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Substance use and common contributors to morbidity: A genetics perspective

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Summary

Excessive substance use and substance use disorders (SUDs) are common, serious and relapsing medical conditions. They frequently co-occur with other diseases that are leading contributors to disability worldwide. While heavy substance use may potentiate the course of some of these illnesses, there is accumulating evidence suggesting common genetic architectures. In this narrative review, we focus on four heritable medical conditions - cardiometabolic disease, chronic pain, depression and COVID-19, which are commonly overlapping with, but not necessarily a direct consequence of, SUDs. We find persuasive evidence of underlying genetic liability that predisposes to both SUDs and chronic pain, depression, and COVID-19. For cardiometabolic disease, there is greater support for a potential causal influence of problematic substance use. Our review encourages de-stigmatization of SUDs and the assessment of substance use in clinical settings. We assert that identifying shared pathways of risk has high translational potential, allowing tailoring of treatments for multiple medical conditions.

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Introduction

Substance Use Disorders (SUDs) are serious and often treatable yet relapsing medical conditions that arise from prolonged use of psychoactive substances (either licit or illicit) that contribute to physiological and psychological impairment.[1] They are associated with high morbidity and mortality, contributing directly or indirectly to the leading causes of disability in developing and developed nations.[2] Excessive substance use and SUDs contribute *directly* to cancers, liver disease, respiratory diseases, infectious diseases (e.g., HIV, HCV), and prenatal exposure can be associated with infant health (e.g., fetal alcohol syndrome) - these feature among the leading contributors to Disability Adjusted Life Years (DALYs) worldwide.[3] SUDs are also associated with other common health conditions, such as cardiometabolic disease,[4–6] depression,[7] and chronic pain,[8] which are also leading contributors to DALYs, and also associated with COVID-19.[9] These medical conditions may not result as a direct consequence of excessive substance use/SUDs; rather, their co-occurrence may arise from a common genetic basis. In this review, we examine the association between substance use, SUDs and these 4 health outcomes - all heritable conditions - from a genetic perspective. First, we introduce the classification of SUDs, their heritability and comorbidities. Second, we outline our strategy for selecting these 4 medical conditions, and terms for inclusion in this narrative review. Then, we present the epidemiological backdrop substantiating associations between SUDs and these medical conditions, including preliminary support for genetic mechanisms from family and twin studies. Our results outline evidence regarding the extent to which genetically-informed methodologies support correlational and causal mechanisms of association between SUDs and these conditions. We close by presenting a few research gaps and the overall implications of our observations.

SUDs are broadly characterized by the transition from occasional or even regular use for pleasure or as prescribed, to compulsive use directed at alleviating

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distress experienced when not using the substance. Clinically, SUDs are typically diagnosed using the Fifth Edition of the Diagnostic and Statistical Manual (DSM-5) when individuals meet 2 or more of 11 criteria that include aspects of physiological response (tolerance to and withdrawal from the substance), escalating use with loss of control, preoccupation with obtaining or using the substance, and continued use despite psychological, physical and social consequences.[10] The DSM-5 also diagnoses a range of mild (2-3 criteria), moderate (4-5 criteria) and severe (6-11 criteria) SUDs. Relatedly, the 11th Edition of the International Classification of Diseases (ICD-11) diagnoses unhealthy substance use as hazardous, harmful (either episodically or chronically) or related to dependence, with the latter being classified by criteria representing impaired control over substance use, increasing prioritization of substance use over other aspects of life and physiological features.[11] Harmful, hazardous or problematic patterns of substance use can also be evaluated in healthcare settings using short patient-reported screeners (e.g., the Alcohol Use Disorders Identification Test, or AUDIT[12]; Drug Use Disorder Identification Test (DUDIT)[13]; the Fagerström Test for Nicotine Dependence[14]) to provide rapid identification of at-risk individuals.

SUDs are heritable conditions (~30-60%) and can present comorbidly with each other, with increasing evidence demonstrating that multiple SUDs may share overlapping genetic architectures.[15,16] In addition, SUDs have neurobehavioral underpinnings that distinguish them from substance use.[17–19] Different substances have different disorder liability (i.e., the proportion of individuals who develop a SUD when they use substances), yet overall, SUDs tend to be underdiagnosed, and therefore, are undertreated,[20] further perpetuating the chronicity of the illness.

SUDs clinically present comorbidly with other psychiatric disorders,[21–23] often further complicating the course of these illnesses. Beyond the brain, SUDs and problematic substance use also have widespread effects on other organ systems.[24] Some of these medical consequences are substance-specific and a result of exposure toxicity. For instance, heavy alcohol use has been linked to liver disease[25] and fetal alcohol syndrome[26]; cigarette smoking is a major contributor to lung cancer[27]; and injection drug use increases risk for HIV/AIDS and Hepatitis B and C.[28] However, there are many other common medical conditions (e.g., cardiometabolic disease, chronic pain, depression, COVID-19) that may not be a direct consequence of a SUD; rather, their co-occurrence in individuals with SUDs or problematic substance use may arise from a common genetic liability to both disorders. For instance, excessive alcohol use has been linked to cardiometabolic disease, although the mechanisms underlying this association remain unclear.[29] Likewise, a growing literature indicates that common reward-related processes may underlie the seemingly causal associations between opioid use and chronic pain.[30] A more thorough epidemiological overview appears below. Notably, these medical conditions are frequently seen by health-care providers and pose a large economic burden.

The assumption that SUDs cause or complicate these medical conditions may have contributed to stigmatization of individuals with SUDs, including deprioritizing them for other medical care.[31] However, the heritable nature of both SUDs and these individual medical conditions suggest alternative polygenic pleiotropic mechanisms (i.e., genetic loci affecting multiple traits) may underlie their associations. Evidence for pleiotropy or causation may have early implications for treatment and prevention. For instance, if purely correlational mechanisms underlie a pair of traits (e.g., genetic correlation between SUDs and depression), then enhanced vigilance towards both disorders in those with a family history of either may prove to be worthwhile. Furthermore, identification of these shared genetic pathways could provide insights into novel pharmacotherapeutics for those with multiple comorbid conditions. On the other hand, if one condition causes the other (e.g., SUDs cause cardiometabolic disease) then patient stratification by exposure may be beneficial.

Selection criteria and search strategy

Selection of medical conditions

We based our selection of medical conditions on the 2019 Global Health Estimates report identifying the top 20 leading contributors to DALYs globally.[3] First, we excluded conditions for which there was limited to no evidence for the influence of SUDs, including diarrhoeal diseases, malaria , tuberculosis, other hearing loss and uncorrected refractive errors. Next, we identified those conditions that could be consequentially related to a specific substance or groups of substances (even if they were not linked to SUDs in the report). These included: neonatal conditions or congenital anomalies , which could partially include the impact of fetal exposure to alcohol or narcotics; road injury and falls, which could be associated with acute alcohol and drug intoxication (i.e., driving under the influence); chronic obstructive pulmonary disease, trachea, bronchus and lung cancers and lower respiratory tract infections, which tend to be elevated in tobacco smokers; and cirrhosis of the liver and kidney diseases, which have been linked to excessive alcohol use. We also excluded HIV/AIDs, because injection drug use has been directly linked to increased likelihood of HIV infection. The remaining 3 conditions we included broadly reflected cardiometabolic disease (ischaemic heart disease, stroke, diabetes mellitus), pain (back and neck), and depressive disorders. To this list, we included COVID-19 infection and severity as, since 2019, severe illness due to COVID-19 has been a major source of DALYs.[32]

General search strategy

To assess the role of common genetic variants in liability to substance use, SUDs and these four medical conditions, we relied only on large-scale (N>50,000) genome-wide association studies (GWAS) of substance use and SUDs, which captured a significant proportion of the heritability of these conditions. As this pool of GWAS is not vast, we used an open-ended search to identify relevant findings. We searched PubMed, MEDLINE, Web of Science, pre-print servers (bioRxiv, medRxiv) and Google. We included pre-prints because genetic approaches to the study of SUD comorbidities is a fairly new area of research and larger GWAS of SUDs are ever-arising. Studies that were included spanned 2017 to 2022. Only articles published in English were considered. We recognize that our search criteria and databases may miss relevant literature not included in these databases. To set the stage for the genetic studies, we briefly review epidemiological support for comorbidity between SUDs and these 4 medical conditions - we did not conduct a systematic review of all studies for this section, which is intended only to provide the impetus for the genetic studies.

SUD search terms

As many of the comorbidities that we selected may be evident in individuals with heavy, excessive or problem substance use (but not necessarily a SUD diagnosis), we included a broad range of terms for SUDs (use disorder OR abuse OR dependence OR addiction OR problem use OR excessive use). We used several terms for substances (alcohol, drinking, nicotine, tobacco, smoking, cannabis, marijuana, heroin, opioid, opiate, prescription opioid misuse, cocaine, stimulants, methamphetamine, drug, illicit, polysubstance).

Medical condition search terms

We report findings that considered cardiometabolic disease (obesity OR body mass index [BMI] OR cardiovascular OR stroke OR heart disease, diabetes OR blood pressure OR hypertension), chronic pain (pain - we did not restrict our search to neck and lower back), depression (major depressive disorder OR depression), COVID-19 OR SARS-CoV-2. The number of GWASs for these conditions is substantial but, for the purposes of this review, we were interested only in studies that linked them to substance use or SUDs; therefore we only included studies reporting genetic analyses of these 4 medical conditions with substance use or SUDs GWASs.

Epidemiologic support for comorbidity

Cardiometabolic disease

There are well documented associations between excessive substance use and the onset and course of heart disease, hypertension, type 2 diabetes and obesity.[33,34]

All levels of tobacco smoking are associated with increased risk for cardiometabolic disease. Post-combustion products from smoking have been shown to contribute to atherogenesis, and cigarette smoking is a leading contributor to cardiovascular disease (CVD)-related mortality.[35] The role of acute and chronic use of cocaine on worsening CVD is indisputable[36]; however, the long-term consequences after cocaine cessation are less well-known. For example, Ritalin, a stimulant medication that was recently used to treat drowsiness, appetite loss and even depression in older adults, contributed to transient but significant increases in CVD.[37]

In contrast, the association between cardiometabolic disease and alcohol consumption is controversial. The hypothesized J-shaped distribution of risk of alcohol use on CVD suggests that light to moderate alcohol consumption exerts cardioprotective effects, lack of drinking (either lifetime or recent) slightly elevates risk, while excessive alcohol consumption dramatically increases risk for CVD. However, numerous studies, including meta-analyses,[29] have failed to replicate the cardioprotective effects of moderate drinking or have not identified the risk-conferring aspects of lifetime or recent abstinence. This paradoxical association may reflect the reverse causal effects of drinking cessation for therapeutic reasons in individuals with CVD onset. A similar, inconclusive literature surrounds the association between alcohol use and type 2 diabetes, with some studies suggesting reduced risk in light to moderate drinkers (e.g.,[38,39]) and others indicating no association or elevated risk (e.g.,[40,41]). Thus, the most robustly replicated associations between alcohol and cardiometabolic disease are observed in heavy drinkers.

Studies of cannabis use provide mixed evidence, with some suggesting significant elevation in risk for coronary artery disease and stroke,[42] and others indicating lower body mass index and improved metabolic outcomes, such as reduced likelihood of type 2 diabetes.[43,44] Finally, exogenous and endogenous opioids can profoundly impact cardiovascular systems, and this has resulted in increasing scrutiny of opioid prescribing for pain in individuals with CVD.[45] However, the role of opioid use in cardiometabolic health is still unclear.

Chronic pain

Chronic pain, which is broadly defined as the experience of pain for longer than 3 months, is a prevalent condition that tends to co-occur (40%) with SUDs.[46] Individuals with chronic pain show worse response to SUD treatment,[47] and experience of pain has been shown to predict heavy drinking relapses.[48–50] Unlike cardiometabolic disease, many of the epidemiological studies between pain and substance use assume that pain is the initial event, followed by substance use (for

instance, the consumption of alcohol to ameliorate pain). This is especially the case for opioids, which are one of the most commonly prescribed medications to treat chronic pain conditions. However, neurobiological studies suggest that common reward mechanisms may underlie both subjective experiences of pain and SUDs.[30] Therefore, the reported phenotypic association between prescription opioids, SUDs, and pain is likely complex, and the possibility of pain arising from, or being exacerbated by SUDs, cannot be excluded.

Depression

Given the mood altering properties of alcohol and other substances, the comorbidity between SUDs and depression is expected. The elevated prevalence of depressive disorders in individuals with alcohol use disorders has been documented in numerous nationally-representative samples (e.g.,[51–54]). Beyond alcohol, tobacco smoking and other SUDs also occur comorbidly with depressive disorders.[21,55] For example, heavy cannabis use has been linked to depression particularly during adolescence.[56] For opioids, comorbid depression is frequent, particularly in those using opioid medications for chronic pain.[57,58] Although negative affect is a notable clinical characteristic of a majority of SUDs, not all of the comorbidity between depression and SUDs reflects substance-induced mood disorders. Similar to pain, the hypothesis of "self-medication" - the voluntary intake of substances to ameliorate dysphoria and anhedonia associated with depression - is also frequently posited as a contributor.[59] These two disorder groups often complicate prognosis, with only modest benefits of antidepressant medications for patients with combined depressive- and substance-use disorders.[60]

COVID-19

The COVID-19 pandemic placed the vulnerabilities associated with SUDs into sharp focus.[61] While anecdotal information indicated protective effects of smoking tobacco and cannabis (in contrast to cannabidiol[62]), clinical data overwhelmingly documented that individuals with SUDs were more likely to require hospitalization or die due to COVID-19 (Wang et al., 2021), those with opioid use disorders being particularly at high risk. Despite expectations that pandemic-related stress would promote heavier substance use, results were mixed for substances such as alcohol[63,64] and indicative of escalating use for others, such as opioids and polysubstance use.[65,66]

Collectively, these epidemiologic studies have shown robust *phenotypic* correlations between SUDs and these four medical conditions. Whereas SUDs are posited to antedate some of these conditions (e.g., heavy drinking and CVD), be a consequence (e.g., pain and higher opioid use) or be the result of bidirectional effects (e.g., depression and substance use, and vice versa), there are limitations to these epidemiological observations. First, despite most epidemiological studies being correlational in nature, phenotypic findings can easily lend themselves to untested causal interpretations because studies might not have the necessary data structure or include methods to test for alternative hypotheses. For example, an association between alcohol use disorder and depression in older adults is confounded by exposure to both heavy alcohol and depressogenic effects of stressful life events, as well as third variables (e.g., socioeconomic status). The study of comorbidities in related individuals (e.g., siblings, twins) have, thus, played a role in establishing the role of genetic influences as an alternative mechanism of association.

Evidence from genetic epidemiology

Twin studies were foundational in demonstrating that SUDs share genetic underpinnings with each other and with numerous other traits, primarily of a psychiatric nature.[67] Just as the heritability of a single trait can be calculated by comparing the twin pair correlation for the trait in identical twins (who share 100% of their segregating genes) and fraternal twins (who share 50% of their segregating genes), the contributions of genetic factors to the correlation between a pair of traits can be estimated by examining cross-trait correlations across identical and fraternal twin pairs. For example, twin studies demonstrated that a significant proportion of the genetic factors that influence SUDs and depression are correlated.[68–70] Beyond psychiatric conditions, twin studies also demonstrated substantial correlations between high alcohol consumption and CVD-related mortality, although the magnitude of the association was no greater in identical than in fraternal twin pairs, suggesting that non-genetic factors (i.e., familial environment) were likely to be relevant.[71] To our knowledge, the majority of twin studies that evaluated SUDs did not also assess pain (or COVID-19, although it is far too contemporary) in the same samples.

There are a few illustrations of the utility of twin data in addressing causal mechanisms for the comorbidities studied in this review. Utilizing the cotwin-as-control approach (i.e., comparing the risk of an outcome in an exposed twin compared to their genetically related unexposed co-twin),[72,73] studies have shown that while SUDs and depression were genetically correlated, twins with alcohol or cannabis use disorder were more likely to also meet criteria for depression, even when compared to their genetically identical co-twin without these SUDs.[70,74] This residual association in the twins with SUDs suggest that factors beyond shared genetics, including possibly causal effects of SUD, play a role. On the other hand, genetic factors explained most of the association between nicotine dependence and depression.[73,75] Again, only a handful of studies have examined both SUDs and non-psychiatric health

outcomes. For instance, a longitudinal study of veteran males found that the alcohol abstaining member of a discordant pair was at a two-fold increased relative risk of all-cause mortality, and also specifically for CVD-related death, when compared to their alcohol-consuming co-twin.[76] Thus, cardioprotective effects of alcohol appeared to be causal in nature, although the study did not assess the origins of alcohol abstinence in this cohort. Furthermore, this decreased mortality was not evident in smokers.[76]

Statistical power is frequently a challenge in discordant twin studies - within-pair analyses necessitate a reasonable number of identical twin pairs where one twin engages in a behavior while the other does not. As SUDs are highly heritable, such discordance can be difficult to identify and therefore investigators have extended the study of discordance to pairs of relatives by leveraging large nationalized registries. In such analyses, instead of relying on identical twins (an infrequent relative type), co-relative comparisons are made in pairs of individuals with varying degrees of relatedness (e.g., cousins vs. half siblings vs. full siblings) and the pattern of associations is extrapolated to project an effect size in identical twin pairs. Using the Swedish national registries, investigators have found that individuals with an AUD are at increased risk for suicide death when compared to their relatives without an AUD, although the magnitude of this association decreased with increasing degree of relatedness, suggesting that genetic factors also played a role.[77]

Family, twin and registry-based studies of relatives have the advantage of being population-representative. However, these designs require that multiple traits are measured in closely related individuals. Complementary to these methods are larger scale GWAS in unrelated cohorts, where traits can be measured in independent samples. This is the methodology that we relied on for the current review.

Results

Evidence from genome-wide methods

Our search strategy identified 27 SUD GWAS, which pertained to problematic tobacco use and nicotine dependence (6), alcohol use, misuse and alcohol use disorders (12), cannabis use and cannabis use disorders (2), problematic opioid use and opioid use disorders (6), and general SUD (1).

Genome-wide association studies (GWASs; Figure 1) are conceptually straightforward. Given the abundance of common variation within the genome, researchers can readily identify genomic variants - represented by single base pair changes - that are more common in individuals with certain medical conditions. GWASs are unbiased because they do not prioritize specific genes or variants, allowing for genome-wide discovery.

GWASs require large datasets and technical capabilities, both of which have increasingly become available via collaborative science. Well-powered GWASs of substance use and SUDs are now available for alcohol, nicotine, cannabis and opioids.[84–95] Beyond identification of associated variants, well-powered GWAS have mobilized a suite of analytic paradigms aimed at studying genetic sources of comorbidity - Figure 1 illustrates these specific approaches.

Genetic underpinnings of SUD and medical diseases

Cardiometabolic disease. While genetic liability to tobacco smoking was reported to be associated with increased susceptibility to cardiometabolic diseases,[91] alcohol, opioid and cannabis use disorders were not genetically correlated with these traits.[88] On the other hand, alcohol consumption has shown *negative* genetic correlations with many cardiometabolic traits.[88,93,96–99] These paradoxical associations, particularly with drinking frequency, have been partially attributed to measurement error, or inaccurate self-reports, or changes in alcohol consumption over time (e.g., individuals who abstain from drinking due to medical reasons, or former drinkers[100,101]), as well as higher socioeconomic status that is frequently associated with drinking frequency in the population-based cohorts where the original GWASs were drawn from.[89,102]

Polygenic risk score (PRS) analyses for cannabis, alcohol and prescription opioid misuse have revealed widespread associations with cardiometabolic conditions (incl. ischemic heart disease, stroke, diabetes mellitus).[86,89,92] With regards to alcohol, genetic liability to alcohol misuse was associated with increased risk for heart disease in a large hospital EHR database.[89] Polygenic liability to how often someone drank alcohol was associated with decreased risk for metabolic conditions.[89] Importantly, these associations did not persist in the absence of the clinical manifestations of AUD (i.e., when covarying for a diagnosis of AUD), suggesting that they may index peripheral effects putatively caused by alcohol, rather than an underlying common genetic architecture, and encouragingly, suggest that treating alcohol misuse could have widespread effects on CVD health. Mendelian randomization (MR) studies using a genetic instrument for alcohol consumption have shown either a causal risk-conferring effect,[33] or a null effect, of alcohol consumption on cardiometabolic outcomes.[103]

With regards to nicotine, a tobacco smoking PRS was associated with circulatory system and metabolic phenotypes, including ischemic heart disease, obesity, and type 2 diabetes.[104] As in the alcohol analyses, when a diagnosis of tobacco use disorder was added as a covariate, many of these associations became non-significant, suggesting that they were driven by the effects of tobacco use rather than an underlying genetic

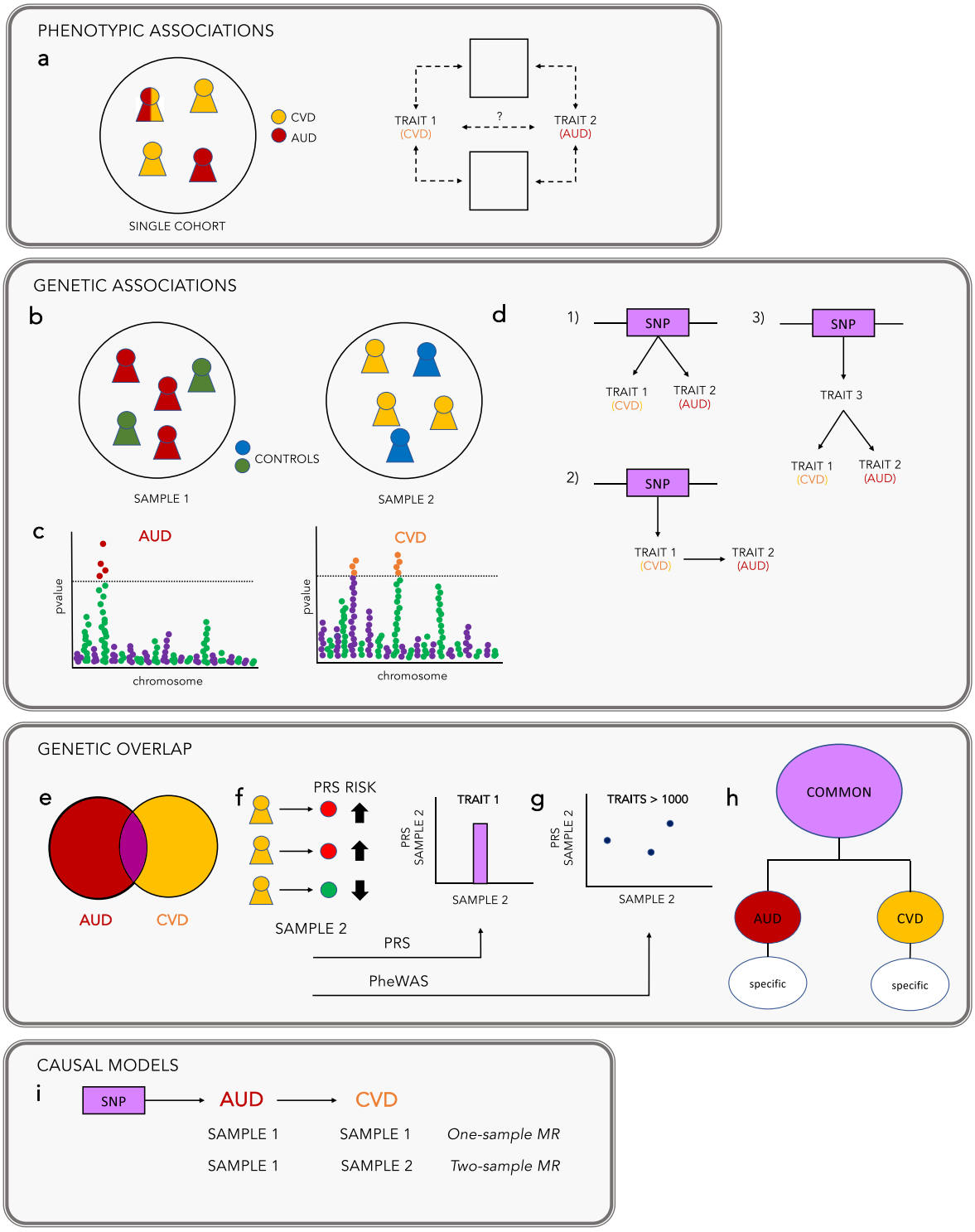

Figure 1. Current methods to capture genetic comorbidity across traits and diseases. Substance use disorders frequently co-occur with other medical conditions. (a) Phenotypic associations are identified in epidemiologic studies as the increased instance of one trait (e.g., alcohol use disorder, AUD) in the presence of another trait (e.g., cardiovascular disease, CVD). However, the factors that cause these traits, and whether they share common causal factors, is not known. (b) Genetic associations can be identified through large scale genome-wide association studies (GWAS) of complex traits. Traits can be defined as either case/control (e.g., AUD) or as a quantitative measure (e.g., alcohol consumption). These provide trait-genotype associations from thousands to millions

architecture. The genetic association between cardiometabolic disease (including type 2 diabetes) and tobacco and alcohol use disorders has been replicated in several other studies.[105,106] Another study found that polygenic risk for prescription opioid misuse was associated with increased risk for cardiometabolic outcomes, with metabolic biomarkers as measured using laboratory values extracted from the EHR.[92] As a measure of prescription opioid use was not available in the PheWAS dataset, the authors instead covaried for diagnoses of OUD and any SUD. Interestingly, the association with cardiometabolic outcomes persisted following correction for these diagnoses, suggesting that genetic liability, beyond its impact on OUD, might be influencing the likelihood of cardiometabolic disease. With regards to cannabis, one study identified that genetic liability for cannabis use disorders was associated with endocrine or metabolic conditions in a health-care system cohort.[86] To date, MR studies of cannabis use or disorder on type 2 diabetes have not been conclusive.[107]

Chronic pain

Recent large-scale GWAS of SUDs have demonstrated positive genetic correlations between chronic pain and substance use. As expected, pain conditions have been associated with genetic liability for OUD and opioid cessation.[84,85,87,108,109] However, these associations also extend to other substances (tobacco, alcohol, general SUD).[85,89,110] A plausible mechanism underlying these associations may be explained by reward mechanisms that substances (particularly, opioids) act upon. To date, there are no studies using causal methods to explore these comorbidities and common pathways. Such approaches could potentially illuminate novel treatments for OUD that could target pain after conditioning on substance use liability; which, if identified, could have tremendous therapeutic value. For example, *KDM4A*, which is a gene that interacts with disulfiram, opioid anesthetics and antidepressants, was recently associated with problematic opioid use.[92]

Depression

There is robust support for genetic influences on the comorbidity between AUD and depression. Recent GWAS have reinforced that there are positive genetic correlations between both problematic alcohol use and AUD, and depression.[89,94,95,97,111] PRS analyses have also consistently found that depression, as well as using substances to relieve negative affect, are amongst the top associations with polygenic liability to several SUDs derived from multiple populations,[15,85,89,92,97,112,113] including studies using samples with detailed psychiatric interviews of major depression.[114] Furthermore, some of these associations persisted even after covarying for a SUD diagnosis, suggesting a shared genetic basis. On the other hand, the association between tobacco use disorder and polygenic risk for major depression was attenuated when controlling for

of genetic markers (also known as single nucleotide polymorphisms, or SNPs). (c) These associations can be visualized using a Manhattan plot, which simply documents the *p*-values of the association between a trait and these individual variants along the genome. Because results from GWAS do not contain personal identifiable information they can be shared and have become the basis for the development of methods aimed at comorbidity studies. (d) Some SNPs are associated with multiple traits (known as pleiotropy). An association between a SNP and two traits may mean: (1) that there is a direct genetic association between the SNP and trait 1 and trait 2; (2) that there is a genetic association between the SNP and trait 1, and a phenotypic association between trait 1 and trait 2; (3) that there is a genetic association between the SNP and an unidentified trait 3, which is then phenotypically associated with trait 1 and trait 2. (e) Genetic correlations estimate how much of the phenotypic correlation between two traits is due to common variants, and can be conducted across the genome or parsed into localized estimates.[78,79] Unlike phenotypic correlations, genetic correlations are calculated between pairs of traits that are generally measured in independent samples. (f) Polygenic risk, or polygenic score (PRS/PGS) analyses aggregate the effects of multiple SNPs to predict individual risk for a given trait.[80,81] From a large discovery GWAS, effect sizes for each SNP are used to weight genotypes in an independent sample. The aggregated effects of these weighted SNPs are summarized in a single score, commonly referred to as PRS/PGS. This approach can be used to assess the association of genetic liability for one trait (e.g., AUD) with a second trait (e.g., CVD). (g) Phenome-wide association studies (PheWAS) extend on PRS analyses by testing the association between a PRS against hundreds to thousands of traits. Because associations between genetic liability for the primary trait and secondary traits may be due to phenotypic correlation, a supplementary analysis can be performed where the first trait is included as a covariate. (h) Other methods[82] use GWAS results to examine the effects of genetic variants that are shared across multiple correlated traits. This framework capitalizes on the genetic correlations between traits to identify the variants that are common across all, from those that are specific to each trait. One such approach is a form of structural equation modeling or factor analysis that models how different SUDs and medical conditions might coalesce based on their genetic correlations. (i) Mendelian randomization (MR) analyses were introduced to infer potentially genetically causal relationships using GWAS results. These analyses can be conducted in a single sample (one-sample MR), assuming both traits have been measured in the same sample, or using GWAS results from two different samples (two-sample MR). These approaches can help to examine evidence about putative causal relations between a single "exposure" (e.g., AUD) or multiple exposures or confounders (e.g., AUD and BMI, referred to as Multiple Variable MR) and "outcome" (e.g., CVD) by using genetic variants as instrumental variables.[83] MR analyses are not affected by reverse causation because genetic variants are fixed at conception. They are also less biased by the environment, compared to traditional observational studies, because genetic instruments are assumed to affect the outcome only via the exposure, independent of confounders.

depression diagnoses,[114] suggesting mediating effects of depression on tobacco use.

Genetic causal studies of SUDs and depression suggest some evidence for genetic causal effects of depression on AUD but not vice versa (e.g.,[90,113]), whereas a bidirectional causal association was found between major depression and OUD[87] and prescription opioid use risk.[115] While replication studies are necessary, these findings may inform prevention and intervention strategies directed toward the SUD epidemic and depression.

COVID-19

The role of shared genomic variants is far more nuanced when studying the elevated probability of severe COVID-19 in individuals with SUDs. Here, we consider evidence regarding the host genome (i.e., the static genome of affected individuals) - these studies explore whether variants within the host genome that modify an individual's COVID-19 susceptibility (to illness upon infection, severity and prognosis) include variants associated with SUDs. Studies report associations between genetic liability to COVID-19 severity and alcohol, tobacco smoking and cannabis use disorder.[85,115,116] For instance, polygenic risk for severe COVID-19 (i.e., requiring hospitalization) has been associated with smoking and alcohol consumption, as well as with cannabis use disorder, even after controlling for covariates. Emerging insights also hint at causal mechanisms, with MR analyses suggesting that a proportion of the association between COVID-19 severity and alcohol and tobacco smoking may be due to causal effects of the latter on the former.[117]

Insights, caveats and outstanding questions

Collectively, genetic studies are providing persuasive evidence that there is underlying genetic liability that predisposes to both SUDs and chronic pain, depression, and COVID-19. For cardiometabolic disease, there is greater support for a potential causal influence of problematic substance use. Despite this impressive array of studies, the wish-list of advances that would facilitate greater resolution between causal and correlational mechanisms is extensive. Here, we highlight a few caveats, key priority areas and considerations.

Our review primarily focuses on SUDs with well-powered GWAS. Without a doubt, larger GWAS of SUDs will be needed to disentangle causal mechanisms from shared genetic influences. In particular, there are currently no well-powered GWAS of cocaine use disorder and other stimulants (e.g., methamphetamine), which dominate in some global regions. In general, the sample size burden is especially high for SUD GWASs because they are highly polygenic (i.e., the effects of individual genetic variants is exceedingly small and distributed across the genome).

Furthermore, data from individuals of European genetic ancestry are almost exclusively responsible for the findings that we have reviewed. Therefore, an urgent requirement is well-powered GWASs of both SUDs and these four medical conditions in other ancestries. The absence of such diverse studies limits our understanding of the global interplay between SUDs and these 4 medical conditions from a genetic perspective. While it is possible that potential ancestry-specific genetic effects will arise (e.g., different causal loci within the same gene, or novel genetic signals), we will have to be cognizant that certain ancestral differences in genetic contributions may reflect differences in ascertainment and environmental (e.g., diet), societal and cultural factors.[118,119] As current methods do not account for the complex sociocultural experiences of individuals that may impact these medical conditions,[120] future studies will need to ensure that these sociocultural factors are considered and that phenotypes in understudied groups are well characterized.

GWAS were intended to probe the effects of individual, commonly occurring variants in the genome. Other forms of genetic variation, such as rare single variants[121] or structural polymorphisms[122] may also be relevant. Furthermore, identifying aggregate genetic overlap or even individual loci that similarly associate with SUDs and these medical conditions provides only limited insight into the pathophysiology of these comorbidities. Downstream *in silico* analyses that leverage curated 'omics data to outline networks of genes that underlie these conditions is a necessary next step before GWAS products can be brought forward to preclinical testing and subsequent drug development.[123] Novel methods towards linking GWAS results to the action of drugs on cell transcriptomes offers one low-cost opportunity to probe the feasibility of repurposed drugs.[124]

In the literature, and in this review, individual medical conditions were conceptualized as independent SUD comorbidities, but the four medical conditions studied in this review also occur concomitantly. For instance, the comorbidity between chronic pain and SUDs likely contributes to the comorbidity between depression and SUDs.[125] The comorbidity between SUDs and cardiometabolic disease is a necessary consideration when assessing the elevated likelihood of COVID-19 complications in individuals with SUDs.[9,126] Thus, despite our attempt to disentangle the mechanisms underlying *pairs* of comorbidities, it is likely that risk is better represented by a *matrix* of comorbidities with many shared genetic and non-genetic pathways. Furthermore, this matrix of medical conditions is likely more extensive, including conditions that are developmentally salient (e.g., Late Onset Alzheimer's Disease or Dementias) or cross-cutting aspects of well being (e.g., sleep health). Future research may wish to explore the

extent to which these comorbidities arise due to genetic influences that extend across multiple SUDs (i.e., a general addiction liability) or those that are substance-specific.[85] Structural equation modeling or subset analyses of genomic data (e.g.,[82,127]) are a few of the approaches for categorizing this web of comorbidities. Such analyses allow for the construction of confirmatory factor models of multiple variables that are found to be genetically correlated in an attempt to identify loci that undergird all or subsets of traits.[82,89,127,128] Likewise, multiple variable causal modeling,[129] which allows for the inclusion of heritable confounders, could be valuable in understanding whether the relationship between SUDs and these medical conditions could be attributed to, or mediated by other underlying factors (e.g., the extent to which causal effects of alcohol on cardiometabolic disease are confounded by tobacco smoking or depression).

We also contemplated various study designs that could be particularly well-suited to further research on SUD comorbidities. Current genetic analyses largely rely on cross-sectional data, particularly from health system biobanks, or data with limited information on timing of onset. Longitudinal studies of within-person change, with data collection spanning the period prior and subsequent to substance use and disorder onset, are widely hailed as a gold-standard approach for disentangling causation from correlational findings. However, such studies, especially with large enough sample sizes to examine the role of varying genetic propensity, can be expensive and resource intensive. Attrition or loss to follow-up in such studies may be correlated with heavy substance use and SUDs, posing another challenge. In particular, large national registries such as those in Denmark[130] and Sweden[131] provide an opportunity for population-based longitudinal analyses. Even within cross-sectional data, tests of causal hypotheses would benefit from access to information on the temporal ordering of onsets, whether through self-recall or EHR registrations and the application of time-variant methodologies, such as survival analysis. However, across all of these large-scale repositories, SUD comorbidity research is disadvantaged by the notoriously low rate of diagnoses and the absence of access to self-reported substance use information.

The need in the field of SUD comorbidity, therefore, is the systematic assessment of substance use in a majority of research and clinical settings, regardless of presenting conditions. Many studies and most physicians gather some information on substance use (e.g., ever using an illicit drug, how much and how often someone drinks or smokes). While such assessments of recent use can identify at-risk individuals, research suggests that they do not fully capture liability to SUDs, especially from a genetic perspective.[89] We suggest the use of short screeners [e.g.,[12,13,132–137]], which provide researchers and clinicians the opportunity to further document an individual participant's or patient's experiences with substances. Most screeners can be administered rapidly (<1 min), and regularly (e.g., at annual well visits), can assess both substance use (e.g., how much, how often) and problematic use (e.g., impairment due to substance use), and have been culturally and linguistically adapted.

Similarly, we encourage the assessment of family history of SUDs in a majority of research and healthcare settings. Many physicians evaluate whether the patient's family members have a history of cardiometabolic disease, pain-related illness, and even depression. If shared genetic pathways link SUDs to medical conditions commonly confronted in clinical settings, then family history of SUDs could serve as an early risk monitoring and preventative tool, not only for SUDs but also for other comorbid medical conditions.

Conclusion

It is undeniable that problematic substance use and SUDs co-occur with cardiometabolic disease, chronic pain, depression and COVID-19 - all leading causes of worldwide disability. Approaching SUDs as medical conditions, similar to cardiometabolic disorders or pain, rather than moral inadequacies or indicators of lack of interest in personal health, will ensure that at-risk individuals are prioritized for treatment of all of their medical comorbidities rather than penalized for their substance use history. A multi-faceted view of the origins of SUDs, and the use of destigmatizing language,[138] could also promote disclosure of substance use behaviors allowing a more accurate assessment of an individual's overall health.

We have shown that rapid advances in genomic studies have allowed researchers to estimate the extent to which comorbidities are due to shared genetic mechanisms or are causally related, which has implications for prevention, intervention and treatment. From a clinical standpoint, if one condition causes another, patient stratification by exposure may be beneficial. However, if comorbidities are due to common genetic factors, then identifying shared pathways of risk has high translational potential. For instance, one could repurpose existing drugs that act on the intersection of genetic pathways for multiple conditions.[139] Similarly, tailoring treatment for multiple medical conditions could be informed by genetics (e.g., in the form of polygenic risk scores) thereby enabling precision medicine. Prior to these advances, GWASs and polygenic risk scores, especially for SUDs, will need to explain a greater amount of variability in genetic risk and be equally informative across ancestries.

Contributors

S.S.R., R.L.K. and A.A. jointly researched, wrote and edited the manuscript. All authors have read and approved the final version of the manuscript.

Declaration of interests

S.S.R. and A.A. report consulting fees and speaker honoraria from NIH. R.L.K. reports honoraria and editorial service fees, outside the submitted work.

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