Association of chronic pain with suicide attempt and death by suicide: A two-sample Mendelian randomization

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A two-sample Mendelian randomization

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Running title

Chronic pain and suicide

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Abstract

Prior studies have suggested an association between chronic pain and suicidal behavior. However, evidence supporting the causal nature of this association, and the role played by depression, remain difficult to establish due to confounding. We investigated associations of chronic pain with suicide attempt and death by suicide as well as the mediating role of depression in this association using a genetically informed method strengthening causal inference. We conducted a two-sample Mendelian randomization. Independent SNPs (N=97) from the Multisite Chronic Pain GWAS (N_{GWAS}=387,649) were used as instrumental variables to test associations of chronic pain with suicide attempt (measured from hospital records; N_{GWAS}=50,264) and death by suicide (measured from official death causes; N_{GWAS}=18,085). Indirect associations of chronic pain with suicide attempt and death by suicide via major depressive disorder (N_{GWAS}=173,005) were estimated. Primary analyses were supported by a range of sensitivity and outlier analyses.We found evidence supporting the contribution of chronic pain to increasing the risk of suicide attempt (OR=1.67, CI=1.21-2.35) and death by suicide (OR=2.00, CI=1.10-3.62). Associations were consistent across sensitivity analysis methods, and no evidence for outliers driving these associations was found. Through mediation analyses, we found that major depressive disorder explained a substantial proportion of the association between chronic pain and suicide attempt (proportion mediated=39%; $OR_{indirect\ association}$=1.32, CI=1.09-1.61) and death by suicide (proportion mediated=34%; $OR_{indirect\ association}$=1.40, CI=1.13-1.73). Our findings suggest that both pain management interventions and prevention of depression are likely to be effective strategies to reduce suicide risk in individuals with chronic pain.

Introduction

Chronic pain, which is an umbrella term that encompasses numerous pain conditions lasting for at least 3 months, affects approximately 1 in 5 adults [1]. Chronic pain conditions like migraine and low back pain are leading causes of disability worldwide [2]. Living with chronic pain may have a profound impact on an individual's mental health, negatively influencing their thoughts, emotions, and overall well-being [3]. A growing body of research consistently links chronic pain to suicidal behavior [4–13], suggesting that individuals with chronic pain experience double the rates of suicide attempt and death by suicide than the general population [4, 5]. Suicide attempt and death by suicide are important public health concerns [14], and understanding whether individuals with chronic pain are at increased risk of these outcomes is critical for targeting prevention efforts.

Although chronic pain has been highlighted as an important risk factor for suicide in clinical practice guidelines [15, 16], it is unclear whether there is a causal mechanism linking chronic pain to suicide risk. The association noticed in previous epidemiological studies could potentially be explained by confounding factors [17, 18]. Environmental factors, such as stressful life experiences, have been linked to both chronic pain [19] and suicide risk [14, 20], and can therefore explain the increased suicide risk of individuals with chronic pain. Additionally, underlying biological mechanisms linked to neuroplasticity and shared genetic liability have been associated with both chronic pain and depression [21–23]. Given that depression is one the strongest predictors of suicide risk [14, 24], it is plausible that such shared biological mechanisms might explain the observed association between chronic pain and suicide. Additionally, most previous studies relied on self-reported measures of both pain and suicidality, which introduces measurement bias due to the subjective nature of both phenomena (a bias arising from common-method variance) [4, 5, 25]. Clarifying whether chronic pain is causally related to suicide risk is important to inform suicide prevention in both somatic and psychiatric care [18], as interventions are likely to be effective only if the targeted risk factor has a casual, rather than correlational, association with the outcome.

As conducting randomized trials to infer causality is unethical and unfeasible in the case of chronic pain and suicide, quasi-experimental design, such as Mendelian randomization, may be used to strengthen the causal inference drawn from observational data [4]. Mendelian randomization is a special case of an instrumental variable design [26] where genetic variants, previously identified as being robustly associated with chronic pain, are used as proxy (i.e., instruments) for chronic pain [27]. To our knowledge, the associations of chronic pain with suicide attempt and death by suicide have not previously been assessed using this design. However, findings from previous Mendelian randomization studies showed that chronic pain is associated with an increased risk of major depressive disorders (MDDs) and that the association is likely to be bidirectional (i.e., MDD is also associated with higher reported pain). This underscores the relevance of examining the potential mediating role of MDD in the putative association between chronic pain and suicide risk.

Drawing on data from large genome-wide association studies (GWASs), the first aim of this study was to investigate the contribution of chronic pain to suicide attempt and death by suicide using Mendelian randomization. The second aim was to conduct a mediation analysis to quantify to what extent the association of chronic pain with suicide attempt and death by suicide was explained by MDD.

Methods

Data sources and phenotypes

This study is based on summary statistics obtained from large GWAS (**Table 1**). Only GWASs of individuals of European ancestry were used, as genetic variants can be differentially associated with a trait in different ancestry groups due to specific linkage disequilibrium structures [28], and due to a lack of available GWAS data for other ancestries. All GWASs were adjusted for ancestry-informed principal components to account for population stratification, age, and gender.

Exposure. Exposure to chronic pain was identified in a GWAS of 387,649 individuals aged 40-79 living in the UK between 2006 and 2010 from the UK Biobank [23]. Here, the phenotype, Multisite Chronic Pain, has been measured through a self-reported questionnaire. Participants were asked about pain at up to 7 non-mutually exclusive body sites (neck/shoulder, headache, back, hip, knee, abdominal, facial), and Multisite Chronic Pain was defined as the sum of body sites at which chronic pain of more than 3 months had been reported. This measure has been used previously and evidence suggests that chronic pain is better studied as a "continuum of widespreadness" rather than distinct pain conditions experienced in specific locations [23].

Outcomes. Suicide attempt and death by suicide were examined as outcomes. The suicide attempt GWAS was conducted using data on 50,264 individuals residing in Denmark and born between May 1, 1981, and December 31, 2012. Residents over 15 years old who had at least one non-fatal suicide attempt within that period were defined as cases (N=6,024), while controls were those over 15 years old for whom no suicide attempt was recorded (N=44,240). Suicide attempts were identified through Danish medical registries using ICD codes for suicide attempts (ICD-10: X60-X84) or hospital contacts for which "reasons of contact" included suicide attempt [29]. The death by suicide GWAS was conducted using data from 3,413 individuals who died by suicide in Utah, US. The cause of death was based on autopsy reports, which included investigation of circumstances and interviews with survivors. Data from the population-based Generation Scotland Scottish Family Health Study and the UK10K Rare Genetic Variants in Health and Disease Project was used to identify controls who did not die by suicide (N = 14,672) [30].

Mediator. The MDD GWAS was conducted using data from 6 different cohorts, each based in either the US, the UK, or Europe. Cases were defined as those with a lifetime diagnosis of MDD (N=59,851), identified based on meeting DSM-III/DSM-IV criteria or ICD-9/ICD-10 codes for MDD. Controls were those with no lifetime diagnosis of MDD (N=113,154), for a total of 173,005 individuals [31].

Statistical analysis

Two-sample Mendelian randomization (details in **Supplementary Methods 1**). We conducted a two-sample Mendelian randomization analysis in R 4.1. In two-sample Mendelian randomization, the SNP-exposure and SNP-outcome associations are obtained from two GWASs (one for the exposure, chronic pain, and one for the outcome, suicide attempt/death by suicide) [32]. First, we used a set of independent (linkage disequilibrium clumping window 10,000 kb; r^2 0.001) instrument SNPs, which were associated with chronic pain at $P < 1x10^{-6}$. In, secondary analyses we applied a significance level of $P < 5x10^{-8}$. The strength of the final set of instruments was evaluated using the F statistic, for which values above ten are indicative of strong instruments [33]. Second, to determine the SNP-outcome associations, the selected SNPs were identified in the outcome (i.e., suicide attempt and death by suicide) GWASs. Third, for each instrument SNP, we computed the ratio between the SNP-exposure and the SNP-outcome association (Wald test), which represents the unconfounded association between exposure and outcomes [32]. Wald estimates for single SNPs were pooled using random-effect inverse-variance weighting (IVW) meta-analysis as the primary analysis and expressed as an Odds Ratio (OR). Heterogeneity across the meta-analyzed estimates was quantified using the Q-statistic, to test for horizontal pleiotropy (i.e., the fact that the same SNPs influence traits other than chronic pain, meaning the association between instrument SNPs and the outcomes of suicide attempt/death by suicide could be due to alternative pathways not entirely explained by chronic pain, violating instrumental variable assumptions) [32]. Pleiotropy does not bias the analysis, unless it is unbalanced.[34] Therefore, to determine whether pleiotropy was unbalanced, we tested the significance of the MR-Egger intercept. A significant test implies a need to validate the results in sensitivity analyses [32]. Fourth, sensitivity analyses were performed by re-estimating associations using alternative methods to account for a possible violation of the instrumental variable assumptions [32]: MR-Egger regression (with SIMEX correction to account for violation of the No Measurement Error Assumption) [35], weighted median regression, Robust Adjusted Profile Score (RAPS) [36]. The main criterion for these sensitivity

analyses was to assess whether the direction and the size of the associations were consistent with those obtained using the IVW estimator, as this would support the validity of the primary analysis. Fifth, we conducted two sets of analyses to test whether specific SNP instruments, i.e., outliers, might be driving all the association. This was done using the leave-one-out and MR Pleiotropy Residual Sum and Outlier (MR-PRESSO) procedures [37].

Mediation analysis. Once computed the associations between chronic pain and suicide attempt/death by suicide (total association), mediation analyses were conducted to estimate a) the indirect association of chronic pain with suicide attempt and death by suicide via MDD, and b) the remaining (direct) association of chronic pain with suicide attempt and death by suicide once MDD was adjusted for. We applied Mendelian randomization to estimate the association between chronic pain and MDD, and the association between MDD and suicide attempt/death by suicide, following the procedure described above [38]. First, the indirect association was computed as the product of these estimated associations, with bootstrapped 95% confidence intervals to determine statistical significance. Second, the direct association was computed as the difference between the total association, and the estimated indirect associations. The ratio between indirect and total associations (proportion mediated) indicates the size of the mediation effect [39]. Since a bidirectional association between chronic pain and MDD is expected, mediation analysis was conducted to quantify to what extent chronic pain mediated the association of MDD with suicide attempt and death by suicide, thus allowing us to compare the two indirect associations.

Results

Instrumental variables

We identified 110 potential independent SNPs associated with chronic pain with $P < 1x10^{-6}$ as instruments. Of those, 82 were used in the analyses for suicide attempt and 97 for the analyses for suicide death, as not all SNPs were measured in the outcome GWASs. The mean F-statistic for these

SNPs was 30 (median, 28.5; range, 24–54.6) for suicide attempt and 29.9 (median, 28.4; range, 24.0-54.6) for death by suicide, indicative of strong instruments (**Table S1**).

Association between chronic pain and suicide attempt

We found evidence for an association between chronic pain and suicide attempt **(Figure 1** and **Table 2)**. Using the IVW approach, an OR of 1.67 (95% confidence interval [CI], 1.21-2.35) was obtained; thus, suggesting a 67% increase in the odds of suicide attempt for each additional unit of increase in the pain scale. Heterogeneity of this estimate was negligible, as suggested by the Q statistic (Q, 98.0; degrees of freedom [DF], 86; $P = 0.178$). The Egger intercept indicated no evidence of unbalanced horizontal pleiotropy (-0.002; SE, 0.001; $P = 0.801$). The findings from the sensitivity analyses supported the primary analysis, as the estimates obtained with alternative estimation methods had the same direction and the magnitude of associations were comparable. Both the leave-one-out (**Figure S1**) and the MR-PRESSO (**Table S2**) analyses did not identify outlier SNPs. Restricting the analyses to a conservative set of SNP instruments (i.e., those associated with chronic pain at $P < 5x10^{-8}$; n = 33) provided comparable results (**Table 2**).

Association between chronic pain and death by suicide

An OR of 2.00 (CI, 1.10-3.62) suggested a significant association between chronic pain and death by suicide (**Figure 1** and **Table 2**). According to the Q statistic, there was plausible evidence of heterogeneity (Q, 177.88; DF, 96; $P <0.001$), but no evidence of unbalanced horizontal pleiotropy (-0.003; SE 0.005; $P = 0.466$). The results of the sensitivity analyses were consistent with the main analyses in terms of the magnitude of the association, although the Weighted median methods found a weaker OR than the other methods. The leave-one-out analyses did not show evidence of outlier SNPs (**Figure S1**). However, the MR-PRESSO procedure suggested the possible presence of one outlier SNP (rs35824797; $P < 0.049$; Global $P <0.001$). Correction for this outlier SNP did not alter our conclusions

(Outlier-corrected OR, 1.91; 95% CI, 1.11-3.27; **Table S2**). Analyses conducted using the more conservative set of SNP instruments (n = 35) yield similar results **(Table 2)**.

Mediation analysis

Mendelian randomization analyses provided evidence for a positive association between chronic pain and MDD (OR 2.07, CI 1.77-2.41; **Table S3**), and for positive associations between MDD and both suicide attempt (OR 1.32, CI 1.09-1.61) and death by suicide (OR 1.40, CI 1.13-1.73; **Table S4**). In the mediation analyses, we found indirect associations of chronic pain with suicide attempt (OR 1.23, CI 1.07-1.43) and death by suicide (OR 1.26, CI 1.05-1.55) via MDD (**Figure 2**) with similar proportions of association mediated (39% for suicide attempt and 34% for death by suicide). After accounting for MDD, the remaining direct associations of chronic pain with suicide attempt and death by suicide were OR 1.37 (CI, 0.95-1.97), and OR 1.58 (CI, 0.84-2.94), respectively. When the inverse pathway was tested, mediation analyses showed that chronic pain accounted for 12.5% (indirect association: OR 1.05, CI 1.01-1.08) and 14.3% (indirect association: OR 1.05, CI 1.01-1.09) of the associations of MDD with suicide attempt and death by suicide, respectively (**Table S5**).

Discussion

Using Mendelian randomization, a robust, genetically informed design to strengthen causal inference with observational data, this study found that for each increase in chronic pain measure unit (number of body sites with pain) the odds of suicide attempt increased by 67% and the odds of death by suicide increased two-fold. Our findings also showed that 39% and 34% of the observed associations between chronic pain and suicide attempt and death by suicide, respectively, was attributable to MDD in individuals experiencing chronic pain.

Our findings of the associations of chronic pain with suicide attempt and death by suicide are in line with previous studies conducted using classical observational designs showing increase suicide risk

for individual with chronic pain [4–13]. For example, Danish registry-based studies have found a four-fold and seven-fold higher incidence rate of suicide attempt and death by suicide, respectively, in individuals with chronic pain compared to the general population [40, 41]. These studies have assessed diagnosed conditions characterized by chronic pain as the exposure, rather that self-reported chronic pain, which may explain why these studies reported stronger associations than the one found in our study. Yet, the fact that the finding of such representative studies based on objective measures (i.e., from administrative registers) and population-based data are in line with our genetically informed findings supports the generalization of our conclusions. However, our findings diverge from those of a recent study showing that the association between chronic pain and suicidal behavior was no longer present when examined within monozygotic twin pairs (i.e., adjusting for genetic and familial confounding factors) [42]. This difference may be explained by the specific strengths and limitations of each study design and methodological choices (e.g., regarding the measurement of pain), and stresses the need for triangulation of evidence obtained using alternative study designs [26, 43].

By providing quasi-experimental evidence that MDD plays an important role as a potential causal mechanism linking chronic pain with both suicide attempt and death by suicide, our study adds support to previous observational studies [44]. MDD is associated with increasing self-reported levels of pain, thus, suggesting a bidirectional association between pain and MDD [7]. We find that about one third of the association is mediated by MDD, while just about one eight of the association of MDD with suicide attempt and death by suicide is mediated by chronic pain. This underscores the importance of the pathways linking chronic pain and suicide risk via increase in MDD, despite the complex, bidirectional associations between pain and suicide.

Our findings suggest that interventions (both pharmacological and not pharmacological) aiming to improve pain management have the potential to decrease suicide risk, since they would target a likely causal risk factor. Decision-making on the provision of such interventions is complex and should consider the benefits and risks of each option, including the risks associated with opioids intake and the

patient's quality of life [45]. Previous RCTs have provided evidence for the efficacy of non-pharmacological interventions for either pain reduction [46] or suicide prevention [47], but evidence directly linking non-pharmacological interventions for pain reduction with decreased suicide risk is still scant at present. Conducting rigorous RCTs is therefore necessary. However, a previous propensity score study suggested that non-pharmacological interventions such as exercise therapy, chiropractic care, and biofeedback are associated with reduction of suicidal ideation and self-harming behavior in veterans with chronic pain [48]. It is worth noting that, to enhance effectiveness of any intervention, it is critical to improve integration between mental and somatic care. Screening for depression and suicide risk assessment should be conducted by healthcare professionals working with individuals with somatic problems involving chronic pain, and adequate protocols for referral should be implemented. Similarly, mental health professionals should be aware that patients with chronic pain are at high suicide risk and can thus consider pain management interventions and, if necessary, referral to specialized pain management services.

Our findings also suggest that suicide risk in individuals with chronic pain might be alleviated through treatment of depression. The links between pain and depression are complex, involving both psychological mechanisms, shared brain circuitry (e.g., anterior insula and anterior cingulate) [49], and genetic vulnerabilities. Future studies might investigate specific psychological mechanisms implicated in the relationships among pain, depression, and suicidality in order to inform clinical interventions. These mechanisms might include pain-related helplessness/hopelessness, perceived burdensomeness on caregiver for individuals for whom pain is also linked to limitations of functioning (mobility, work), catastrophizing, increased fearlessness about death, and mental imagery [50]. Developing a better understanding of such specific psychological mechanisms would help with tailoring therapeutic approaches for suicide prevention. Finally, depression is only one of the mechanisms linking chronic pain to suicide risk. Living with chronic pain complicates various aspects of living, such as employment, the ability to perform daily tasks, including physical activity, and the ability to engage in

social activities. As such, individuals living with chronic pain may face increased socioeconomic stressors, have reduced capacity to cope, experience a reduction of meaning in life, and diminished exposure to protective factors (such as physical activity) [50]. Understanding the role of these psychosocial mechanisms may open alternative avenues for suicide prevention for individuals suffering from chronic pain.

Our study is based on a robust quasi-experimental approach based on large high-quality GWAS data from international consortia and uses a range of sensitivity analyses to support the main findings. However, we acknowledge the following limitations. First, our findings are valid under specific assumptions of the instrumental variable approach, including the absence of bias due to horizontal pleiotropy (i.e., alternative pathways explaining the associations between instrument SNPs and outcomes). Despite our results remaining robust after a series of sensitivity analyses challenging these assumptions, horizontal pleiotropy cannot be completely ruled out, as the biological action of most included SNPs is not fully understood yet. Related to this, confounding effects arising from population stratification and dynastic effects may have introduced bias. Second, despite the known sex dimorphism in suicide, pain, and MDD, we were not able to conduct disaggregated analyses by sex since sex-specific GWASs were not available. In a similar way, the effect of age could not be specifically investigated. Third, large GWASs of our phenotypes of interest were only available for individuals of European ancestry, which restricts generalizability and calls for replication of our results in more ethnically diverse samples. Fourth, the GWASs used in this study come from very large samples in which measurement of the phenotypes may be heterogeneous (including regarding sex and age distributions) or affected by measurement errors. For example, measuring suicide attempt with hospital records does not allow one to capture cases that never reached medical attention. Furthermore, chronic pain was self-reported and measured the presence of pain in different cumulative body sites, but this does not specify the intensity, duration, and localization of pain. Since previous studies have suggested the association between chronic pain and suicide may vary depending on the pain condition

and duration [7, 8, 10], future quasi-experimental investigations should account for such specificities of pain.

In summary, using a quasi-experimental approach strengthening causal inference, this study provides robust evidence of the contribution of chronic pain to suicide attempt and death by suicide as well as the mediating role of MDD in this association. Screening for depression and assessment of suicide risk in individuals with chronic pain can lead to the identification of those in need for interventions.

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Conflict of Interest

The authors report no conflict of interest to disclosure.

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Table 1. Characteristics of the genome-wide association studies used in our analyses

Phenotype	Source GWAS	Sample size	Cases	Phenotype assessment
Chronic pain[23]	UK Biobank	387,649	-	Self-reports
Suicide attempt[29]	iPSYCH	50,264	6032 (12%)	National register-based data and hospital records
Death by suicide[30]	Utah OME, GSSFHS, UK10K Project	18,085	3418 (18.9%)	Medical and public reports, police investigation, autopsy
Major depressive disorder[31]	PGC, deCODE, GenScotland, GERA, iPSYCH, UK Biobank (pilot data release)	173,005	59,851 (34.6%)	Structured diagnostic interviews, National inpatient electronic records, From self-reported symptoms or treatment

All GWASs were adjusted for ancestry-informed principal components to account for population stratification, age, and gender

GWAS, Genome Wide Association Study; iPSYCH, Lundbeck Foundation Initiative for Integrative Psychiatric Research; Utah OME, Utah Office of the Medical Examiner; GSSFHS, Generation Scotland Scottish Family Health Study; UK10K, Project UK10K Rare Genetic Variants in Health and Disease Project; PGC, Psychiatric Genetics Consortium

Table 2. Mendelian randomization estimates of the association of chronic pain and suicide attempt and death by suicide

	Suicide attempt			Death by suicide		
	N SNPs	**OR (95% CI)**	**P**	**N SNPs**	**OR (95% CI)**	**P**
Main analysis ($P < 1\times10^{-6}$)						
IVW	87	1.67 (1.21-2.35)	0.002	97	2.00 (1.10-3.62)	0.022
RAPS	87	1.72 (1.24-2.38)	0.001	97	2.09 (1.34-3.27)	0.001
MR Egger	87	1.74 (1.23-2.46)	0.002	97	2.02 (1.09-3.74)	0.029
Weighted median	87	1.51 (0.96-2.38)	0.077	97	1.07 (0.54-2.10)	0.853
Sensitivity analysis ($P < 5\times10^{-8}$)						
IVW	33	1.63 (1.00-2.68)	0.051	35	2.88 (1.23-6.74)	0.015
RAPS	33	1.66 (1.03-2.68)	0.038	35	3.02 (1.55-5.91)	0.001
MR Egger	33	1.72 (1.01-2.93)	0.054	35	3.10 (1.27-7.58)	0.018
Weighted median	33	1.89 (0.96-3.75)	0.066	35	2.33 (0.86-6.30)	0.097

IVW, Inverse Variance Weighting; RAPS, Robust Adjusted Profile Score

Figure 1. Mendelian randomization scatter plots for the associations of chronic pain with suicide attempt (A) and death by suicide (B)

IVW, Inverse Variance Weighting; RAPS, Robust Adjusted Profile Score

Figure 2. Mediation analysis

Representation of the mediation analysis quantifying the indirect association of chronic pain with suicide attempt (A) and death by suicide (B). The figure shows the total associations (i.e., unadjusted association between chronic pain and suicide attempt, A1, and death by suicide B1), and their decomposition into indirect (i.e., mediated by major depressive disorder) and direct (remaining association non mediated) associations (A2 and B2). Numbers are log Odds Ratios with 95% Confidence Intervals as estimated using two-sample Mendelian randomization Inverse-Variance Weighting.

Figures

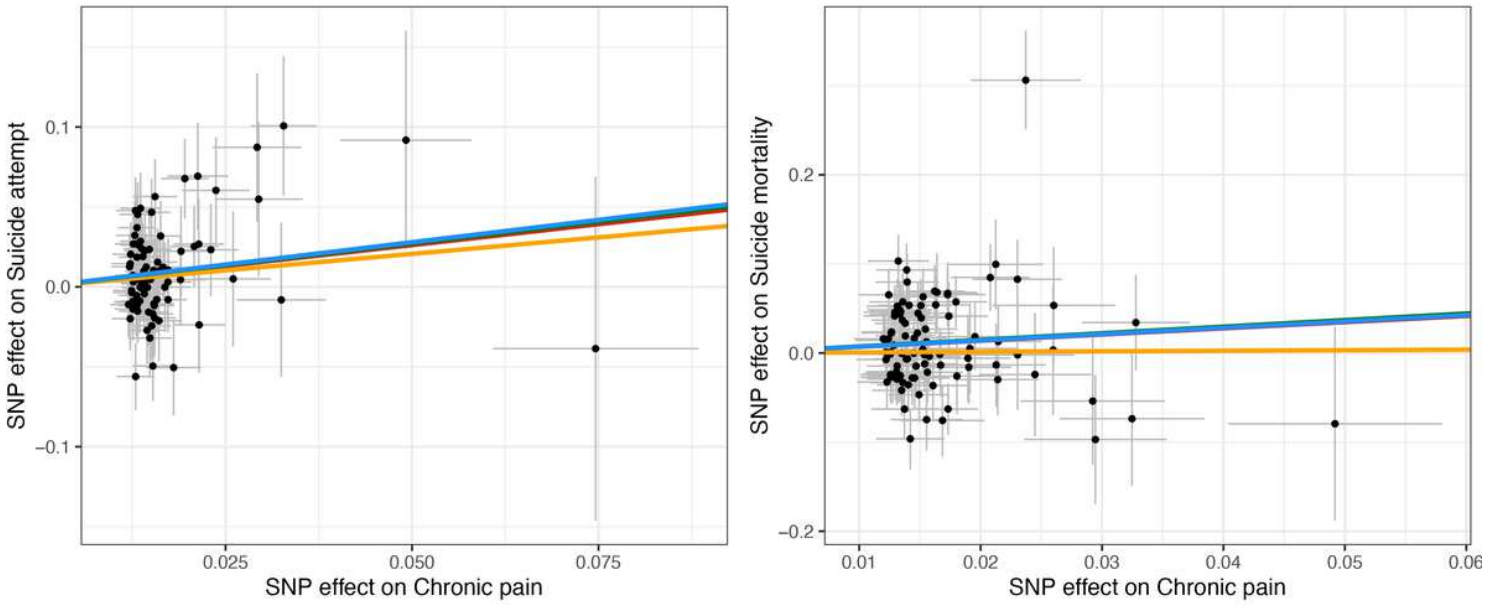

Figure 1

Mendelian randomization scatter plots for the associations of chronic pain with suicide attempt (A) and death by suicide (B)

IVW, Inverse Variance Weighting; RAPS, Robust Adjusted Profile Score

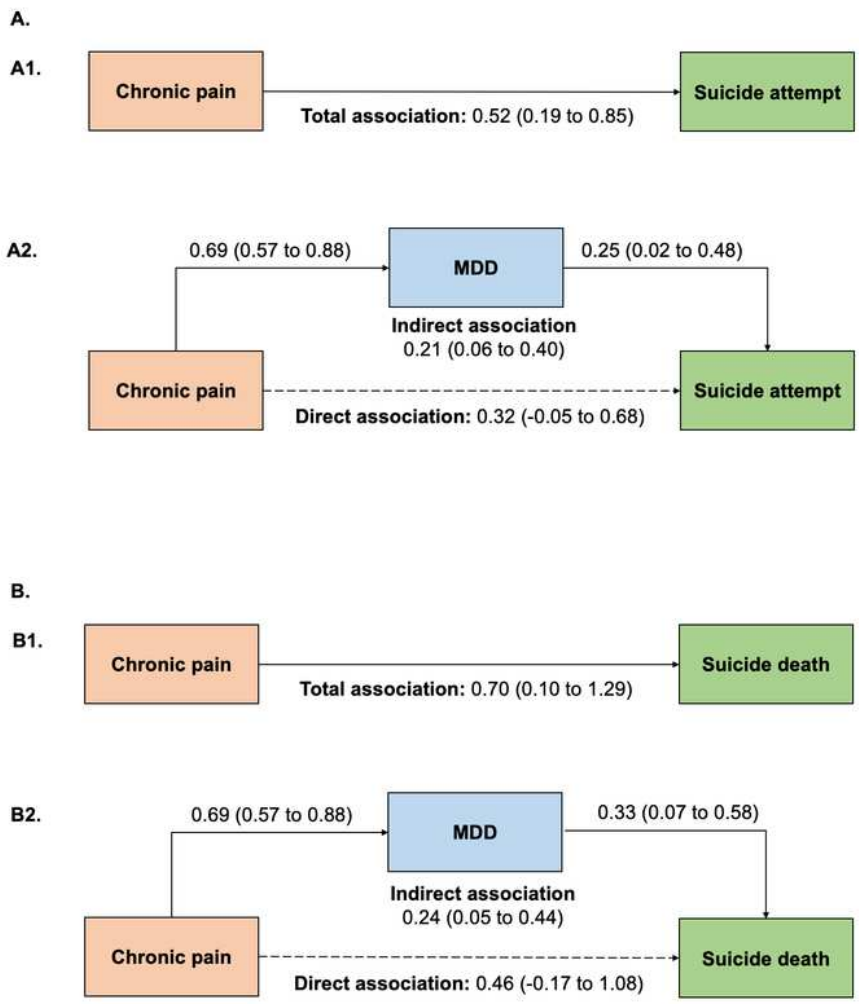

Figure 2

Mediation analysis

Representation of the mediation analysis quantifying the indirect association of chronic pain with suicide attempt (A) and death by suicide (B). The figure shows the total associations (i.e., unadjusted association between chronic pain and suicide attempt, A1, and death by suicide B1), and their decomposition into

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Supplementary Files

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- 20230717MRpainsuicidesupplementary.pdf