

# No evidence of a causal relationship between negative emotions and glaucoma: evidence triangulation from genetic correlation, Mendelian randomisation and colocalisation

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## ABSTRACT

**Purpose** Observational studies suggest that anxiety and depression disorders have significant correlation, but these results may have been influenced by confounding factors, and negative emotions that do not meet the criteria for clinical mental disease diagnosis are more common, the evidence for this association is unclear. This study employed whole-genome linkage disequilibrium score regression (LDSC), Mendelian randomisation (MR), Bayesian colocalisation (colocalisation) to explore association between common negative emotions and glaucoma.

**Design** Bidirectional genetic associations between negative emotion and glaucoma.

**Participants** Data from UK Biobank and FinnGen R10.

**Methods** MR, whole-genome LDSC, Bayesian colocalisation.

**Main outcome measures** Genetic causal associations between negative emotion and glaucoma.

**Result** At Bonferroni-corrected levels of significance, there was no genetic correlation, causal association or shared genetic mechanism between any negative emotions and glaucoma, except for depression, which showed a genetic link but no causal evidence.

**Conclusions** Depression, anxiety and eight other common negative emotions may not be causally associated with glaucoma and there may be no genetic correlation between them.

## INTRODUCTION

Glaucoma is a common ophthalmic disease that often leads to irreversible vision loss and ranks as the second leading cause of blindness globally.<sup>1–3</sup> In 2020, the prevalence of primary open-angle glaucoma (POAG) in Europe was estimated at 2.60%,<sup>4</sup> with an increasing trend observed annually. It is projected that by 2040, the global number of patients with glaucoma will rise to 111.8 million.<sup>5</sup> Challenges persist in the prevention, diagnosis and treatment of glaucoma. While current surgical therapies effectively mitigate vision loss caused by glaucoma, identifying new risk factors to

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Observational studies have suggested links between depression, anxiety and glaucoma, but these associations may reflect bias or confounding, and the role of common negative emotions remains unclear.

## WHAT THIS STUDY ADDS

⇒ Using genetic correlation, Mendelian randomisation and colocalisation analyses from large genome-wide association study datasets, we found no evidence of a causal relationship or shared genetic mechanisms between negative emotions and glaucoma.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings indicate that negative emotions are unlikely to be direct risk factors for glaucoma, suggesting clinical care should prioritise established risk factors and quality-of-life management, while future studies should confirm these results in larger and more diverse populations.

pre-emptively target high-risk populations remains crucial.<sup>1</sup> Glaucoma can be classified based on aetiology into primary open-angle, angle-closure and congenital forms, and these can also be further subdivided according to the different characteristics.<sup>6</sup> This categorisation underscores the complexity and diversity of glaucoma; however, previous studies have primarily focused on a limited number of types or overall risk factors, leaving characteristics of more specific subtypes largely unexplored.

Emotions possess the capability to regulate various physiological systems such as the endocrine and immune systems.<sup>7</sup> Consequently, fluctuations in emotions have been associated with numerous diseases including psychiatric disorders, neurological conditions and cancers.<sup>8–10</sup> Psychological disorders, particularly depression disorders and anxiety

disorders, have garnered substantial support from observational studies and genetic analyses for their association with glaucoma.<sup>11–16</sup> However, the relationship between negative emotions, which do not meet clinical diagnostic criteria for disease, and glaucoma remains unclear and causative links have yet to be established. Given the complexity of human negative emotions and diseases, and the severity of glaucoma, further research into the associations between different types of negative emotions and glaucoma risk is warranted.

Previous studies on emotions and glaucoma have predominantly relied on observational research, and their results suggest that there may be a significant correlation between the two, but observational research may be subject to biases and has not comprehensively covered all types of glaucoma.<sup>11 12 14 16</sup> Therefore, investigating causal relationships between different phenotypes of glaucoma and various negative emotions is essential for a more comprehensive understanding of the links between emotions and glaucoma. Increasingly, researchers are combining genetic correlation analyses with MR or MR with colocalisation analyses as frameworks to elucidate causal relationships.<sup>17–20</sup> Linkage disequilibrium score regression (LDSC) is a method to assess genetic correlation from summary statistics of genome-wide association study (GWAS) that is unaffected by sample overlap.<sup>21</sup> MR

is a method unaffected by environmental confounding and reverse causation biases, estimating correlations and causal relationships between traits using statistical methods from GWAS.<sup>22 23</sup> Bayesian colocalisation analysis identifies whether two or more traits or diseases share the same genetic variants as potential causal variants.<sup>24</sup> Thus, this study integrates evidence from these three approaches to comprehensively infer the genetic causal relationship between negative emotions and glaucoma.

This study used summary data from the UK Biobank (UKB) GWAS on eight common human negative emotions as exposure (table 1). Simultaneously, summary data from the FinnGen Consortium GWAS on glaucoma served as the outcome (table 1). Through MR, LDSC and colocalisation methods, the study investigates the causal relationship and genetic correlation between negative emotions and glaucoma. Besides, we conducted post hoc MR to explore their reverse causal relationship.

## METHODS

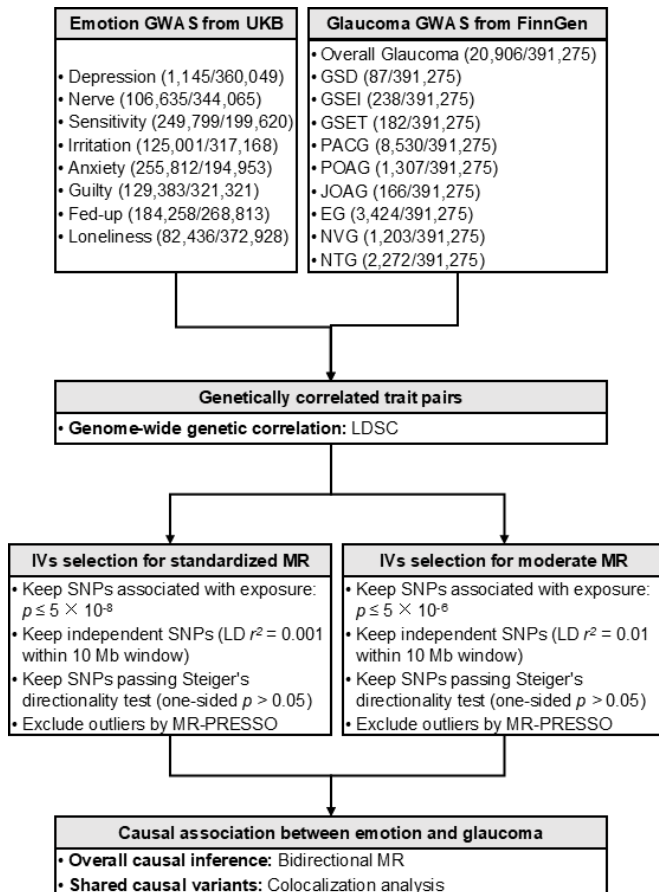
### Study design

This study used GWAS data from European populations to explore potential causal relationships between eight types of negative emotions and the risk of 10 types of glaucoma. The eight negative emotions examined were depression, irritation, sensitivity, anxiety, fed-up feeling,

**Table 1** Genome-wide association study data source and heritability

Traits	Data source	Number of case	Number of control	Total number	Build	Race	h <sup>2</sup>
Depression	UKB	1145	360049	361 194	HG19/GRCh37	European	0.0047 (0.0012)
Nervousness	UKB	106635	344065	450 700	HG19/GRCh37	European	0.0625 (0.0032)
Sensitivity	UKB	249799	199620	449 419	HG19/GRCh37	European	0.0607 (0.003)
Irritation	UKB	125001	317168	442 169	HG19/GRCh37	European	0.0661 (0.0035)
Anxiety	UKB	255812	194953	450 765	HG19/GRCh37	European	0.0758 (0.0038)
Guilty	UKB	129383	321321	450 704	HG19/GRCh37	European	0.0508 (0.0025)
Fed-up	UKB	184258	268813	453 071	HG19/GRCh37	European	0.0694 (0.0032)
Loneliness	UKB	82436	372928	455 364	HG19/GRCh37	European	0.0367 (0.0021)
Overall glaucoma	FinnGen	20906	391 275	412 181	HG19/GRCh37	European	0.0319 (0.0028)
Glaucoma secondary to drugs	FinnGen	87	391 275	391 362	HG19/GRCh37	European	0.0011 (0.0011)
Glaucoma secondary to eye inflammation	FinnGen	238	391 275	391 513	HG19/GRCh37	European	0.0002 (0.0011)
Glaucoma secondary to eye trauma	FinnGen	182	391 275	391 457	HG19/GRCh37	European	0.0003 (0.0011)
Primary angle-closure glaucoma	FinnGen	8530	391 275	399 805	HG19/GRCh37	European	0.0064 (0.0013)
Primary open-angle glaucoma	FinnGen	1307	391 275	392 582	HG19/GRCh37	European	0.0246 (0.0026)
Juvenile open-angle glaucoma	FinnGen	166	391 275	391 411	HG19/GRCh37	European	0.002 (0.001)
Exfoliative glaucoma	FinnGen	3424	391 275	395 149	HG19/GRCh37	European	0.0117 (0.005)
Neovascular glaucoma	FinnGen	1203	391 275	392 478	HG19/GRCh37	European	0.0019 (0.0012)
Normotensive glaucoma	FinnGen	2272	391 275	393 547	HG19/GRCh37	European	0.0116 (0.0018)

h<sup>2</sup>, heritability; UKB, UK Biobank.



**Figure 1** An overview of our analysis. EG, exfoliative glaucoma; GSD, glaucoma secondary to drugs; GSEI, glaucoma secondary to eye inflammation; GSET, glaucoma secondary to eye trauma; GWAS, genome-wide association study; IV, instrumental variable; JOAG, juvenile open-angle glaucoma; LD, linkage disequilibrium; LDSC, linkage disequilibrium score regression; MR, mendelian randomisation; MR-PRESSO, mendelian randomisation pleiotropy residual sum and outlier; NTG, normotensive glaucoma; NVG, neovascular glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma; SNP, single nucleotide polymorphism; UKB, UK Biobank.

nervousness, loneliness and guilt (table 1). The types of glaucoma included were POAG, glaucoma secondary to drug use, glaucoma secondary to eye inflammation (GSEI), glaucoma secondary to eye trauma (GSET), exfoliation glaucoma, juvenile open-angle glaucoma, neovascular glaucoma, normal-tension glaucoma, primary angle-closure glaucoma and POAG (table 1).

Whole-genome LDSC was employed to assess the genetic correlation between negative emotions and glaucoma. Standard two-sample MR analysis was conducted to elucidate the causal relationship between negative emotions and the risk of glaucoma. Bayesian colocalisation analysis was used to explore shared local genetic structures between negative emotions and glaucoma, and to evaluate whether the observed causal relationships were likely to be incidental. Figure 1 outlines the study's

analytical design and procedures. This study adheres to the Strengthening the Reporting of Observational Studies in Epidemiology-MR guidelines<sup>25</sup> (online supplemental table S1).

### Data collection

The GWAS summary statistics used in this study were obtained from publicly available databases. GWAS data concerning common human negative emotions were derived from the UKB, with sample sizes ranging from 345 231 to 361 194 individuals (table 1). GWAS summary data for various types of glaucoma were obtained from FinnGen release R10. Detailed disease definitions can be found in the corresponding databases.

Given that glaucoma does not exhibit gender differences, stratification by sex was not applied to avoid collider bias. Regarding age, individuals with JOAG were aged between 4 and 40 years, while other glaucoma cases were not stratified by age. Emotion-related exposures were based on self-reported questionnaire data and treated as binary variables (presence vs absence of the trait). All human data were obtained with ethical approval as part of their original studies.

Furthermore, for defining emotions, we relied on self-reported results from questionnaire measurements, which were as binary exposure (present or absent), and glaucoma was also reported as binary exposure. For binary variables (presence vs absence of the trait), we could only test the causal null hypothesis, because the causal estimates do not have a clear interpretation.<sup>21</sup> All human data were obtained with ethical approval as part of their original experiments.

### Whole-genome genetic correlation

LDSC was employed to calculate single nucleotide polymorphism (SNP) heritability and assess the genetic correlation between negative emotions and glaucoma.<sup>22</sup> Whole-genome LDSC calculates genetic correlations by considering the effects of all SNPs, regardless of whether individual SNPs reach genome-wide significance. SNPs that were not merged with common autosomal SNPs in HapMap3 and SNPs with minor allele frequency  $<0.01$  were excluded, excluding the MHC region.<sup>19 20</sup> Study results are presented as genetic correlations with SE. If traits exhibit low heritability for one or both traits, LDSC analysis may not yield conclusive results.<sup>20 26</sup> A  $p < 0.05$  indicates potential genetic correlation.

### MR analysis

In the primary analysis, SNP clumping was performed using PLINK software (<https://www.cog-genomics.org/plink/>) to extract instrumental variables (IVs) highly associated with negative emotions ( $p \leq 5 \times 10^{-8}$ ) and independent ( $kb=10\,000$ ,  $r^2=0.001$ ). LD proxies for clumping were defined using the 1000 Genomes European samples. Additionally, a secondary analysis relaxed the criteria for genetic IVs, extracting those significantly associated with negative emotions ( $p \leq 5 \times 10^{-6}$ ) and independent

( $kb=10\,000$ ,  $r^2=0.01$ ). Steiger's directional test was used to exclude IVs with directional pleiotropy, and MR-PRESSO was employed to assess IV horizontal pleiotropy and remove outliers.

For estimating causal effects, seven main MR methods were employed.<sup>27</sup> The inverse variance-weighted (IVW) or Wald ratio model served as the primary assessment method for causal relationships. The Wald ratio was used to estimate causal effects when the number of IVs was 1. When the number of IVs exceeded 1, IVW was considered the primary evaluation method.<sup>28–29</sup> Additionally, weighted median (WM), MR-Egger, Bayesian weighted MR and robust adjusted profile score (RAPS) analyses were used to enhance result credibility.<sup>30–33</sup> Ideally, in the absence of horizontal pleiotropy affecting outcomes through multiple pathways via genetic variants, IVW analysis results are considered reliable. In the presence of horizontal pleiotropy, MR-Egger regression provided estimates, and additional scrutiny was applied to MR-Egger results to mitigate the influence of outliers.<sup>28</sup> Furthermore, heterogeneity arising from shared biological pathways involving unmeasured confounders between exposure and outcome was assessed using Cochran's Q test on genetic IVs. If heterogeneity existed, random-effects IVW analysis was considered reliable.<sup>30</sup> Moreover, WM was capable of identifying genuine causal relationships by measuring the WM of IV ratios and using only the largest IV group to estimate causal effects, ensuring statistical reliability even in the presence of ineffective IVs.<sup>30</sup> Consistency of results between simple mode and weighted mode further bolstered result reliability.

### Secondary MR analysis

In the secondary MR analysis, IVs selected with less stringent criteria as described ( $p=5\times 10^{-8}$ ,  $r^2=0.01$ ,  $kb=10\,000$ ) were used. While this approach enhances statistical power, it may also introduce weak instrument bias, potentially violating MR assumptions.<sup>30</sup> Therefore, in the secondary MR analysis, the RAPS method was employed to correct for biases introduced by weak instruments.

### Post hoc MR analysis

To assess the possibility of reverse causation, SNPs significantly associated with glaucoma were selected based on the screening criteria. Subsequently, IVW, MR-Egger, WM, simple mode, weighted mode and RAPS methods were employed to analyse the reverse causal relationships between different types of glaucoma and negative emotions. Both main and less stringent secondary analyses were conducted simultaneously to explore additional potential outcomes.

### Statistical power

The strength of each genetic instrument was estimated using the F-statistic ( $F=\beta^2/SE^2$ ). An F-statistic  $>10$  indicates sufficient strength of the IV in relation to the exposure, ensuring that MR analysis results are robust

against weak instrument bias.<sup>31</sup> All IVs used in this study across all methods had F-statistics  $>10$ .

### Multiple testing correction

For genetic correlation analysis, MR analysis and coloc analysis, a  $p<0.05$  was considered nominally significant. However, to correct for multiple comparisons, Bonferroni correction was applied. P values corrected to maintain significance were adjusted to  $p<6.25\times 10^{-4}$  ( $0.05/8\times 10$ ), indicating evidence suggestive of potential causal relationships.

### Sensitivity analysis

To ensure the reliability of MR results, sensitivity analyses were conducted to identify and address potential pleiotropy and heterogeneity. In this study, Cochran's Q-test and MR-Egger regression were used for sensitivity analysis. Cochran's Q-test evaluated the presence of heterogeneity among IVs, with  $p>0.05$  indicating no significant heterogeneity.<sup>32</sup> MR-Egger regression assessed horizontal pleiotropy, with  $p<0.05$  suggesting the presence of horizontal pleiotropy.<sup>17–33</sup>

### Bayesian colocalisation analysis

Coloc analysis was employed to assess the colocalisation of causal genetic variants shared between two correlated traits and IVs. This method tested five mutually exclusive hypotheses: (1) neither trait has a causal genetic variant (H0); (2) only trait 1 has a causal genetic variant (H1); (3) only trait 2 has a causal genetic variant (H2); (4) each trait has two distinct causal genetic variants (H3); (5) both traits share the same causal genetic variant (H4). Posterior probabilities (PP) quantified the evidence for each hypothesis and were expressed as PPH0, PPH1, PPH2, PPH3 and PPH4.<sup>34</sup> For MR, regions within 500 kb upstream and downstream of each trait were analysed, and the average PPH4 across all regions was considered the final coloc result. PPH4  $>0.75$  was considered evidence suggestive of causal genetic variants shared between the two traits.

### Statistical software

All analyses were conducted using R (V.4.3.1). IVW method, sensitivity analysis (excluding MR-RAPS) and Steiger's directional test were implemented using the 'TwoSampleMR' package (V.0.5.7). MR-RAPS analysis was performed using the 'mr.raps' package (V.0.2). Bayesian colocalisation analysis used the 'coloc' package (V.5.2.3). LDSC analysis was conducted using LDSC V.1.0.1 software.

### Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

## RESULT

### Genetic correlation between negative emotions and glaucoma

We employed LDSC to explore the results of the genetic correlation analysis between negative emotions

**Table 2** The genetic correlations between negative emotion and glaucoma analysed by LDSC.

	Depression			Fed-up			...			Anxiety		
	$r_g$	SE	P value	$r_g$	SE	P value	...	...	...	$r_g$	SE	P value
Overall glaucoma	0.0457	0.0495	0.3555	0.0217	0.0173	0.209	...	...	...	0.0577	0.0166	0.0005
GSD	-	-	-	-	-	-	...	...	...	-	-	-
GSEI	-	-	-	-	-	-	...	...	...	-	-	-
GSET	-	-	-	-	-	-	...	...	...	-	-	-
EG	0.0643	0.0828	0.4377	-0.0114	0.0253	0.6519	...	...	...	0.0153	0.0245	0.5305
JOAG	-	-	-	-	-	-	...	...	...	-	-	-
NVG	0.0536	0.2713	0.8433	0.0711	0.0969	0.463	...	...	...	0.0646	0.1025	0.5285
NTG	0.0845	0.0737	0.2519	-0.0607	0.027	0.0246	...	...	...	0.0405	0.0245	0.0973
PACG	0.1489	0.0998	0.1357	0.0104	0.0323	0.7477	...	...	...	0.0004	0.0298	0.9881
POAG	0.1189	0.0516	0.0213	0.0139	0.0186	0.4543	...	...	...	0.0441	0.0179	0.0137

For details, see online supplemental table S2.

$r_g$  is the genetic correlation between two traits.

-, no instrumental variables for analysis; EG, exfoliative glaucoma; GSD, glaucoma secondary to drug; GSEI, glaucoma secondary to eye inflammation; GSET, glaucoma secondary to eye trauma; JOAG, juvenile open-angle glaucoma; NTG, normotensive glaucoma; NVG, neovascular glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma.

and glaucoma (table 2). We found that depression has significant genetic correlation with overall glaucoma ( $p=5\times 10^{-4}$ ).

### MR analysis results

Following the methods described, MR analysis was conducted on eight types of negative emotions and 10 types of glaucoma, using all eligible IVs identified. The number of IVs considered ranged from 1 to 18, with F-statistics ranging from 15.35 to 72.11. The results reveal that there is no statistically significant causal relationship between negative emotions and the risk of glaucoma (table 3, online supplemental file 4). Detailed results for all methods are provided in online supplemental table S2, online supplemental file 5. This suggests that there is no evidence of a causal relationship between negative emotions and glaucoma. Sensitivity analyses did not reveal horizontal pleiotropy or heterogeneity (online supplemental table S3, online supplemental file 6), supporting the reliability of the IVW or Wald ratio analysis results.

### Post hoc MR analysis results

Using a screening threshold of  $p=5\times 10^{-8}$ , the statistical values for all IVs ranged from 21.54 to 361.98, with IV counts ranging from 2 to 26. Results suggest potential associations between EG and loneliness (IVW:  $p=0.037$ , OR 1.003, 95% CI 1.000, 1.006), GSET and guilt (IVW:  $p=0.004$ , OR 1.004, 95% CI 1.001, 1.006), GSEI and anxiety (IVW:  $p=0.025$ , OR 0.996, 95% CI 0.995, 1.000) and GSEI and irritation (IVW:  $p=0.019$ , OR 0.996, 95% CI 0.994, 0.999) (table 4). However, after Bonferroni correction for multiple testing, these p values were no longer significant. Sensitivity analysis supported the reliability of these findings, showing no evidence of horizontal pleiotropy or heterogeneity (online supplemental table S8).

When the threshold was set to  $p=5\times 10^{-6}$  for secondary analysis, three to 125 IVs were selected for different traits, with F-statistics ranging from 21.54 to 85.39. Consistent with the main analysis, results did not show significant associations between glaucoma and negative emotions after Bonferroni correction (online supplemental table S9). Detailed results for different methods are provided in online supplemental table S10. Sensitivity analysis further supported the reliability of these findings (online supplemental table S11). Thus, it is inferred that there may be no reverse association between glaucoma and negative emotions.

### Bayesian colocalisation analysis

In the Bayesian colocalisation analysis using the average PPH value, no shared causal genetic variants were found between negative emotions as exposure and glaucoma as outcome (PPH4 <75%; table 3). Similarly, when glaucoma was considered as exposure and negative emotions as outcome, no shared causal genetic variants were identified (PPH4 <75%; table 4). This suggests that there may be no shared genetic mechanisms underlying negative emotions and glaucoma. Detailed results of all colocalisation analyses can be found in online supplemental table S12.

### DISCUSSION

In this study focusing on the risk of eight types of negative emotions and 10 types of glaucoma, we found no statistically significant genetic correlation or causal relationship between negative emotions and glaucoma. Our analyses using LDSC, MR and colocalisation failed to provide genetic evidence linking negative emotions with glaucoma. Even with a more lenient threshold in MR analysis, we still did not identify any potential causal relationships.

**Table 3** The IVW result of main MR analysis

Exposure	Outcome	No. of SNP	P value	OR (95% CI)	CO <sup>+</sup> PPH4
Depression	Overall glaucoma	1	0.825	1.62e-03 (2.86e-28, 9.21e+21)	5.32e-02
Depression	GSD	1	0.836	1.21e-02 (7.81e-21, 1.88e+16)	2.92e-04
Depression	GSEI	4	0.931	0.63 (1.71e-05, 2.31e+04)	4.61e-03
Depression	GSET	3	0.841	2.35 (5.39e-04, 1.03e+04)	4.40e-04
Depression	JOAG	3	0.828	0.37 (4.64e-05, 2.95e+03)	2.94e-04
Depression	NVG	1	0.527	5.15e+31 (3.37e-67, 7.86e+129)	6.70e-02
Depression	NTG	1	0.312	1.83e-37 (1.29e-108, 2.60e+34)	7.21e-02
Depression	PACG	1	0.651	1.65e-21 (1.66e-111, 1.63e+69)	7.20e-02
Depression	POAG	1	0.595	4.16e-11 (1.99e-49, 8.71e+27)	6.57e-02
Fed-up	EG	8	0.942	1.09 (9.65e-02, 1.24e+01)	1.51e-02
Fed-up	Overall glaucoma	12	0.404	7.04e-01 (3.08e-01, 1.61)	9.27e-03
Fed-up	GSD	1	0.970	2.16 (1.60e-17, 2.91e+17)	4.99e-02
Fed-up	GSEI	1	0.930	3.39 (5.41e-12, 2.12e+12)	3.66e-02
Fed-up	GSET	2	0.880	2.28e-01 (1.09e-09, 4.76e+07)	3.96e-02
Fed-up	JOAG	2	0.979	1.34 (4.43e-10, 4.03e+09)	3.38e-02
Fed-up	NVG	6	0.937	1.2 (1.20e-02, 1.21e+02)	2.12e-02
Fed-up	NTG	7	0.756	0.6 (2.41e-02, 1.50e+01)	1.65e-02
Fed-up	PACG	5	0.969	1.1 (8.22e-03, 1.48e+02)	1.69e-02
Fed-up	POAG	11	0.299	4.94e-01 (1.30e-01, 1.87)	1.13e-02
Guilty	EG	4	0.371	8.23 (8.16e-02, 8.29e+02)	2.76e-02
Guilty	Overall glaucoma	7	0.500	1.66 (0.38, 7.27)	3.06e-02
Guilty	GSD	1	0.859	116 (1.80e-21, 7.44e+24)	5.52e-02
Guilty	GSEI	1	0.784	1.76e-02 (4.80e-15, 6.45e+10)	3.24e-02
Guilty	GSET	1	0.986	1.55 (7.38e-22, 3.25e+21)	4.85e-02
Guilty	JOAG	1	0.946	3.07e-01 (3.75e-16, 2.52e+14)	3.51e-02
Guilty	NVG	3	0.705	4.79 (1.43e-03, 1.61e+04)	2.47e-02
Guilty	NTG	2	0.787	3.73e-01 (2.86e-04, 4.85e-02)	2.17e-02
Guilty	PACG	1	0.821	1.47e-01 (8.72e-09, 2.47e+06)	3.46e-02
Guilty	POAG	5	0.397	2.84 (2.53e-01, 3.19e+01)	3.14e-02
Irritation	EG	11	0.799	1.34 (1.42e-01, 1.26e+01)	1.51e-02
Irritation	Overall glaucoma	15	0.147	1.92 (7.96e-01, 4.63)	2.47e-02
Irritation	GSD	3	0.962	1.84 (2.39e-11, 1.42e+11)	4.94e-02
Irritation	GSEI	2	0.939	4.93e-01 (5.75e-09, 4.22e+07)	4.33e-02
Irritation	GSET	5	0.955	1.5 (1.24e-06, 1.80e+06)	4.71e-02
Irritation	JOAG	2	0.976	1.39 (7.46e-10, 2.58e+09)	4.30e-02
Irritation	NVG	6	0.805	5.35e-01 (3.76e-03, 76.1)	1.93e-02
Irritation	NTG	10	0.502	2.72 (1.46e-01, 50.6)	1.34e-02
Irritation	PACG	9	0.740	1.96 (3.64e-02, 1.06e+02)	2.01e-02
Irritation	POAG	11	0.142	2.96 (6.95e-01, 12.6)	1.03e-02
Loneliness	EG	1	0.711	5.96 (4.75e-04, 7.47e+04)	9.25e-03
Loneliness	Overall glaucoma	1	0.254	0.11 (2.46e-03, 4.90)	8.00e-03
Loneliness	GSD	1	0.832	503 (5.05e-23, 5.01e+27)	3.61e-02
Loneliness	GSEI	2	0.670	177 (8.10e-09, 3.86e+12)	3.35e-02
Loneliness	GSET	3	0.888	0.126 (3.23e-14, 4.89e+11)	1.33e-02
Loneliness	JOAG	2	0.982	1.48 (2.70e-15, 8.14e+14)	2.87e-02
Loneliness	NVG	1	0.883	3.11 (8.62e-07, 1.12e+07)	1.65e-02
Loneliness	NTG	2	0.159	293 (1.08e-01, 7.93e+05)	1.92e-02

Continued

**Table 3** Continued

Exposure	Outcome	No. of SNP	P value	OR (95% CI)	CO* PPH4
Loneliness	PACG	1	0.831	0.21 (1.25e-07, 3.54e+05)	2.31e-02
Loneliness	POAG	2	0.940	0.784 (1.40e-03, 4.40e+02)	9.39e-03
nervousness	EG	15	0.902	0.883 (1.22e-01, 6.38)	1.29e-02
nervousness	Overall glaucoma	17	0.420	1.39 (6.27e-01, 3.06)	1.39e-02
nervousness	GSD	4	0.968	0.568 (5.98e-13, 5.40e+11)	4.68e-02
nervousness	GSEI	4	0.888	0.411 (1.77e-06, 9.55e+04)	2.38e-02
nervousness	GSET	1	0.794	84.6 (3.00e-13, 2.38e+16)	3.82e-02
nervousness	JOAG	5	0.963	0.708 (3.69e-07, 1.36e+06)	3.99e-02
nervousness	NVG	10	0.983	1.04 (2.03e-02, 5.36e+01)	1.88e-02
nervousness	NTG	11	0.822	0.715 (3.87e-02, 1.32e+01)	1.82e-02
nervousness	PACG	7	0.860	0.676 (8.76e-03, 5.22e+01)	2.03e-02
nervousness	POAG	12	0.143	0.345 (8.31e-02, 1.43)	5.77e-02
Sensitivity	EG	5	0.317	4.67 (2.28e-01, 9.59e+01)	1.48e-02
Sensitivity	Overall glaucoma	15	0.250	0.643 (3.03e-01, 1.37)	1.05e-02
Sensitivity	GSD	1	0.907	10.6 (7.11e-17, 1.59e+18)	4.43e-02
Sensitivity	GSEI	5	0.977	0.846 (1.07e-05, 6.67e+04)	3.45e-02
Sensitivity	GSET	3	0.914	2.63 (5.82e-08, 1.19e+08)	4.30e-02
Sensitivity	JOAG	3	0.994	0.939 (4.22e-08, 2.09e+07)	3.31e-02
Sensitivity	NVG	7	0.701	0.398 (3.61e-03, 4.39e+01)	2.32e-02
Sensitivity	NTG	9	0.812	1.42 (7.75e-02, 2.62e+01)	1.57e-02
Sensitivity	PACG	9	0.996	0.991 (2.20e-02, 4.47e+01)	1.85e-02
Sensitivity	POAG	13	0.636	0.742 (2.16e-01, 2.55e)	8.67e-03
Anxiety	EG	16	0.644	0.68 (1.32e-01, 3.50e)	1.30e-02
Anxiety	Overall glaucoma	18	0.318	1.43 (7.10e-01, 2.87e)	8.86e-03
Anxiety	GSD	2	0.947	2.59 (1.58e-12, 4.26e+12)	5.04e-02
Anxiety	GSEI	2	0.899	0.425 (8.11e-07, 2.23e+05)	3.18e-02
Anxiety	GSET	4	0.900	2.07 (2.54e-05, 1.68e+05)	3.76e-02
Anxiety	JOAG	4	0.722	0.0846 (1.04e-07, 6.87e+04)	4.27e-02
Anxiety	NVG	8	0.896	1.3 (2.59e-02, 6.53e+01)	2.21e-02
Anxiety	NTG	17	0.679	0.668 (9.87e-02, 4.52)	1.64e-02
Anxiety	PACG	6	0.491	4.14 (7.29e-02, 2.35e+02)	1.81e-02
Anxiety	POAG	15	0.696	0.788 (2.39e-01, 2.60)	1.04e-02

The average of all regions of PPH4 is considered as the final colocalisation result.

CO\*, colocalisation analysis; EG, exfoliative glaucoma; GSD, glaucoma secondary to drug; GSEI, glaucoma secondary to eye inflammation; GSET, glaucoma secondary to eye trauma; IVW, inverse variance-weighted; JOAG, juvenile open-angle glaucoma; NTG, normotensive glaucoma; NVG, neovascular glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma.

This suggests that negative emotions may not causally influence the risk of glaucoma.

Previous MR studies have explored causal relationships between mental disorders such as depression and glaucoma.<sup>35 36</sup> However, we argue that everyday emotions like depression, loneliness and other negative feelings may not meet the clinical threshold but could still contribute to disease onset.<sup>12 37</sup> Furthermore, we hypothesised that other negative emotions, such as anger and isolation, which could influence internal secretion, might have relationship with glaucoma. Therefore, we included a broader range of non-pathological emotional states in our analysis. Our findings contradict previous cohort

and observational studies reporting associations between mood disorders and the risk of glaucoma.<sup>11 12 14</sup> Considering potential mechanisms through which emotions might trigger disease and our experimental results, we suggest that emotions are not direct aetiological factors for glaucoma.<sup>38 39</sup> Similarly, disease occurrence does not directly lead to changes in emotional states. The observed high prevalence of glaucoma associated with emotions in clinical settings might be influenced by other factors rather than direct emotional links. Future research should investigate common risk factors or confounding factors such as risky behaviours, intraocular pressure, blood pressure, cardiovascular diseases, etc, to determine

**Table 4** The IVW result of main post hoc MR analysis

Exposure	Outcome	No. of SNP	P value	OR (95% CI)	CO <sup>+</sup> PPH4
EG	Fed-up	5	0.335	1.001 (0.999, 1.004)	1.17e-03
EG	Guilty	5	0.686	1.001 (0.998, 1.004)	1.52e-02
EG	Irritation	5	0.370	1.001 (0.999, 1.003)	1.14e-03
EG	Loneliness	5	0.037	1.003 (1.000, 1.006)	1.96e-02
EG	Nervousness	5	0.998	1 (0.998, 1.002)	2.14e-03
EG	Sensitivity	5	0.209	1.002 (0.999, 1.006)	2.17e-03
EG	Anxiety	5	0.768	1 (0.997, 1.002)	1.51e-03
Overall glaucoma	Depression	26	0.821	1 (0.999, 1.001)	3.00e-04
Overall glaucoma	Fed-up	23	0.497	1.003 (0.994, 1.012)	4.28e-03
Overall glaucoma	Guilty	24	0.788	0.999 (0.992, 1.006)	2.65e-03
Overall glaucoma	Irritation	25	0.331	1.004 (0.996, 1.012)	3.27e-03
Overall glaucoma	Loneliness	26	0.374	1.003 (0.997, 1.009)	4.26e-03
Overall glaucoma	Nervousness	23	0.870	1.001 (0.993, 1.009)	2.01e-03
Overall glaucoma	Sensitivity	26	0.798	0.999 (0.991, 1.007)	3.28e-03
Overall glaucoma	Anxiety	24	0.397	1.003 (0.996, 1.010)	1.63e-03
GSEI	Depression	4	0.843	1 (1.000, 1.001)	4.17e-03
GSEI	Fed-up	4	0.675	0.999 (0.995, 1.003)	4.73e-02
GSEI	Guilty	4	0.791	0.999 (0.996, 1.003)	9.17e-03
GSEI	Irritation	4	0.019	0.996 (0.994, 0.999)	2.41e-03
GSEI	Loneliness	4	0.416	1.001 (0.999, 1.004)	6.12e-03
GSEI	Nervousness	4	0.099	0.998 (0.995, 1.000)	8.24e-03
GSEI	Sensitivity	4	0.739	0.999 (0.996, 1.003)	8.44e-02
GSEI	Anxiety	4	0.025	0.996 (0.993, 1.000)	3.86e-02
GSET	Depression	5	0.992	1 (1.000, 1.000)	9.58e-03
GSET	Fed-up	5	0.988	1 (0.997, 1.003)	2.35e-03
GSET	Guilty	5	0.004	1.004 (1.001, 1.006)	2.89e-03
GSET	Irritation	5	0.357	1.001 (0.999, 1.004)	2.92e-03
GSET	Loneliness	5	0.364	0.999 (0.997, 1.001)	1.86e-03
GSET	Nervousness	5	0.832	1 (0.997, 1.002)	6.96e-03
GSET	Sensitivity	5	0.505	0.999 (0.996, 1.002)	2.06e-03
GSET	Anxiety	5	0.714	0.999 (0.997, 1.002)	6.37e-03
JOAG	Depression	3	0.760	1 (1.000, 1.001)	3.97e-04
JOAG	Fed-up	3	0.778	0.999 (0.990, 1.007)	2.59e-03
JOAG	Guilty	3	0.535	0.999 (0.995, 1.003)	1.85e-03
JOAG	Irritation	3	0.985	1 (0.996, 1.004)	2.27e-03
JOAG	Loneliness	3	0.792	0.999 (0.994, 1.005)	2.17e-03
JOAG	Nervousness	3	0.949	1 (0.996, 1.003)	1.97e-03
JOAG	Sensitivity	3	0.564	1.001 (0.997, 1.005)	2.86e-03
JOAG	Anxiety	3	0.800	0.999 (0.995, 1.004)	2.66e-03
NVG	Depression	2	0.717	1 (0.999, 1.002)	6.49e-04
NVG	Fed-up	2	0.603	1.002 (0.995, 1.009)	4.04e-03
NVG	Guilty	2	0.699	0.999 (0.992, 1.005)	2.89e-03
NVG	Irritation	2	0.597	0.998 (0.990, 1.006)	1.99e-03
NVG	Loneliness	2	0.677	0.999 (0.993, 1.004)	1.01e-02
NVG	Nervousness	2	0.631	1.002 (0.995, 1.008)	1.08e-03
NVG	Sensitivity	2	0.610	0.998 (0.991, 1.005)	2.26e-03
NVG	Anxiety	2	0.605	1.002 (0.995, 1.009)	7.23e-04

Continued

**Table 4** Continued

Exposure	Outcome	No. of SNP	P value	OR (95% CI)	CO <sup>+</sup> PPH4
NTG	Depression	3	0.198	1 (1.000, 1.001)	8.86e-05
NTG	Fed-up	3	0.327	0.997 (0.991, 1.003)	8.04e-04
NTG	Guilty	3	0.358	1.003 (0.997, 1.008)	1.29e-03
NTG	Irritation	3	0.945	1 (0.987, 1.013)	1.99e-02
NTG	Loneliness	3	0.661	0.999 (0.992, 1.005)	8.91e-04
NTG	Nervousness	3	0.084	0.995 (0.990, 1.001)	1.61e-03
NTG	Sensitivity	3	0.282	1.007 (0.994, 1.021)	1.48e-01
NTG	Anxiety	3	0.661	1.001 (0.995, 1.007)	6.16e-04
PACG	Depression	9	0.770	1 (1.000, 1.001)	8.46e-03
PACG	Fed-up	8	0.862	1 (0.996, 1.005)	2.52e-03
PACG	Guilty	9	0.563	1.001 (0.998, 1.004)	2.56e-03
PACG	Irritation	9	0.939	1 (0.996, 1.004)	2.39e-03
PACG	Loneliness	8	0.347	1.002 (0.998, 1.005)	1.76e-03
PACG	Nervousness	9	0.143	1.002 (0.999, 1.006)	1.59e-03
PACG	Sensitivity	9	0.747	1.001 (0.997, 1.005)	4.56e-03
PACG	Anxiety	9	0.923	1 (0.996, 1.004)	4.42e-03
POAG	Depression	23	0.397	1 (1.000, 1.001)	2.27e-04
POAG	Fed-up	22	0.359	1.003 (0.997, 1.008)	5.90e-03
POAG	Guilty	21	0.267	0.997 (0.992, 1.002)	3.82e-03
POAG	Irritation	21	0.891	1 (0.996, 1.005)	2.39e-03
POAG	Loneliness	23	0.526	1.001 (0.997, 1.006)	2.02e-03
POAG	Nervousness	22	0.854	1 (0.995, 1.004)	1.80e-03
POAG	Sensitivity	22	0.261	0.997 (0.991, 1.002)	3.04e-03

The average of all regions of PPH4 is considered as the final colocalisation result.

Co<sup>+</sup>, colocalisation analysis; EG, exfoliative glaucoma; GSEI, glaucoma secondary to eye inflammation; GSET, glaucoma secondary to eye trauma; JOAG, juvenile open-angle glaucoma; NTG, normotensive glaucoma; NVG, neovascular glaucoma; PACG, primary angle-closure glaucoma; POAG, primary open-angle glaucoma.

potential biases in these findings. These studies should use randomised controlled trials, other population studies or animal experiments to verify these results. The contradictions between our results and previous studies on the emotional or psychiatric disease and glaucoma risk show that previous studies may be influenced by detection bias, unobserved confounding factors and pleiotropy. Moreover, we provide more reliable conclusions and fill gaps in the understanding of the causal relationship between emotions and glaucoma by integrating the results of genetic correlation, MR and colocalisation analyses.

Overall, our study suggests that negative emotions may not be causal triggers for glaucoma, and caution should be exercised in interpreting the association between these two conditions in clinical practice, which guide the management of emotional regulation and care for high-risk populations and patients with glaucoma. We indicated that there is no evidence of a causal relationship between these two conditions within the power limits of our data, and developing glaucoma does not necessarily lead to increased negative emotions. Therefore, subsequent emotional changes in patients should

focus more on ensuring quality of life related to vision to avoid psychological changes that may arise from glaucoma consequences.

This study has significant strengths compared with previous articles. First, we used data from large GWAS databases, enhancing the credibility of our results. Second, we integrated GWAS of eight common negative emotions and common glaucoma diseases for analysis, filling this gap in research. Third, standard MR analysis and more lenient secondary MR analysis were employed, enhancing the reliability of our results. Finally, MR, genetic correlation analysis and Bayesian colocalisation analysis have complementary aspects, reducing the likelihood of false negatives and false positives. These advantages make our analysis of the association between emotions and glaucoma more accurate and less biased.

However, our results still have some limitations. First, due to database limitations, the aggregated data we used did not allow for stratification by factors such as age, diet, underlying diseases, etc, which could lead to bias. Even though we considered this aspect, no MR study can completely eliminate the bias of pleiotropy.<sup>40</sup> Second, due to lack of data on other emotional GWAS, such as



misery, jealousy, etc, we could not discuss more about the connection between various negative emotions and the risk of glaucoma. Third, due to the very small sample sizes and low heritability estimates for several glaucoma subtypes in FinnGen (eg, drug-induced, juvenile, traumatic and inflammatory glaucoma), the statistical power of our analyses was limited, and our findings should therefore be interpreted as showing no evidence of a causal relationship within these constraints, while small or subtype-specific effects cannot be excluded. Fourth, due to the definition of negative emotions as binary self-reported traits (yes/no), the complexity and spectrum of emotional states could not be fully captured. This dichotomisation may reduce sensitivity, introduce misclassification and attenuate associations, thereby contributing to potential false negatives. Future studies using more nuanced quantitative scales or longitudinal assessments will be needed to better characterise these traits.

Lastly, due to the restriction of our analyses to European ancestry cohorts (UKB and FinnGen), the generalisability of our findings is limited. While this provides internal consistency, it does not account for potential differences in genetic architecture or environmental modifiers across populations. At present, GWAS data for negative emotional traits in non-European cohorts remain scarce and underpowered for robust Mendelian randomisation analyses. Future studies with larger and more diverse populations will therefore be essential to validate our findings and determine their applicability on a global scale. Additionally, studying the risk of glaucoma with other emotions is also essential.

## CONCLUSION

This study suggests that depression, anxiety and eight other common negative emotions may not be causally associated with glaucoma and there may be no genetic correlation between them.

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**Data availability statement** Data are available in a public, open access repository. Data are available on reasonable request. Our research used available public database. Negative emotion GWAS data can be downloaded at UK Biobank website (<https://www.ukbiobank.ac.uk/>),<sup>41</sup> glaucoma GWAS data can be downloaded at FinnGen R10 website (<https://www.finnngen.fi/en>).<sup>42</sup>

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