**Supplementary Material**

**Figure 1. Supplementary Information**

All analyses were conducted in R version 3.3.2 using its package ‘MendelianRandomization’ (Yavorska & Burgess, 2017) for the Mendelian Randomization (MR) analysis. In MR analysis, the estimates were derived using both the inverse variance weighted (IVW) and the MR-Egger method.

**Figure 1a/b.** We conducted MR analysis to replicate the findings from univariable and multivariable MR on coronary heart disease (CHD) risk as reported by Rees et al. (2017). To obtain the beta estimates for the risk variants associated with CHD, we used the same GWAS (Genome Wide Association Study) summary data from the CARDIoGRAMplusC4D consortium (Nikpey, 2017, data online available under: <http://www.cardiogramplusc4d.org/data-downloads/>). The beta estimates for genetic variants associated with high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) were derived from a more recently published GWAS (Liu et al. 2017, data online available under: <https://www.nature.com/articles/ng.3977#supplementary-information>). We conducted univariable MR (IVW, random effects model), to estimate the causal effect of **(1a)** LDL-C on CHD (including 138 SNPs that were significant at *p*<5 x 10-8) and **(1b)** HDL-C on CHD (183 SNPs, significant at *p*<5 x 10-8). In multivariable MR, we included 386 SNPs that were significant at *p*<5 x 10-8 for either LDL-C, HDL-C or TG. Multivariable MR-Egger to assess **(1a)** the causal effect of LDL-C on CHD, controlling for the effects of HDL-C and TG and **(1b)** HDL-C on CHD, controlling for the effects of LDL-C and TG.

**Figure 1c/d.** To visualize the findings reported by Gage et al. (2017), we re-analysed the data included in the study, which were either reported in the paper or were provided by the authors upon request. The effects were estimates for the link between **(1c)** initiation of cannabis use and schizophrenia (21 SNPs; est.IVW=1.04, 95% 1.01-1.07; est.MR-Egger =1.01, 95% 0.93-1.10) and **(1d)** between schizophrenia and initiation of cannabis use (107 SNPs; est.IVW=1.10, 95% 1.05-1.14; est.MR-Egger=1.17, 95%CI 0.96-1.43).

**Figure 2. Supplementary Information**

**Figure 2a.** The genetic correlation results were obtained from LD Hub (data on genetic correlations between 49 traits available under: <http://ldsc.broadinstitute.org/lookup/>), originally reported in Bulik-Sullivan et al. (2015). Only significant (*p*<0.001) estimates are reported in the Figure.

**Figure 2b.** The estimates for the different pathways were obtained from MR analysis in R version 3.3.2. We used its package TwoSampleMR (cf. <https://mrcieu.github.io/TwoSampleMR/>), which allows to access GWAS data available on the MR-Base database (cf. Hemani et al., 2016). The data was accessed on the 06/03/2018. In MR analysis, the bi-directional relationships of 11 variables of interest (cf. below sTable 1.) were tested. A protocol of the different steps involved in the MR analysis are detailed in Table 2. (below). Only significant (*p*<0.001) estimates are reported in the Figure.

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| GWAS references for Figure 2 | |
| Schizophrenia | Ripke, Stephan, Benjamin M. Neale, Aiden Corvin, James TR Walters, Kai-How Farh, Peter A. Holmans, Phil Lee et al. "Biological insights from 108 schizophrenia-associated genetic loci." *Nature* 511, no. 7510 (2014): 421. |
| Cigarette use | Ben Neale (2017), UK Biobank (cf. <http://ldsc.broadinstitute.org/gwashare/>) |
| Years of schooling | Okbay, Aysu, Jonathan P. Beauchamp, Mark Alan Fontana, James J. Lee, Tune H. Pers, Cornelius A. Rietveld, Patrick Turley et al. "Genome-wide association study identifies 74 loci associated with educational attainment." *Nature* 533, no. 7604 (2016): 539. |
| Infant head circumference | Taal, H. Rob, Beate St Pourcain, Elisabeth Thiering, Shikta Das, Dennis O. Mook-Kanamori, Nicole M. Warrington, Marika Kaakinen et al. "Common variants at 12q15 and 12q24 are associated with infant head circumference." *Nature genetics* 44, no. 5 (2012): 532. |
| Childhood intelligence | Benyamin, Beben, BSt Pourcain, Oliver S. Davis, Gail Davies, Narelle K. Hansell, M-JA Brion, R. M. Kirkpatrick et al. "Childhood intelligence is heritable, highly polygenic and associated with FNBP1L." *Molecular psychiatry* 19, no. 2 (2014): 253. |
| Body mass index | Locke, Adam E., Bratati Kahali, Sonja I. Berndt, Anne E. Justice, Tune H. Pers, Felix R. Day, Corey Powell et al. "Genetic studies of body mass index yield new insights for obesity biology." *Nature* 518, no. 7538 (2015): 197. |
| Plasma cortisol | Bolton, Jennifer L., Caroline Hayward, Nese Direk, John G. Lewis, Geoffrey L. Hammond, Lesley A. Hill, Anna Anderson et al. "Genome wide association identifies common variants at the SERPINA6/SERPINA1 locus influencing plasma cortisol and corticosteroid binding globulin." *PLoS genetics* 10, no. 7 (2014): e1004474. |
| Fasting glucose | Dupuis, Josée, Claudia Langenberg, Inga Prokopenko, Richa Saxena, Nicole Soranzo, Anne U. Jackson, Eleanor Wheeler et al. "New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk." *Nature genetics* 42, no. 2 (2010): 105. |
| Coronary heart disease | Nikpey, A Goel, H Won, LM Hall C. Willenborg, S Kanoni, D Saleheen et al. A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015 47:1121-1130 |
| Type 2 diabetes | Morris, Andrew P., Benjamin F. Voight, Tanya M. Teslovich, Teresa Ferreira, Ayellet V. Segre, Valgerdur Steinthorsdottir, Rona J. Strawbridge et al. "Large-scale association analysis provides insights into the genetic architecture and pathophysiology of type 2 diabetes." *Nature genetics* 44, no. 9 (2012): 981. |
| LDL cholesterol | Willer, Cristen J., Ellen M. Schmidt, Sebanti Sengupta, Gina M. Peloso, Stefan Gustafsson, Stavroula Kanoni, Andrea Ganna et al. "Discovery and refinement of loci associated with lipid levels." *Nature genetics* 45, no. 11 (2013): 1274. |

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| **Table 2.** MR analysis using MR-Base | |
| Step | Description |
| 1: Extract the instrument | First, GWAS significant SNPs (*p* < 5 x 10-8) for a specified outcome (e.g. body mass index, BMI) are extracted from the MR base database. Clumping is conducted at a threshold of r2=0.001 and with a distance cutoff of kb = 10000. |
| 2: Extract the outcome | Second, the corresponding beta and standard error for the identified SNP IV’s are extracted from the outcome of interest (e.g. CHD). |
| 3: Harmonisation | Third, harmonisation of the effect of the exposure and the outcome data is carried out. This ensures that the effect of a SNP on the exposure and the effect of that SNP on the outcome correspond to the same allele. |
| 4: MR analysis | Fourth, the MR analysis is conducted, using the harmonised dataset. The IVW method was used for all MR analyses. This returns the causal effect of the exposure (BMI) on the outcome (CHD): *b*=0.44; se=0.05 *p*<0.0001 |

**References**

* Gage, Suzanne H., Hannah J. Jones, Stephen Burgess, Jack Bowden, G. Davey Smith, Stanley Zammit, and Marcus R. Munafò. "Assessing causality in associations between cannabis use and schizophrenia risk: a two-sample Mendelian randomization study."*Psychological medicine* 47, no. 5 (2017): 971-980.
* [Hemani G, Zheng J, Wade KH, Laurin C, Elsworth B, Burgess S, Bowden J, Langdon R, Tan V, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC, The MR-Base Collaboration.  
  MR-Base: a platform for systematic causal inference across the phenome using billions of genetic associations. bioRxiv. doi:](http://biorxiv.org/content/early/2016/12/16/078972) <https://doi.org/10.1101/078972>
* Liu, Dajiang J., Gina M. Peloso, Haojie Yu, Adam S. Butterworth, Xiao Wang, Anubha Mahajan, Danish Saleheen et al. "Exome-wide association study of plasma lipids in> 300,000 individuals." *Nature genetics* 49, no. 12 (2017): 1758.
* Nikpey, A Goel, H Won, LM Hall C. Willenborg, S Kanoni, D Saleheen et al. A comprehensive 1000 Genomes–based genome-wide association meta-analysis of coronary artery disease. Nat Genet 2015 47:1121-1130.
* Rees, Jessica, Angela M. Wood, and Stephen Burgess. "Extending the MR‐Egger method for multivariable Mendelian randomization to correct for both measured and unmeasured pleiotropy."Statistics in medicine 36, no. 29 (2017): 4705-4718.
* Bulik-Sullivan, Brendan, Hilary K. Finucane, Verneri Anttila, Alexander Gusev, Felix R. Day, Po-Ru Loh, Laramie Duncan et al. "An atlas of genetic correlations across human diseases and traits." *Nature genetics* 47, no. 11 (2015): 1236.
* Yavorska, Olena O., and Stephen Burgess. "MendelianRandomization: an R package for performing Mendelian randomization analyses using summarized data." *International journal of epidemiology* 46, no. 6 (2017): 1734-1739.