Socioeconomic status and severe mental disorders: a bidirectional multivariable Mendelian randomisation study

Álvaro Andreu-Bernabeu,1 Javier González-Peñas,1 Celso Arango,1,2 Covadonga M Díaz-Caneja1,2

ABSTRACT

**Background** Despite the evidence supporting the relationship between socioeconomic status (SES) and severe mental disorders (SMD), the directionality of the associations between income or education and mental disorders is still poorly understood.

**Objective** To investigate the potential bidirectional causal relationships between genetic liability to the two main components of SES (income and educational attainment (EA)) on three SMD: schizophrenia, bipolar disorder (BD) and depression.

**Methods** We performed a bidirectional, two-sample univariable Mendelian randomisation (UVMR) and multivariable Mendelian randomisation (MVMR) study using SES phenotypes (income, n=397,751 and EA, n=766,345) and SMD (schizophrenia, n=127,906; BD, n=51,710 and depression, n=500,119) genome-wide association studies summary—statistics to dissect the potential direct associations of income and EA with SMD.

**Findings** UVMR showed that genetic liability to higher income was associated with decreased risk of schizophrenia and depression, with a smaller reverse effect of schizophrenia and depression on income. Effects were comparable after adjusting for EA in the MVMR. UVMR showed bidirectional negative associations between genetic liability to EA and depression and positive associations between genetic liability to EA and BD, with no significant effects on schizophrenia. After accounting for income, MVMR showed a bidirectional positive direction between genetic liability to EA and BD and schizophrenia but not with depression.

**Conclusions** Our results suggest a heterogeneous link pattern between SES and SMD. We found a negative bidirectional association between genetic liability to income and the risk of schizophrenia and depression. On the contrary, we found a positive bidirectional relationship of genetic liability to EA with schizophrenia and BD, which only becomes apparent after adjusting for income in the case of schizophrenia.

**Clinical implications** These findings shed light on the directional mechanisms between social determinants and mental disorders and suggest that income and EA should be studied separately in relation to mental illness.

BACKGROUND

Social determinants and their potential aetiological role in mental disorders have been a major topic since the inception of psychiatry. Socioeconomic status (SES) plays a fundamental role in the performance of an individual in society, affecting well-being, longevity and health. Extensive evidence based on survey data, large cohort observational studies and family-level studies supports the association between mental disorders and lower income, disadvantaged socioeconomic position and homelessness. Recent work has also reported an association of parental SES with offspring mental health selection in the risk of severe mental disorders, with a smaller reverse effect. Conversely, we found bidirectional positive associations of genetic liability for educational attainment with bipolar disorder and, only after adjusting for income, with schizophrenia. When including cognitive ability in the model, we observed a protective effect of genetic liability for cognitive ability against these two disorders.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Despite previous evidence linking low socioeconomic status to mental disorders, the nature of their association remains controversial. Health selection theories propose that mental disorders lead to lower education and income, whereas social causation theories suggest that societal inequality and stress are possible causes of these disorders.

WHAT THIS STUDY ADDS

- This bidirectional multivariable Mendelian randomisation study showed a heterogeneous pattern of causal links between socioeconomic status and severe mental disorders. Genetic liability for income was associated with lower risk for schizophrenia and major depressive disorder, with a smaller reverse effect.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Our results support both social causation and health selection in the risk of severe mental disorders but only in domain-specific ways and suggest that income and educational attainment should be studied separately in relation to mental illness. These findings shed light on the role of genetics in social determinants and mental health, providing potentially useful information for future public mental health initiatives.
disorders such as major depressive disorder or schizophrenia disorder (SCZ). However, the specific pattern of relationships is heterogeneous, as some disorders such as ASD or bipolar disorder (BD) are associated with higher parental or individual SES, while depression or SCZ are associated with lower levels of education and income.

Two classic theories have attempted to explain the nature of the relationship between SES and mental health: health selection and social causation. The health selection theory posits that individuals with mental disorders might be predisposed to reduced educational attainment (EA) and lower income. The social causation theory, in contrast, posits that social inequality, health resources gaps and context-related stress may increase the risk of mental disorders. The general consensus to date suggests that health selection could play a stronger role in severe mental disorders (SMD) like SCZ, whereas social causation would be more relevant for common mental disorders such as anxiety or depressive symptoms.

Although researchers have considered socioeconomic factors mainly environmental, the two core phenotypes comprising SES, income and EA, are substantially heritable (40%-60%). Likewise, family and twin studies have estimated that genetics account for a large portion of the phenotypic variation of mental disorders, with heritability estimates of 65%-80% in SCZ and 30%-40% for depression. Genome-wide association studies (GWASs) have supported observational evidence of heterogeneous patterns of genetic correlations between income and mental disorders, with positive genetic correlation for BD (rg=0.11) and anorexia nervosa (rg=0.05) and negative correlations for attention deficit hyperactivity disorder (rg=-0.36), depression (rg=-0.24) and SCZ (rg=-0.14)). Two recent studies using Conditional Genome-wide Complex Trait Analysis and Genomic Structural Equation Modelling have also reported that genetic associations among mental disorders may be influenced by genetic overlap with SES traits, highlighting the polygenic and pleiotropic links between mental disorders and SES.

Despite the efforts to disentangle the complex relationship between SES and mental disorders, there is still ongoing debate due to the disparity of results and lack of replication. Further, conventional observational studies are affected by unmeasured confounders that preclude adequate assessment of the direction of associations between SES and mental disorders. The use of univariable Mendelian randomisation (UVMR) has become popular for analysing causality between exposures to risk or protective factors and outcomes such as diseases in recent years, to overcome the limitations of observational studies. An extension of MR called multivariable Mendelian randomisation (MVMR) has recently been developed to allow the analysis of the independent causal effects of correlated exposures simultaneously.

We performed bidirectional two-sample UVMR to determine whether genetic liability to household income and EA were causally linked to three SMD (ie, SCZ, BD and depression) with onset in adolescence or young adulthood and differing effects across the psychotic, cognitive and affective spectra. We used MVMR to disentangle the independent contribution of income and EA to SMD and the independent reverse effects of SMD on each SES trait.

Figure 1 Directional associations between socioeconomic status (SES) and mental disorders: (A) Total (UVMR, blue) and direct effects (MVMR, red) of genetic liability to educational attainment on the risk of severe mental disorders (SMD). (B) Total (UVMR, blue) and direct effects (MVMR, red) of genetic liability to household income on the risk of SMD. (C) Total (UVMR, blue) and direct effects (MVMR, red) of genetic liability to severe mental disorder (SMD) on EA. (D) Total (UVMR, blue) and direct effects (MVMR, red) of genetic liability to SMD on household income. MR estimates and 95% CIs for the effects of genetic liability to EA and income on the risk of SMD (A-B) per 1-SD increase in each SES component (ie, household income 33181 pounds, EA 4.2 education years) on the odds of each SMD. For analysis investigating the effects of genetic liability of mental disorders to SES (C-D), estimates are provided per doubling (twofold increase) of the prevalence of the exposure. Significant effects after false discovery rate (FDR) correction (FDR < 0.05) for total effects and after non-parametric 1000 iteration bootstrap permutations for direct effects are marked with an asterisk. EA, educational attainment; MVMR, multivariable Mendelian randomisation; SES, socioeconomic status; UVMR, univariable Mendelian randomisation.
Table 1  (A) Estimates of the total and direct effects of genetic liability to mental disorders on genetic liability to income and (B) estimates of the total and direct effects of genetic liability to mental disorders on genetic liability to educational attainment

(A) UVMR (IVW)|total effect | Outcome: income | MVMR|direct effect (mental disorder not mediated by income)| Outcome: income

<table>
<thead>
<tr>
<th>Exposure</th>
<th>NSNP</th>
<th>beta</th>
<th>SE</th>
<th>95% CI</th>
<th>P value</th>
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<th>SE</th>
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<th>P value</th>
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<td>-0.048 to -0.022</td>
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<td>0.013321</td>
<td>-0.002 to 0.049</td>
<td>0.078648</td>
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<td>0.0344</td>
<td>-0.182 to -0.047</td>
<td>8.70E-04</td>
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<td>-0.0849</td>
<td>-0.127 to -0.05</td>
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(B) UVMR (IVW)|total effect | Outcome: educational attainment | MVMR|direct effect (mental disorder not mediated by income)| Outcome: educational attainment

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<th>beta</th>
<th>SE</th>
<th>95% CI</th>
<th>P value</th>
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<td>Depression</td>
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*In MVMR 95% Confidence interval after non-parametric 1000 iteration bootstrap permutations. Bold (UVMR pFDR<0.05 and MVMR with 95% CIs included after non-parametric 1000 permutations).

METHODS

Study design

MR is an instrumental variable analysis method based on genetic variants (single-nucleotide polymorphisms, SNPs). MR enables causal estimates between exposure and an outcome thanks to the natural randomisation of genetic variants that takes place in meiosis. MVMR is an extension of the MR method that allows the inclusion of instrumental variables of different exposures that are phenotypically and genetically associated in the same model in order to obtain the independent direct effects of each exposure on the outcome. We performed bidirectional two-sample UVMR and MVMR analyses to assess the causal links between SES (income and EA) and SMD in public datasets of European population. We performed follow-up analyses including genetic liability to cognitive ability and intelligence in MVMR models to assess the causal links independently of cognitive ability. For more information on MR, see online supplemental eMethods and MR guidelines.

Data sources

SES phenotypes

We used the largest publicly available GWAS summary statistics of household income from the UK Biobank (UKB) (n=3 977 51) estimated from the household income Phenat-derived phenotype which comprised five ordinal midpoints from ‘less than £18 000’ up to ‘more than £100 000’ with an estimated mean income of £44 409 (SD: £33 181). For EA, we used the largest available GWAS from European Ancestry (n=766 345). The EA phenotype was a meta-analysis of 70 GWAS with standardised measures of years of schooling (weighted mean 16.8 years, SD 4.2), including 442 183 individuals from the UKB cohort.

Mental disorders

We selected the latest GWAS from the Psychiatric Genomics Consortium (PGC) for (1) SCZ (wave-3, only European ancestry), comprising 52 017 cases and 75 889 controls) from 76 European cohorts from the PGC; (2) BD wave 3 419 197 cases and 371 549 controls recruited in Europe, North America and Australia of European ancestry and (3) depression, 17 0756 cases and 329 443 controls. For depression, we used a meta-analysis of the two largest GWAS of depression (excluding 23andMe) which includes the PGC major depressive disorder cohort and cohorts with a broader definition of depression.

Cognitive ability and intelligence

We used a cognitive ability GWAS meta-analysis and the most extensive GWAS meta-analysis of intelligence. The cognitive ability phenotype included a general cognitive ability study (n=35 298) conducted by the COGENT consortium, as well as a cognitive performance sample from the UKB (n=222 543). Intelligence phenotype included 14 independent epidemiological cohorts of European ancestry (n=269 867). General cognitive ability was captured by a latent variable, termed the ‘g-factor’ captured the shared variance across cognitive tasks indicative of general intelligence.

The ethics declarations for each public dataset used in the present research can be found in their original publications. For more details, see online supplemental eMethods.

Genetic instruments and statistical analysis

We extracted genome-wide significant SNPs as instrumental variables at p<5×10−8. For each exposure, we calculated the F statistic to analyse the instrument’s strength and used the rule of thumb of F>10 adopted in previous studies to define weak instrument bias. Univariable Mendelian randomisation

We conducted a bidirectional two-sample UVMR analysis to assess putative causality between household income and EA and the three SMD. We used an inverse-variance weighted method (IVW) as the main analysis, as recommended by available guidelines due to its robustness. However, as IVW may generate biased results in case of heterogeneity or violation of any assumption, we used weighted median (WM) MR-Egger, simple mode (SM), weighted mode (WMO), heterogeneity tests and horizontal pleiotropy tests as sensitivity analyses. Additionally, we conducted
Mendelian Randomisation Pleiotropy RESidual Sum and Outlier analysis which enables correction of horizontal pleiotropy via outlier removal. All analyses were performed using the ‘TwoSampleMR’ package V.0.5.6, with R V.4.1.2.

Multivariable Mendelian randomisation
The total effects provided by a classical UVMR method can suffer from bias when there is a high correlation between exposures, as is the case of income and EA. Hence, we evaluated (1) the direct effect independent of EA of genetic liability to income on each SMD and the direct effect of genetic liability to each SMD on income and (2) the direct effect independent of income of genetic liability to EA on each SMD and the direct effect of genetic liability to each SMD on EA. Finally, we conducted post hoc analyses including genetic liability to cognitive ability and intelligence in the MVMR models to assess the association of EA and income with SMD independently of cognitive performance.

For each MVMR analysis, we applied the same LD-Clumping, harmonised method and palindromic SNPs exclusion as for UVMR using the ‘TwoSampleMR’ package. We then followed Sanderson et al to estimate causal effects and to correct for potentially weak and pleiotropic instruments through various sensitivity analyses. We estimated the instrumental variable strength using conditional-F statistics and heterogeneity as well as horizontal pleiotropy using a modified Cochran’s Q-statistic. We performed IVM-MVMR regression of each model and robust-to-weak-instrument Q-statistic minimisation, using non-parametric 1000 iteration bootstrap permutations. All MVMR analyses were performed with the MVMR package (more details in online supplemental eMethods and (https://github.com/WSpiller/MVMR)).

Interpretation of the estimates
For the analyses exploring the effect of genetic liability to income and EA on the risk of SMD, causal effects and 95% CIs, we expressed the increase in the odds of developing each mental disorder in SD. Analyses exploring the effect of SMD on EA and income were first multiplied by the SD of income (SD=£33 181) and EA (SD=4.2 years of education) to convert them to British pounds and months and then expressed as the effect of a doubling (twofold increase) of genetic liability to each SMD on the odds of income and EA, as recommended in previous studies. Finally, we defined significance at a false discovery rate of 0.05 for each UVMR analysis. For the MVMR analyses, we considered significant results included in the CI after non-parametric 1000-iteration bootstrap permutation. For more details, see online supplemental eMethods.

RESULTS
Effect of genetic liability to SES on the risk of SMD
The results of the bidirectional UVMR (total effects) and MVMR (direct effects) analysis of genetic liability to cognitive ability, educational attainment (EA) and income on the risk of each SMD are shown in figure 1A,B.

![Figure 2](https://example.com)  
**Figure 2** Direct effects of genetic liability to cognitive ability and socioeconomic status (SES) on the risk of severe mental disorder (SMD): follow-up multivariable Mendelian randomisation analyses of genetic liability to cognitive ability, educational attainment (EA) and income on the risk of each SMD. 95% CIs included after non-parametric 1000 iteration bootstrap permutations are marked with an asterisk.
Effects of genetic liability to EA on mental disorders

Using the inverse-variance-weighted (IVW) method, genetic liability to EA was univariately associated with a lower risk of depression per SD-increase-unit (~4.2 years schooling) (IVW-ORDEP=0.78, p=1.89E–10) and a higher risk of BD (IVW-ORBIP=1.84, p=0.0017), but not with SCZ risk (IVW-ORSCZ=1.11, p=0.263) Sensitivity analyses mirrored the results of the IVW method and egger-intercept showed nonsignificant results indicating that there was little evidence for directional genetic pleiotropy. After accounting for income, genetic liability to EA was associated with an almost 1.7-fold increased risk of BD (MVMR-ORBIP=1.67, p=1.76E–03), and a 2-fold increased risk of SCZ (MVMR-ORSCZ=2.09, p=0.00108), with no significant effects on depression risk. These results were consistent with the corresponding confidence intervals of the robust-to-weak instruments MVMR sensitivity analyses (see figure 1A and online supplemental eTables 1 and 2 for more details).

Effects of genetic liability to household income on mental disorders

Genetic liability to household income was associated with lower risk of SCZ (IVW-ORSCZ=0.58 per SD-increase, p=0.016) and depression (IVW-ORDEP=0.66 per SD-increase, p=9.81e–08). We found heterogeneity for both disorders, but there was limited evidence of horizontal pleiotropy, as suggested by the MR-Egger intercept (see online supplemental eTables 1 and 3). Using MVMR, the estimated direct effect of genetic liability to income, independent of EA, was nearly comparable to the total effect for both disorders (MVMR-ORSCZ: 0.32 per SD-increase, p=0.00042; MVMR-ORDEP: 0.66, p=9.96E–05). We found no significant associations between income and BD in the UVMR or MVMR analyses (see figure 1B and online supplemental eTables 1 and 3).

Effect of genetic liability to SMD on SES

The results of the bidirectional UVMR and MVMR analysis of the effects of genetic liability to SCZ, depression and BD on income and EA are shown in table 1 and figure 1B,C.

Effects of genetic liability to SMD on EA

We found that genetic liability to SCZ had a small positive effect on EA only after including income in the model (MVMR-IVMSCZ=1.046 months per doubling of genetic liability to SCZ, p=0.0000057), while genetic liability to BD had significant total and direct effects on EA (MVMR-IVMBIP=1.912 months, p=9.84E–06). Genetic liability to depression had a small negative total effect on EA in the univariate analyses (IVWDEP=−2.79 months, p=0.0211) that was no longer significant after accounting for income (see online supplemental eTables 1 and 4 and figure 1C).

Effects of genetic liability to SMD on household income

Genetic liability to SCZ had significant total and direct negative effects on household income (IVWSCZ=−819.99£, p=7.53E–08, MVMR-IVMSCZ=−960.41£, p=5.27E–09). We also found that genetic liability to depression had a significant negative total effect on income (IVWDEP=−263.96£, p=8.69E–04), with comparable although slightly lower direct effects after accounting for EA in the MVMR models. There was no significant effect of genetic liability to BD on income (see Table 1, online supplemental eTable 5 and figure 1D).

Direct effects of genetic liability to SES and cognitive ability on the risk of SMD

Considering previous inconsistent evidence of a protective effect of education on mental disorders,47 we conducted supplementary post hoc MVMR analyses to assess the potential role of cognitive ability in the positive association found between genetic liability to EA and the risk of SCZ and BD. We found that the direct effect of EA on the risk of BD and SCZ, not mediated through cognitive ability, was larger than that found in the original model (MVMR-ORSCZ=3.95 per SD-increase, p=4.55E–09; IVW-ORBIP=2.73, p=1.47E–06). There was a direct negative effect of cognitive ability, not mediated by EA or income, with around 0.50-fold decreased risk per SD-increase on SCZ (MVMR-ORSCZ=0.50, p=1.58E–05) and around 0.30-fold decreased risk per SD-increase on bipolar disorder (MVMR-ORBIP=0.31, p=0.010375). Income effects were practically unchanged. Further sensitivity analyses using an alternative intelligence phenotype suggested that genetic liability to intelligence, not mediated by EA, was associated with increased risk of depression (MVMR-ORDEP=1.25 per SD-increase, p=3.03E–05). Both analyses were consistent in terms of the direction and strength of the effects, supporting the robustness of our findings (see figure 2, online supplemental eTables 6 and 7).

DISCUSSION

Despite the well-established relationship of SES to mental disorders,17 18 considerable debate remains about the causal links between key SES constituents income and education with SMD.37 48 49 We used MVMR to address the potential influence of SES multidimensionality on mental disorders by analysing the independent effects of genetic liability to income and EA on three SMD. Our study revealed different patterns of bidirectional associations between SES constituents and the three SMD. We observed a negative bidirectional association between household income on the risk of SCZ and depression, with a smaller reverse causal effect. On the contrary, we found a positive bidirectional relationship of genetic liability to EA with BD in UVMR and MVMR and with SCZ, which only becomes apparent after adjusting for income. These findings are in line with a recent nationwide study in Finland supporting contributions of both social causation and health selection mechanisms to the risk of mental disorders,49 and may contradict, at least in terms of genetic liability, widespread social causation versus health selection theories.18

EA MVMR estimates were in agreement with previous positive genetic correlations with SCZ and BD.50 However, as SCZ has been classically associated with premorbid cognitive deficits and cognitive decline,51 52 we conducted post hoc analyses including genetic liability to cognitive ability in the MVMR model to assess these apparently counterintuitive results. We found an even greater positive direct effect of EA (independently of cognitive ability and income, and thus probably reflecting non-cognitive skills53) on the risk of BD and SCZ. By contrast, we found that, after adjusting for EA and income, cognitive ability was associated with decreased risk for SCZ and BD. These results are consistent with genetic correlations of BD and SCZ with cognitive and non-cognitive skills latent factors shown by the recent GWAS-by-subtraction method54 and also support findings from genetic studies showing a polygenic contribution of SCZ and BD liability to creative and artistic careers55 as opposed to the negative association of genetic liability to SCZ with general cognitive function.32 56 Our results suggest that non-cognitive skills such as creativity, higher tolerance of risk or perseverance towards...
an activity, which may provide evolutionary benefits, could also lead to an increased susceptibility to SCZ or BD.\textsuperscript{55,57}

Overall, our research supports previous evidence linking socioeconomic inequality and poor mental health.\textsuperscript{7,11,17} In the USA, the estimated economic burden of SCZ was around US$150 billion per year, mainly due to indirect costs associated with unemployment and lack of productivity.\textsuperscript{58} Our results support an association between genetic liability to SCZ and depression and lower household income, with smaller effects than those expected from the observational data. This is consistent with recent research suggesting that genetic liability to higher EA could affect health and social outcomes independently of educational milestones or changes in wages.\textsuperscript{36} A combined liability-threshold model which includes putative rare variants with large effects\textsuperscript{59} and involves potential gene–environmental interaction effects such as the stigma and discrimination associated with some diagnostic categories,\textsuperscript{60} the disability associated with early symptoms and drug abuse,\textsuperscript{61} \textsuperscript{62} the potential impact of isolation and social defeat\textsuperscript{62,64} and a likely negative expectation effect towards SMD such as SCZ\textsuperscript{64} could provide more accurate estimates in the future.

Our findings are also consistent with previous GWAS showing that income-related genetic variants are more strongly associated with better mental health than education genetic variables.\textsuperscript{62} We found that the total effects of genetic liability to EA on the three mental disorders tended to diverge from direct effects after accounting for income. For instance, we only found a positive bidirectional connection between SCZ and EA after adjusting for income, while the bidirectional negative association of depression with EA was only significant in the unadjusted analyses and was thus probably confounded by income. On the contrary, the pattern of bidirectional associations between household income and SMD was less influenced by EA overall. Our results suggest that we should assess the independent and joint effects of income and EA to better address the complexity of their causal links to SMD. They also underscore the role of novel multivariate methods such as MVMR in disentangling the effects of complex phenotypes with highly correlated subphenotypes such as SES.

The use of genetic information tools in the social field remains a subject of ongoing debate.\textsuperscript{65} In MR analyses, genetic variants serve as proxies for an underlying liability to EA or income. This genetic liability can affect outcomes either by changing exposure categories, acting independently or both. Consequently, causal estimates are unlikely to reflect the direct effects of additional years of education or shifts in household income.\textsuperscript{66} Furthermore, due to limitations inherent to their design, GWAS studies may not accurately identify causal variants, nor capture the full range of genetic determinants for complex traits such as cognitive ability or EA.\textsuperscript{67} Nevertheless, genetic liability to complex traits such as education and income can play a role in perpetuating inequality and affect mental health outcomes.\textsuperscript{67} Accordingly, public health strategies could benefit from a nuanced application of socio-environmental genetic studies in the future.

CONCLUSIONS

We provide evidence that genetically predicted income was associated with a lower risk of SCZ and depression and that SCZ and depression were associated with decreased income. On the contrary, a positive bidirectional association of genetic liability to EA with SCZ and BD was found, but only after adjusting for income in the case of SCZ. Even if our results need to be interpreted in terms of genetic liability, our study may advance knowledge of the mechanisms by which social determinants influence mental health by dissecting the independent effects of genetic liability to income and EA on different SMD and could provide useful information for allocating mental health resources and addressing social inequality.

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Contributors AA-B is guarantor and was responsible for the planning, conception, analysis and writing of the article. JG-P contributed to the analysis and provided critical revisions to the manuscript. CA contributed to the interpretation of results and provided critical revisions to the manuscript. CMD-C was involved in the conception, critical manuscript revisions and editing of the article.

Funding This work was supported by the Spanish Ministry of Science and Innovation. Instituto de Salud Carlos III (SAF1607C1, PI16/02012, PI17/00997, PI19/01024, PI20/00712), co-financed by ERDF Funds from the European Commission, ‘A way of making Europe’, CIBERSAM, Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds. European Union Seventh Framework Program under grant agreements FP7-HEALTH-2009-2.2.1-2.2-241909 (Project EU-GEI), FP7-HEALTH-2013-2.2.1-2-603196 (Project PSYSCAN), and FP7-HEALTH-2013-2.2.1-2-602478 (Project METSYS), and European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking (grant agreement No 115916, Project PRISM, and grant agreement No 777394, Project AMIS-2-TRIALS), Fundación Familia Alonso, Fundación Alicia Koplowitz, and Fundación Mutua Madrileña. The authors acknowledge the valuable commentaries provided by Nicolas Crossley. AA-B
held a Rio Hortega Grant during the development of the research from Instituto de Salud Carlos III (CM20/00114). CMD-C holds a Juan Rodés Grant from Instituto de Salud Carlos III (JR19/00024).

Competing interests CA has been a consultant to or has received honoraria or grants from Acadia, Angelini, Gedeon Richter, Janssen Cilag, Lundbeck, Minevra, Otsuka, Roche, Sage, Servier, Shire, Scheering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda. CMD-C has received honoraria from AbbVie, Sanofi and Exelixis. The rest of the authors declare no competing interests.

Patient consent for publication Not applicable.

Ethics approval This study involved human participants and the ethics declarations for each public dataset used in the present research can be found in their original publications. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository.

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