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Original Article

Phenome-wide screening of the putative causal determinants of depression using genetic data

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Abstract

Depression is one of the most common mental health disorders and one of the top causes of disability throughout the world. The present study sought to identify putative causal associations between depression and hundreds of complex human traits through a genome-wide screening of genetic data and a hypothesis-free approach. We leveraged genome-wide association studies summary statistics for depression and 1504 complex traits and investigated potential causal relationships using the latent causal variable method. We identified 559 traits genetically correlated with depression risk at FDR < 5%. Of these, 46 were putative causal genetic determinants of depression, including lifestyle factors, diseases of the nervous system, respiratory disorders, diseases of the musculoskeletal system, traits related to the health of the gastrointestinal system, obesity, vitamin D levels and the use of prescription medications, among others. No phenotypes were identified as potential outcomes of depression. Our results suggest that genetic liability to multiple complex traits may contribute to a higher risk for depression. In particular, we show a putative causal genetic effect of pain, obesity and inflammation on depression. These findings provide novel insights into the potential causal determinants of depression and should be interpreted as testable hypotheses for future studies to confirm, which may facilitate the design of new prevention strategies to reduce depression's burden.

Introduction

Depression is one of the most common mental health disorders and one of the top causes of disability throughout the world (1). Its 12-month prevalence is estimated to be 4.4% worldwide, affecting 5.1% of females and 3.6% of males (2–4). Depression is characterized by a persistent low mood or anhedonia (i.e. loss of pleasure and interest) and other symptoms such as fatigue or loss of energy, significant weight loss and sleep disturbance (5).

Epidemiological studies have identified factors that contribute to the development of depression. For instance, there is evidence that social isolation, alcohol dependence, psychological stress and medical conditions, such as cancer, are risk factors for depression (6–9). Furthermore, several hypotheses propose mechanisms to explain the pathogenesis of depression, suggesting that genes, psychosocial stress and inflammation may play a role in the development of depression (10–12).

Depression is a heritable trait, with twin and family studies estimating its heritability around 38% (13). In addition, genome-wide association studies (GWAS) have identified 223 independent genetic variants related to depression (14) and have pointed out genetic correlations between depression and other complex traits such as anxiety, autism, ADHD, schizophrenia, bipolar disorder, coronary artery disease and body fat (15–18).

Pleiotropic effects, which can be either vertical or horizontal, explain genetic correlations (19). Horizontal pleiotropy refers to genetic variants that have an independent and direct effect on both traits (i.e. owing to a shared biological pathway). In contrast, vertical pleiotropy can be understood as a causal cascade in which the effect of a genetic variant on one trait is mediated by its effect on another trait (Fig. 1) (20).

Mendelian randomization methods, which employ genetic variants as instrumental variables, are commonly used in genetic epidemiological studies to infer potential causal relationships between a pair of traits. One of the essential assumptions of traditional Mendelian randomization methods is that vertical

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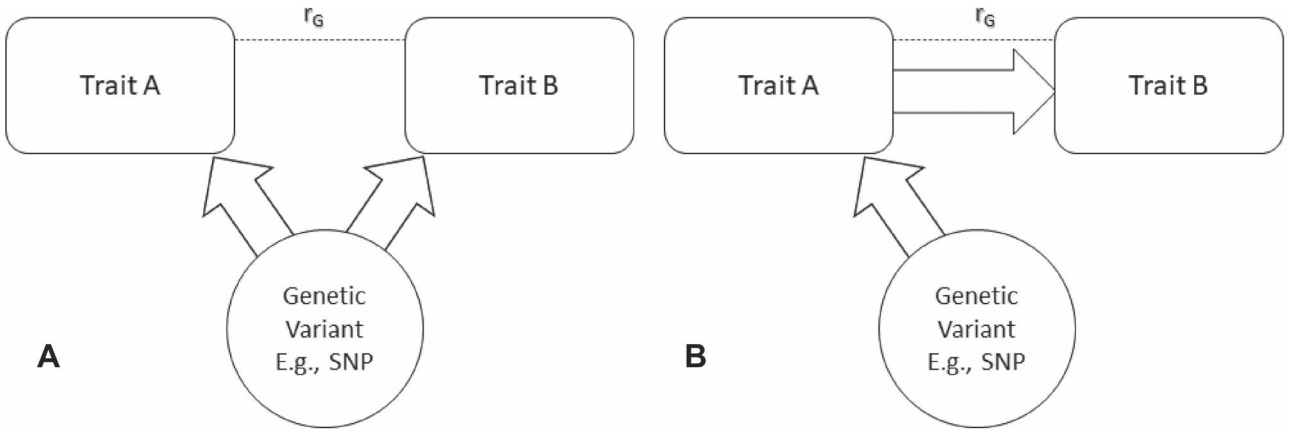

Figure 1. Illustration of horizontal and vertical pleiotropy concepts. (**A**) Horizontal pleiotropy: genetic variants independently influence the risk of traits A and B. (**B**) Vertical pleiotropy: genetic variants contribute to the risk of trait B through trait A, showing a potential causal relationship. r_G = genetic correlation.

pleiotropy drives the association between both traits (i.e. genetic variants are only associated with the outcome through the exposure) (21,22). If this assumption is violated through horizontal pleiotropic effects, results can be biased, increasing the risk for false-positive findings (23). Therefore, the latent causal variable (LCV) method was developed as an alternative to Mendelian randomization. LCV aims to assess potential causal associations between complex traits while accounting for potential horizontal pleiotropy. Advantages of the LCV method include that it is less susceptible to confounding by horizontal pleiotropy, it leverages genome-wide data and it is robust to sample overlap (24).

Despite the extensive efforts made to identify potential risk factors and outcomes of depression in previous observational and Mendelian randomization studies (25,26), there is still a need to uncover disease-modifying traits to screen individuals at a higher risk and enhance the design of prevention strategies. Here, we leverage a vast collection of GWAS summary statistics ($N = 1504$) and a larger sample size for depression than previous studies to perform LCV analyses and infer putative causal relationships between depression and other complex phenotypes. Our results should be interpreted as a set of testable hypotheses for future epidemiological and interventional studies.

Results

We identified 559 traits genetically correlated with depression risk at False Discovery Rate (FDR) < 5% (Supplementary Material, File S1). Of those traits, 37 revealed a putative causal genetic association with depression [genetic causality proportion (GCP); |GCP| > 0.60], while 9 showed evidence for limited partial genetic causality (|GCP| < 0.60). No phenotypes were identified as outcomes of depression. Putative risk factors of depression included physical health conditions, such as respiratory disorders, diseases of the musculoskeletal system, diseases of the nervous system and phenotypes related to the health of the gastrointestinal system, among others (Fig. 2). Similarly, lifestyle factors and the use of several medications increased the likelihood of depression (Table 1).

Physical health conditions inferred to increase risk of depression included malignant neoplasm of bronchus and lung (ICD10) (GCP = −0.60, $r_G = 0.29$), self-reported ulcerative colitis (GCP = −0.83, $r_G = 0.19$), high triglyceride levels (GCP = −0.72, $r_G = 0.15$), self-reported susceptibility to *Helicobacter pylori* infection (GCP = −0.82, $r_G = 0.38$), self-reported psoriasis (GCP = −0.77, $r_G = 0.19$), polyneuropathies and disorders of the peripheral nervous system (GCP = −0.70, $r_G = 0.25$) and obesity (GCP = −0.70, $r_G = 0.32$), among others. In contrast, high vitamin D levels were inferred to potentially decrease the risk of depression (GCP = −0.66, $r_G = -0.15$).

Among lifestyle-related phenotypes, we observed that being a fruit consumer (GCP = −0.69, $r_G = -0.32$) or rarely/never worked with materials containing asbestos (GCP = −0.70, $r_G = -0.43$) decreased the risk for depression. In addition, potential vertical pleiotropic effects were observed between phenotypes related to alcohol consumption and depression. These included substances taken for anxiety: drugs or alcohol (more than once) (GCP = −0.90, $r_G = 0.81$) and mental and behavioral disorders owing to use of alcohol (ICD10) (GCP = −0.61, $r_G = 0.23$), increasing the likelihood of depression. Consistently, never being injured or injuring someone else through drinking alcohol (GCP = −0.75, $r_G = -0.36$) decreased the risk of depression.

The use of several medications potentially increased the risk of depression. These medications included gabapentin (GCP = −0.63, $r_G = 0.32$), which is usually prescribed for epilepsy and peripheral neuropathy; dihydrocodeine (GCP = −0.66, $r_G = 0.49$), an opioid analgesic indicated for moderate to severe pain; beclometasone (GCP = −0.78, $r_G = 0.30$), a corticosteroid prescribed for several conditions including asthma; and diazepam (GCP = −0.85, $r_G = 0.57$), which is commonly prescribed for anxiety-related traits. In addition, medications

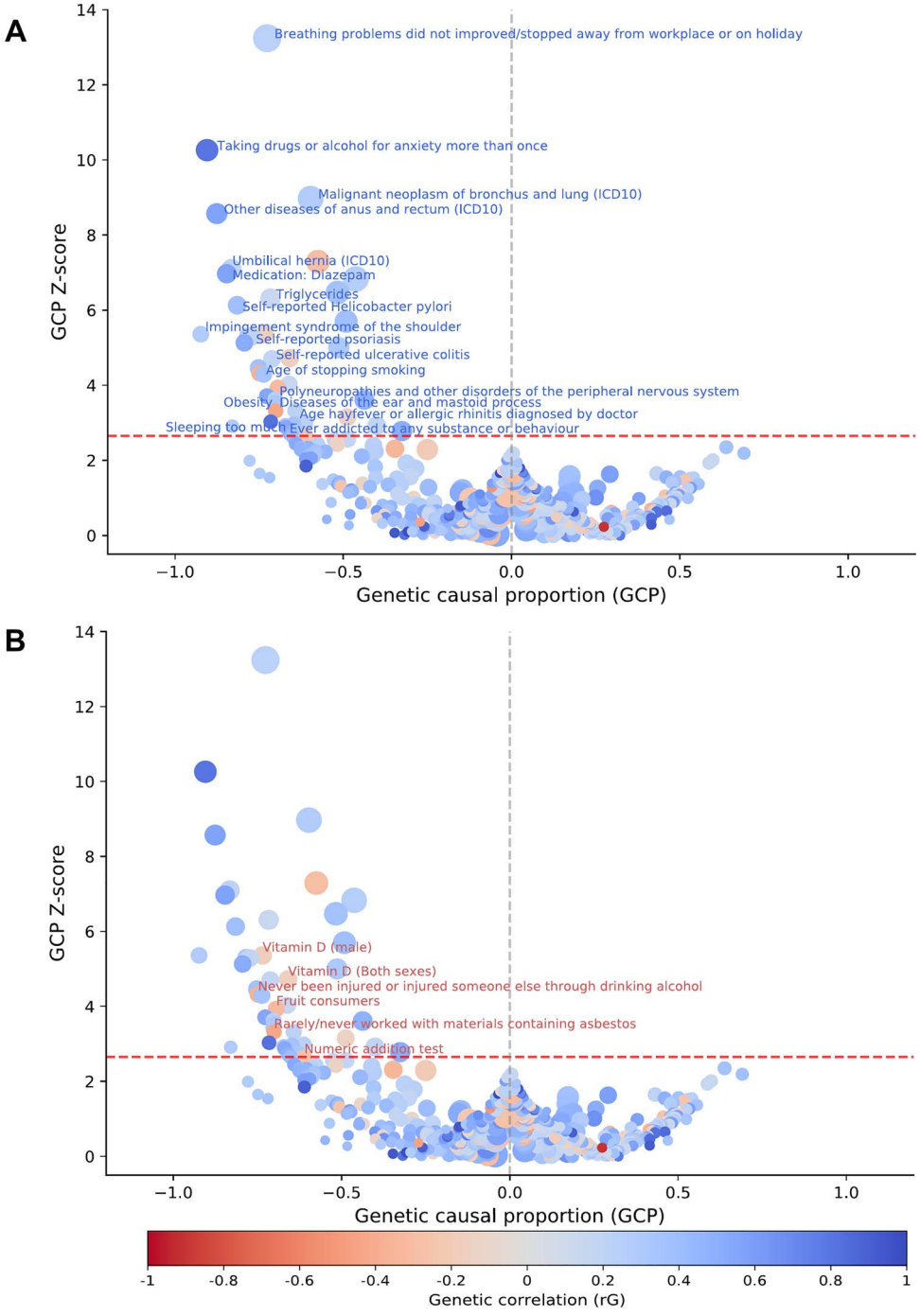

Figure 2. Putative causal associations for depression. Each dot represents a trait with a significant genetic correlation with depression. The x-axis shows GCP values, while the y-axis shows the GCP-related Z-scores as a measurement of statistical significance. The horizontal red dashed lines represent the statistical significance threshold (FDR < 5%). The vertical gray dashed lines divide traits that are potential causal determinants of depression (on the left) and traits that are putative consequences of depression (on the right). Results are shown separately for traits (**A**) with a positive genetic correlation with depression and (**B**) with a negative genetic correlation with depression.

prescribed for gastrointestinal ulcers, such as gaviscon liquid (GCP = −0.52, r_G = 0.37) and ranitidine (GCP = −0.73, r_G = 0.55), potentially increased the likelihood of depression.

Sensitivity analysis

As a sensitivity analysis, we performed LCV analyses to further explore potential causal associations identified in this study using publicly available GWAS summary statistics with larger sample sizes than those available in CTG-VL (Table 2). Overall, we did not observe any direct potential causal effects between depression and substance use–related phenotypes, such as cigarettes per day, smoking cessation, smoking initiation and drinks per week. Similarly, despite the large genetic overlap between phenotypes (r_G = 0.91), we did not identify potential

Table 1. Traits with an inferred potential causal relationship with depression

Phenotype	GCP	GCP *P*-value	r_G
Impingement syndrome of the shoulder	-0.92	1.69E−06	0.29
Taking drugs or alcohol for anxiety more than once	-0.90	1.42E−22	0.81
Other diseases of anus and rectum (ICD10)	-0.88	7.18E−16	0.57
Medication: diazepam	-0.85	1.24E−10	0.57
Umbilical hernia (ICD10)	-0.83	5.87E−11	0.21
Other and unspecified injuries of head (ICD10)	-0.83	2.52E−02	0.30
Self-reported *H. pylori*	-0.82	2.30E−08	0.38
Chest pain felt during physical activity	-0.79	4.73E−06	0.52
Medication: beclomethasone	-0.78	2.15E−06	0.30
Self-reported psoriasis	-0.77	2.15E−06	0.19
Leg pain when walking uphill or hurrying	-0.75	1.08E−04	0.37
Diaphragmatic hernia (ICD10)	-0.75	1.06E−04	0.41
Never been injured or injured someone else through drinking alcohol	-0.75	1.86E−04	-0.36
Age of stopping smoking	-0.74	2.11E−04	0.35
Vitamin D (male)	-0.73	1.69E−06	-0.17
Medication: ranitidine	-0.73	2.12E−03	0.55
Breathing problems did not improve/stopped away from workplace or on holiday	-0.73	1.37E−37	0.23
Triglycerides	-0.72	7.97E−09	0.15
Medication: fluoxetine	-0.72	1.98E−02	0.82
Self-reported ulcerative colitis	-0.71	3.58E−05	0.19
Obesity	-0.70	5.39E−03	0.32
Polyneuropathies and other disorders of the peripheral nervous system	-0.70	2.94E−03	0.25
Diseases of the ear and mastoid process	-0.70	3.85E−03	0.32
Rarely/never worked with materials containing asbestos	-0.70	7.69E−03	-0.43
Fruit consumers	-0.69	9.30E−04	-0.32
Osteoporosis without pathological fracture (ICD10)	-0.67	2.48E−02	0.35
Ever addicted to any substance or behavior	-0.67	2.73E−02	0.54
Triglycerides (male)	-0.66	6.12E−04	0.15
Vitamin D (both sexes)	-0.66	3.49E−05	-0.15
Medication: dihydrocodeine	-0.66	4.19E−02	0.49
Other diseases of intestine (ICD10)	-0.65	4.92E−02	0.40
Sleeping too much	-0.65	2.23E−02	0.37
Age hay fever or allergic rhinitis diagnosed by doctor	-0.64	7.69E−03	0.22
Medication: gabapentin	-0.63	3.64E−02	0.32
Mental and behavioral disorders owing to alcohol (ICD10)	-0.61	2.15E−02	0.23
Numeric addition test	-0.61	4.92E−02	-0.26
Malignant neoplasm of bronchus and lung (ICD10)	-0.60	2.86E−17	0.29

This table shows traits with a significant (FDR < 5%) and strong GCP (|GCP| > 0.60) with depression. Owing to space restrictions, all nominally significant genetic correlations (i.e. *P*-value < 0.05 before multiple testing correction) for depression are shown in Supplementary Material, File S1. Phenotype, phenotype with a potential causal association with depression; GCP *P*-value, GCP *P*-value after multiple testing correction; r_G, genetic correlation.

causal effects between lifetime anxiety and depression. Nonetheless, we replicated the causal association in which high vitamin D levels potentially decrease the risk for depression (GCP = −0.59, $r_G = -0.12$). Consistent with our previous results, our sensitivity analysis failed to identify evidence for a causal association between BMI and depression.

Table 2. Latent casual variable results for depression and other complex traits in sensitivity analysis

Phenotype	GCP	GCP *P*-value	r_G
Vitamin D	-0.59	1.00E−300	-0.12
Cigarettes per day	0.06	0.53	-0.23
Smoking initiation	-0.04	0.54	-0.31
Drinks per week	0.11	0.61	-0.06
Smoking cessation	-0.07	0.62	-0.24
BMI	0.26	0.87	0.11

This table shows results for the LCV method between depression and other complex traits.

Discussion

In this work, we conducted a phenome-wide screening and LCV analyses between depression and 1504 other complex traits to shed light on the putative causal architecture of depression. Previous genetic epidemiological studies have proposed different risk factors for depression using traditional Mendelian randomization methods (25,27,28). For instance, inflammatory gastrointestinal diseases, anxiety disorders and asthma have been associated with a higher risk for depression (27,29). Here, we sought to assess the robustness to the modeling of horizontal pleiotropy of findings from previous studies and provide novel insights into the potential causal determinants and outcomes of depression by uncovering a set of testable hypotheses for future studies.

In the present study, traits such as difficulty stopping worrying during the worst period of anxiety and taking drugs or alcohol for anxiety more than once potentially increased the risk of depression. In particular, for the first phenotype, half of its genetic correlation with depression was explained by potential vertical pleiotropic effects, while for the latter, almost all of the genetic overlap is consistent with vertical pleiotropic effects. These symptoms are observed in anxiety disorders, which are highly comorbid with depression (30,31). For instance, previous studies suggested that both disorders have a substantial genetic overlap (15,32). In the present study, we did not identify potential vertical pleiotropic effects between lifetime anxiety and depression. Although it can be challenging to establish causal associations between co-occurring disorders, it could be the case here that indirect anxiety-related phenotypes serve as a proxy for depression. In addition, it has been suggested that taking drugs or alcohol to overcome depression and anxiety may exacerbate their symptoms and influence the development of other mental disorders, perhaps as a consequence of intoxication or withdrawal (7,33).

Mental and behavioral disorders owing to alcohol (ICD10) were a potential causal determinant for depression in which 60% of the genetic overlap with depression is explained by vertical pleiotropic effects. In addition, in the present study, never being injured or injuring someone else through drinking alcohol, which indirectly suggests a lower alcohol consumption, decreased the risk of depression (three-quarters of its genetic correlation with depression was explained by potential vertical pleiotropic effects). Previous studies have observed that depressive episodes were prevalent after alcohol drinking, withdrawal and intoxication (7,33–35), which suggests that a higher alcohol intake is associated with an increase in the incidence of depression (36). However, our sensitivity analysis did not show any potential causal effects between drinks per week and depression. Therefore, another plausible explanation for the indirect effect we originally observed of alcohol on depression could be a common genetic factor or a shared environment between heavy alcohol drinkers and depression patients (37). Regarding the relationship between smoking and depression, our sensitivity analysis did not show any potential causal effects between smoking phenotypes (cigarettes per day, smoking initiation and smoking cessation) and depression.

It has been shown that depression has a higher incidence and prevalence among lung cancer patients (9,38–40). A likely explanation for this is that lung cancer patients face a relatively low survival rate of around 21%, which has a detrimental psychological effect (41,42). In some cases, patients may be subjected to high financial stress related to treatment costs, which has been associated with an increased risk of developing depressive symptoms (41,42). Our results show malignant neoplasm of bronchus and lung (ICD10) and lung cancer and mesothelioma, potentially increasing the likelihood of depression, perhaps as a consequence of a detrimental psychological effect on patients upon diagnosis. Both phenotypes revealed a moderate genetic correlation with depression. In particular, for the first phenotype, three-fifths of the genetic overlap was explained by potential vertical pleiotropic effects, while for the latter, 46% of the genetic overlap is consistent with potential vertical pleiotropic effects.

There is accumulating observational and genetic evidence showing that atypical features of depression, such as increased appetite and/or weight during an active depressive episode, are associated with obesity-related traits (43). In the present study, obesity influenced a higher risk of depression (70% of its genetic correlation with depression is consistent with vertical pleiotropic effects), which may be explained by psychological and inflammatory factors. From a psychological perspective, obesity can affect self-esteem and body image perception. It could, in some instances, lead to depressive symptoms, particularly for individuals in communities where their body image is compared with cultural beauty standards, which are often defined by a low body mass index (44–47). On the other side, inflammation has also been suggested as a putative mechanism underlying depression (48). For instance, patients with depression are known to show higher levels of inflammatory biomarkers in peripheral blood (10), and it is well established that obesity leads to a chronic inflammatory state (49) which in turn increases the production of pro-inflammatory cytokines and c-reactive protein (50). Therefore, our results align with the hypothesis that an inflammatory state may contribute to a higher risk of depression, perhaps as a consequence of obesity. Nonetheless, further research is required to pinpoint the potential molecular underpinnings underlying the association between depression and inflammation.

Previous studies have reported an association between high triglycerides, low HDL cholesterol levels and high risk for depression (51,52), while some other studies found an inverse association with depression (53). Our results support the hypothesis in which high HDL cholesterol levels could be protective for depression (Supplementary Material, File S1), while high triglyceride levels might increase the likelihood of depression (54). In particular, for the first phenotype, half of its genetic overlap with depression was explained by potential vertical pleiotropic effects, while for the latter, around 70% of the genetic overlap is consistent with vertical pleiotropic effects. This finding is most likely explained by obesity-related effects, which are well known to lower HDL cholesterol and increase triglyceride levels (55,56).

The association between chronic pain and depression has been investigated before (57,58). For instance, it has been reported that neuropathic pain and depression share common pathogenic and inflammatory pathways, and neuroimaging findings suggest that common brain areas are responsible for regulating emotions and pain experiences (59). Chronic pain is associated with

higher rates of depression, and comorbid chronic pain and depression are associated with poorer outcomes, including higher rates of suicidality and unsatisfactory antidepressant response both on the phenotypic (60) and genetic levels (61). Pain related to chronic musculoskeletal disorders has been associated with a high psychological distress level (62). In the present study, musculoskeletal disorders, such as meniscus derangement, impingement syndrome of the shoulder and osteoporosis without pathological fracture (ICD10), were potential causal determinants of depression, as were disorders of the peripheral nervous system. In particular, for the first phenotype, two-fifths of its genetic overlap with depression was explained by potential vertical pleiotropic effects, while for the last two phenotypes, 66 and 70% of the genetic overlap are explained by potential vertical pleiotropic effects, respectively. In addition, almost all of the genetic overlap for the impingement syndrome of the shoulder phenotype with depression is consistent with potential vertical pleiotropic effects. Consistently, medications usually prescribed for easing chronic pain symptoms, such as gabapentin and dihydrocodeine, which can be used as proxies for neuropathic pain and moderate to severe pain, respectively, potentially increased the risk of depression. These findings suggest that identifying and addressing pain as a potential risk factor for depression could be of great importance.

We observed putative causal associations in which gastrointestinal disorders increased the risk for depression. These included susceptibility to *H. pylori* infection, ulcerative colitis and the use of gaviscon liquid and ranitidine, which can be interpreted as proxies for peptic ulcers (63,64). In particular, for the previously mentioned traits, 82, 71, 52 and 73% of their genetic overlap with depression was explained by potential vertical pleiotropic effects, respectively. Previous studies have proposed a mechanism underlying the relationship between *H. pylori* infection and depression, suggesting that the infection plays a role in immunity and serotonin receptors upregulation, which may increase the risk of psychiatric disorders, including depression (65). Furthermore, evidence from a previous Mendelian randomization study supported that depression could potentially increase the risk of developing peptic ulcer disease. However, combined gastrointestinal disorders (i.e. peptic ulcer and inflammatory bowel diseases) showed potential causal associations with depression in both directions (66). Our results suggest that gastrointestinal disorders could be a putative causal determinant of depression; this association is most likely explained by immune-inflammatory pathways (12,67) and the detrimental psychological effect of physical illness on vulnerable individuals (68).

Previous studies have investigated the potential supportive role of vitamin D supplementation (69,70), suggesting that vitamin D has homeostatic and immunomodulatory effects (71). Furthermore, a Mendelian randomization study found a putative causal indirect effect of depression decreasing vitamin D concentrations, which is most likely explained by behaviors that are well known to lead to reduced production of vitamin D, such as less outdoor and physical activities decreasing sun exposure (72). Our results are consistent with previous findings in which vitamin D may have a protective direct effect on depression, and our results suggest that two-thirds of the genetic correlation between vitamin D and depression was explained by vertical pleiotropic effects. Nonetheless, we cannot rule out the possibility of sun exposure (i.e. through outdoor activities) underlying this association.

Previous studies have observed that a low socioeconomic status (SES) is associated with a higher prevalence of depression (73,74). Individuals with lower SES are more likely to work in an environment exposed to hazardous substances and involuntarily tend to consume less healthy food, as its price is more accessible compared with nutritious meals (75–77). In the present study, traits such as being a fruit consumer and rarely/never worked with materials containing asbestos influenced a potentially lower risk for depression. Around 70% of the genetic overlap of each of the aforementioned phenotypes with depression is consistent with potential vertical pleiotropic effects. These findings add up to previous reports of a positive association between higher fruit consumption and better mental health (78,79), suggesting that fruit, which is rich in minerals and vitamins, may have a role in modulating neurotransmitter receptors associated with depressive symptoms (80). In addition, fruit consumption may protect the body from oxidative stress, which has been suggested to contribute to depression through inflammation and neurodegeneration (81–83).

Similarly, previous studies suggest that depression is closely related to occupational environments (84). In fact, depression is prevalent among individuals working with asbestos (85). Our results are consistent with observations in previous studies, suggesting a putative protective effect of healthy food choices and non-hazardous work environments on depression risk.

Epidemiological studies commonly use randomized controlled trials (RCTs) as the standard approach to identify risk factors of several diseases. However, RCTs have shortcomings as it could be expensive to conduct large RCTs, or it may be unethical to randomly allocate participants to a well-known harmful exposure or give a placebo to seriously ill patients (86,87). In addition, observational studies, such as case–control or cohort studies, have limited capacity to identify causal associations owing to potential confounding variables and biases (88). As an alternative to this, causal inference methods used in statistical genetics are based on genetic data to provide a different approach in the light of the limitations of interventional and observational studies (21). As previous studies have noted, we note that potential causal associations identified with the LCV method should be

used as testable hypotheses for future studies to confirm. Therefore, we stress the importance of triangulating results from several studies with different study designs before establishing a causal relationship between complex traits.

We recognize that there are potential limitations to our study. First, most GWAS summary statistics used in the present study were retrieved from the UK Biobank cohort, which primarily includes participants of European ancestry. Therefore, results should not be generalized to other populations until findings are confirmed using data for different populations. Second, owing to its nature, the LCV method assesses the predominant causal pathway between two phenotypes and assumes no bidirectional causality (24). However, it is unclear whether bidirectional associations would still be captured by the LCV. In the future, this assumption should be tested in a systematic manner. Null findings in the present study may be explained owing to a lack of power because there is truly no causal relationship or because the relationship is bidirectional. Null findings in the present study must be addressed with caution.

Third, it is important to consider the complexity of genotype–phenotype associations, in which a GWAS may capture other traits beyond the one under study, potentially reflecting other risk factors. For instance, it is likely that the relationship between fruit consumption and depression is influenced by SES-related variables, and the association between lung cancer and depression is most likely explained by a detrimental psychological effect upon diagnosis and financial stress. In addition, in the present study, we identified a potential causal association between depression and obesity but not between depression and BMI. This discrepancy has been observed in previous studies (49) and is explained by the difference in phenotype definition. For example, obesity refers to the dichotomization of BMI based on the International Classification of Diseases, whereas BMI represents BMI as a continuous measurement which in turn does not entirely reflect obesity as a disease. Another example for this is that, as suggested in previous studies (89), phenotypes related to the use of medications were interpreted as a proxy for the trait they are most commonly prescribed for.

Lastly, although the LCV method offers increased statistical power owing to the use of genetic information across the whole genome, it is tied to the statistical power of the original GWAS included in the analysis. Thus, the ability to infer potential causal associations for phenotypes with an underpowered GWAS is limited. This might explain the absence of evidence for potential outcomes of depression, particularly the absence of a statistically significant association for suicide attempt as a potential outcome of depression (Supplementary Material, File S1), which comes in contrast with documented evidence in which suicidal behaviors are frequent among patients with depressive symptoms (90). This could be owing to the low statistical power of the suicide attempt GWAS. Nonetheless, previous studies report that the association between suicidal behaviors and depression could be confounded by traits such as hopelessness (91), which adds up to evidence suggesting that the association between suicide and depression is likely explained by horizontal pleiotropic effects (92). In addition, the etiology of individual suicide-related phenotypes, such as suicide ideation, suicide attempt and death by suicide, might differ and thus cannot all be captured by the suicide attempt GWAS only (93).

In summary, we provide evidence for potential causal genetic effects between depression and 1504 complex phenotypes. Our findings uncovered respiratory and gastrointestinal disorders potentially increasing depression risk. Also, we identified that obesity and pain might increase the likelihood of depression. Our analyses provide evidence for causal relationships observed in previous studies and provide novel testable hypotheses, increasing our understanding of depression and contributing to the design of new prevention and treatment strategies to reduce depression's burden.

Materials and Methods

Depression dataset

We leveraged publicly available GWAS summary statistics for depression from the Psychiatric Genomics Consortium (PGC). Briefly, an inverse-variance weighted meta-analysis was performed on samples from the UK Biobank, the PGC and 23andMe. After excluding the data from 23andMe, the total sample size was 500 199 individuals of which 170 756 were cases and 329 443 were controls. Full details for these GWAS summary statistics are available at their corresponding publication (17). The summary statistics for depression can be freely accessed via the PGC's website (https://www.med.unc.edu/pgc/download-results/).

Other datasets

This study used a compilation of 1504 phenotypes available at the Complex Traits Genetics Virtual Lab (CTG-VL) web-based tool (https://genoma.io) (94), which provides free access to public GWAS summary statistics and post-GWAS analyses to improve research collaboration and reproducibility (94). Most of the GWAS summary statistics available in CTG-VL were retrieved from the second wave of GWAS results from the UK Biobank released by Neale's Lab (www.nealelab.is/uk-biobank/) (95), and the rest were retrieved from GWAS consortia. Therefore, most of these GWAS summary statistics represent individuals of European ancestry which in turn prevents putative biases owing to differences between genetic ancestries (94). Phenotypes in the CTG-VL include objective laboratory measurements, self-reported traits and consortia meta-analysis. UK Biobank GWAS were adjusted for age, age-squared, inferred sex (i.e. sex is inferred from the sex chromosomes in the genome), age

∗ inferred sex, age-squared ∗ inferred sex and 20 genetic ancestry principal components (94,95). CTG-VL platform included only GWAS with a nominally significant heritability (i.e. heritability estimate with a P-value < 0.05 before multiple testing correction) derived from LD-score regression to ensure that analyses such as LCV and genetic correlations can be performed (94).

Latent causal variable

The LCV method determines whether a genetic correlation between traits can be explained by a putative causal relationship rather than horizontal pleiotropic effects. The method fits a latent variable L that mediates the genetic correlation between two traits (trait A and trait B), assuming that L is causal for both traits (24). In particular, L represents the degree to which a one-way potential causal relationship explains a genetic correlation (i.e. the genetic effects of trait A are proportional on B but not vice versa). Furthermore, the GCP parameter, which is estimated by comparing the correlation between L and trait A and the correlation between L and trait B (24), indicates whether the genetic correlation is more likely explained by horizontal or vertical pleiotropy.

Under the assumption of no bi-directional causality, a GCP value equal to zero suggests the genetic correlation is explained by horizontal pleiotropic effects, implying the absence of potential causal genetic effects. In contrast, a |GCP| = 1 indicates the detection of vertical pleiotropic effects and full genetic causality. Furthermore, |GCP| values between 0 and 1 indicate partial genetic causality (24). A |GCP| > 0.6 is considered to be robust, which indicates a lower likelihood of false-positive findings, and interventions targeting trait A are likely to affect trait B owing to potential causal genetic effects (24). Therefore, to interpret LCV results, it is important to take into consideration three factors: the magnitude of the genetic correlation, the value of the GCP estimate and the direction of the GCP estimate, which can be positive or negative. The GCP value is not a measure of the magnitude of the potential causal effects but indicates the proportion of a genetic correlation that can be explained by potential causal effects. For instance, associations with a small genetic correlation ($|r_G| < 0.30$) and a large |GCP| estimate close to 1 suggest that almost all of the genetic overlap between two traits, even though it is small, is explained by potential vertical pleiotropic effects. In addition, in the present study, a negative GCP between depression and trait A suggests potential causal genetic effects from trait A on depression, while a positive GCP value between depression and trait A would imply potential causal genetic effects from depression on trait A.

In the present study, we estimated the GCP between depression and 1504 complex traits. We used the phenome-wide analysis pipeline publicly available in CTG-VL as described in previous studies (96,97). The phenome-wide analysis pipeline was created using the original R script for the LCV method made available by the original authors in a GitHub repository (https://github.com/lukejoconnor/LCV) (24). Consistency of alleles and variants for all GWAS summary statistics was ensured using munge_sumstats.py, which is available in the LD score regression software. Also, HapMap SNPs were extracted using the list of SNPs w_hm3_noMHC.snplist (https://github.com/bulik/ldsc/wiki). In this study, to conduct the analyses, we uploaded GWAS summary statistics for depression to CTG-VL. Then, we used the phenome-wide analysis pipeline to perform LD score regression (98) and LCV analyses (24) to estimate genetic correlations and potential causal relationships, respectively. Finally, we created causal architecture plots to visualize the results. Full details on using and interpreting results from the publicly available phenome-wide analysis pipeline are available elsewhere (96,97). The LCV was applied to all phenotypes that showed a genetic correlation with depression at Benjamini-Hochberg FDR < 5%. Similarly, we applied FDR < 5% on all GCP estimates obtained from the LCV method.

Sensitivity analysis

As a sensitivity analysis, we performed LCV analyses to further explore potential causal associations identified in this study using publicly available GWAS summary statistics with larger sample sizes. These included cigarettes per day (N = 403 928) (99), smoking cessation (N = 820 192) (99), smoking initiation (N = 1 359 002) (99), drinks per week (N = 1 039 210) (99), vitamin D (N = 417 580) (72), lifetime anxiety (N = 83 566) (100) and BMI (N = ∼700 000) (101).

Supplementary Material

Supplementary Material are available at *HMGJ* online.

Data availability statement

Summary-level data used in the present study are publicly available at the Complex Traits Genomics Virtual Lab (https://genoma.io/) platform. Summary-level data for depression are publicly available at the PGC website (https://www.med.unc.edu/pgc/shared-methods/open-source-philosophy/).

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Conflict of Interest statement. G.C.-P. contributed to this study while employed at The University of Queensland. He is now an employee of 23andMe Inc., and he may hold stock or stock options. All other authors declare no conflicts of interest.

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