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Observational Study

Causal relationship between feelings and cognitive decline: An univariable and multivariable Mendelian randomization study

Liu J *et al*. Cognition and feelings: Genetic causation

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Abstract

BACKGROUND

While the impact of depression on cognition is well-documented, the relationship between feelings and cognition has received limited attention.

AIM

To explore the potential association between feelings and cognition with a two-sample Mendelian randomization (MR) analysis.

METHODS

Our analysis utilized genome-wide association data on various feelings (fed-up feelings, n = 453071; worrier/anxious feelings, n = 450765; guilty feelings, n = 450704; nervous feelings, n = 450700; sensitivity/hurt feelings, n = 449419; miserableness, n = 454982; loneliness/isolation, n = 455364; happiness, n = 152348) in the European population and their impact on cognitive functions (intelligence, n = 269867). Conducting a univariable MR (UVMR) analysis to assess the relationship between feelings and cognition. In this analysis, we applied the inverse variance weighting (IVW), weighted median, and MR

Egger methods. Additionally, we performed sensitivity analysis (leave-one-out analysis), assessed heterogeneity (using MR-PRESSO and Cochran's *Q* test), and conducted multiple validity test (employing MR-Egger regression). Subsequently, a multivariable MR (MVMR) analysis was employed to examine the impact of feelings on cognition. IVW served as the primary method in the multivariable analysis, complemented by median-based and MR-Egger methods.

RESULTS

In this study, UVMR indicated that sensitivity/hurt feelings may have a negative causal effect on cognition (OR = 0.63, 95%CI = 0.43-0.92, *P* = 0.017). After adjustment of other feelings using MVMR, a direct adverse causal effect on cognition was observed (OR_{MVMR} = 0.39, 95%CI = 0.17-0.90, P_{MVMR} = 0.027). While a potential increased risk of cognitive decline was observed for fed-up feelings in the UVMR analysis (OR_{UVMR} = 0.64, 95%CI = 0.42-0.97, P_{UVMR} = 0.037), this effect disappeared after adjusting for other feelings (OR_{MVMR} = 1.42, 95%CI = 0.43-4.74, P_{MVMR} = 0.569). These findings were generally consistent across MV-IVW, median-based, and MR-Egger analyses. MR-Egger regression revealed pleiotropy in the impact of worrier/anxious feelings on cognition, presenting a challenge in identifying the effect. Notably, this study did not demonstrate any significant impact of guilty feelings, nervous feelings, miserableness, or loneliness/isolation on cognition. Due to a limited number of instrumental variables for happiness, this study was unable to analyze the relationship between happiness and cognition.

CONCLUSION

This MR study finds that sensitivity/hurt feelings are associated with cognitive decline, while the link between worrier/anxious feelings and cognition remains inconclusive. Insufficient evidence supports direct associations between happiness, guilty feelings, nervous feelings, miserableness, loneliness/isolation, and cognition.

Key Words: Mendelian randomization analysis; Feelings; Cognition; Intelligence

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Core Tip: Our two-sample Mendelian randomization (MR) analysis investigated the relationship between various emotions and cognitive function in the European population. We found compelling genetic evidence suggesting that sensitivity/hurt feelings may have a negative causal effect on cognition, even after adjusting for other emotional factors. In contrast, the causal link between worrier/anxious feelings and cognition remains inconclusive due to pleiotropy. Additionally, we did not find significant associations between happiness, guilty feelings, nervous feelings, miserableness, loneliness/isolation, and cognitive decline. This study sheds light on the complex interplay between emotions and cognition, highlighting the importance of sensitivity/hurt feelings in cognitive health.

INTRODUCTION

Intelligence encompasses a spectrum of cognitive functions, including reasoning, planning, problem-solving, abstract thinking, experiential learning, and the comprehension of intricate concepts[1]. Intelligence or cognition can be assessed by a variety of neurocognitive tests[2,3]. Given the expanding elderly population, cognitive health has become a paramount concern. Mild cognitive impairment (MCI) and dementia represent discrete stages of cognitive decline. MCI prevalence varies, ranging from 4% to 19% among individuals aged 65 and older[4-6]. Globally, around 50 million individuals live with dementia, and this number is expected to reach 152 million by 2050[7]. MCI serves as an intermediary stage between healthy cognitive aging and early-stage dementia. Individuals with MCI, also known as those with cognitive impairment without dementia, maintain their functional daily activities. However, they report

objective cognitive deficits, either self-reported or observed by their relatives[8,9]. While some individuals with MCI may revert to a state of healthy cognition, a substantial proportion (22%) progress to dementia within a span of 3 to 10 years[10]. Both modifiable risk factors, including factors like smoking, diabetes, and depression, as well as non-modifiable factors like age, can contribute to cognitive decline[11]. Furthermore, neuropsychiatric symptoms frequently accompany cognitive decline, with their severity often escalating alongside cognitive impairment[11,12].

Feelings represent psychological experiences linked to physiological states, aiding in adaptation to changes in bodily conditions, and enabling effective responses in complex scenarios[13]. Several critical health conditions, such as depression, substance addiction, and intractable pain, center on disturbances in feelings. Numerous neuropsychiatric disorders exhibit marked deficits in both cognitive and emotional domains. These included Alzheimer's disease, autism, and schizophrenia. The central challenge in comprehending these disorders revolves around unraveling the intricate interplay between cognitive and emotional processes in both normal and pathological contexts[14]. Currently, the precise influence of feelings on cognition remains a subject of ongoing investigation.

Mendelian randomization (MR), an innovative tool for evaluating causal relationships between exposure factors and outcomes, employs genetic variants as instrumental variables[15]. MR essentially functions as a natural randomized controlled trial, built on the assumption that genetic variant alleles associated with exposure are randomly distributed. Consequently, MR methodology serves to mitigate common pitfalls associated with confounding and reverse causation often encountered in observational studies[16]. In this study, we conduct a two-sample MR analysis to delve into the causal relationship between feelings and cognitive function.

MATERIALS AND METHODS

Study design

The study design overview is depicted in Figure 1. To comprehensively assess the causal role of feelings in cognition, we initially conducted univariable MR (UVMR) analyses. Subsequent multivariable MR (MVMR) analyses, considering the genetic interrelationships among these feelings, were conducted to examine their independent effects. All MR analyses followed a two-sample approach. To ensure unbiased causal assessments, the MR study must satisfy three key assumptions: (1) the genetic variants are highly associated with exposures; (2) genetic variants are not associated with potential confounders; and (3) genetic variants influencing the outcome exclusively through the exposure pathway. Our MR analyses relied on publicly available Genome-Wide Association Study (GWAS) data, obviating the need for additional approvals or informed consent.

Data source

Intelligence: The summary-level data on intelligence were derived from a GWAS meta-analysis involving 14 independent epidemiological cohorts of European ancestry[17]. These cohorts assessed intelligence through a range of neurocognitive tests, including mathematical reasoning, verbal fluency, digit span, immediate and delayed recall tests, among others. In most of these 14 cohorts, intelligence was treated as a continuous variable, quantified by cognitive test scores. However, in the high IQ/health and retirement study, which differed from the other cohorts, individuals were categorized as either high-IQ or unselected, rather than being assessed with a specific intelligence score. Comprehensive GWAS information related to intelligence is available on the public GWAS website, with the ID ebi-a-GCST006250 (https://gwas.mrcieu.ac.uk/).

Feelings: GWAS information pertaining to feelings can be accessed on the website (https://gwas.mrcieu.ac.uk/), with the following identifiers: Happiness (ID: ukb-b-4062), fed-up feelings (ID: ukb-b-19809), worrier/anxious feelings (ID: ukb-b-6519), guilty feelings (ID: ukb-b-10169), nervous feelings (ID: ukb-b-20544), sensitivity/hurt feelings (ID: ukb-b-9981), miserableness (ID: ukb-b-18994), and loneliness/isolation (ID:

ukb-b-8476). It is worth noting that, except for Happiness, which is classified as categorical ordered, the remaining feelings are represented as binary variables. These variables were derived from GWAS pipeline using phesant-derived variables from UK Biobank (Table 1).

Selection of genetic instruments

Single-nucleotide polymorphisms: We selected valid instrumental variables (IVs) according to the following criteria: (1) Single-nucleotide polymorphisms (SNPs) were required to exhibit strong associations with the exposure and possess significant *P*-values of $< 5 \times 10^{-8}$; (2) To evaluate linkage disequilibrium (LD) between the selected SNPs, we utilized a clumping process ($r^2 = 0.001$, clumping distance = 10000 kb); (3) We employed PhenoScanner (http://www.phenoscanner.medschl.cam.ac.uk/) to assess whether the selected SNPs were associated with other traits at genome-wide significance levels, thereby eliminating genetic variants associated with the outcome and potential confounders; and (4) For SNPs to be considered meaningful, a minor allele frequency threshold of 0.01 was set, and the *F*-test statistic was employed to quantify the strength of IVs, with a threshold of $F > 10$ for MR analyses. All SNPs were harmonized for the exposure and the outcome by alleles to ensure alignment of allele effects. In cases where a specific IV could not be matched in the outcome dataset, proxy SNPs with high LD ($r^2 > 0.8$) were identified for inclusion.

Statistical analysis

All statistical analyses were conducted using the following R software packages: TwoSampleMR (version 0.5.6), MendelianRandomization (version 0.9.0), and MRPRESSO (version 1.0), implemented in R software version 4.2.2. Statistical significance was defined by a *P*-value < 0.05.

For the UVMR analysis, we employed three distinct methods: inverse-variance weighted (IVW), weighted median, and MR-Egger approaches[18-20]. The primary analysis, using IVW, was conducted to investigate the causal relationship between

feelings and intelligence. We assessed heterogeneity among IVs through Cochran's *Q* test. In cases where no evidence of heterogeneity was observed, we utilized fixed-effect IVW models; otherwise, random-effect IVW models were applied[18]. To assess horizontal pleiotropy, we examined the intercept of MR-Egger regression and conducted MR-PRESSO analysis[20,21]. We also employed a leave-one-out analysis to assess whether the results were significantly influenced by any specific SNP. In the UVMR, we carried out a total of seven MR analyses, applying a Bonferroni-corrected threshold of $P < 0.007$ (0.05/7). Associations with *P* values ranging from ≥ 0.007 to < 0.05 were considered suggestive associations.

Considering potential correlations among feelings that may impact intelligence, we conducted a MVMR analysis to assess the independent causal influence of feelings on cognition[22,23]. In this analysis, we employed three different MVMR methods: MR-IVW, the MR-Egger method, and the median-based method.

RESULTS

SNP selection

Following the removal of SNPs exhibiting LD, the feelings-related SNPs obtained from GWAS in Supplementary Table 1. The final selection of independent SNPs, meticulously excluding any confounding factors, is thoughtfully presented in Supplementary Table 2. Notably, the F-statistics associated with the included SNPs in this study all exceeded the threshold of 10. However, when it comes to the analysis of Happiness, it is worth mentioning that only one instrumental variable (IV), namely rs685031, met the criteria with a *P*-value < 5×10^{-8}, an $r^2 = 0.001$, and kb = 10000, rendering the analysis considerably challenging. Furthermore, the excluded confounding factors in this study encompassed a wide array of variables, including education, hearing impairment, diabetes, hypertension, high cholesterol, body mass index, smoking, alcohol intake, coronary artery disease, as well as an assortment of neuropsychiatric disorders, such as progressive supranuclear palsy, neuroticism,

depressive symptoms or depression, schizophrenia, Parkinson's disease, multiple sclerosis, autism, bipolar disorder, epilepsy, Alzheimer's disease, and spinal cord injuries.

UVMR analysis of the causal relationship between feelings and cognitive function

The results from the IVW-mre (multiplicative random effects) method suggested that fed-up feelings have a potential effect on cognitive function, with an OR of 0.64 (95%CI: 0.42-0.97; P = 0.037). Similarly, sensitivity/hurt feelings showed an OR of 0.63 (95%CI: 0.43-0.92; P = 0.017), as detailed in Figure 2. Conversely, feelings such as guilty feelings, miserableness, loneliness/isolation, and nervous feelings showed no significant impact on cognitive function (see Figure 2). These findings were corroborated by other MR analysis methods. Sensitivity analysis revealed heterogeneity in the analysis of these feelings and intelligence (see Table 2). Consequently, we employed a multiplicative random-effects inverse-variance weighted method in this study. Intercepts from MR-Egger regression and MR-PRESSO analyses indicated directional pleiotropy in the relationship between worrier/anxious feelings and cognitive function. Importantly, no outliers were identified in the analysis of sensitivity/hurt feelings (see Table 2). Leave-one-out analysis demonstrated that the effects of fed-up feelings and sensitivity/hurt feelings on cognitive function were not driven by a single SNP. Scatter plots, forest plots, and leave-one-out plots that illustrate the analysis of sensitivity/hurt feelings and fed-up feelings can be found in the Supplementary Figure.

Multivariable MR analysis of the causal relationship between feelings and cognitive function

Worrier/anxious feelings were excluded from the multivariable MR analysis due to pleiotropy concerns. Eventually, we included a total of 36 SNPs in the multivariable MR analysis. The intercept derived from the MR-Egger regression indicated no evidence of pleiotropy in the multivariable MR (MVMR) analysis. However, the heterogeneity test revealed the presence of heterogeneity (see Supplementary Table 3).

Even with adjustments for other feelings, sensitivity/hurt feelings still showed a negative direct effect on cognitive function (OR_{IVW} = 0.39, 95%CI: 0.17-0.90, P_{IVW} = 0.027). Both MR-Egger and median-based analyses were consistent with the results obtained from IVW method. On the other hand, Fed-up feelings, along with other factors, showed no significant association with cognitive function in the multivariable MR analysis (see Figure 3).

DISCUSSION

In this study, our examination of the influence of feelings on cognitive function revealed genetic evidence that links sensitivity/hurt feelings with cognitive decline. However, after accounting for the genetic effects of other feelings in the MVMR analysis, the direct causal effect of Fed-up feelings did not persist. Furthermore, our findings show no associations between various feelings - happiness, guilty, nervous, miserableness, and loneliness/isolation - and cognitive function.

It is well-documented that the upper brainstem and hypothalamus serve as the structural basis for generating feelings, while the cerebral cortex facilitates complex cognitive processes such as memory, language, reasoning, and imagination[24,25]. These cognitive processes enhance emotional states, aiding the body's adaptation to changes. Feelings are vital in understanding shifts in bodily states due to environmental changes and in applying this knowledge to predict future situations, thereby enhancing behavioral adaptability. Feelings lay the foundation for establishing higher levels of cognition and consciousness[13].

Hurt feelings, also known as social pain, often arise in unfavorable circumstances and intertwine closely with cognitive functionslike perception, judgment, expectations, and beliefs[26,27]. The perception of hurt feelings and high sensitivity to rejection have been shown to predict more verbal aggression but less physical aggression[28]. Researchers have proposed the "interactive influence model of emotion and cognition", which suggests that feelings can override cognition, influencing decision-making from the bottom-up, particularly in emotion exaggeration context[29]. Using the MR approach,

our study strengthened the evidence for a causal effect of hurt feelings on cognitive decline.

Loneliness is a psychological condition resulting from a disconnect between an individual's desired and actual social relations, leading to the negative experience of feeling alone or socially isolated, even in the presence of family or friends[30]. Research has indicated that loneliness and depression are distinct, with loneliness increasing the risk of depression[31,32]. Loneliness is also a risk factor for cognitive decline and Alzheimer's disease progression[33]. Social isolation, on the other hand, relates to the structural aspects of one's social network. An observational study revealed that social isolation was independently associated with a 1.26-fold increased risk of dementia over an average follow-up period of 11.7 years, while the fully adjusted hazard ratio for dementia specifically associated with loneliness was 1.04[34]. However, due to insufficient instrumental variables, this study could not conclusively explore a causal relationship between loneliness/isolation and cognition, highlighting the need for further investigation.

Guilt feelings emergewhen a person feel responsible perceives responsibility for a negative outcome impacting others[35]. Guilt is often viewed as a detrimental emotion that should be avoided, yet it is also associated with a desire to improve subsequent performance, apologize, and rectify misdeeds. Guilt feelings can influence interpersonal decision-making[36]. However, our study did not find any impact of guilt on cognition.

Furthermore, there is limited research on the cognitive implications of miserableness, nervous feelings, and fed-up feelings. Our univariate MR research initially suggested that fed-up feelings might lead to decreased cognition. However, after adjusting for various factors, we observed no significant impact on cognition.

Study limitations

Data generalizability: Since this study's data were sourced exclusively from European populations, the generalizability of the findings to other ethnic groups may be limited.

Pleiotropy challenges: Completely eliminating pleiotropy in MR analysis is challenging, and horizontal pleiotropy can notably affect the stability of MR results. In this study, univariate MR research indicates that worrier/anxious feelings may influence cognition. However, their effects appear to be pleiotropic. Consequently, it is not possible to conclusively assert that worrier/anxious feelings directly affect cognition, warranting further investigation.

CONCLUSION

These MR findings provide causal evidence linking sensitivity/hurt feelings with cognitive decline. However, the causal relationship between worrier/anxious feelings and cognition remains inconclusive. Insufficient evidence exists to suggest a direct association of happiness, guilty feelings, nervous feelings, miserableness, and loneliness/isolation with cognition.

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