Causal relationships between blood lipids and depression phenotypes: A Mendelian randomization analysis

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Abstract

Depression is one of the most significant contributors to disability worldwide, yet its etiology is not well understood. Changes in blood lipid levels such as reduced cholesterol have long been suspected to be associated with depression and suicide. Here we performed a two-sample bi-directional MR analysis to investigate their causal relationship, based on large-scale GWAS summary statistics (*N* up to 188,577 and 480,359 for lipid and depression traits respectively). Five depression-related phenotypes were included, namely major depressive disorder (MDD), depressive symptoms (DS), longest duration and number of episodes of having low mood, and history of deliberate self-harm (DSH) or suicide. MR was conducted with several approaches including inverse-variance weighted, Egger regression and Generalized Summary-data-based MR (GSMR).

We found that reduced low-density lipoprotein cholesterol (LDL-c) and total cholesterol (TC) were causally related to higher risks of MDD (OR for 1-SD decrease in LDL-c: 1.07, 95% CI 1.05-1.10, p= 3.15E-08; OR for 1-SD decrease in TC: 1.08, 95% CI 1.04-1.12, p=2.94E-04) and more prolonged depressed/low mood. Lower LDL-c was also found to be causally linked to more severe DS. In addition, we observed that lower levels of high-density lipoprotein cholesterol (HDL-c) was casually related to increased DS, as well as heightened risks of DSH or suicide (OR=2.17, CI: 1.40-3.39). As for triglycerides (TG), we observed positive causal associations with DS, number of episodes of low mood and risks of DSH or suicide (OR=1.58, CI: 1.16-2.17). We did not detect any significant associations when depression phenotypes were treated as the exposure.

Taken together, the current study suggests a causal relationship between reduced cholesterol and raised TG with risks of depression and related phenotypes. Further studies on its mechanistic basis and the clinical effects of lipid-lowering therapies may be warranted.

INTRODUCTION

Major depressive disorder (MDD) is one of the most common psychiatric disorders worldwide. It is estimated that the condition affects more than 300 million, or 4.4% of the global population. Consequences of MDD in term of lost health are huge. Depression has been ranked as the largest contributor to global disability according to a recent WHO report, and is also a major cause underlying suicidal deaths[1].

Despite its high public health importance, the pathophysiology and etiology of depression remains unclear. Blood lipid levels is one of the risk factors that have long been suspected to be associated with depression and related traits, especially suicide. The topic has received much research attention as a large number of people are on lipid-lowering therapies[2] and lipid levels are very commonly measured in clinical practice. In an early study, Muldoon et al.[3] examined the effects on lowering cholesterol concentration on mortality, and revealed a significant rise in deaths due to accidental causes including suicide. Engelberg [4] proposed that reduced peripheral cholesterol levels may contribute to a decrease in brain serotonin, and that low membrane cholesterol may reduce the number of serotonin receptors, leading to elevated suicidal risks. Subsequently, a number of clinical studies have been conducted to investigate the association of blood lipids with depression or suicidal risks. The results were however mixed, with studies showing positive, inverse or non-significant associations[5-8]. A few meta-analyses have also been performed in this area. Shin et al.[7] found that total cholesterol (TC) was inversely associated with levels of depression, especially among the drug-naïve patients. They also observed an inverse relationship of low density lipoprotein cholesterol (LDL-c) with depression, but the result did not reach statistical significance. Interestingly, they reported a positive association of high density lipoprotein cholesterol (HDL-c) with depression in women. A more recent meta-analysis also reported that lower LDL-c is associated with higher risk of depression[6]. As for suicidal risks, Wu et al. reported lower serum lipids are generally associated with heightened suicidality[8].

Although numerous studies have investigated the relationship between lipids and depression risk, there are several important limitations. One key limitation is that *cause-effect* relationships cannot be reliably determined from previous studies. Many studies are case-control or cross-sectional in nature and the temporal relationship between depression onset and lipid changes cannot be ascertained. In addition, confounding variables may not be completely controlled for in every study, which hinders causal inference. For example, medications, including some antidepressants, may affect the lipid profiles of patients[9]. It is difficult to control for drug effects unless the study only involves drug-naïve cases. In addition, publication bias might be present, and previous meta-analyses did reveal statistical evidence of such bias[6,8]. Although the effects of cholesterol levels on depression were investigated in a number of works, the effects of triglyceride, another major lipid marker, were less well-studied. Moreover, relatively few studies (except e.g.[10,11]) focused on other depression phenotypes such as duration of depressive episode or symptoms**.**

In this study, we aim to analyze *causal relationships* between lipid levels and depression-related phenotypes. We will employ Mendelian randomization (MR) for causal inference. MR makes use of genetic variants as

"instruments" to represent the exposure of interest, and infers causal relationship between the exposure and the outcome[12]. MR is much less susceptible to confounding bias and reverse causality when compared to observational studies. The principle of MR may be considered similar to a randomized controlled trial (RCT): for example, a person who has inherited a lipid-lowering allele (or allelic score) is analogous to receiving lipid-lowering medication(s), and vice versa[13]. The random allocation of alleles at conception is analogous to random assignment of treatment in an RCT. Another advantage is that MR can be conducted with summary statistics from genome-wide association studies (GWAS), which are commonly of large sample sizes. Here we studied five depression-related phenotypes, including major depressive disorder (MDD), depressive symptoms (DS), longest duration of depressed mood, number of episodes having depressed mood and history of suicide or deliberate self-harm. The aim of studying multiple phenotypes is to gain a comprehensive understanding of the effects of lipids on depression traits and to triangulate the results from different aspects.

METHODS

GWAS study samples

Four lipid traits are studied, including LDL-c, HDL-c, triglyceride (TG) and total cholesterol (TC). GWAS was performed by the Global Lipids Genetics Consortium, with a sample size (*N*) of 188,577. We downloaded summary statistics of joint GWAS and Metabochip analysis from http://csg.sph.umich.edu/willer/public/lipids2013/. For details of the study please refer to Willer et al.[14].

We included five depression-related phenotypes as follows:

(1) Major depression disorder (MDD): We employed the results from the latest GWAS from Wray et al.[15] Due to privacy concerns, full summary statistics are only available for a subset of subjects excluding 23andMe participants (59851 cases and 113154 controls). We employed this set of summary statistics for MR analysis with lipid traits as exposure. We also performed MR with MDD as the exposure, which only requires access to the genome-wide significant SNPs; we used the 'top 10k SNPs' dataset derived from the entire sample (135458 cases and 344901 controls) for this analysis.

(2) Depressive symptoms (DS): GWAS results were taken from Okbay et al.[16]. This is a meta-analysis that included the MDD-PGC study (*N*=18,759) and a case-control sample from the Genetic Epidemiology Research on Aging (GERA) Cohort (*N*=56,368); it also comprised an UK BioBank (UKBB) sample made up of general population (*N*=105,739), which represented the largest proportion of the total sample (~ 58% of total sample size). Depressive symptoms were measured by a self-reported questionnaire.

GWAS of phenotypes (3) to (5) was based on the UKBB sample. We downloaded GWAS summary statistics from the Neale Lab (https://sites.google.com/broadinstitute.org/ukbbgwasresults/). GWAS analysis was performed using linear models with adjustment for population stratification; details of the analytic approach is given in https://github.com/Nealelab/UK_Biobank_GWAS/tree/master/imputed-v2-gwas. For binary outcome (phenotype 5), we converted the regression coefficients obtained from the linear model to those under a

logistic model, based on methodology presented in [17].

(3) Longest period of depressed/low mood: This item was based on response to a question from the self-reported questionnaire for UKBB participants. The question was 'How many weeks was the longest period when you were feeling depressed or down?' (N = 104,190). Response to this question was only collected from participants who indicated they have felt depressed or down for at least one whole week. Inverse-rank normal transformation was performed prior to analysis.

(4) Number of episodes with depressed/low mood: This item was based on response to the question 'How many periods have you had when you were feeling depressed or down for at least a whole week? (N = 104,190) in the UKBB questionnaire. Again information was only collected for those who indicated having felt depressed or down for one whole week.

(5) History of deliberate self-harm (DSH) or suicide: The analyses was based on self-reported history of deliberate self-harm or suicide attempt among UKBB participants. There were 224 positive responses among 381,462 participants (according to https://biobank.ctsu.ox.ac.uk/crystal/field.cgi?id=20002). The low number of positive cases may be due to under-reporting of such events. The control subjects are likely mixed with positive cases, and may be considered analogous to being only weakly 'screened' or almost 'unscreened'. This does not render the analysis invalid, and the use of unscreened subjects is quite common in GWAS[18]. However the power of the study will be improved if reporting bias can be eliminated.

Mendelian randomization (MR) analysis

As described above, MR is an analytic approach to causal inference, using genetic variants as 'instruments' to represent the exposure. We first performed MR with lipid traits as the exposure and depression phenotypes as the outcome, then did MR in the reverse direction.

We conducted MR with several different methods, including the 'inverse-variance weighted' (MR-IVW)[19], Egger regression (MR-Egger)[20] and Generalized Summary-data-based Mendelian Randomization (GSMR)[21] approaches. Note that MR-Egger and GSMR are able to give valid estimates of causal effects in the presence of imbalanced horizontal pleiotropy.

The IVW framework is very widely used in MR studies. Here we used an IVW approach that is able to account for SNP correlations as described in Burgess et al.[22]. Briefly, assume $\hat{\beta}_{YG}$ to be the vector of estimated regression coefficients when the outcome is regressed on genetic instruments and σ_{YG} to be the corresponding standard errors (SE), and $\hat{\beta}_{XG}$ to be the estimated coefficients when the risk factor is regressed on the genetic instruments with SE σ_{XG}. We also assume the correlation between two genetic variants G_1 and G_2 to be ρ_{G1G2}, and $\Sigma_{G_1G_2} = \rho_{G_1G_2}\sigma_{YG_1}\sigma_{YG_2}$.

The estimate from a weighted generalized linear regression can be formulated by

$$\hat{\beta} = \left(\hat{\beta}'_{XG}\Sigma\hat{\beta}_{XG}\right)^{-1}\hat{\beta}'_{XG}\Sigma^{-1}\hat{\beta}_{YG}$$

with SE

$$SE(\hat{\beta}) = \sqrt{\left(\hat{\beta}'_{XG}\Sigma\hat{\beta}_{XG}\right)^{-1}}$$

A similar approach may be used for MR-Egger, which allows an intercept term in the weighted regression. Please also refer to ref. [20,23] for details. The presence of imbalanced horizontal pleiotropy could be assessed by whether the intercept term is significantly different from zero.

As remarked by Burgess et al.[22], inclusion of a larger panel of variants in partial LD as instruments may enable higher variance to be explained, thus improving the power of MR. Including "redundant" SNPs in addition to the causal variant(s) do not improve power but also will not invalidate the results. However, including too many variants with high correlations may also result in unstable causal estimates[24]. In this study, we performed LD-clumping of genetic instruments at a primary r^2 threshold of 0.1, but also repeated the analysis with r^2=0.05 and 0.15 to ensure that the results are robust to the choice of clumping threshold. Only SNPs that passed genome-wide significance (p< 5E-8) were included as instruments. Analysis was performed with the R packages "MendelianRandomization"[25] and "TwoSampleMR"[26]. If a SNP was not available in the outcome GWAS, we allowed the use a "proxy SNP" provided the r^2 was at least 0.8 with the original SNP. LD information was taken from the 1000 Genomes European samples. For this set of analyses, we primarily present the results from MR-IVW if there is no significant directional pleiotropy (p>0.05); otherwise the estimates from MR-Egger are reported.

Another recently developed analytic framework, called GSMR, also takes into account of horizontal pleiotropy but operates based on the exclusion of 'outlier' or heterogeneous genetic instruments that are likely pleiotropic (the technique is also known as 'HEIDI-outlier')[21]. The GSMR framework also employed a slightly different formula from the conventional IVW approach by modelling variance of both $\hat{\beta}_{XG}$ and $\hat{\beta}_{YG}$. Correlated variants can be accommodated. We employed the GSMR R package from http://cnsgenomics.com/software/gsmr/. Please refer to Zhu et al.[21] for details.

For MR analysis with < 3 genetic instruments, we employed MR-IVW as MR-Egger and GSMR cannot be reliably performed. For single genetic instrument, the Wald ratio approach was used.

We performed bi-directional MR in this study by considering lipid levels and depression-related traits as the exposure in turn.

Multiple testing control by FDR

Multiple testing was controlled by the false discovery rate (FDR) approach according to the Benjamini-Hochberg method[27], which controls the expected *proportion* of false positives among the rejected

hypotheses. For example, if we performed a total of 100 hypothesis tests, and 20 achieved FDR<0.05; then among these 20 tests, we expect on average (~ 20*0.05=) 1 result to be falsely positive. In this study we set a FDR threshold of 0.05 to declare significance. Note that FDR control by the Benjamini-Hochberg method is also valid under positive (regression) dependency of hypothesis tests[28].

RESULTS

Lipid traits as exposure and depression-related phenotypes as outcome

LDL-c as exposure

The MR results are presented in Table 1. We employed a primary LD-clumping r^2 threshold of 0.1, but also performed further analysis with other thresholds (0.05 or 0.15). We expect that for true positive associations, the results will be largely consistent regardless of the choice of clumping thresholds. We observed that lower LDL-c is casually associated with MDD (MR-IVW, OR for one SD *de*crease in LDL-c=1.073, 95% CI 1.047 - 1.100, *p*=3.15E-8; GSMR, OR=1.066, CI 1.043-1.089, *p*=1.13E-08; r^2=0.1). We also observed similar inverse associations with depressive symptoms (DS) and duration of the longest period of depressed/low mood. We observed consistently significant results (FDR<0.05) for the above phenotypes regardless of the analytic method and the r^2 threshold used. Of note, a strongly significant association with MDD was observed using GSMR at r^2 = 0.15 (OR = 1.076, CI 1.058-1.094, *p* = 7.13E-18, FDR = 2.14E-16).

HDL-c as exposure

We observed inverse causal associations between HDL-c and DS with GSMR (beta = 0.0183 for every SD *de*crease in HDL-c, CI: 0.0061-0.0301; r^2=0.1) (Table 2). Similar results were observed with the r^2 threshold was changed to 0.05 or 0.15. Also, we found inverse associations of HDL-c with self-reported deliberate self-harm or suicide by MR-Egger (OR for one SD *de*crease in HDL-c = 2.173, CI 1.395-3.385; r^2=0.1); similar significant association was also observed when r^2 = 0.15. No other significant results that passed FDR correction were found. We noted nominally significant associations of HDL-c with MDD in a positive direction, however the results did not withstand FDR control at the preset threshold.

Total cholesterol (TC) as exposure

Results are presented in Table 3. We found an inverse association between TC and MDD (MR-Egger, OR for one SD *de*crease in TC = 1.079, CI: 1.035-1.124; GSMR, OR=1.034, CI:1.009-1.0604; r^2=0.1) as well as the longest duration of depressed mood (MR-IVW, beta=0.0451 for every SD decrease in TC, CI: 0.0252-0.0650). Similar significant associations were found with GSMR and at a higher r^2 threshold of 0.15.

TG as exposure

As shown in Table 4, TG was causally associated with higher DS (MR-IVW, beta for every SD increase in TG=0.0394, CI: 0.0207-0.0582), increased number of episodes of depressed mood (beta=0.0571, CI: 0.0302-0.0841) and increased risks self-reported DSH or suicide (OR for every SD increase in TG=1.582,

CI: 1.156-2.166). GSMR and MR-IVW gave comparable effect size estimates. Again similar significant findings were observed at a different r^2 thresholds, and with different analytic methods.

Depression phenotypes as exposure and lipid traits as outcome

To assess whether depression or related phenotypes cause changes in lipid levels, we performed MR analysis in the reversed direction. For depression phenotypes (3) and (4) (i.e. longest duration of low/depressed mood and number of episodes of low/depressed mood), there are no genome-wide significant SNPs which also matched to the set of SNPs included in the lipid GWAS; we therefore did not include these two phenotypes in this analysis.

MDD as exposure

Results are given in Table 5. No results reached significance at FDR threshold of 0.05. MDD was positively associated with raised TG at nominal significance (p = 0.034) using GSMR, however this association did not survive multiple testing control by FDR.

Depressive symptoms and DSH/suicide as exposure

We also did not find any results reaching significance in this set of analyses. Note that we only have 2 and 1 SNP(s) respectively as instruments for MR analysis of DS and DSH/suicide, hence tests for pleiotropy cannot be carried out. We employed MR-IVW and Wald ratio for this set of analysis.

DISCUSSIONS

In this study, we have employed MR to reveal causal relationships between lipid levels and depression-related phenotypes. Interestingly, we found evidence that lower LDL-c and TC were causally related to higher risks of MDD and more prolonged depressed/low mood. Lower LDL-c was also causally linked to more severe DS. As for HDL-c, we also observed lower levels of HDL-c being casually related to increased DS, as well as heightened risks of DSH or suicide. It is reassuring that most of the significant findings are robust to different analytic approaches or r^2 thresholds used.

As introduced earlier, a number of clinical studies have investigated the link between cholesterol levels and depression. Notably, meta-analyses have reported inverse associations of LDL-c[6] and TC[7] with depression, consistent with the current findings. This study provided further evidence of such associations with very large sample sizes, and showed for the first time that the relationship is likely causal.

The mechanisms underlying the relationship of cholesterol levels and depression remain unclear, but some studies suggested that reduction in cholesterol may lead to decrease serotonergic transmission[4,29]. It was suggested that the ligand binding function of $5HT_{1A}$ receptor may be affected by cholesterol depletion[30], and other works also reported the involvement of other types of serotonin receptors such as $5\text{-}HT_{2A}$[31,32] and $5\text{-}HT_7$[33]. Nevertheless, serotonergic dysfunction alone may not be sufficient in explaining the development of

depression. For example, many patients do not respond to antidepressants targeting the serotonergic system. Further experimental studies are required to elucidate the exact mechanisms underlying the associations.

As for TG, we observed positive causal associations with DS, number of episodes of depressed/low mood and risks of DSH or suicide, which is in the opposite direction of association as compared to cholesterol levels. A previous meta-analysis[8] showed that suicidal psychiatric *patients* had lower TG than non-suicidal *patients*, but such difference was not significant when comparing suicidal patients with healthy controls. However, there was significant heterogeneity in the analysis and statistical evidence of publication bias; also as many studies are cross-sectional or case-control in nature, casual relationship may not be accurately determined. Our analysis is *not* focused on suicidal risks *within* patients, so is not contradictory with findings from Wu et al. Some studies have found raised TG in depression (e.g.[34-37]), but systematic review and meta-analysis on the topic is lacking. Of note, a prospective study in Finnish young adults showed that steeply rising TG levels throughout childhood and adulthood was associated with increased DS in adulthood[35], consistent with the present finding of a causal role of TG in the development of depression.

We also studied causal relationship in the reversed direction, but did not find evidence that depression and related traits cause changes to lipid levels. The number of instrument SNPs included is relatively small especially for DS and history of DSH/suicide, which may lead to lower power to detect potential causal relationships. Repeating the MR analysis based on larger GWAS samples may be warranted in the future.

Limitations

There are several limitations to the current study. First of all, there is likely heterogeneity within each study sample. For example, within the sample of MDD patients, they might be substantial differences with respect to disease etiology, clinical symptoms, course of illness and so on. Here we have not studied how the causal relationship with lipids may differ with different depression subtypes or symptoms. In a similar vein, we have not studied how the causal relationship may be affected by the clinical background of patients. For instance, age, sex, baseline metabolic profile, family history, past medical and drug history etc. may all affect the relationship between lipid levels and depression. One possible direction is for future studies is more in-depth analysis on stratified samples (e.g. male or female-only; young or elderly subjects only).

Another limitation is that for studies that included the UKBB sample, depression traits are self-reported instead of being assessed by a health-care professional according to certain clinical criteria. There may be heterogeneity in the definition of ‘feeling depression or down’ for different people. However, detailed clinical assessment is very costly and some subjectivity is still inevitable; the current approach allows much larger sample sizes to be studied.

With regards to the MR approach used in this study, it is also not without limitations. As we employed genetic instruments to model the risk factor, the analysis reflects effects of a *chronic* exposure of (genetically)

lowered lipid levels to the outcomes. The effects of shorter-term exposures, such as taking a LDL-lowering drug for 1 year, cannot be inferred with full confidence from MR analysis alone. Also, non-linear relationships between the exposure and outcome are not captured with the present method. Our analysis mainly found that low cholesterol and high TG may be causal risk factors for increased depression risks or symptoms; however the relationship in the opposite direction (effects of depression traits on lipids) is less clear due to inadequate or relatively small number of genetic instruments for most analyses.

We note that previous epidemiological studies are not all consistent and a few revealed higher cholesterol in depressed subjects (e.g.[38,39]). Heterogeneity in samples and study design may partially explain this phenomenon; it is also possible that that some shared (but non-causal) genetic or environmental risk factors are present for both depression and dyslipidemia.

Clinical implications

We believe the current study has clinical importance as both lipid disorders and depression are common medical conditions, and lipid levels are widely measured in daily clinical practice. We highlight a few areas of potential clinical relevance here, but we also caution that due to various limitations, one should not over-interpret the current findings.

One area of interest is that cholesterol or TG levels may serve as predictive biomarkers for depression or suicide. Since the relationship is likely causal, altered lipid levels are likely present before the onset of depression. However, the effect size observed in this study are relatively modest. For example, for every SD unit decrease in LDL-c (38.7 mg/dL), the risk of MDD is roughly increased by ~ 7%. The observed effects sizes for DSH/suicide were higher, but the estimates are less precise due to small number of cases. However, the predictive value could be improved by combining with other biomarker or clinical risk factors and will be an interesting topic for further studies.

Another relevant topic is whether lipid-lowering therapies may contribute to increased depression or suicidal risks. This is a controversial topic and no consistent conclusions have been reached despite numerous studies[40-42]. While our findings did suggest lower cholesterol levels are causal risk factors for depression or suicide, this study is *less* suited to infer the effects of lipid-lowering therapies, owing to several limitations. Firstly, as already discussed earlier, MR models the effects of long-term exposure to an outcome, and effects of shorter exposure at later stages of life may not be reliably determined. In addition, different lipid-lowering drugs act in different pathways, and the effects on depression could also differ. Also, many lipid-lowering drugs have effects on more than one type of lipids, for example statins lower LDL-c but also have effects on reducing TG[43] and raising HDL-c[42]. According to the current study, the latter two effects may reduce DS although lowered LDL-c may result in the opposite. The overall effect is however difficult to judge. Finally, the effects and side-effects of lipid-lowering drugs may differ from patient to patient, and careful judgement of cardiovascular benefit vs other side-effects is important.

However, this study suggests that increased awareness and surveillance for psychiatric problems might be needed for patients at high risk for depression and/or suicide who also have low cholesterol levels or high TG. Similarly, if aggressive lowering of LDL-c is required for such patients, it might be prudent for the clinician to be aware of possible emergence or worsening of depressive symptoms. From a therapeutic point of view, it will also be interesting to study whether TG-lowering therapies may ameliorate DS in patients with comorbid hypertriglyceridemia and depression.

In conclusion, through an MR analysis with large sample sizes, we found that low cholesterol levels and high TG may be causal risk factors for depression and related traits. The findings helped shed light on the mechanisms underlying depression, and might also have clinical implications.

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Author contributions

Conceived and designed the study: HCS. Study supervision: HCS. Main data analysis: HCS, CKLC. Data interpretation: HCS, YYC. Drafted the manuscript: HCS, YYC.

Conflicts of interest

The author declares no conflict of interest.

Table 1 Mendelian randomization (MR) result with LDL-c as exposure and depression traits as outcome

Exposure	Outcome	r^2	bxy	bxy_se	bxy_pval	FDR	nsnps	n_pleio	Pleio.p	Method
MR-IVW/Egger										
LDL	**MDD-2018**	0.1	**-0.0706**	**0.0128**	**3.15E-08**	**3.15E-07**	189	-	0.128	IVW
LDL	**DepSymptoms**	0.1	**-0.0198**	**0.0059**	**7.96E-04**	**2.65E-03**	180	-	0.091	IVW
LDL	**LongestDepression**	0.1	**-0.0449**	**0.0096**	**2.70E-06**	**2.03E-05**	188	-	0.806	IVW
LDL	NumOfDepressionEpisodes	0.1	0.0100	0.0077	1.95E-01	2.78E-01	188	-	0.427	IVW
LDL	SelfReported_DSH_Suicide	0.1	-0.1750	0.1702	3.04E-01	3.80E-01	188	-	0.006	Egger
GSMR										
LDL	**MDD-2018**	0.1	**-0.0638**	**0.0112**	**1.13E-08**	**1.70E-07**	188	1	-	GSMR
LDL	**DepSymptoms**	0.1	**-0.0126**	**0.0052**	**1.61E-02**	**3.44E-02**	180	0	-	GSMR
LDL	**LongestDepression**	0.1	**-0.0350**	**0.0088**	**7.33E-05**	**2.75E-04**	187	1	-	GSMR
LDL	NumOfDepressionEpisodes	0.1	0.0057	0.0082	4.87E-01	5.84E-01	188	0	-	GSMR
LDL	SelfReported_DSH_Suicide	0.1	0.0689	0.1109	5.35E-01	6.17E-01	186	2	-	GSMR
Analysis with other r^2 thresholds										
LDL	**MDD-2018**	0.05	**-0.0623**	**0.0155**	**5.99E-05**	**2.57E-04**	145	-	0.313	IVW
LDL	**DepSymptoms**	0.05	**-0.0167**	**0.0077**	**3.07E-02**	**5.75E-02**	139	-	0.806	IVW
LDL	**LongestDepression**	0.05	**-0.0367**	**0.0110**	**8.91E-04**	**2.67E-03**	144	-	0.387	IVW
LDL	NumOfDepressionEpisodes	0.05	0.0041	0.0094	6.62E-01	7.36E-01	144	-	0.191	IVW
LDL	SelfReported_DSH_Suicide	0.05	-0.3276	0.2027	1.06E-01	1.68E-01	144	-	0.023	Egger
LDL	**MDD-2018**	0.05	**-0.0361**	**0.0142**	**1.10E-02**	**2.54E-02**	144	1	-	GSMR
LDL	DepSymptoms	0.05	-0.0101	0.0067	1.30E-01	1.94E-01	139	0	-	GSMR
LDL	LongestDepression	0.05	-0.0210	0.0113	6.21E-02	1.03E-01	144	0	-	GSMR
LDL	NumOfDepressionEpisodes	0.05	0.0021	0.0105	8.38E-01	8.67E-01	144	0	-	GSMR
LDL	SelfReported_DSH_Suicide	0.05	-0.0380	0.1417	7.88E-01	8.45E-01	142	2	-	GSMR
LDL	**MDD-2018**	0.15	**-0.0469**	**0.0109**	**1.72E-05**	**8.62E-05**	224	-	0.152	IVW
LDL	**DepSymptoms**	0.15	**-0.0115**	**0.0050**	**2.31E-02**	**4.62E-02**	215	-	0.703	IVW
LDL	**LongestDepression**	0.15	**-0.0335**	**0.0078**	**1.69E-05**	**8.62E-05**	223	-	0.751	IVW
LDL	NumOfDepressionEpisodes	0.15	0.0072	0.0068	2.86E-01	3.72E-01	223	-	0.431	IVW
LDL	SelfReported_DSH_Suicide	0.15	-0.1670	0.1469	2.56E-01	3.48E-01	223	-	0.001	Egger
LDL	**MDD-2018**	0.15	**-0.0733**	**0.0085**	**7.13E-18**	**2.14E-16**	223	1	-	GSMR
LDL	**DepSymptoms**	0.15	**-0.0107**	**0.0042**	**1.09E-02**	**2.54E-02**	213	2	-	GSMR
LDL	**LongestDepression**	0.15	**-0.0200**	**0.0070**	**4.56E-03**	**1.24E-02**	221	2	-	GSMR
LDL	NumOfDepressionEpisodes	0.15	0.0130	0.0064	4.02E-02	7.09E-02	222	1	-	GSMR
LDL	SelfReported_DSH_Suicide	0.15	-0.0055	0.0842	9.48E-01	9.48E-01	221	2	-	GSMR

MDD-2018: Major depressive disorder (GWAS data from Wray et al. 2018); DepSymptoms: depressive symptoms; LongestDepression, longest duration of depressed or low mood (UK Biobank data; NumOfDepressionEpisodes, number

of episodes with depressed or low mood for at least one week (UK BioBank data); SelfReported_DSH_Suicide, history of deliberate self-harm or suicide (UK BioBank data).

r^2: LD-clumping r^2 threshold; bxy: regression coefficient from MR; bxy_se: standard error of bxy; bxy_pval: p-value of bxy; FDR, false discovery rate (ie *q*-value) corresponding to the observed p-value; nsnps: total number of SNPs used as genetic instruments; n_pleio: number of SNPs that are likely pleiotropic and excluded based on HEIDI-outlier test in GSMR; Pleio_p, pleiotropy p-value based on testing whether the intercept from Egger regression is significantly different from zero; Method: MR method used.

IVW: inverse variance weighted approach; Egger, Egger regression approach; GSMR, Generalized Summary-data-based Mendelian Randomization.

Results with FDR < 0.05 (i.e. passed FDR control for multiple testing) are in bold.

Table 2 MR result with HDL-c as exposure and depression traits as outcome

Exposure	Outcome	r^2	bxy	bxy_se	bxy_pval	FDR	nsnps	n_pleio	Pleio.p	Method
MR-IVW/Egger										
HDL	MDD-2018	0.1	0.0147	0.0175	4.01E-01	5.73E-01	214	-	0.980	IVW
HDL	DepSymptoms	0.1	0.0036	0.0115	7.56E-01	8.40E-01	204	-	0.003	Egger
HDL	LongestDepression	0.1	-0.0123	0.0121	3.11E-01	4.90E-01	215	-	0.750	IVW
HDL	NumOfDepressionEpisodes	0.1	-0.0036	0.0114	7.51E-01	8.40E-01	215	-	0.496	IVW
HDL	**SelfReported_DSH_Suicide**	0.1	**-0.7760**	**0.2263**	**6.04E-04**	**9.05E-03**	215	-	0.009	Egger
GSMR										
HDL	MDD-2018	0.1	0.0217	0.0140	1.21E-01	2.43E-01	213	1	-	GSMR
HDL	**DepSymptoms**	0.1	**-0.0183**	**0.0062**	**3.32E-03**	**2.49E-02**	199	5	-	GSMR
HDL	LongestDepression	0.1	-0.0124	0.0112	2.67E-01	4.49E-01	214	1	-	GSMR
HDL	NumOfDepressionEpisodes	0.1	0.0092	0.0104	3.78E-01	5.66E-01	213	2	-	GSMR
HDL	SelfReported_DSH_Suicide	0.1	-0.2484	0.1387	7.34E-02	2.00E-01	215	0	-	GSMR
Analysis with other r^2 thresholds										
HDL	MDD-2018	0.05	0.0128	0.0181	4.79E-01	6.54E-01	169	-	0.685	IVW
HDL	DepSymptoms	0.05	0.0068	0.0125	5.88E-01	7.35E-01	163	-	0.014	Egger
HDL	LongestDepression	0.05	-0.0081	0.0121	5.05E-01	6.58E-01	170	-	0.455	IVW
HDL	NumOfDepressionEpisodes	0.05	0.0027	0.0132	8.39E-01	8.49E-01	170	-	0.497	IVW
HDL	SelfReported_DSH_Suicide	0.05	-0.2957	0.1602	6.50E-02	2.00E-01	170	-	0.706	IVW
HDL	MDD-2018	0.05	0.0189	0.0159	2.37E-01	4.44E-01	168	1	-	GSMR
HDL	**DepSymptoms**	0.05	**-0.0213**	**0.0070**	**2.37E-03**	**2.37E-02**	160	3	-	GSMR
HDL	LongestDepression	0.05	-0.0045	0.0128	7.25E-01	8.40E-01	169	1	-	GSMR
HDL	NumOfDepressionEpisodes	0.05	0.0131	0.0118	2.69E-01	4.49E-01	168	2	-	GSMR
HDL	SelfReported_DSH_Suicide	0.05	-0.2984	0.1562	5.61E-02	2.00E-01	170	0	-	GSMR
HDL	MDD-2018	0.15	0.0356	0.0156	2.27E-02	9.73E-02	249	-	0.498	IVW
HDL	DepSymptoms	0.15	-0.0138	0.0077	7.26E-02	2.00E-01	236	-	0.070	IVW
HDL	LongestDepression	0.15	-0.0173	0.0105	1.01E-01	2.43E-01	250	-	0.154	IVW
HDL	NumOfDepressionEpisodes	0.15	0.0239	0.0154	1.21E-01	2.43E-01	250	-	0.002	Egger
HDL	**SelfReported_DSH_Suicide**	0.15	**-0.5458**	**0.2060**	**8.08E-03**	**4.85E-02**	250	-	0.022	Egger
HDL	MDD-2018	0.15	0.0301	0.0126	1.69E-02	8.46E-02	248	1	-	GSMR
HDL	**DepSymptoms**	0.15	**-0.0229**	**0.0057**	**6.22E-05**	**1.87E-03**	229	7	-	GSMR
HDL	LongestDepression	0.15	-0.0019	0.0101	8.49E-01	8.49E-01	250	0	-	GSMR
HDL	NumOfDepressionEpisodes	0.15	0.0025	0.0094	7.92E-01	8.48E-01	248	2	-	GSMR
HDL	SelfReported_DSH_Suicide	0.15	-0.1942	0.1244	1.18E-01	2.43E-01	249	1	-	GSMR

Please refer to table 1 for legends.

Table 3 MR result with total cholesterol (TC) as exposure and depression traits as outcome

Exposure	Outcome	r^2	bxy	bxy_se	bxy_pval	FDR	nsnps	n_pleio	Pleio.p	Method
MR-IVW/Egger										
TC	**MDD-2018**	0.1	**-0.0759**	**0.0210**	**2.94E-04**	**2.21E-03**	228	-	0.046	Egger
TC	DepSymptoms	0.1	0.0134	0.0097	1.67E-01	3.34E-01	222	-	0.022	Egger
TC	**LongestDepression**	0.1	**-0.0451**	**0.0102**	**9.05E-06**	**1.41E-04**	236	-	0.266	IVW
TC	NumOfDepressionEpisodes	0.1	0.0019	0.0087	8.28E-01	8.87E-01	236	-	0.196	IVW
TC	SelfReported_DSH_Suicide	0.1	-0.1631	0.1787	3.61E-01	5.86E-01	236	-	0.032	Egger
GSMR										
TC	**MDD-2018**	0.1	**-0.0337**	**0.0127**	**8.29E-03**	**3.11E-02**	225	3	-	GSMR
TC	DepSymptoms	0.1	-0.0017	0.0057	7.72E-01	8.58E-01	219	3	-	GSMR
TC	**LongestDepression**	0.1	**-0.0374**	**0.0098**	**1.34E-04**	**1.34E-03**	235	1	-	GSMR
TC	NumOfDepressionEpisodes	0.1	0.0058	0.0091	5.21E-01	7.14E-01	236	0	-	GSMR
TC	SelfReported_DSH_Suicide	0.1	0.0732	0.1216	5.47E-01	7.14E-01	235	1	-	GSMR
Analysis with other r^2 thresholds										
TC	MDD-2018	0.05	-0.0289	0.0179	1.06E-01	2.65E-01	173	-	0.089	IVW
TC	DepSymptoms	0.05	-0.0119	0.0083	1.50E-01	3.21E-01	165	-	0.065	IVW
TC	LongestDepression	0.05	-0.0244	0.0131	6.27E-02	1.71E-01	174	-	0.243	IVW
TC	NumOfDepressionEpisodes	0.05	0.0000	0.0101	1.00E+00	1.00E+00	174	-	0.087	IVW
TC	SelfReported_DSH_Suicide	0.05	-0.4013	0.2079	5.35E-02	1.61E-01	174	-	0.024	Egger
TC	MDD-2018	0.05	-0.0068	0.0156	6.64E-01	7.97E-01	171	2	-	GSMR
TC	DepSymptoms	0.05	-0.0063	0.0070	3.71E-01	5.86E-01	162	3	-	GSMR
TC	LongestDepression	0.05	-0.0256	0.0120	3.23E-02	1.08E-01	174	0	-	GSMR
TC	NumOfDepressionEpisodes	0.05	0.0074	0.0111	5.07E-01	7.14E-01	174	0	-	GSMR
TC	SelfReported_DSH_Suicide	0.05	-0.0748	0.1490	6.16E-01	7.70E-01	170	4	-	GSMR
TC	**MDD-2018**	0.15	**-0.0372**	**0.0127**	**3.52E-03**	**1.51E-02**	267	-	0.746	IVW
TC	DepSymptoms	0.15	0.0106	0.0088	2.26E-01	4.24E-01	258	-	0.001	Egger
TC	**LongestDepression**	0.15	**-0.0421**	**0.0095**	**9.38E-06**	**1.41E-04**	277	-	0.729	IVW
TC	NumOfDepressionEpisodes	0.15	0.0025	0.0078	7.54E-01	8.58E-01	277	-	0.493	IVW
TC	SelfReported_DSH_Suicide	0.15	0.0026	0.1617	9.87E-01	1.00E+00	277	-	0.008	Egger
TC	**MDD-2018**	0.15	**-0.0356**	**0.0108**	**1.01E-03**	**6.04E-03**	262	5	-	GSMR
TC	DepSymptoms	0.15	-0.0077	0.0050	1.26E-01	2.90E-01	253	5	-	GSMR
TC	**LongestDepression**	0.15	**-0.0249**	**0.0084**	**3.01E-03**	**1.50E-02**	276	1	-	GSMR
TC	NumOfDepressionEpisodes	0.15	0.0086	0.0078	2.71E-01	4.79E-01	276	1	-	GSMR
TC	SelfReported_DSH_Suicide	0.15	0.0664	0.1046	5.26E-01	7.14E-01	273	4	-	GSMR

Please refer to table 1 for legends.

Table 4 MR result with triglycerides (TG) as exposure and depression traits as outcome

Exposure	Outcome	r^2	bxy	bxy_se	bxy_pval	FDR	nsnps	n_pleio	Pleio.p	Method
MR-IVW/Egger										
TG	MDD-2018	0.1	0.0381	0.0194	5.01E-02	8.35E-02	125	-	0.058	IVW
TG	**DepSymptoms**	**0.1**	**0.0394**	**0.0096**	**3.83E-05**	**1.28E-04**	121	-	0.181	IVW
TG	LongestDepression	0.1	0.0161	0.0150	2.85E-01	3.29E-01	139	-	0.341	IVW
TG	**NumOfDepressionEpisodes**	**0.1**	**0.0571**	**0.0138**	**3.31E-05**	**1.24E-04**	139	-	0.375	IVW
TG	**SelfReported_DSH_Suicide**	**0.1**	**0.4588**	**0.1603**	**4.21E-03**	**1.15E-02**	139	-	0.101	IVW
GSMR										
TG	MDD-2018	0.1	0.0345	0.0175	4.83E-02	8.35E-02	124	1	-	GSMR
TG	**DepSymptoms**	**0.1**	**0.0379**	**0.0080**	**1.99E-06**	**1.19E-05**	120	1	-	GSMR
TG	LongestDepression	0.1	-0.0047	0.0138	7.33E-01	7.33E-01	138	1	-	GSMR
TG	**NumOfDepressionEpisodes**	**0.1**	**0.0548**	**0.0125**	**1.24E-05**	**6.20E-05**	139	0	-	GSMR
TG	**SelfReported_DSH_Suicide**	**0.1**	**0.4679**	**0.1672**	**5.14E-03**	**1.29E-02**	138	1	-	GSMR
Analysis with other r^2 thresholds										
TG	MDD-2018	0.05	0.0290	0.0230	2.07E-01	2.82E-01	105	-	0.121	IVW
TG	DepSymptoms	0.05	0.0052	0.0137	7.02E-01	7.26E-01	98	-	0.018	Egger
TG	LongestDepression	0.05	-0.0192	0.0159	2.27E-01	2.96E-01	113	-	0.294	IVW
TG	NumOfDepressionEpisodes	0.05	0.0261	0.0150	8.13E-02	1.28E-01	113	-	0.133	IVW
TG	SelfReported_DSH_Suicide	0.05	0.2099	0.1788	2.40E-01	3.00E-01	113	-	0.505	IVW
TG	MDD-2018	0.05	0.0299	0.0195	1.25E-01	1.79E-01	103	2	-	GSMR
TG	**DepSymptoms**	**0.05**	**0.0304**	**0.0089**	**6.04E-04**	**1.81E-03**	97	1	-	GSMR
TG	LongestDepression	0.05	-0.0114	0.0152	4.53E-01	5.03E-01	113	0	-	GSMR
TG	NumOfDepressionEpisodes	0.05	0.0240	0.0141	8.89E-02	1.33E-01	113	0	-	GSMR
TG	SelfReported_DSH_Suicide	0.05	0.3910	0.1873	3.68E-02	7.90E-02	113	0	-	GSMR
TG	**MDD-2018**	**0.15**	**0.0375**	**0.0154**	**1.48E-02**	**3.42E-02**	155	-	0.235	IVW
TG	DepSymptoms	0.15	0.0241	0.0120	4.44E-02	8.35E-02	145	-	0.024	Egger
TG	LongestDepression	0.15	0.0062	0.0122	6.12E-01	6.56E-01	178	-	0.417	IVW
TG	**NumOfDepressionEpisodes**	**0.15**	**0.0446**	**0.0107**	**3.17E-05**	**1.24E-04**	178	-	0.053	IVW
TG	**SelfReported_DSH_Suicide**	**0.15**	**0.7192**	**0.1292**	**2.60E-08**	**2.60E-07**	178	-	0.214	IVW
TG	MDD-2018	0.15	0.0230	0.0116	4.66E-02	8.35E-02	154	1	-	GSMR
TG	**DepSymptoms**	**0.15**	**0.0390**	**0.0059**	**3.98E-11**	**1.19E-09**	143	2	-	GSMR
TG	LongestDepression	0.15	0.0107	0.0094	2.56E-01	3.08E-01	176	2	-	GSMR
TG	**NumOfDepressionEpisodes**	**0.15**	**0.0505**	**0.0090**	**1.92E-08**	**2.60E-07**	177	1	-	GSMR
TG	**SelfReported_DSH_Suicide**	**0.15**	**0.6070**	**0.1134**	**8.75E-08**	**6.56E-07**	177	1	-	GSMR

Please refer to table 1 for legends.

Table 5 MR result with MDD as exposure and lipid traits as outcome

Exposure	Outcome	r^2	bxy	bxy_se	bxy_pval	FDR	nsnps	n_pleio	Pleio.p	Method
MR-IVW/Egger										
MDD-2018	HDL	0.1	-0.0233	0.0310	4.52E-01	7.81E-01	39	-	0.650	IVW
MDD-2018	LDL	0.1	-0.3693	0.1932	5.59E-02	4.45E-01	39	-	0.049	Egger
MDD-2018	TC	0.1	-0.0339	0.0348	3.29E-01	7.81E-01	39	-	0.155	IVW
MDD-2018	TG	0.1	0.0526	0.0325	1.05E-01	4.45E-01	39	-	0.394	IVW
GSMR										
MDD-2018	HDL	0.1	-0.0220	0.0263	4.04E-01	7.81E-01	39	0	-	GSMR
MDD-2018	LDL	0.1	-0.0015	0.0286	9.57E-01	9.71E-01	39	0	-	GSMR
MDD-2018	TC	0.1	-0.0150	0.0279	5.91E-01	7.88E-01	39	0	-	GSMR
MDD-2018	TG	0.1	0.0548	0.0259	3.41E-02	4.45E-01	39	0	-	GSMR
Analysis with other r^2 thresholds										
MDD-2018	HDL	0.05	-0.0182	0.0328	5.79E-01	7.88E-01	37	-	0.519	IVW
MDD-2018	LDL	0.05	-0.0162	0.0370	6.61E-01	8.13E-01	37	-	0.069	IVW
MDD-2018	TC	0.05	-0.0282	0.0366	4.41E-01	7.81E-01	37	-	0.340	IVW
MDD-2018	TG	0.05	0.0380	0.0335	2.56E-01	7.81E-01	37	-	0.320	IVW
MDD-2018	HDL	0.05	-0.0190	0.0275	4.88E-01	7.81E-01	37	0	-	GSMR
MDD-2018	LDL	0.05	0.0011	0.0298	9.71E-01	9.71E-01	37	0	-	GSMR
MDD-2018	TC	0.05	-0.0103	0.0291	7.25E-01	8.28E-01	37	0	-	GSMR
MDD-2018	TG	0.05	0.0428	0.0269	1.11E-01	4.45E-01	37	0	-	GSMR
MDD-2018	HDL/LDL/TC/TG	0.15	Same results as above							

Please refer to table 1 for legends.

Table 6 MR result with depressive symptoms or self-reported DSH/suicide as exposure and lipid traits as outcome

Exposure	Outcome	r^2	bxy	bxy_se	bxy_pval	FDR	nsnps	Method
DepSymptoms	HDL	0.1	-0.1415	0.1420	3.19E-01	7.71E-01	2	IVW
DepSymptoms	LDL	0.1	-0.0848	0.1520	5.77E-01	7.71E-01	2	IVW
DepSymptoms	TC	0.1	0.0286	0.1486	8.47E-01	8.47E-01	2	IVW
DepSymptoms	TG	0.1	0.1570	0.1352	2.46E-01	7.71E-01	2	IVW
SelfReported_DSH_Suicide	HDL	0.1	-0.0220	0.0277	4.28E-01	7.71E-01	1	Wald ratio
SelfReported_DSH_Suicide	LDL	0.1	0.0158	0.0284	5.79E-01	7.71E-01	1	Wald ratio
SelfReported_DSH_Suicide	TC	0.1	-0.0072	0.0281	7.97E-01	8.47E-01	1	Wald ratio
SelfReported_DSH_Suicide	TG	0.1	-0.0416	0.0237	7.88E-02	6.30E-01	1	Wald ratio

The results were identical when SNPs are clumped at r^2 thresholds of 0.05 or 0.15.

GSMR and MR-Egger are not applicable as there are too few SNPs.

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