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A Preliminary Report on Alcohol-Associated DNA Methylation Changes and Suicidal Behavior: Evidence Using Mendelian Randomization

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Abstract

Suicide is a major public health concern. In 2015, it was the 10th leading cause of death in the US. The number of suicides increased by 30% in the US from 1999 to 2016, and a greater uptick in suicides is predicted to occur as a result of the COVID-19 crisis, for which the primary public-health strategy is physical distancing and during which alcohol sales have soared. Thus, current strategies for identifying at-risk individuals and preventing suicides, such as relying on self-reported suicidal ideation, are insufficient, especially under conditions of physical distancing, which exacerbate isolation, loneliness, economic stress, and possibly alcohol consumption. New strategies are urgent now and into the future. To that aim, here, a two-sample Mendelian randomization (an instrumental variables technique using public genome-wide association study data as data sources) was performed to determine whether alcohol-associated changes in DNA methylation mediate risk for suicidal behavior. The results suggest that higher alcohol-associated DNA methylation levels at cg18120259 confer a weak causal effect. Replication and triangulation of the results, both experimentally and with designs other than Mendelian randomization, are

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needed. If the findings replicate, the information might be utilized to raise awareness about the biological links between alcohol and suicide and possibly explored as a biomarker of risk, perhaps especially for early detection of those who may not self-report suicidal intent.

Keywords
DNA methylation, Mendelian randomization, alcohol, suicidality, VEGF

Suicide is a major public health concern. In 2015, it was the 10th leading cause of death in the US. The number of suicides increased by 30% in the US from 1999 to 2016, and a greater uptick in suicides is predicted to occur as a result of the COVID-19 crisis (Reger et al., 2020), for which the primary public-health strategy is physical distancing and during which alcohol sales have soared (Bremner, 2020). Thus, current strategies for identifying individuals at-risk for suicide are insufficient, especially under conditions of physical distancing, which exacerbate isolation, loneliness, economic stress, and possibly alcohol consumption (Garcia-Alvarez et al., 2020). For instance, one common tool for assessing risk for suicide relies on self-reported suicidal ideation. However, about 75% of those who die by suicide express no documented suicidal intent (Schuck et al., 2019). Novel strategies for early detection of those at risk for suicide and for its prevention are, therefore, urgently needed now and into the future.

To that aim, the present paper uses Mendelian randomization (MR) to investigate whether alcohol-associated changes in DNA methylation cause suicidal behavior and considers possibilities that could explain the findings, including vertical, horizontal, and confounding pleiotropy (Figure 1). Specifically, alcohol consumption is a strong risk factor for suicide (Borges et al., 2017) and is associated with changes in DNA methylation (Xu et al., 2019) and chronic inflammation (Wang et al., 2010), both of which may play a role in the pathophysiology of suicidality. For instance, lower plasma concentrations of vascular endothelial growth factor (VEGF) have been documented for suicide attempters versus controls (Isung et al., 2012). Thus, a better understanding of these relationships could strengthen our understanding of the pathophysiology of suicidality, which could amplify efforts to increase awareness of the biological link between alcohol and suicide and possibly lead to the development of novel biomarkers for detecting at-risk individuals.

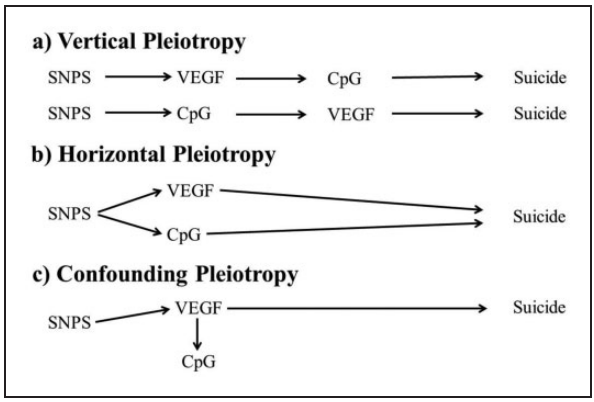

Figure 1. Possible pathways that might explain pleiotropy between DNA methylation, VEGF levels, and suicidal behavior. The pathways depicted here do not preclude confounding by unmeasured traits. "CpG" denotes a site in the genome where a cytosine nucleotide is followed by a guanine nucleotide in the linear sequence of bases. CpGs can be methylated and their levels measured.

Conceptual Framework

MR is an instrumental variables technique, heuristically analogous to a randomized-controlled trial (RCT). It uses genetic variants (typically single-nucleotide polymorphisms, SNPs) strongly associated with traits in statistical models instead of traits themselves. Doing so avoids most environmental sources of confounding and averts reverse causation (Davey Smith & Ebrahim, 2003; Hemani, Bowden et al., 2018; Schooling et al., 2013). Two-sample MR is an extension of the procedure that uses summary statistics from two genome-wide association (GWA) studies (Bowden et al., 2015; Burgess et al., 2013; Burgess & Thompson, 2017; Davey Smith & Hemani, 2014; Hemani, Zheng, et al., 2018; Johnson, 2012). For example, the causal effect of DNA (CpG) methylation on suicidality can be assessed as follows (Figure 2): Estimates of the SNP-CpG associations ($\hat{\beta}_{ZX}$) can be calculated in Sample 1, a GWA study of DNA methylation levels (SNPs strongly associated with CpG levels are termed methylation quantitative trait loci (mQTL)). The association between these same SNPs and suicidality ($\hat{\beta}_{ZY}$) can then be estimated in a GWA study of a suicidality phenotype (Sample 2). These estimates can be combined into Wald ratios ($\hat{\beta}_{XY}=\hat{\beta}_{ZY}/\hat{\beta}_{ZX}$) to produce a causal estimate of CpG methylation on suicidality.

Mendelian Randomization Assumptions

Three assumptions must hold for MR to be valid: (i) the SNPs acting as the instrumental variables must be strongly associated with the exposure; (ii) the

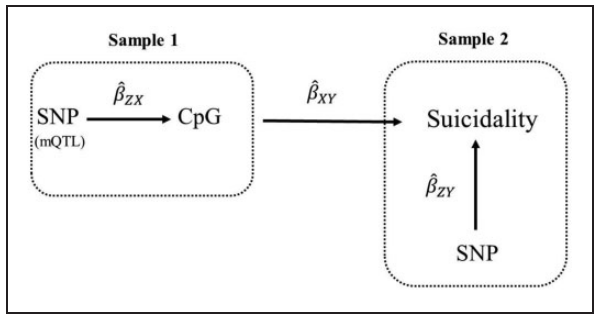

Figure 2. Two-sample MR depicting the use of methylation quantitative trait loci (mQTL) to instrument DNA methylation (CpG) levels (Sample 1) to test the effect of alcohol-associated DNA methylation changes on suicidality. mQTL identified in Sample 1 ($\hat{\beta}_{ZX}$) are extracted from Sample 2 ($\hat{\beta}_{ZY}$). The effect estimates are combined into Wald ratios ($\hat{\beta}_{XY}=\hat{\beta}_{ZY}/\hat{\beta}_{ZX}$).

instrumental variables must be independent of confounders of the exposure and the outcome; and (iii) the instrumental variables must be associated with the outcome only through the exposure (Bowden et al., 2015; Didelez & Sheehan, 2007).

Methods

70 CpGs associated with alcohol consumption in 1,135 European American male veterans were extracted from the manuscript by Xu et al. (2019) (Supplementary Table 3) (Xu et al., 2019). To determine whether the CpGs were associated with cis-methylation quantitative trait loci (mQTLs), the list of 70 CpGs were uploaded to the mQTL database (http://www.mqtldb.org/) (Gaunt et al., 2016), revealing that 8/70 CpGs have cis-mQTLs associated with them at genome-wide significance ($P < 5$ x 10-8) (Supplementary Tables 4 and 5). Trans-mQTLs were excluded. Summary statistics for these eight CpGs functioned as data sources for SNP-CpG associations and used in two-sample Mendelian randomization (MR). For each of the eight CpG instruments, only cis-mQTLs that were independent (those not in linkage disequilibrium, LD; $R^2 < 0.01$) were kept.

A genome-wide association (GWA) study performed by the Neale Lab (2017) on UK Biobank data field 41205 (Collins, 2012; Sudlow et al., 2015) for ICD-9 code E9500 ("suicide, self-inflicted poisoning by analgesics, antipyretics, anti-rheumatics") was accessed via MR-Base (http://www.mrbase.org/) (Hemani, Zheng, et al., 2018) and served as the outcome data source for the SNP-suicidality associations (sample size = 462,859 of which 151 were cases). Harmonized SNP-CpG and SNP-outcome associations were analyzed as Wald ratios or combined with the inverse-variance weighted (IVW) method

when more than one SNP instrumented a CpG site (Figure 2). This was done within the "TwoSampleMR" package (Hemani, Zheng, et al., 2018). To correct for running eight tests, a Bonferroni threshold was set to $P < 0.006$ (0.05/8). Analyses were performed in in R version 3.5.2 (R Core Team, 2013).

Sensitivity Analyses

None of the DNA methylation instruments contained a sufficient number of SNPs to perform typical MR sensitivity analyses for pleiotropy, such as MR-Egger regression. To address this, a second two-sample MR was run as a replication for each instrument using a different UK Biobank ICD-9 code for a closely related suicidality phenotype (E9503: "suicide and self-inflicted poisoning by tranquillizers, other psychotropic agents"; sample size = 462,569 of which 141 are cases). In addition, PhenoScanner, a curated database of GWA studies containing SNP-phenotype associations, was used to ascertain potential pleiotropic confounders for the SNP instrument for cg18120259 (rs9472155) (Kamat et al., 2019; Staley et al., 2016). PhenoScanner revealed that the SNP instrumenting cg18120259 (rs9472155) is associated with VEGF, altered levels of which have been documented in those who attempt suicide. Therefore, to investigate the possibility that alcohol-induced DNA methylation at cg18120259 is confounded by the influence of VEGF, an MR of VEGF levels on suicidality was performed as a sensitivity test. For this, an instrument for circulating VEGF levels was constructed from a GWA study of 3,527 individuals of European descent in the Framingham Heart Study (Debette et al., 2011).

The number of cases of suicide are small in the outcome GWA studies. To probe the possibility that outcome GWA studies with few cases of suicide could be used with biologically probable hypotheses, a final sensitivity test was performed among those who consume alcohol. In the UK Biobank, those who indicated they consumed alcohol were asked how frequently they drank with meals (data field 1618; sample size 172,454). An MR of frequency of drinking with meals on suicidality was run using a GWA study for ICD-9 code E9509: "Suicide and self-inflicted poisoning by other/unspecified solid and liquid substances" (the suicidality GWA study was performed by the Neale Lab, 2017).

The same methods for instrument construction listed above for the DNA methylation instruments were used to instrument VEGF levels and frequency of alcohol consumed with meals.

Instrument Strength

F-statistics, which provide a measure of instrument strength, and R^2 statistics (how much variance in a trait is explained by an instrument) (Burgess & Thompson, 2011) were calculated for each primary test (Table 1). *F*-statistics <10 are weak (Pierce & Burgess, 2013). All instruments used in this analysis are

Table 1. Instrument Strength.

Trait	R^2	*F*-statistic
cg18120259	0.03	32
cg02583484	0.03	35
cg07626482	0.04	42
cg14476101	0.18	252
cg16246545	0.15	199
cg26170244	0.01	17
cg11701312	0.03	35
cg06469895	0.02	27
VEGF	0.40	794
Frequency of drinks with meals	0.003	38

aptly strong. Detailed characteristics of the SNP instruments are available in Supplementary Tables 6 to 14, and 16.

Data Availability

All data sources are publicly available. The data for the Xu et al. (2019) instrument of alcohol-associated DNA methylation levels (Xu et al., 2019) and the data for the VEGF instrument (Debette et al., 2011) were obtained directly from the supplementary files accompanying their primary papers. The remaining data used for these analyses are accessible within MR-Base http://www.mrbase.org/ (Hemani, Zheng, et al., 2018). Template code for performing these analyses is also available through the MR-Base app.

Results

Higher alcohol-associated methylation at cg18120259 is suggestively weakly causal for suicide (OR per beta-level increase in DNA methylation: 1.0005; 95% CI 1.0002, 1.0008; $P = 0.001$). These findings replicated with a sensitivity test using a closely related ICD-9 outcome GWA study for suicidality (OR per beta-level increase in DNA methylation: IVW: 1.0003; 95% CI 1.00003, 1.0007; $P = 0.03$). None of the seven remaining CpGs showed evidence for causality (Table 2).

Sensitivity Analyses

The sensitivity analysis of circulating VEGF levels on risk for suicide was null (Table 3): IVW estimate 1.0000, 95% CI 0.9999, 1.0001; $P = 0.6776$). The sensitivity analysis for frequency of alcohol consumed with meals on risk for suicide demonstrates a causal effect for more drinks consumed (OR for suicide per

Table 2. Causal Effect Estimates for the Association of Alcohol-Associated DNA Methylation on Risk for Suicide.

CpG	Suicide phenotype	MR method	Num. SNPs	Odds Ratio	Lower 95% CI	Upper 95% CI	*P*-value
cg18120259	ICD-9 E9500	Wald ratio	1	1.0005	1.0002	1.0008	0.001
cg18120259	ICD-9 E9503[a]	Wald ratio	1	1.0003	1.0000	1.0006	0.030
cg02583484	ICD-9 E9500	Wald ratio	1	1.0000	0.9996	1.0003	0.866
cg02583484	ICD-9 E9503[a]	Wald ratio	1	0.9998	0.9994	1.0001	0.155
cg07626482	ICD-9 E9500	Wald ratio	1	0.9999	0.9996	1.0001	0.312
cg07626482	ICD-9 E9503	Wald ratio	1	1.0000	0.9997	1.0003	0.973
cg14476101	ICD-9 E9500	IVW	2	1.0000	0.9999	1.0001	0.663
cg14476101	ICD-9 E9503[a]	IVW	2	1.0000	0.9999	1.0001	0.519
cg16246545	ICD-9 E9500	Wald ratio	1	1.0000	0.9998	1.0001	0.484
cg16246545	ICD-9 E9503[a]	Wald ratio	1	1.0000	0.9999	1.0001	0.770
cg26170244	ICD-9 E9500	Wald ratio	1	1.0000	0.9996	1.0004	0.916
cg26170244	ICD-9 E9503[a]	Wald ratio	1	1.0001	0.9997	1.0005	0.670
cg11701312	ICD-9 E9500	Wald ratio	1	1.0002	0.9999	1.0005	0.235
cg11701312	ICD-9 E9503[a]	Wald ratio	1	0.9999	0.9996	1.0002	0.654
cg06469895	ICD-9 E9500	Wald ratio	1	1.0001	0.9997	1.0004	0.674
cg06469895	ICD-9 E9503[a]	Wald ratio	1	0.9998	0.9995	1.0001	0.255

[a]Sensitivity replication. IVW = inverse-weighted variance; CI = confidence interval.

Table 3. Causal Effect Estimates for VEGF Levels on Risk for Suicide.

MR test	SNPs	Odds ratio	Lower 95% CI	Upper 95% CI	*P*-value
IVW	3	1.0000	0.9999	1.0001	0.6776
MR-Egger	3	1.0000	0.9998	1.0001	0.7416
Weighted median	3	1.0000	0.9999	1.0001	0.8373
Weighted mode	3	1.0000	0.9999	1.0001	0.7791

IVW = inverse-variance weighted; CI = confidence interval.

category higher of drinking: IVW estimate 1.0013; 95% CI 1.0002, 1.0024; $P = 0.0184$) (Table 4).

Discussion

Regarding the relationships between DNA methylation, VEGF levels, and suicidality, four possibilities are considered: (i) VEGF levels could influence suicide through cg18120259 (vertical pleiotropy); (ii) cg18120259 could regulate VEGF levels and hence suicidality (vertical pleiotropy); (iii) cg18120259 and VEGF levels could have independent, direct influences on suicidality (horizontal

Table 4. Causal Effect Estimates for Frequency of Alcohol Consumed With Meals Among Those Who Drink on Risk for Suicide.

MR test	SNPs	Odds ratio	Lower 95% CI	Upper 95% CI	*P*-value
IVW	14	1.0013	1.0002	1.0024	0.0184
MR-Egger	14	1.0052	0.9943	1.0163	0.3694
Weighted median	14	1.0008	0.9994	1.0021	0.2783
Weighted mode	14	1.0004	0.9981	1.0026	0.7633

IVW = inverse-variance weighted; CI = confidence interval.

pleiotropy); (iv) and the findings implicating methylation of cg18120259 in suicidality could be explained by confounding from an unmeasured trait; i.e., the hypermethylation of cg18120259 could be a biomarker associated with a causal trait in individuals who are at-risk for suicide.cg18120259 is instrumented by a cis-mQTL (rs9472155) that is associated with VEGF levels. Since higher methylation levels typically downregulate expression, these findings might imply that alcohol-associated higher methylation of cg18120259 acts to downregulate *VEGFA*. However, from the MR results, there is no evidence for a direct, causal effect of VEGF levels on risk for suicide, suggesting the lower levels of VEGF that have been previously reported in suicide attempters are marking but not causing the behavior. This is evidence against explanations (i), (ii), and (iii); i.e., the finding for hypermethylation of cg18120259 increasing risk for suicide does not appear to be confounded by VEGF levels or occurring through them. Because VEGF levels are the only documented trait associated with rs9472155 (Supplementary Table 15), the null MR provides some evidence against horizontal pleiotropy. Notwithstanding, the numbers of suicide cases in the two outcome GWA are small. Exploring the possibility that VEGF confers a causal effect should be reconsidered when more cases are available in public GWA studies of suicide. Further, the small number of suicide cases for the tests of DNA methylation on suicidality might also have led to Type 1 error. This possibility is mitigated some by the replication with the MR analysis of the closely related suicidality phenotype and by the MR of frequency of alcohol consumed with meals on suicidality, which showed that frequency of drinking among drinkers does increase risk for suicide. It is unlikely that these separate and biologically plausible tests performed with three separate outcome GWA studies of suicidality are chance artefacts.

That leaves confounding by an unmeasured endophenotype (iv). A look-up of rs9472155 in the UCSC Genome Browser reveals that it is at transcription factor binding site for the estrogen receptor alpha (ERα), encoded by *ESR1* (6q25.1) (Kent et al., 2002). However, while estrogen has been hypothesized to play a role in the pathophysiology of suicidality, a case-control study examining genetic variants in *ESR1* among suicide attempters and healthy controls

found no evidence that ERα contributes strongly to the risk for suicide (Giegling et al., 2008). Thus, while a limitation of the present study is that computational methods to test pleiotropy directly were unavailable for investigation of DNA methylation, probing biologically plausible confounders revealed little evidence for confounding (iv). Since the possibility cannot be ruled out, hypermethylation of cg18120259 could be a biomarker that tags a true underlying causal factor or itself a molecular driver of alcohol-associated suicide. Either way, should these preliminary findings replicate in future studies, this information might be harnessed for early detection of at-risk individuals, thereby possibly reducing the burden of suicide – it could help save lives.

Replication of these findings is crucial, as is triangulation of evidence experimentally and with epidemiologic approaches other than MR. Perhaps the biggest unknown limitation and potential bias inherent to the present to the study, and yet to be mentioned, is whether male veterans differ substantially from the population in the UK Biobank used to obtain the GWA study data for suicidal behavior. It is unknown what type of bias differences between male veterans and a population of non-veterans that includes females could introduce in the context of alcohol-associated changes in methylation.

A strength of this study is that there is unlikely to be much participant overlap between the exposure and outcome GWA studies used in the primary two-sample MR designs (Burgess et al., 2016). This means that bias from sample overlap is minimized. Also, the study points to two promising molecular mechanisms that might be explored in future studies.

Future MR investigations of alcohol-associated DNA methylation changes on suicidality would best be done using multivariable MR – with full summary data for alcohol-induced DNA methylation and full summary data of VEGF levels (currently not available publicly) – and include an outcome GWA study of suicidality that includes many more cases of suicide. Multivariable MR would permit a formal statistical assessment of the pleiotropy between DNA methylation and VEGF. Though the sensitivity analyses here already do this, including more cases would reduce concerns for both Type 1 and 2 error from a possible lack of statistical power. Since the data for alcohol-associated changes in methylation already exists for male veterans, the best GWA study of suicidal behavior for a replication study would use the summary statistics from a GWA study of suicidal behavior among male veterans.

Declaration of Conflicting Interests

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Supplemental Material

Supplemental material for this article is available online.

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