SUPPLEMENTAL MATERIAL

Data S1. STROBE-MR Reporting Guidelines

1. TITLE and ABSTRACT

Indicate Mendelian randomization as the study's design in the title and/or the abstract.

Mendelian randomization is present in both the title and abstract of the manuscript.

INTRODUCTION

2. Background

Explain the scientific background and rationale for the reported study. Is causality between exposure and outcome plausible? Justify why MR is a helpful method to address the study question.

Addressed in the Introduction and Methods section of the main manuscript.

3. Objectives

State specific objectives clearly, including pre-specified causal hypotheses (if any).

Addressed in the Introduction section of the main manuscript.

METHODS

4. Study design and data sources

Present key elements of study design early in the paper. Consider including a table listing sources of data for all phases of the study. For each data source contributing to the analysis, describe the following:

a) Describe the study design and the underlying population from which it was drawn.

Describe also the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection, if available.

b) Give the eligibility criteria, and the sources and methods of selection of participants.

c) Explain how the analyzed sample size was arrived at.

d) Describe measurement, quality and selection of genetic variants.

e) For each exposure, outcome and other relevant variables, describe methods of assessment and, in the case of diseases, the diagnostic criteria used.

f) Provide details of ethics committee approval and participant informed consent, if relevant.

Addressed in the Methods section of the main manuscript.

5. Assumptions

Explicitly state assumptions for the main analysis (e.g. relevance, exclusion, independence, homogeneity) as well assumptions for any additional or sensitivity analysis.

Addressed in the Methods section of the main manuscript.

6. Statistical methods: main analysis

Describe statistical methods and statistics used.

a) Describe how quantitative variables were handled in the analyses (i.e., scale, units, model).

b) Describe the process for identifying genetic variants and weights to be included in the analyses (i.e, independence and model). Consider a flow diagram.

c) Describe the MR estimator, e.g. two-stage least squares, Wald ratio, and related statistics.

Detail the included covariates and, in case of two-sample MR, whether the same covariate set was used for adjustment in the two samples.

d) Explain how missing data were addressed.

e) If applicable, say how multiple testing was dealt with.

Addressed in the Methods section of the main manuscript.

7. Assessment of assumptions

Describe any methods used to assess the assumptions or justify their validity.

Addressed in the Methods section of the main manuscript.

8. Sensitivity analyses

Describe any sensitivity analyses or additional analyses performed.

Addressed in the Methods section of the main manuscript.

9. Software and pre-registration

a) Name statistical software and package(s), including version and settings used.

Addressed in the Methods section of the main manuscript.

b) State whether the study protocol and details were pre-registered (as well as when and where).

Addressed in the Methods section of the main manuscript.

RESULTS

10. Descriptive data

a) Report the numbers of individuals at each stage of included studies and reasons for exclusion. Consider use of a flow-diagram.

b) Report summary statistics for phenotypic exposure(s), outcome(s) and other relevant variables (e.g. means, standard deviations, proportions).

c) If the data sources include meta-analyses of previous studies, provide the number of studies, their reported ancestry, if available, and assessments of heterogeneity across these studies. Consider using a supplementary table for each data source.

d) For two-sample Mendelian randomization:

i. Provide information on the similarity of the genetic variant-exposure associations between the exposure and outcome samples.

ii. Provide information on extent of sample overlap between the exposure and outcome data sources.

Addressed in the Methods and Results sections of the main manuscript and Supplemental Tables.

11. Main results

a) Report the associations between genetic variant and exposure, and between genetic variant and outcome, preferably on an interpretable scale (e.g. comparing 25th and 75th percentile of allele count or genetic risk score, if individual-level data available).

b) Report causal effect estimate between exposure and outcome, and the measures of uncertainty from the MR analysis. Use an intuitive scale, such as odds ratio, or relative risk, per standard deviation difference.

c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time-period.

d) Consider any plots to visualize results (e.g. forest plot, scatterplot of associations between genetic variants and outcome versus between genetic variants and exposure).

Addressed in the Results section of the main manuscript and Supplemental Tables.

12. Assessment of assumptions

a) Assess the validity of the assumptions.

b) Report any additional statistics (e.g., assessments of heterogeneity, such as I2, Q statistic).

Addressed in the Results and Discussion section of the main manuscript and Supplemental Tables.

13. Sensitivity and additional analyses

a) *Use sensitivity analyses to assess the robustness of the main results to violations of the assumptions.*

b) Report results from other sensitivity analyses (e.g., replication study with different dataset, analyses of subgroups, validation of instrument(s), simulations, etc.).

c) Report any assessment of direction of causality (e.g., bidirectional MR).

d) When relevant, report and compare with estimates from non-MR analyses.

e) Consider any additional plots to visualize results (e.g., leave-one-out analyses).

Addressed in the Results section of the main manuscript and Supplemental Tables.

DISCUSSION

14. Key results

Summarize key results with reference to study objectives.

Addressed in the Discussion section of the main manuscript.

15. Limitations

Discuss limitations of the study, taking into account the validity of the MR assumptions, other sources of potential bias, and imprecision. Discuss both direction and magnitude of any potential bias, and any efforts to address them.

Addressed in the Discussion section of the main manuscript.

16. Interpretation

a) Give a cautious overall interpretation of results considering objectives and limitations.

Compare with results from other relevant studies.

b) Discuss underlying biological mechanisms that could be modelled by using the genetic variants to assess the relationship between the exposure and the outcome.

c) Discuss whether the results have clinical or policy relevance, and whether interventions could have the same size effect.

Addressed in the Discussion section of the main manuscript.

17. Generalizability

Discuss the generalizability of the study results (a) to other populations (i.e. external validity),

(b) across other exposure periods/timings, and (c) across other levels of exposure.

Addressed in the Discussion section of the main manuscript.

OTHER INFORMATION

18. Funding

Give the source of funding and the role of the funders for the present study and, if applicable, for the original study or studies on which the present article is based.

Addressed in the Funding section of the main manuscript.

19. Data and data sharing

Present data used to perform all analyses or report where and how the data can be accessed. State whether statistical code is publicly accessible and if so, where.

Addressed in the Methods section of the main manuscript.

20. Conflicts of Interest

All authors should declare all potential conflicts of interest.

Addressed in the Conflicts of Interest section of the main manuscript.

Table S1. Phenotype descriptives and sources

Table S2. PCSK9 instruments

Table S3. Polygenic LDL instrument

Table S4. SVMR results for PCSK9 in LDL-C on sex-stratified neuropsychiatric outcomes aligned with PCSK9 inhibition with the primary 2021 GLGC LDL-C instrument

Table S5. Statistical power to detect odds ratio of OR 2.00, 1.20, and 1.10 per standard deviation decrease in exposure levels at a 5% false positive rate

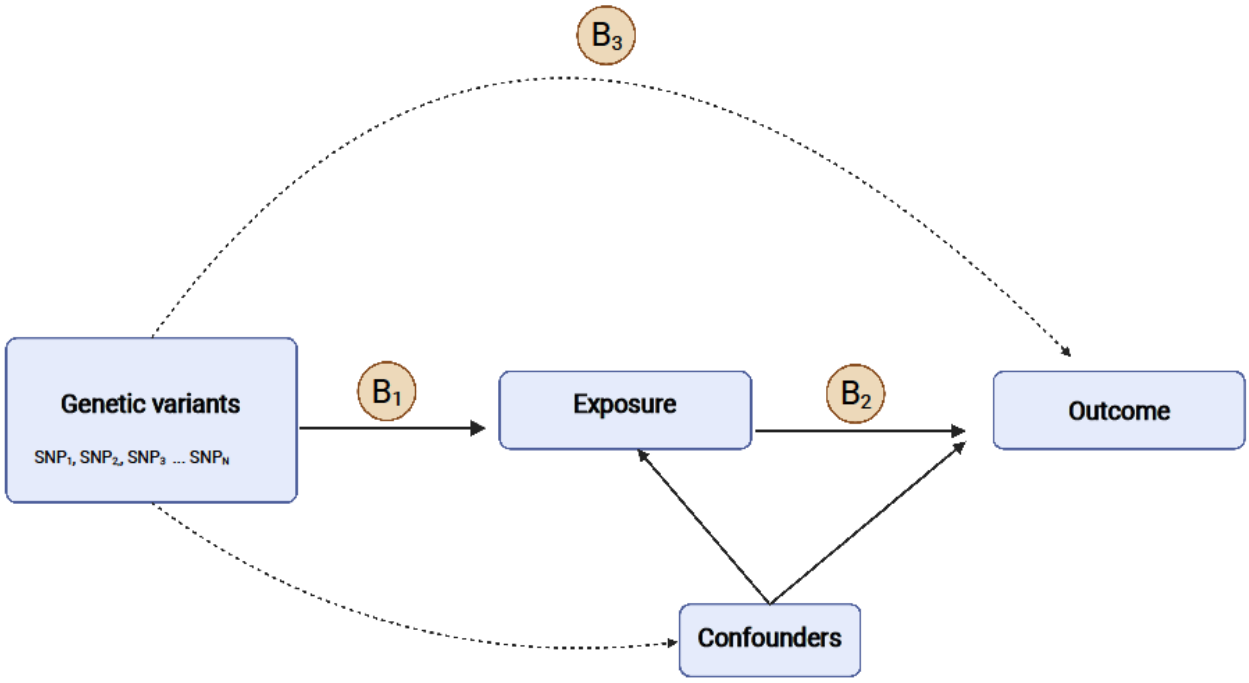
Table S6. Results of sex-specific drug-target MR on all outcomes from secondary PCSK9 LDL-C instrument derived from 2013 GLGC data

Table S7. SVMR results for LDL-C on sex-stratified neuropsychiatric outcomes

Table S8. SVMR results for PCSK9 cis-located instruments in EQTL/liver, EQTL/whole blood, and PQTL/whole blood on LDL-C

Table S9. SVMR results for PCSK9 in liver EQTL, whole blood PQTL, whole blood EQTL, and cortex and meta-brain EQTLs on sex-stratified neuropsychiatric outcomes aligned with PCSK9 inhibition

Figure S1. Mendelian Randomization Model and Assumptions



B_2 is the genetic association of interest, estimated by $B_2=B_1/B_3$. B_1 and B_3 are the associations of the genetic variants with the exposure and the outcome. MR assumes that the genetic variants comprising the instrument for the exposure only impact the outcome of interest via the exposure and not directly, or via confounders (dotted lines).[53]