EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Smoking quantitatively increases risk for COVID-19

Fuquan Zhang, Ancha Baranova

Please cite this article as: Zhang F, Baranova A. Smoking quantitatively increases risk for COVID-19. *Eur Respir J* 2021; in press (https://doi.org/10.1183/13993003.01273-2021).

This manuscript has recently been accepted for publication in the *European Respiratory Journal*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJ online.

Copyright ©The authors 2021. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

Smoking quantitatively increases risk for COVID-19

Fuquan Zhang, MD[1]; Ancha Baranova, PhD[2,3]

1. Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, Nanjing, 210029, China

2. School of Systems Biology, George Mason University, Manassas, 20110, USA

3. Research Center for Medical Genetics, Moscow, Russia

* Correspondence: Fuquan Zhang (zhangfq@njmu.edu.cn), Department of Psychiatry, The Affiliated Brain Hospital of Nanjing Medical University, 264 Guangzhou Road, Nanjing, 210029, China

TO THE EDITOR:

The COVID-19 pandemic has raised concern about the influence of smoking and alcohol drinking behavior on the susceptibility to coronavirus infection and its severity. Widely debated, the connection remains highly controversial. Conclusions derived from observational studies commonly suffer from limited ability to discern causes and effects.

We used two-sample Mendelian randomization (MR) to investigate individual causal relationships between multiple traits of smoking and alcohol intake and COVID-19 outcomes, and meta-analysis to evaluate overall causal effects of smoking or alcohol consumption on COVID-19 outcomes. We have analyzed summary results of GWAS, with seven datasets on smoking, including four quantitative datasets providing the age of smoking (AOS, the age at which an individual started smoking cigarettes regularly, 341,427 participants) from Liu et al. [1], cigarettes per day from Liu et al. (CPD1, 337,334 participants) [1] and Erzurumluoglu et al. (CPD2, 134,316 participants) [2], and cigarette pack-years (CPY, 622,409 participants) [2], and three datasets reporting the smoking status in binary form (regular smoker (current or former) vs participant who reported never being a regular smoker), namely, these by Liu et al. (SMK1, 1,232,091 participants) [1], Erzurumluoglu et al. (SMK2, 353,630 participants) [2], and Karlsson Linnér et al. (SMK3, 518,633 participants) [3]. To analyze alcohol intake, three datasets were employed, including alcohol drinks per week from Liu et al. [1] (DPW1, 941,280 participants) and Karlsson Linnér et al. (DPW2, 414,343 participants) [3], and alcohol intake per day from Evangelou et al. (DPD, 480,843 participants) [4]. For COVID-19, three datasets were obtained from the COVID-19 Host Genetic Initiative (round 4) [5], including three separate COVID-19 outcomes: severe COVID-19 (4,438 very severe respiratory COVID-19 cases and 718,232 controls), COVID-19 hospitalization (6,406 hospitalized COVID-19 cases and 902,088 controls), and SARS-CoV-2 infection (14,134 cases with reported SARS-CoV-2 infection and 1,284,876 controls). The controls in the COVID-19 datasets were from genetically ancestry-matched samples without known SARS-CoV-2 infection. The participants of MR analysis should come from the same population across studies. All or majority of the participants in the datasets were of European origins.

The main analyses were performed using the inverse-variance weighted (IVW) method and complemented with the weighted median and MR-Egger methods implemented in TwoSampleMR [6]. The intercept from the MR-Egger model was used as a measure of directional pleiotropy (a SNP influencing both the exposure and outcome through independent pathways). Single-nucleotide polymorphisms (SNPs) associated with smoking at genome-wide significance ($P<5\times10^{-8}$) were selected as instrumental variants and further pruned using a clumping r^2 cutoff of 0.01. The P value threshold of 1×10^{-5} was used for the CPY dataset due to the number of instrumental variants being less than five.

We performed meta-analyses for the causal effects in two quantitative smoking datasets (CPD1 and CPD2), three categorical smoking status datasets (SMK1, SMK2, and SMK3), and three alcohol drinking datasets on each of the three COVID-19 conditions, separately. A meta-analysis of the MR results was conducted using a random-effect model implemented in metafor [7].

As shown in Figure 1A, our MR analysis detected eight causal associations between smoking traits and the COVID-19 outcomes: CPD1 (OR [95CI%] = 2.69 [1.27-5.67]) and CPY (OR [95CI%] =1.87 [1.15-3.02]) with severe COVID-19; CPD1 (OR [95CI%] = 1.92 [1.04-3.55]); CPY (OR [95CI%] = 1.84 [1.19-2.85]), SMK1 (OR [95CI%] = 2.46 [1.22-4.98]), and SMK2 (OR [95CI%] = 2.49 [1.23-5.04]) with COVID-19 hospitalization; SMK1 (OR [95CI%] = 1.47 [1.01-2.13] and SMK2 (OR [95CI%] = 1.76 [1.15-2.70]) with SARS-CoV-2 infection. Smoking status displayed mixed associations with COVID-19 outcomes, with smoking-related features in SMK1 and SMK2 tending to increase the risk for COVID-19 hospitalization and in SMK3 tending to decrease this risk.

For alcohol traits, our MR analysis across the three alcohol datasets yielded inconsistent results. Within the Karlsson et al. dataset (DPW2), alcohol consumption has shown a protective effect both on severe COVID-19 (OR [95CI%] = 0.44 [0.25-0.80]) and COVID-19 hospitalization (OR [95CI%] = 0.48 [0.26-0.88]), while the analysis of Liu et al. dataset (DPW1) pointed that consumption of alcohol may increase risk for COVID-19 susceptibility (OR [95CI%] = 1.53 [1.03-2.28]). No causal effects were detected, when the Evangelou et al. dataset was analyzed.

The sensitivity analyses suggested that directions of causal effect estimates across the methods were predominantly consistent (Figure 1A). Tests of MR-Egger regression intercepts did not support the directional pleiotropy of the genetic instrumental variables.

Our meta-analysis indicated that incremental increases in smoking intensity are positively associated with increased risk for severe COVID-19 (OR [95CI%] = 2.47 [1.43-4.28], $P = 1.26 \times 10^{-3}$) and hospitalized COVID-19 (OR [95CI%] = 2.01 [1.19-3.40], $P = 9.56 \times 10^{-3}$), while the binary smoking status and all the alcohol drinking traits had no associations with any kind of COVID-19 outcomes (Figure 1B).

Our study reveals that the amount of smoking causally and positively influences the risk of COVID-19 severity, presumably due to reduced lung function caused by smoking of the tobacco, which is proportional to cigarette pack-years. However, the binary defined smoking status does not show any effect on susceptibility to COVID-19 or its severity. This inconsistency may reflect a balanced effect of possible protective effects of cigarette smoking as such, including intermittent ones, on susceptibility to COVID-19 and the extent of smoking-related lung damage which is evident in heavy smokers. Our study suggests that heavy smokers have an increased risk for the development of severe outcomes after the SARS-CoV-2 infection. For heavy smokers, attention should be paid to avoidance of the contact with the virus.

Our study reveals that the individual effects of alcohol consumption on COVID-19 susceptibility and severity are mixed, and may be cohort-specific. It is possible that in certain populations alcohol's immunosuppression [8] may provide some protection, while in others alcohol-related toxicity may outweigh this putative benefit. Overall, our study did not support a causal effect of alcohol consumption on COVID-19.

Several limitations are also to be acknowledged. Pleiotropy is a potential source of bias capable of threatening the validity of any MR study. However, our results were consistent in all analyses when performed by different MR methods, with no statistical indications of directional pleiotropy revealed in the case of smoking and COVID-19 connections.

In conclusion, our study indicated that one standard deviation (SD) increase in cigarettes per day is associated with 2.5-fold increased risk for severe COVID-19 and 2-fold increased risk for hospitalized COVID-19, while the smoking status and alcohol drinking traits have no associations with any kind of COVID-19 outcomes.

Author contributions

FZ conceived the study and performed the analyses; FZ and AB drafted the manuscript. Both authors assisted with interpretation, commented on drafts of the manuscript. Both authors approved the final version.

Acknowledgements

We thank members of the HGI and other teams, who generously shared the GWAS data. This work was supported by the National Natural Science Foundation of China (81471364). The funders had no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Conflict of interest

The authors have declared that no conflict of interest exists.

References

1. Liu M, Jiang Y, Wedow R, Li Y, Brazel DM, Chen F, Datta G, Davila-Velderrain J, McGuire D, Tian C, Zhan X, andMe Research T, Psychiatry HA-I, Choquet H, Docherty AR, Faul JD, Foerster JR, Fritsche LG, Gabrielsen ME, Gordon SD, Haessler J, Hottenga JJ, Huang H, Jang SK, Jansen PR, Ling Y, Magi R, Matoba N, McMahon G, Mulas A, Orru V, Palviainen T, Pandit A, Reginsson GW, Skogholt AH, Smith JA, Taylor AE, Turman C, Willemsen G, Young H, Young KA, Zajac GJM, Zhao W, Zhou W, Bjornsdottir G, Boardman JD, Boehnke M, Boomsma DI, Chen C, Cucca F, Davies GE, Eaton CB, Ehringer MA, Esko T, Fiorillo E, Gillespie NA, Gudbjartsson DF, Haller T, Harris KM, Heath AC, Hewitt JK, Hickie IB, Hokanson JE, Hopfer CJ, Hunter DJ, Iacono WG, Johnson EO, Kamatani Y, Kardia SLR, Keller MC, Kellis M, Kooperberg C, Kraft P, Krauter KS, Laakso M, Lind PA, Loukola A, Lutz SM, Madden PAF, Martin NG, McGue M, McQueen MB, Medland SE, Metspalu A, Mohlke KL, Nielsen JB, Okada Y, Peters U, Polderman TJC, Posthuma D, Reiner AP, Rice JP, Rimm E, Rose RJ, Runarsdottir V, Stallings MC, Stancakova A, Stefansson H, Thai KK, Tindle HA, Tyrfingsson T, Wall TL, Weir DR, Weisner C, Whitfield JB, Winsvold BS, Yin J, Zuccolo L, Bierut LJ, Hveem K, Lee JJ, Munafo MR, Saccone NL, Willer CJ, Cornelis MC, David SP, Hinds DA, Jorgenson E, Kaprio J, Stitzel JA, Stefansson K, Thorgeirsson TE, Abecasis G, Liu DJ, Vrieze S. 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(2): 237-244.

2. Erzurumluoglu AM, Liu M, Jackson VE, Barnes DR, Datta G, Melbourne CA, Young R, Batini C, Surendran P, Jiang T, Adnan SD, Afaq S, Agrawal A, Altmaier E, Antoniou AC, Asselbergs FW, Baumbach C, Bierut L, Bertelsen S, Boehnke M, Bots ML, Brazel DM, Chambers JC, Chang-Claude J, Chen C, Corley J, Chou YL, David SP, de Boer RA, de Leeuw CA, Dennis JG, Dominiczak AF, Dunning AM, Easton DF, Eaton C, Elliott P, Evangelou E, Faul JD, Foroud T, Goate A, Gong J, Grabe HJ, Haessler J, Haiman C, Hallmans G, Hammerschlag AR, Harris SE, Hattersley A, Heath A, Hsu C, Iacono WG, Kanoni S, Kapoor M, Kaprio J, Kardia SL, Karpe F, Kontto J, Kooner JS, Kooperberg C, Kuulasmaa K, Laakso M, Lai D, Langenberg C, Le N, Lettre G, Loukola A, Luan J, Madden PAF, Mangino M, Marioni RE, Marouli E, Marten J, Martin NG, McGue M, Michailidou K, Mihailov E, Moayyeri A, Moitry M, Muller-Nurasyid M, Naheed A, Nauck M, Neville MJ, Nielsen SF, North K, Perola M, Pharoah PDP, Pistis G, Polderman TJ, Posthuma D, Poulter N, Qaiser B, Rasheed A, Reiner A, Renstrom F, Rice J, Rohde R, Rolandsson O, Samani NJ, Samuel M, Schlessinger D, Scholte SH, Scott RA, Sever P, Shao Y, Shrine N, Smith JA, Starr JM, Stirrups K, Stram D, Stringham HM, Tachmazidou I, Tardif JC, Thompson DJ, Tindle HA, Tragante V, Trompet S, Turcot V, Tyrrell J, Vaartjes I, van der Leij AR, van der Meer P, Varga TV, Verweij N, Volzke H, Wareham NJ, Warren HR, Weir DR, Weiss S, Wetherill L, Yaghootkar H, Yavas E, Jiang Y, Chen F, Zhan X, Zhang W, Zhao W, Zhao W, Zhou K, Amouyel P, Blankenberg S, Caulfield MJ, Chowdhury R, Cucca F, Deary IJ, Deloukas P, Di Angelantonio E, Ferrario M, Ferrieres J, Franks PW, Frayling TM, Frossard P, Hall IP, Hayward C, Jansson JH, Jukema JW, Kee F, Mannisto S, Metspalu A, Munroe PB, Nordestgaard BG, Palmer CNA, Salomaa V, Sattar N, Spector T, Strachan DP, Understanding Society Scientific Group E-CVDGCfGoSBCHDEc, van der Harst P, Zeggini E, Saleheen D,

Butterworth AS, Wain LV, Abecasis GR, Danesh J, Tobin MD, Vrieze S, Liu DJ, Howson JMM. Meta-analysis of up to 622,409 individuals identifies 40 novel smoking behaviour associated genetic loci. *Mol Psychiatry* 2020: 25(10): 2392-2409.

3. Karlsson Linner R, Biroli P, Kong E, Meddens SFW, Wedow R, Fontana MA, Lebreton M, Tino SP, Abdellaoui A, Hammerschlag AR, Nivard MG, Okbay A, Rietveld CA, Timshel PN, Trzaskowski M, Vlaming R, Zund CL, Bao Y, Buzdugan L, Caplin AH, Chen CY, Eibich P, Fontanillas P, Gonzalez JR, Joshi PK, Karhunen V, Kleinman A, Levin RZ, Lill CM, Meddens GA, Muntane G, Sanchez-Roige S, Rooij FJV, Taskesen E, Wu Y, Zhang F, and Me Research T, e QC, International Cannabis C, Social Science Genetic Association C, Auton A, Boardman JD, Clark DW, Conlin A, Dolan CC, Fischbacher U, Groenen PJF, Harris KM, Hasler G, Hofman A, Ikram MA, Jain S, Karlsson R, Kessler RC, Kooyman M, MacKillop J, Mannikko M, Morcillo-Suarez C, McQueen MB, Schmidt KM, Smart MC, Sutter M, Thurik AR, Uitterlinden AG, White J, Wit H, Yang J, Bertram L, Boomsma DI, Esko T, Fehr E, Hinds DA, Johannesson M, Kumari M, Laibson D, Magnusson PKE, Meyer MN, Navarro A, Palmer AA, Pers TH, Posthuma D, Schunk D, Stein MB, Svento R, Tiemeier H, Timmers P, Turley P, Ursano RJ, Wagner GG, Wilson JF, Gratten J, Lee JJ, Cesarini D, Benjamin DJ, Koellinger PD, Beauchamp JP. Genome-wide association analyses of risk tolerance and risky behaviors in over 1 million individuals identify hundreds of loci and shared genetic influences. *Nat Genet* 2019: 51(2): 245-257.

4. Evangelou E, Gao H, Chu C, Ntritsos G, Blakeley P, Butts AR, Pazoki R, Suzuki H, Koskeridis F, Yiorkas AM, Karaman I, Elliott J, Luo Q, Aeschbacher S, Bartz TM, Baumeister SE, Braund PS, Brown MR, Brody JA, Clarke TK, Dimou N, Faul JD, Homuth G, Jackson AU, Kentistou KA, Joshi PK, Lemaitre RN, Lind PA, Lyytikainen LP, Mangino M, Milaneschi Y, Nelson CP, Nolte IM, Perala MM, Polasek O, Porteous D, Ratliff SM, Smith JA, Stancakova A, Teumer A, Tuominen S, Theriault S, Vangipurapu J, Whitfield JB, Wood A, Yao J, Yu B, Zhao W, Arking DE, Auvinen J, Liu C, Mannikko M, Risch L, Rotter JI, Snieder H, Veijola J, Blakemore AI, Boehnke M, Campbell H, Conen D, Eriksson JG, Grabe HJ, Guo X, van der Harst P, Hartman CA, Hayward C, Heath AC, Jarvelin MR, Kahonen M, Kardia SLR, Kuhne M, Kuusisto J, Laakso M, Lahti J, Lehtimaki T, McIntosh AM, Mohlke KL, Morrison AC, Martin NG, Oldehinkel AJ, Penninx B, Psaty BM, Raitakari OT, Rudan I, Samani NJ, Scott LJ, Spector TD, Verweij N, Weir DR, Wilson JF, Levy D, Tzoulaki I, Bell JD, Matthews PM, Rothenfluh A, Desrivieres S, Schumann G, Elliott P. New alcohol-related genes suggest shared genetic mechanisms with neuropsychiatric disorders. *Nat Hum Behav* 2019: 3(9): 950-961.

5. Initiative C-HG. The COVID-19 Host Genetics Initiative, a global initiative to elucidate the role of host genetic factors in susceptibility and severity of the SARS-CoV-2 virus pandemic. *Eur J Hum Genet* 2020: 28(6): 715-718.

6. Hemani G, Zheng J, Elsworth B, Wade KH, Haberland V, Baird D, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC. The MR-Base platform supports systematic causal inference across the human phenome. *Elife* 2018: 7.

7. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software* 2010: 36(3): 1–48.

8. Zhang P, Bagby GJ, Happel KI, Summer WR, Nelson S. Pulmonary host defenses and alcohol. *Front Biosci* 2002: 7: d1314-1330.

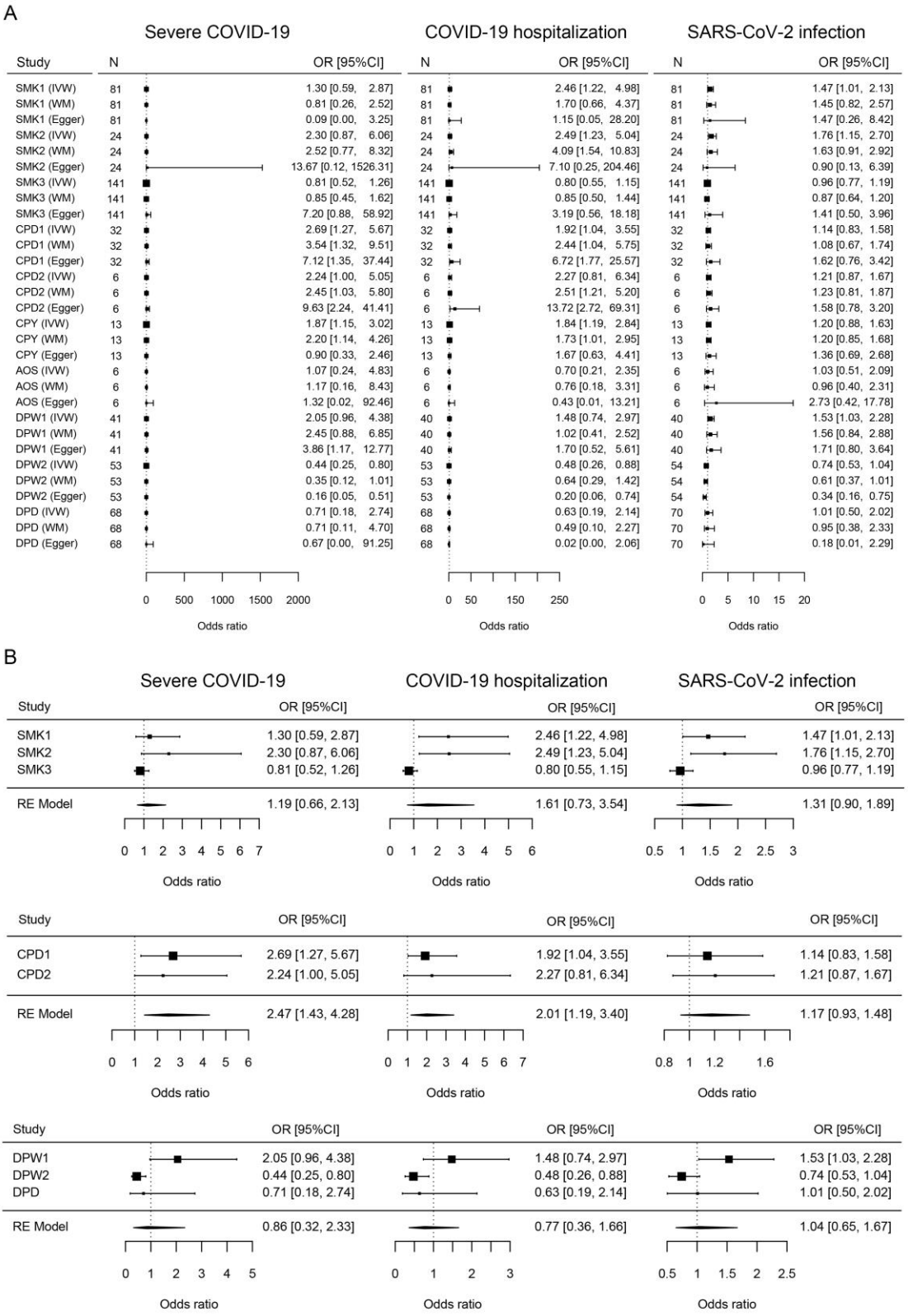

Figure 1. Causal associations between COVID-19 and smoking and alcohol drinking. CPD1: cigarettes per day from Liu et al.; CPD2: cigarettes per day from Erzurumluoglu et al.; CPY: cigarette pack-years from Erzurumluoglu et al.; SMK1: smoking from Liu et al.; SMK2: smoking from Erzurumluoglu et al.; SMK3: smoking

from Karlsson Linnér et al.; DPW1: alcohol drinks per week from Liu et al.; DPW2: alcohol drinks per week from Karlsson Linnér et al.; DPD: alcohol drinking per day from Evangelou et al.; IVW: inverse variance weighted; WM: weighted mean; Egger: MR Egger. A: Mendelian randomization analysis. Rows are exposures with different methods and columns are outcomes. B: Meta-analysis of the causal effects from IVW model. Rows are exposures with different methods and columns are outcomes.