



Wootton, R. E., Munafò, M. R., Treur, J. L., & al., E. (2020). Bi-directional effects between loneliness, smoking and alcohol use: Evidence from a Mendelian randomisation study. *Addiction*.
<https://doi.org/10.1111/add.15142>

Publisher's PDF, also known as Version of record

License (if available):
CC BY

Link to published version (if available):
[10.1111/add.15142](https://doi.org/10.1111/add.15142)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the final published version of the article (version of record). It first appeared online via Wiley at <https://onlinelibrary.wiley.com/doi/full/10.1111/add.15142?af=R>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Bidirectional effects between loneliness, smoking and alcohol use: evidence from a Mendelian randomization study

Robyn E. Wootton^{1,2,3,*} , Harriet S. R. Greenstone^{4*}, Abdel Abdellaoui⁵, Damiaan Denys⁵, Karin J. H. Verweij⁵, Marcus R. Munafò^{1,2,3}  & Jorien L. Treur⁵

School of Psychological Science, University of Bristol, MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK,¹ National Institute for Health Research Biomedical Research Centre, University Hospitals Bristol NHS Foundation Trust and University of Bristol, Bristol, UK,² MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK,³ Avon and Wiltshire Mental Health Partnership NHS Trust, Bath, UK⁴ and Department of Psychiatry, Amsterdam UMC, University of Amsterdam, Amsterdam, the Netherlands⁵

ABSTRACT

Background and Aims Loneliness is associated with cigarette smoking and problematic alcohol use. Observational evidence suggests these associations arise because loneliness increases substance use; however, there is potential for reverse causation (problematic drinking damages social networks, leading to loneliness). With conventional epidemiological methods, controlling for (residual) confounding and reverse causality is difficult. This study applied Mendelian randomization (MR) to assess bidirectional causal effects among loneliness, smoking behaviour and alcohol (mis)use. MR uses genetic variants as instrumental variables to estimate the causal effect of an exposure on an outcome, if the assumptions are satisfied. **Design** Our primary method was inverse-variance weighted (IVW) regression and the robustness of these findings was assessed with five different sensitivity methods. **Setting** European ancestry. **Participants** Summary-level data were drawn from the largest available independent genome-wide association studies (GWAS) of loneliness ($n = 511\,280$), smoking (initiation ($n = 249\,171$), cigarettes per day ($n = 249\,171$) and cessation ($n = 143\,852$), alcoholic drinks per week ($n = 226\,223$) and alcohol dependence ($n = 46\,568$). **Measurements** Genetic variants predictive of the exposure variable were selected as instruments from the respective GWAS. **Findings** There was weak evidence of increased loneliness leading to higher likelihood of initiating smoking, smoking more cigarettes, and a lower likelihood of quitting smoking. Additionally, there was evidence that initiating smoking increases loneliness [IVW, $\beta = 0.30$, 95% confidence interval (CI) = 0.22–0.38, $P = 2.8 \times 10^{-13}$]. We found no clear evidence for a causal effect of loneliness on drinks per week (IVW, $\beta = 0.01$, 95% CI = -0.11, 0.13, $P = 0.865$) or alcohol dependence (IVW, $\beta = 0.09$, 95% CI = -0.19, 0.36, $P = 0.533$) nor of alcohol use on loneliness (drinks per week IVW, $\beta = 0.09$, 95% CI = -0.02, 0.22, $P = 0.076$; alcohol dependence IVW, $\beta = 0.06$, 95% CI = -0.02, 0.13, $P = 0.162$). **Conclusions** There appears to be tentative evidence for causal, bidirectional, increasing effects between loneliness and cigarette smoking, especially for smoking initiation increasing loneliness.

Keywords Alcohol dependence, alcohol use, health behaviours, loneliness, Mendelian randomization, smoking behaviour, social isolation.

Correspondence to: Robyn E Wootton, School of Psychological Science, University of Bristol, 12a Priory Road, Bristol, BS8 1TU, UK; MRC Integrative Epidemiology Unit, University of Bristol, Oakfield House, Oakfield Grove, Bristol, BS8 2BN, UK; National Institute for Health Research Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol, Oakfield Grove, Bristol, BS8 2BN, UK. E-mail: robyn.wootton@bristol.ac.uk
Submitted 12 September 2019; initial review completed 19 December 2019; final version accepted 19 May 2020

*Joint first authors.

BACKGROUND

Extreme and prolonged loneliness is associated with worse physical and mental health [1,2], with evidence that loneliness and social isolation are comparable in magnitude to other well-established risk factors for

mortality [3]. One proposed explanation is that loneliness is associated with poor health behaviours [4]. Studies indicate that 5–30% of adults are lonely [5–8]. Therefore, identifying causal links between loneliness and health behaviours could have high public health relevance [6,7].

In particular, there is an association between loneliness and tobacco smoking and alcohol use: two of the most detrimental health behaviours world-wide. Lonely individuals are more likely to be cigarette smokers [4,9], potentially resulting from smokers' attempts to regain belonging in environments where smoking is socially acceptable [10]. Feelings of loneliness are associated with higher smoking in a nationally representative sample of adults [10] and social support appears to be beneficial when considering and maintaining smoking cessation [11]. Similarly, greater daily alcohol use is associated with lack of social activity among older adults in the general population [12] and clinical samples [13].

Furthermore, there are strong genetic correlations between loneliness and increased alcohol dependence, smoking heaviness, likelihood to initiate smoking and decreased likelihood of smoking cessation [5], suggesting possible causal pathways. However, in order to support a causal effect, we must first rule out residual confounding. For example, alcohol consumption is partly determined by societal attitudes to alcohol [14], and stress (perhaps exacerbated by loneliness) may also play an indirect role in risky behaviours [15], such as excessive drinking. Furthermore, there remains potential for reverse causality, as problematic drinking may cause damage to and limit social networks, leading to loneliness.

To date, only observational studies have examined associations between smoking, alcohol use and loneliness. With observational data, results are probably biased by residual confounding and reverse causation. One way to reduce this bias is by using Mendelian randomization (MR) [16]. The MR method uses genetic variants as instrumental variables for the exposure [17]. In this study, we applied MR to assess bidirectional causal effects between loneliness, smoking behaviour and alcohol (ab)use.

METHODS

MR is an instrumental variable method, using genetic variants as a proxy for an exposure to estimate the effect of that exposure on an outcome [18]. MR can provide evidence of a causal effect that avoids bias from confounding and reverse causation if the following hold: (1) genetic variants robustly predict the exposure, (2) genetic variants are not associated with confounders and (3) genetic variants are only associated with the outcome through the exposure. The latter two assumptions can be violated by horizontal pleiotropy, which occurs when one genetic variant directly influences two traits, inducing spurious causal effects. We conducted multiple sensitivity analyses, each with different assumptions, to test for pleiotropy.

Data

We applied bidirectional MR using summary-level data of published genome-wide association studies (GWAS) of loneliness ($n = 511\,280$) [5], smoking [initiation ($n = 249\,171$), cigarettes per day ($n = 249\,171$ smokers) and cessation ($n = 143\,852$)] [19] and alcohol use (drinks per week ($n = 226\,223$) [19] and alcohol dependence ($n = 46\,568$) [20]). The sample sizes for the smoking variables and for alcoholic drinks per week are considerably lower than in the original GWAS because we based our analyses on summary-level data, with UKBiobank and 23andMe, Inc. samples removed. This was to avoid sample overlap, which can cause bias towards the observational association.

Statistical analyses

Analyses were conducted using the TwoSampleMR package for R [21,22]. Briefly, independent variants that passed the genome-wide level of significance ($P < 5 \times 10^{-8}$) in the exposure GWAS were selected as instruments. This provided 16 single nucleotide polymorphisms (SNPs) for loneliness [5], 378 SNPs for smoking initiation [19], 99 SNPs for drinks per week [19] and 11 SNPs for alcohol dependence [20]. Because there were relatively few genome-wide significant SNPs for loneliness and alcohol dependence, we added instruments with relaxed P -value thresholds of $P < 1 \times 10^{-5}$ for both. SNPs were clumped for independence at $r^2 < 0.01$ and 10000 kb [21]. Next, these sets of SNPs were identified in the outcome GWAS. When a particular exposure SNP was not available in the outcome dataset, we used a proxy SNP in high linkage disequilibrium with the target SNP ($R^2 \geq 0.8$, based on information in the SNIiPA database [23]). Cigarettes per day and smoking cessation could only be used as outcome variables because those GWAS only contained 'ever-smokers', and there was insufficient information to stratify by smoking status in the loneliness GWAS.

The main analysis was an inverse-variance weighted (IVW) regression model (SNP–outcome association/SNP–exposure, whereby each SNP is weighted according to the inverse of its variance). We applied five sensitivity methods: weighted median [24], weighted mode [25], MR-Egger [26], Steiger filtering [27] and generalized summary-based MR (GSMR) [28]. First-order weights are used for the IVW, weighted median and MR-Egger methods. The weighted mode method uses second-order weights. A consistent result across these methods would provide the greatest confidence in a causal effect. The reliability of MR-Egger is evaluated using the I^2_{GX} statistic [29]. We also calculated the mean F -statistic to test instrument strength ($F > 10$ being sufficiently strong) [30] and Cochran's Q to estimate heterogeneity between the SNP effects, which could suggest pleiotropy [31].

The analysis plan for this study was not pre-registered, and therefore all results should be considered exploratory.

RESULTS

Causal effects of loneliness on smoking and alcohol use

With the $P < 1 \times 10^{-5}$ threshold only, there was weak evidence of increased loneliness leading to a higher likelihood of initiating smoking [IVW, $P < 1 \times 10^{-5}$, $\beta = 0.10$, 95% confidence interval (CI) = 0.06–0.13, $P = 4.6 \times 10^{-05}$; see Table 1] and smoking more cigarettes per day once started (IVW, $P < 1 \times 10^{-5}$, $\beta = 0.09$, 95% CI = 0.03–0.15, $P = 0.005$). With both P -value thresholds, there was weak evidence for increased loneliness decreasing the odds of smoking cessation (IVW, $P < 5 \times 10^{-08}$, $\beta = -0.09$, 95% CI = -0.19 to 0.01, $P = 0.075$; IVW, $P < 1 \times 10^{-05}$, $\beta = -0.09$, 95% CI = -0.13 to -0.05, $P = 1.3 \times 10^{-04}$). Results were mainly consistent across the weighted median and GSMR sensitivity methods in effect size and direction of effect (with slightly weaker statistical evidence), but not with the weighted mode method. MR-Egger results were not reported due to low reliability based on the I_{GX}^2 (Supporting information, Table S3). For loneliness-smoking initiation and loneliness-cigarettes per day there was evidence of heterogeneity (Cochran's $Q = 209.61$, $P = 1.2 \times 10^{-08}$ and $Q = 165.77$, $P = 1.1 \times 10^{-04}$, respectively, at $P < 1 \times 10^{-05}$), while for loneliness-smoking cessation that was not the case (Cochran's $Q = 91.04$, $P = 0.70$, Supporting information, Table S2). Steiger filtering showed that all except one of the SNPs explained more variance in the exposure than in the outcomes, suggesting that the effects were not due to reverse causation (Supporting information, Table S5). We found no clear evidence for causal effects of loneliness on drinks per week (IVW, $P < 5 \times 10^{-8}$, $\beta = 0.01$, 95% CI = -0.11 to 0.13, $P = 0.87$) or alcohol dependence (IVW, $P < 5 \times 10^{-8}$, $\beta = 0.09$, 95% CI = -0.19 to 0.36, $P = 0.53$) at either P -value threshold for loneliness.

Causal effects of smoking and alcohol use on loneliness

There was evidence for a causal influence of smoking initiation on increased loneliness across each of the MR sensitivity methods (IVW, $\beta = 0.30$, 95% CI = 0.22–0.38, $P = 2.8 \times 10^{-13}$, see Table 1), despite the instrument being relatively weak (F -statistic = 7.58, see Supporting information, Table S1). Weak instruments in non-overlapping samples can bias results towards the null, therefore these estimates are probably conservative. However, there was strong evidence of SNP-heterogeneity (Cochran's $Q = 29.30$, $P = 1.5 \times 10^{-40}$). Horizontal pleiotropy is one possible explanation for the heterogeneity. Alternatively, there could be multiple true causal pathways from the exposure to outcome. With Steiger

filtering, the majority of SNPs (277 of 287) explained more variance in the exposure than the outcome. There was very weak evidence of an increasing effect of drinks per week on loneliness using the IVW method ($\beta = 0.09$, 95% CI = -0.02 to 0.22, $P = 0.076$), but this did not hold up with any of the MR sensitivity methods. Finally, there was no clear evidence for causal effects of alcohol dependence on loneliness at either P -value threshold (e.g. IVW, $P < 5 \times 10^{-8}$, $\beta = 0.06$, 95% CI = -0.02 to 0.13, $P = 0.162$).

DISCUSSION

This is the first MR study, to our knowledge, exploring bidirectional associations between loneliness, smoking and alcohol use. We report tentative evidence for bidirectional effects between loneliness and smoking behaviour. There was very weak evidence to suggest that loneliness increases the odds of initiating smoking, heavier smoking once started and finding it difficult to quit. These potential causal effects should be investigated further once stronger instruments for loneliness are available. There was strong evidence for an effect of smoking initiation increasing the odds of experiencing loneliness.

The fact that our evidence was not consistent for all sensitivity methods could be due to limited power, and warrants further replication when larger sample sizes are available. Our suggestive evidence that loneliness increases smoking is in line with pre-existing observations that a lack of social connectedness may lead to increased smoking and difficulty in quitting [32,33]. Our finding of potential causal effects of smoking initiation on loneliness is particularly interesting, and consistent with recent results from an MR study that found that smoking increases depressive symptoms [34]. The mechanism for this may result from inhaled nicotine acting on nicotinic cholinergic receptors, dysregulating neurotransmitters such as dopamine and serotonin, involved in the aetiology of depression. Feelings of loneliness and depressive symptoms are highly phenotypically and genetically correlated [5,35], so it seems that the (biological) effects of smoking that could lead to depressive feelings could plausibly also lead to higher odds of experiencing loneliness. Other constituents of tobacco smoke could also impact neurotransmitters, with suggestions that MAO inhibition is also implicated [35].

There was no clear evidence of causal effects between loneliness and alcohol use. Further studies with better-powered genetic instruments are needed to fully assess the link between drinks per week and loneliness. Future work should also look at drinking frequency as there may be complexities such that loneliness is associated with extremes of drinking frequency rather than moderate drinking [36]. There may also be differences when

Table 1 Results of the two sample, bidirectional Mendelian randomization between loneliness, smoking and alcohol use.

Exposure	Outcome	IVW		Weighted median		Weighted mode		MR-Egger		GSMR			
		n SNPs	beta (95% CI)	P	beta (95% CI)	P	beta (95% CI)	P	beta (95% CI)	P	n SNPs	beta (95% CI)	P
Loneliness $P < 5 \times 10^{-08}$	Smoking initiation	14	0.03 (-0.09 to 0.15)	0.574	0.08 (-0.02 to 0.18)	0.133	0.10 (-0.08 to 0.27)	0.284	NA	NA	12	0.05 (-0.03 to 0.13)	0.191
Loneliness $P < 1 \times 10^{-05}$	Smoking initiation	108	0.10 (0.06 to 0.13)	4.6×10^{-05}	0.08 (0.02 to 0.13)	0.003	0.06 (-0.06 to 0.18)	0.339	NA	NA	97	0.10 (0.06 to 0.14)	4.0×10^{-08}
Loneliness $P < 5 \times 10^{-08}$	Cigarettes per day	13	0.09 (-0.09 to 0.27)	0.312	0.00 (-0.17 to 0.18)	0.970	-0.02 (-0.28 to 0.24)	0.883	NA	NA	13	0.08 (-0.04 to 0.19)	0.222
Loneliness $P < 1 \times 10^{-05}$	Cigarettes per day	105	0.09 (0.03 to 0.15)	0.005	0.02 (-0.06 to 0.10)	0.623	-0.03 (-0.23 to 0.17)	0.804	NA	NA	98	0.09 (0.03 to 0.14)	0.002
Loneliness $P < 5 \times 10^{-08}$	Smoking cessation	13	-0.09 (-0.19 to 0.01)	0.075	-0.06 (-0.20 to 0.08)	0.374	0.04 (-0.19 to 0.28)	0.715	NA	NA	13	-0.08 (-0.18 to 0.02)	0.099
Loneliness $P < 1 \times 10^{-05}$	Smoking cessation	100	-0.09 (-0.13 to -0.05)	1.3×10^{-04}	-0.06 (-0.12 to 0.00)	0.060	-0.02 (-0.18 to 0.13)	0.750	NA	NA	95	-0.08 (-0.12 to 0.04)	0.001
Loneliness $P < 5 \times 10^{-08}$	Drinks per week	14	0.01 (-0.11 to 0.13)	0.865	0.01 (-0.12 to 0.15)	0.801	0.04 (-0.15 to 0.24)	0.690	NA	NA	13	-0.02 (-0.11 to 0.08)	0.729
Loneliness $P < 1 \times 10^{-05}$	Drinks per week	107	-0.03 (-0.07 to 0.01)	0.269	-0.03 (-0.09 to 0.03)	0.359	-0.03 (-0.19 to 0.13)	0.703	NA	NA	99	-0.03 (-0.07 to 0.01)	0.189
Loneliness $P < 5 \times 10^{-08}$	Alcohol dependence	16	0.09 (-0.19 to 0.36)	0.533	0.26 (-0.09 to 0.61)	0.140	0.34 (-0.23 to 0.91)	0.259	NA	NA	15	0.07 (-0.20 to 0.34)	0.602
Loneliness $P < 1 \times 10^{-05}$	Alcohol dependence	120	0.10 (-0.02 to 0.22)	0.114	0.16 (-0.01 to 0.34)	0.060	0.19 (-0.24 to 0.62)	0.399	NA	NA	110	0.11 (-0.01 to 0.23)	0.070
Smoking initiation	Loneliness	287	0.30 (0.22 to 0.38)	2.8×10^{-13}	0.22 (0.12 to 0.31)	2.2×10^{-06}	0.21 (0.03 to 0.38)	0.022	NA	NA	255	0.23 (0.17 to 0.29)	1.1×10^{-14}
Drinks per week	Loneliness	68	0.09 (-0.02 to 0.22)	0.076	0.07 (-0.05 to 0.19)	0.286	0.08 (-0.10 to 0.26)	0.357	0.00 (-0.31 to 0.32)	0.992	56	0.04 (-0.04 to 0.12)	0.289
Alcohol dependence	Loneliness	6	0.06 (-0.02 to 0.13)	0.162	0.06 (-0.02 to 0.14)	0.082	0.03 (-0.07 to 0.13)	0.578	0.11 (-0.32 to 0.54)	0.644	6	0.05 (-0.03 to 0.13)	0.139
Alcohol dependence	Loneliness	16	0.00 (-0.04 to 0.04)	0.911	0.00 (-0.06 to 0.06)	0.865	-0.01 (-0.08 to 0.07)	0.880	-0.06 (-0.25 to 0.14)	0.576	16	0.00 (-0.04 to 0.04)	0.972

IVW = inverse variance weighted regression; GSMR = generalized summary-based Mendelian randomisation; SNP = single nucleotide polymorphism; CI = confidence interval; NA: MR-Egger results not reported because of limited reliability based on the I-squared measure being < 0.60.

considering frequency compared with quantity of alcohol consumption per occasion, with evidence indicating that the former is generally positively correlated with health outcomes, while the latter is negatively correlated [37]. In addition, we found no clear evidence overall for effects between loneliness and alcohol dependence. While this could be due to low statistical power, it aligns with some literature showing no evidence of an association between loneliness and at-risk drinking, binge drinking and extreme alcohol use [36,38].

There are some important strengths to our study. We are the first, to our knowledge, to apply MR using the largest available GWAS to examine bidirectional results between smoking, alcohol use and loneliness. We maximized the robustness of our findings by using a wide range of MR sensitivity methods, attempting to overcome the issue of horizontal pleiotropy. Applying multiple different MR methods, which each make different assumptions about the nature of pleiotropy, aims to overcome any individual limitation of a specific method. As required for MR, we also excluded overlapping samples; for example, if the GWAS for the exposure had contained the same people as for the outcome, then this result would be biased towards the observed estimate [18].

However, there are some limitations. First, the genetic instrument for loneliness was relatively weak due to the small number of genome-wide significant SNPs. Therefore, we relaxed *P*-value thresholds for instrument selection to increase the number of SNPs in the instrument. This could increase the likelihood of pleiotropy, which we attempted to overcome by using a variety of sensitivity methods. While the instrument for smoking initiation was also of arguably low strength (given the *F*-statistic < 10), we found considerable evidence for causal effects. While it therefore did not appear to have limited our findings, replication of these results with stronger genetic instruments is advised. The loneliness GWAS is predominately based on the UKBiobank cohort; even after controlling for population structure, coincident structure and geographic clustering remain [39,40], potentially introducing bias. We attempted to overcome this by ensuring that the outcome sample did not overlap with UKBiobank. Additionally, there may be selection bias; UKBiobank participants are well-educated, healthier and less likely to be smokers compared to the general population [41]. Loneliness rates may therefore not be representative. If smoking, alcohol use and/or loneliness reduce the likelihood of participating in the UKBiobank, we would lack results for those most significantly affected—meaning that our results may underestimate the association. Finally, our judgement of loneliness as a nominal variable is arguably flawed, failing to account for those intermittently but intensely lonely, or those with limited social connectedness, but who enjoy or benefit from this solitude [37,38].

CONCLUSIONS

In conclusion, we are first, to our knowledge, to examine bidirectional effects between loneliness and health behaviours with an MR framework. Although there was no clear evidence for effects between loneliness and alcohol (neither drinks per week nor alcohol dependence), there was moderate evidence for bidirectional effects between loneliness and smoking, which is supported by the existing literature. We recommend that our analyses be repeated using a stronger genetic instrument for loneliness in the future, which would increase the power of these findings. For now, however, our findings are of relevance for population health. The negative health impacts of both smoking and loneliness have been established, and addressing these factors in conjunction with a newfound understanding of their interrelatedness seems an important public health goal. This could include an increased emphasis on social and interpersonal methods for smoking cessation and a greater recognition of the impact of loneliness on individuals using existing smoking cessation services.

Declaration of interests

None.

Acknowledgements

M.R.M. is a member of the UK Centre for Tobacco and Alcohol Studies, a UKCRC Public Health Research: Centre of Excellence. Funding from British Heart Foundation, Cancer Research UK, Economic and Social Research Council, Medical Research Council and National Institute for Health Research, under the auspices of the UK Clinical Research Collaboration, is gratefully acknowledged. This work was supported by the Medical Research Council Integrative Epidemiology Unit at the University of Bristol, which is supported by the Medical Research Council and the University of Bristol (grant MC_UU_12013/7). J.L.T. is supported by a Rubicon grant from the Netherlands Organization for Scientific Research (NWO; grant number 446-16-009) as well as a Veni grant (NWO; grant number 016.Veni.195.016). K.J.H.V., A.A. and J.L.T. are supported by the Foundation Volksbond Rotterdam. A.A. is supported by ZonMw grant 849200011 from the Netherlands Organization for Health Research and Development. This study was supported by the NIHR Biomedical Research Centre at the University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research or the Department of Health and Social Care.

References

- Cacioppo J. T., Hughes M. E., Waite L. J., Hawkley L. C., Thisted R. A. Loneliness as a specific risk factor for depressive symptoms: cross-sectional and longitudinal analyses. *Psychol Aging* 2006; **21**: 140–51.
- James B. D., Wilson R. S., Barnes L. L., Bennett D. A. Late-life social activity and cognitive decline in old age. *J Int Neuropsychol Soc* 2011; **17**: 998–1005.
- Holt-Lunstad J., Smith T. B., Baker M., Harris T., Stephenson D. Loneliness and social isolation as risk factors for mortality: a meta-analytic review. *Perspect Psychol Sci* 2015; **10**: 227–37.
- Lauder W., Mummery K., Jones M., Caperchione C. A comparison of health behaviours in lonely and non-lonely populations. *Psychol Health Med* 2006; **11**: 233–45.
- Abdellaoui A., Sanchez-Roige S., Sealock J., Treur J. L., Dennis J., Fontanillas P. *et al.* Phenome-wide investigation of health outcomes associated with genetic predisposition to loneliness. *Hum Mol Genet* 2019; **28**: 3853–65.
- Office for National Statistics. Loneliness—what characteristics and circumstances are associated with feeling lonely? Analysis of characteristics and circumstances associated with loneliness in England using the Community Life Survey, 2016–2017 [internet]. UK; Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/articles/lonelinesswhatcharacteristicsandcircumstancesareassociatedwithfeelinglonely/2018-04-10#which-factors-independently-affect-loneliness> (Accessed May 2019).
- Office for National Statistics. Technical report: logistic regression and latent class analysis of loneliness using the Community Life Survey August 2016 to March 2017. National Measurement of Loneliness: 2018 [internet]. UK; Available at: <https://www.ons.gov.uk/peoplepopulationandcommunity/wellbeing/methodologies/technicalreportlogisticregressionandlatentclassanalysisoflonelinessusingthecommunitylifesurveyaugust2016tomarch2017> (Accessed May 2019).
- Beutel M. E., Klein E. M., Brähler E., Reiner I., Jünger C., Michal M. *et al.* Loneliness in the general population: prevalence, determinants and relations to mental health. *BMC Psychiatry* 2017; **17**: 97.
- Dyal S. R., Valente T. W. A systematic review of loneliness and smoking: small effects, big implications. *Subst Use Misuse* 2015; **50**: 1697–716.
- DeWall C. N., Pond R. S. Jr. Loneliness and smoking: the costs of the desire to reconnect. *Self Identity* 2011; **10**: 375–85.
- Mitchell S. A., Kneipp S. M., Giscombe C. W. Social factors related to smoking among rural, low-income women: findings from a systematic review. *Public Health Nurs* 2016; **33**: 214–23.
- Kuerbis A., Padovano H. T., Shao S., Houser J., Muench F. J., Morgenstern J. Comparing daily drivers of problem drinking among older and younger adults: an electronic daily diary study using smartphones. *Drug Alcohol Depend* 2018; **183**: 240–6.
- Laudet A. B., Magura S., Vogel H. S., Knight E. L. Perceived reasons for substance misuse among persons with a psychiatric disorder. *Am J Orthopsychiatry* 2004; **74**: 365–75.
- McCrary B. S. To have but one true friend: implications for practice of research on alcohol use disorders and social network. *Psychol Addict Behav* 2004; **18**: 113–21.
- Segrin C., McNelis M., Pavlich C. A. Indirect effects of loneliness on substance use through stress. *Health Commun* 2018; **33**: 513–8.
- Davey Smith G., Ebrahim S. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int J Epidemiol* 2003 Feb; **32**: 1–22.
- Lawlor D. A., Harbord R. M., Sterne J. A., Timpson N., Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. *Stat Med* 2008; **27**: 1133–63.
- Katikireddi S. V., Green M. J., Taylor A. E., Davey Smith G., Munafò M. R. Assessing causal relationships using genetic proxies for exposures: an introduction to Mendelian randomization. *Addiction* 2018; **113**: 764–74.
- Liu M., Jiang Y., Wedow R., Li Y., Brazel D. M., Chen F. *et al.* Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet* 2019; **51**: 237–44.
- Walters R. K., Polimanti R., Johnson E. C., McClintick J. N., Adams M. J., Adkins A. E. *et al.* Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci* 2018; **21**: 1656–69.
- Hemani G., Zheng J., Elsworth B., Wade K. H., Haberland V., Baird D. *et al.* The MR-base platform supports systematic causal inference across the human phenome. *eLife* 2018; **7**: e34408.
- R. Core Team. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. 2013.
- Arnold M., Raffler J., Pfeufer A., Suhre K., Kastenmuller G. SNIIPA: an interactive, genetic variant-centered annotation browser. *Bioinformatics* 2014; **31**: 1334–6.
- Bowden J., Davey Smith G., Haycock P. C., Burgess S. Consistent estimation in Mendelian randomization with some invalid instruments using a weighted median estimator. *Genet Epidemiol* 2016; **40**: 304–14.
- Hartwig F. P., Davey Smith G., Bowden J. Robust inference in summary data Mendelian randomization via the zero modal pleiotropy assumption. *Int J Epidemiol* 2017; **46**: 1985–98.
- Bowden J., Davey Smith G., Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. *Int J Epidemiol* 2015; **44**: 512–25.
- Hemani G., Tilling K., Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. Li J, editor. *PLOS Genet* 2017; **13**: e1007081.
- Zhu Z., Zheng Z., Zhang F., Wu Y., Trzaskowski M., Maier R. *et al.* Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat Commun* 2018; **9**: 224.
- Bowden J., Del Greco M. F., Minelli C., Davey Smith G., Sheehan N. A., Thompson J. R. Assessing the suitability of summary data for two-sample Mendelian randomization analyses using MR-Egger regression: the role of the I² statistic. *Int J Epidemiol* 2016; **45**: 1961–74.
- Pierce B. L., Ahsan H., VanderWeele T. J. Power and instrument strength requirements for Mendelian randomization studies using multiple genetic variants. *Int J Epidemiol* 2011; **40**: 740–52.
- Bowden J., Hemani G., Davey S. G. Invited commentary: detecting individual and global horizontal pleiotropy in Mendelian randomization—a job for the humble heterogeneity statistic? *Am J Epidemiol* 2018; **187**: 2681–5.

32. Tay L., Tan K., Diener E., Gonzalez E. Social relations, health behaviors, and health outcomes: a survey and synthesis. *Appl Psychol Health Well-Being* 2013; 5: 28–78.
33. Stanton C. A., Moadel A. B., Kim R. S., Weinberger A. H., Shuter J. Loneliness in HIV-infected smokers. *AIDS Care* 2015; 27: 268–72.
34. Wootton R. E., Richmond R. C., Stuijffzand B. G., Lawn R. B., Sallis H. M., Taylor G. M. *et al.* Evidence for causal effects of lifetime smoking on risk for depression and schizophrenia: a Mendelian randomisation study. *Psychol Med* 2019; 1–9; <https://doi.org/10.1017/S0033291719002678>
35. Fowler J. S., Volkow N. D., Wang G.-J., Pappas N., Logan J., Shea C. *et al.* Brain monoamine oxidase a inhibition in cigarette smokers. *Proc Natl Acad Sci USA* 1996; 93: 14065–9.
36. Canham S. L., Mauro P. M., Kaufmann C. N., Sixsmith A. Association of alcohol use and loneliness frequency among middle-aged and older adult drinkers. *J Aging Health* 2016; 28: 267–84.
37. Marees A. T., Smit D. J., Ong J.-S., MacGregor S., An J., Denys D. *et al.* Potential influence of socioeconomic status on genetic correlations between alcohol consumption measures and mental health. *Psychol Med* 2020; 50: 484–98.
38. Akerlind I., Hörnquist J. O. Loneliness and alcohol abuse: a review of evidences of an interplay. *Soc Sci Med* 1992; 34: 405–14.
39. Haworth S., Mitchell R., Corbin L., Wade K. H., Dudding T., Budu-Aggrey A. *et al.* Common genetic variants and health outcomes appear geographically structured in the UK biobank sample: old concerns returning and their implications. *bioRxiv* 2018; 11. <https://doi.org/10.1101/294876>
40. Abdellaoui A., Hugh-Jones D., Yengo L., Kemper K. E., Nivard M. G., Veul L. *et al.* Genetic correlates of social stratification in Great Britain. *Nat Hum Behav* 2019; 3: 1332–42.
41. Munafò M. R., Tilling K., Taylor A. E., Evans D. M., Davey Smith G. Collider scope: when selection bias can substantially influence observed associations. *Int J Epidemiol* 2018; 47: 226–35.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 F-statistic, indicating instrument strength, for Mendelian randomization analyses from loneliness to substance use, and from substance use to loneliness.

Table S2 Cochran's heterogeneity statistic for Inverse Variance Weighted (IVW) Mendelian randomization analyses from loneliness to substance use, and from substance use to loneliness.

Table S3 I_{GX}^2 statistic for Mendelian randomization analyses from loneliness to substance use, and from substance use to loneliness.

Table S4 MR-Egger intercept, indicating horizontal pleiotropy, for Mendelian randomization analyses from loneliness to substance use, and from substance use to loneliness.

Table S5 Steiger filtering sensitivity analysis from loneliness to substance use, and from substance use to loneliness.

Figure S1 a. Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 5e-08$) to smoking initiation. **b.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 1e-05$) to smoking initiation. **c.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 5e-08$) to cigarettes per day. **d.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 1e-05$) to cigarettes per day. **e.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 5e-08$) to smoking cessation. **f.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 1e-05$) to smoking cessation. **g.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 5e-08$) to drinks per week. **h.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 1e-05$) to drinks per week. **i.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 5e-08$) to alcohol dependence. **j.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from loneliness ($P < 1e-05$) to alcohol dependence. **k.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from smoking initiation to loneliness. **l.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from drinks per week to loneliness. **m.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from alcohol dependence ($P < 5e-08$) to loneliness. **n.** Scatterplot showing SNP-exposure versus SNP-outcome associations and the estimated regression lines for IVW and the relevant sensitivity analyses, from alcohol dependence ($P < 1e-05$) to loneliness.