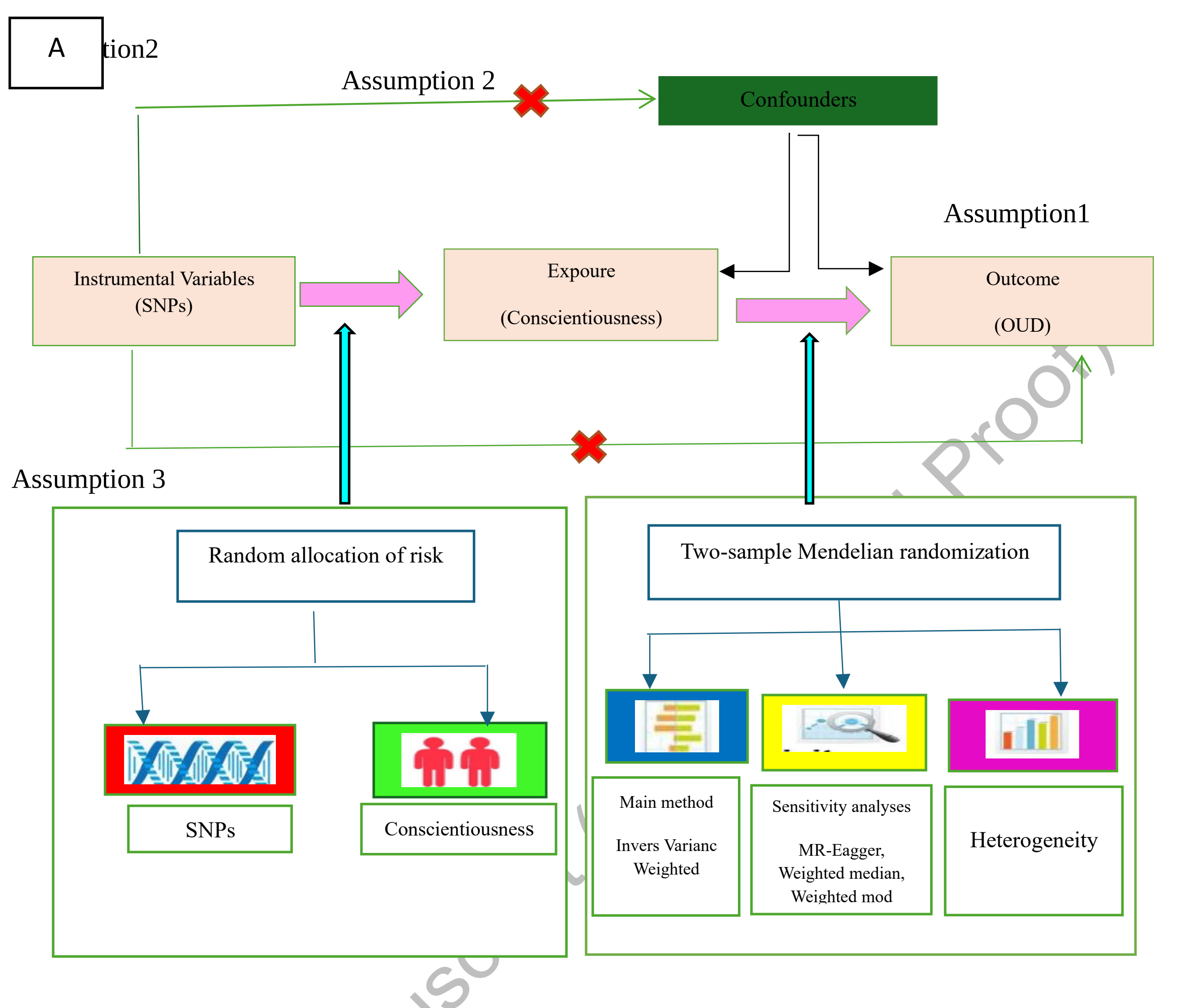

Figure 1. Directed acyclic graph illustrating the instrumental variable assumptions in the Mendelian randomization framework.
Genetic variants (instrumental variables, IVs) are used to estimate the causal effect of conscientiousness (exposure) on OUD (outcome). Three core assumptions are required: **(1) Relevance** — IVs are robustly associated with conscientiousness; **(2) Independence** — IVs are independent of confounders of the exposure–outcome relationship; and **(3) Exclusion Restriction** — IVs influence OUD exclusively through conscientiousness, with no horizontal pleiotropic pathways (direct effect indicated by the crossed dashed arrow). Assumption 3 was formally evaluated using pleiotropy and sensitivity analyses.

Results

- **Instrumental Variable Screening**

Genetic instruments for conscientiousness were selected based on established MR criteria: genome-wide significance ($P < 5 \times 10^{-7}$), independence ($r^2 < 0.001$), and instrument strength (F-statistic > 10). Potentially confounding variants were excluded through manual screening. SNPs were harmonized to align effect alleles across datasets, and palindromic SNPs with intermediate allele frequencies were removed to avoid strand ambiguity. All retained instruments demonstrated adequate strength (F-statistic > 10), reducing the risk of weak instrument bias. Leave-one-out analysis was performed to evaluate the influence of individual

SNPs on the overall estimates. This process resulted in 13 independent SNPs being selected as valid instruments for conscientiousness (Table 1).

Table 1. SNPs associated with conscientiousness in OUD

SNP	Effect Allele	Other Allele	EAF	Conscientiousness			OUD			F_statistic
				β	SE	P value	β	SE	P value	
rs1350134	A	T	0.554468	0.0314	0.0057	4.40E-08	-0.014238	0.006025	0.01811	30.34
rs1005958	A	G	0.557602	0.0321	0.0058	4.09E-08	-0.019208	0.006025	0.001433	30.63
rs1005959	T	G	0.558394	0.0322	0.0058	3.82E-08	-0.019587	0.006025	0.001151	30.82
rs12705975	T	C	0.445416	-0.0314	0.0057	4.36E-08	0.014804	0.006025	0.01403	30.35
rs13226763	T	C	0.445532	-0.0314	0.0057	4.40E-08	0.014575	0.006025	0.01554	30.36
rs12705971	T	G	0.446167	-0.0314	0.0057	4.49E-08	0.014491	0.006025	0.01617	30.34
rs4730637	A	G	0.443501	-0.0323	0.0058	3.35E-08	0.018696	0.006025	0.001914	30.36
rs2396766	A	G	0.4462	-0.0313	0.0057	4.77E-08	0.014539	0.006025	0.01583	30.15
rs1378771	T	C	0.443475	-0.0322	0.0058	3.43E-08	0.014129	0.006025	0.01903	30.84
rs12705973	A	G	0.545197	0.0311	0.0056	3.62E-08	-0.014738	0.006025	0.01444	30.85
rs12705974	T	G	0.55436	0.0315	0.0057	4.10E-08	-0.014756	0.006025	0.01433	30.54
rs12705970	C	G	0.557158	0.0324	0.0058	3.07E-08	-0.014382	0.006025	0.01698	31.21
rs4236599	T	C	0.445466	-0.0314	0.0057	4.49E-08	0.015057	0.006025	0.01246	30.35

Causal Effect of conscientiousness on OUD

Using the IVW approach as the primary two sample MR analysis was observed strong evidence of a causal effect of conscientiousness on the risk of OUD ($\beta = -0.493$; 95% CI: −0.597 to −0.389; $P = 7.8 \times 10^{-21}$). The magnitude and precision of this estimate indicate that higher genetically predicted conscientiousness is associated with a substantially lower risk of OUD.

The weighted median estimator yielded a comparable effect size ($\beta = -0.468$; 95% CI: −0.607 to −0.329; $P = 5.3 \times 10^{-11}$), supporting the robustness of the primary finding under assumptions that allow up to 50% of the instruments to be invalid. Similarly, both the weighted mode (β =

−0.467; 95% CI: −0.683 to −0.251; P = 1.2 × 10^{-3}) and simple mode (β = −0.467; 95% CI: −0.692 to −0.242; P = 1.6 × 10^{-3}) approaches demonstrated statistically significant associations in the same direction. Although the MR-Egger regression did not reach statistical significance (β = −2.487; 95% CI: −9.927 to 4.953; P = 0.526), the direction of effect was consistent with the other estimators.

Overall, the consistency in effect direction and magnitude across all five MR methods strengthens the inference that higher conscientiousness causally reduces the risk of OUD (Table 2; Figure 2).

Table 2. Mendelian randomization estimates for the effect of conscientiousness on OUD

MR method	SNPs	B	SE	95% CI	P value
Inverse variance weighted (IVW)	13	-0.493	0.053	-0.597 to -0.389	7.8 × 10^{-21}
MR-Egger regression	13	-2.487	3.796	-9.927 to 4.953	0.526
Weighted median	13	-0.468	0.071	-0.607 to -0.329	5.3 × 10^{-11}
Weighted mode	13	-0.467	0.110	-0.683 to -0.251	1.2 × 10^{-3}
Simple mode	13	-0.467	0.115	-0.692 to -0.242	1.6 × 10^{-3}

Note: β represents the log-odds change in OUD per unit increase in genetically predicted conscientiousness. IVW was considered the primary analysis. The weighted median provides consistent estimates if at least 50% of the weight derives from valid instruments. MR-Egger regression allows for directional pleiotropy under the InSIDE assumption but has lower statistical power. Mode-based estimators (simple and weighted mode) provide valid estimates when the largest cluster of instruments with similar effects is valid. SE: standard error; CI: confidence interval.

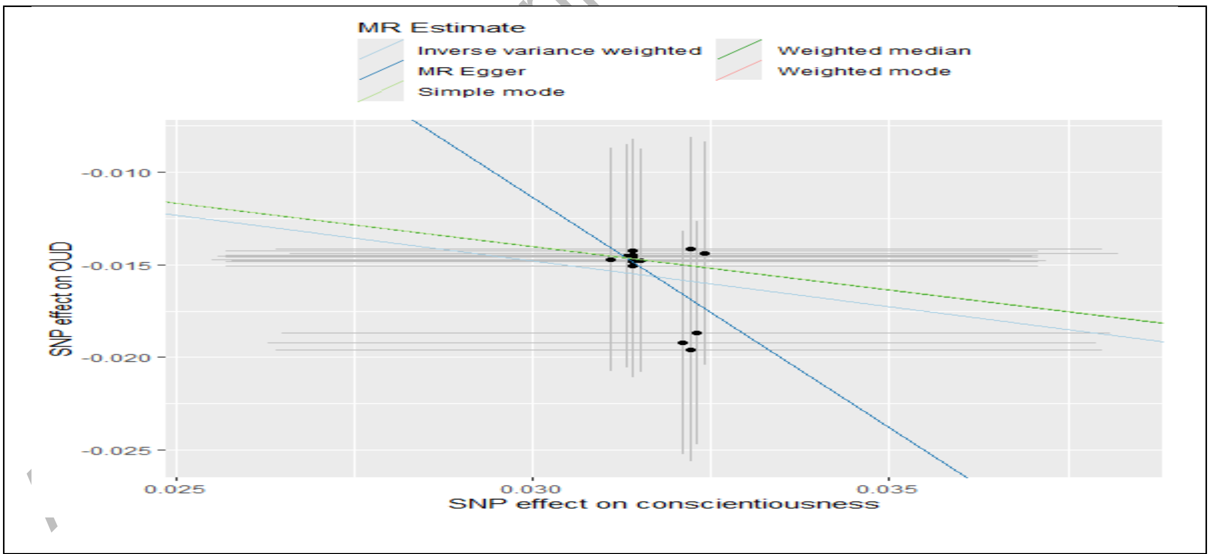

Figure 2. Scatter plot of SNP-specific associations between genetically predicted conscientiousness and OUD. Each point represents a single SNP. Regression lines correspond to IVW, MR-Egger, weighted median, weighted mode, and simple mode estimates. The overall negative slope indicates an inverse causal association.

3.3 Sensitivity Analyses

To evaluate the robustness of the primary IVW estimates and potential violations of Mendelian randomization assumptions, we performed complementary sensitivity analyses, including MR-Egger regression, leave-one-out analysis, and Cochran's Q test (Table 3).

Cochran's Q test showed no evidence of heterogeneity among SNP-specific estimates (IVW: Q = 1.22, df = 12, P = 0.999; MR-Egger: Q = 0.94, df = 11, P = 0.999), indicating consistency across genetic instruments. The MR-Egger intercept test did not detect directional pleiotropy (intercept = 0.063, SE = 0.120, P = 0.609), suggesting that horizontal pleiotropy is unlikely to have biased the causal estimates.

Overall, these findings support the robustness of the primary IVW results. MR-Egger intercept and Cochran's Q tests indicated no evidence of horizontal pleiotropy, and leave-one-out analyses confirmed the robustness of causal estimates.

Table3. Sensitivity analysis of the causal association

Analysis	Method	Q-value	Df	P-value	Intercept	SE	P-value
Heterogeneity	IVW	1.22	12	0.999	-	-	-
Heterogeneity	MR-Egger	0.94	11	0.999	0.063	0.120	0.609
Pleiotropy	MR-Egger	-	-	-	0.063	0.120	0.609

Furthermore, leave-one-out analyses demonstrated that the observed association was not disproportionately influenced by any individual genetic instrument. Iterative exclusion of each SNP produced effect estimates that remained directionally consistent and comparable in magnitude to the primary IVW estimate, indicating that the overall finding was not driven by a single variant (Figure 3).

Taken together, the absence of heterogeneity, lack of evidence for directional pleiotropy, and stability in leave-one-out analyses collectively enhance the internal validity of the Mendelian randomization framework applied in this study. These results provide converging evidence for a robust and potentially causal inverse association between genetically predicted conscientiousness and the risk of OUD.

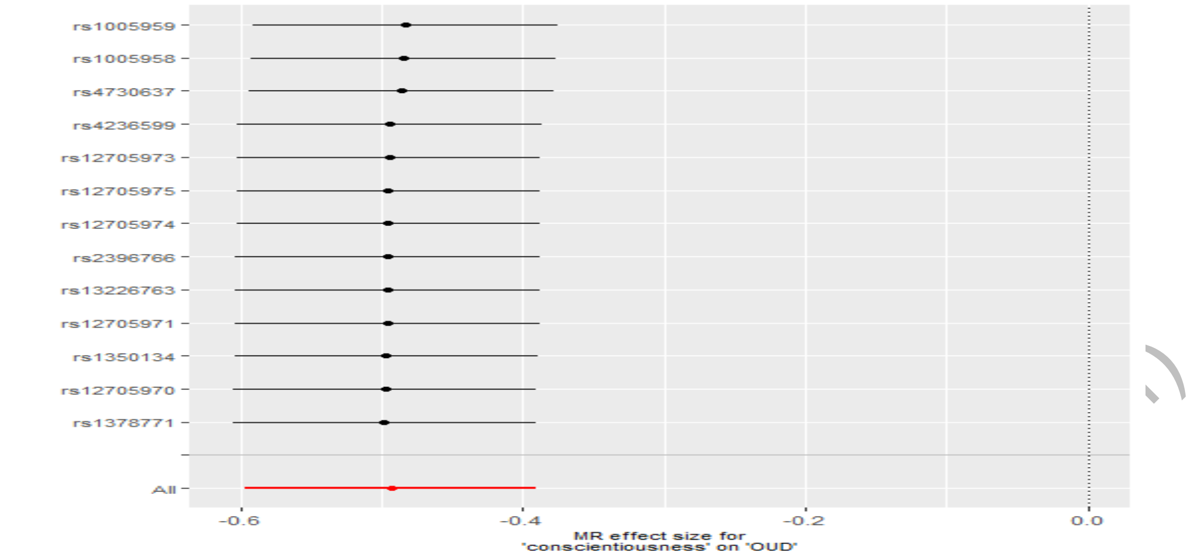

Figure 3: Leave-one-out analysis illustrating the influence of sequential SNP exclusion on the causal estimate of conscientiousness on OUD risk.

Discussion

In this two-sample MR analysis, we found strong evidence that genetically predicted conscientiousness is causally associated with a reduced risk of OUD. The IVW estimate demonstrated a highly significant protective effect ($\beta = -0.493$; 95% CI: −0.597 to −0.389; $P = 7.8 \times 10^{-21}$). This effect persisted across multiple complementary MR methods weighted median, weighted mode, and simple mode supporting the robustness of the causal inference. Although the MR-Egger estimate did not reach statistical significance, its effect direction was consistent, and formal pleiotropy tests did not indicate directional bias, suggesting that horizontal pleiotropy is unlikely to explain the observed association.

Personality traits, including conscientiousness, are highly polygenic and genetically correlated with other behavioral phenotypes, particularly externalizing dimensions such as impulsivity and risk-taking. Impulsivity shares genetic overlap with other psychiatric and substance use traits, situating it as a potential pleiotropic pathway that could influence the observed association between conscientiousness and OUD (20).

Our findings extend previous research, both genomic and epidemiological, linking personality traits to substance use outcomes. Genome-wide analyses have confirmed a polygenic architecture for personality traits, including conscientiousness, and their genetic overlap with psychiatric and behavioral phenotypes (21). Although most genetic loci explain a small portion of trait variance, personality traits have been shown to be heritable and genetically correlated with psychiatric conditions(14, 21).

Observational studies consistently find that higher conscientiousness is inversely associated with substance use and related disorders (22-24). For example, cohort studies show that individuals with higher conscientiousness exhibit lower rates of drug misuse and substance-related problems in adulthood (22). Research also suggests that individuals with higher conscientiousness tend to avoid risk-taking behaviors that predict later addiction(24). Similar patterns have been identified in longitudinal samples showing protective psychological profiles against chronic substance use (25).

Specific to opioid use, earlier observational work indicated that personality characteristics influence the likelihood of developing opioid dependence (3). One study found that individuals who used opioids but never became dependent reported higher self-directedness and self-efficacy traits conceptually aligned with conscientiousness than those with dependence (26).

In contrast, impulsivity—a related but distinct personality dimension has been repeatedly implicated as a risk factor for substance misuse in general and opioid-related misuse in particular (27, 28). Research on impulsivity facets such as urgency, lack of premeditation, and sensation seeking has shown associations with opioid misuse and OUD symptoms in clinical settings (29, 30). These findings highlight the importance of considering multidimensional personality architectures when interpreting trait associations with addiction risk.

Personality traits such as conscientiousness reflect neural processes involved in self-regulation, executive functioning, and inhibitory control (31, 32). Structural and functional neuroimaging studies have linked conscientiousness to cortical thickness and brain connectivity patterns, particularly in frontal regions associated with planning, decision-making, and behavioral regulation (33, 34).

Personality neuroscience frameworks posit that traits such as conscientiousness have underlying neural correlates reflecting coordinated activity in prefrontal cortex networks responsible for impulse control and goal-directed behavior. Impulsivity, by contrast, is characterized by reduced inhibitory control and heightened reward sensitivity, which have been linked to neurobiological mechanisms relevant to addictive behaviors (32, 35).

Although our MR design does not directly test neural mechanisms, the 13 SNPs used as instruments for conscientiousness are located within or near genes previously implicated in prefrontal and striatal brain circuits that support self-regulation. The medial prefrontal cortex (mPFC) is a key hub for conscientiousness-related traits, with its structural integrity and activation patterns closely tied to self-regulatory capacity (36) . Dopaminergic pathways bridging striatal and prefrontal regions modulate reward-based learning and impulse control, and genetic variation in these circuits influences behavioral regulation (37). Furthermore, functional variants affecting prefrontal systems have been associated with impulsivity-related phenotypes and conscientiousness (38). Collectively, this evidence suggests that genetic instruments for conscientiousness may exert their protective effect on OUD through prefrontal and striatal circuits governing executive control and reward processing. Direct imaging genetics studies are needed to confirm these pathway-specific mechanisms.

Strengths and Limitations

This study has several methodological strengths. First, the use of large, well-powered GWAS summary statistics for both conscientiousness (N = 234,880) and OUD (20,686 cases; 77,026 controls) reduces random error and enhances precision of causal estimates. Second, the two-sample MR design strengthens causal inference by minimizing confounding and reverse causation compared with traditional observational designs. Third, multiple sensitivity analyses (MR-Egger intercept, Cochran's Q, leave-one-out) confirmed the robustness of findings.

However, several limitations warrant consideration. First, personality traits are highly polygenic, and currently available GWAS capture only a modest proportion of their heritability. Second, analyses were restricted to European ancestry; therefore, results are not generalizable to non-European populations, including Iranians, without replication. Third, partial sample overlap between exposure and outcome GWAS (both include MVP participants) cannot be entirely excluded; however, strong instruments ($F > 30$) and consistent sensitivity analyses mitigate substantial bias. Fourth, residual bias due to dynastic effects or assortative mating cannot be entirely excluded. Fifth, our MR analyses assume linear, homogeneous, and monotonic effects; violations could bias estimates. Finally, although sensitivity analyses suggest minimal horizontal pleiotropy, MR cannot fully exclude pleiotropic or gene–environment interaction effects.

Conclusion

Our MR analysis provides robust genetic evidence that higher conscientiousness causally reduces the risk of opioid use disorder. These findings integrate personality psychology, behavioral genetics, and addiction epidemiology and suggest that self-regulatory traits may serve as upstream protective factors in the development of OUD. From a public health perspective, early psychological and behavioral interventions that strengthen self-regulatory capacities could complement conventional prevention strategies for opioid misuse. Future research should aim at cross-ancestry replication, finer dissection of personality subcomponents, and investigation into the neurobiological mechanisms that mediate these causal pathways.

Data availability statement

The summary-level GWAS data analyzed in this study are publicly accessible. Genetic associations for conscientiousness were obtained from Gupta et al. (2024) [MVP](14), and OUD data were sourced from Deak et al. (2022) [MVP and PGC] (15). Harmonized SNP lists and all MR analysis scripts supporting the findings of this study are available from the corresponding author upon reasonable request.

Author contributions

RK and AM were responsible for the concept and design. RK and AM assisted with carrying out the analyses. RK drafted the early version of the manuscript. AM, AH and MA jointly supervised the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that they have no commercial or financial relationships that could be construed as a potential conflict of interest with respect to the research, authorship, or publication of this study

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