Impact of schizophrenia genetic liability on the association between schizophrenia and physical illness: data-linkage study


Background
Individuals with schizophrenia are at higher risk of physical illnesses, which are a major contributor to their 20-year reduced life expectancy. It is currently unknown what causes the increased risk of physical illness in schizophrenia.

Aims
To link genetic data from a clinically ascertainment sample of individuals with schizophrenia to anonymised National Health Service (NHS) records. To assess (a) rates of physical illness in those with schizophrenia, and (b) whether physical illness in schizophrenia is associated with genetic liability.

Method
We linked genetic data from a clinically ascertained sample of individuals with schizophrenia (Cardiff Cognition in Schizophrenia participants, \( n = 896 \)) to anonymised NHS records held in the Secure Anonymised Information Linkage (SAIL) database. Physical illnesses were defined from the General Practice Database and Patient Episode Database for Wales. Genetic liability for schizophrenia was indexed by (a) rare copy number variants (CNVs), and (b) polygenic risk scores.

Results
Individuals with schizophrenia in SAIL had increased rates of epilepsy (standardised rate ratio (SRR) = 5.34), intellectual disability (SRR = 3.11), type 2 diabetes (SRR = 2.43), congenital disorders (SRR = 1.77), ischaemic heart disease (SRR = 1.57) and smoking (SRR = 1.44) in comparison with the general SAIL population. In those with schizophrenia, carrier status for schizophrenia-associated CNVs and neurodevelopmental disorder-associated CNVs was associated with height \( (P = 0.015-0.017) \), with carriers being 7.5-7.7 cm shorter than non-carriers. We did not find evidence that the increased rates of poor physical health outcomes in schizophrenia were associated with genetic liability for the disorder.

Conclusions
This study demonstrates the value of and potential for linking genetic data from clinically ascertained research studies to anonymised health records. The increased risk for physical illness in schizophrenia is not caused by genetic liability for the disorder.

Keywords
Schizophrenia; psychotic disorders; genetics; physical health.

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Study aims
In this study, we aimed to link genetic data from a clinically ascertained sample of individuals with schizophrenia to anonymised NHS and administrative data-sets in the Secure Anonymised Information Linkage (SAIL) database in Wales, with a focus on the rich physical health outcome data held in primary care electronic health resources. We then aimed to examine the association between physical health outcomes and genetic liability for schizophrenia as indexed by (a) rare (frequency <1%) CNVs, and (b) polygenic risk scores.

Method

Participants
Study individuals (n = 958, aged 17–84 years, 41% female) from the Cardiff Cognition in Schizophrenia (CardiffCOGS) sample were recruited from community, in-patient and voluntary sector mental health services in the UK and underwent detailed phenotypic assessment including a Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview. In brief, data from CardiffCOGS study individuals who had consented to linkage were imported into SAIL in line with permissions already granted to SAIL relating to good practice in research governance and privacy protection. We adopted a split file approach to separate participants for genetic research and linkage of their genetic information to the SAIL databank. Further information on the CardiffCOGS sample has been published elsewhere.

Electronic cohort from SAIL
Data source and data linkage
The SAIL databank (http://www.sail databank.com) is a national data repository containing anonymised, person-based, linkable data in Wales for over 3 million people. The procedure for linking research study data to SAIL has been described elsewhere.9,17,18 In brief, data from CardiffCOGS study individuals who had consented to linkage were imported into SAIL in line with permissions already granted to SAIL relating to good practice in research governance and privacy protection. We adopted a split file approach to separate individual identifiers from the interview data. Identity matching and creation of pseudonymised linkage keys (anonymised linking fields) were performed by a trusted third party prior to linkage and further encryption of data sets using deterministic matching based on NHS number or probabilistic matching using available demographics based on the Welsh Demographic Service data-set (all individuals registered with a general practice (GP) surgery). We included participants whose data were probabilistically linked with an adequate level of matching accuracy (matching score ≥0.9).18

We used the General Practice Database (GPD), containing diagnoses, symptoms, investigations, prescribed medication, referrals, coded hospital contacts and test results. At time of analysis, 77% (333/432) of GP surgeries in Wales supplied their data to SAIL. We also extracted data from the Patient Episode Database for Wales (PEDW), an NHS Wales hospital admissions data-set consisting of clinical information from all hospital admissions (in-patient and day cases) covering the entire population of Wales.

Measures for health outcomes
We used ICD-10 and Read codes for GDP and PEDW data-sets, respectively, to ascertain health outcomes.18 For schizophrenia, we adopted the codes that were validated and used in previous studies.18,20,21 We selected smoking, type 2 diabetes mellitus, ischaemic heart disease and body mass index (BMI) because of their high frequency in clinical samples of individuals with schizophrenia and their potential to contribute to increased mortality either directly, or via phenomena such as metabolic syndrome. We selected congenital disorders, intellectual disability and epilepsy as they are neurodevelopmental phenotypes with direct relevance to CNV carrier status. All of these variables also had either established SAIL algorithms or were considered to have high-quality data available in SAIL. We identified individuals with intellectual disability,18,23,50 ischaemic heart disease,17 epilepsy,24 diabetes mellitus25 and determined smoking status26 based on previously published works.

The list of codes used for extracting height, BMI and for identifying individuals with congenital disorders are given in supplementary Table 1 available at https://doi.org/10.1192/bjo.2020.42. For identifying schizophrenia, intellectual disability, ischaemic heart disease, epilepsy, diabetes mellitus and congenital disorders, we combined both the GPD and PEDW data-sets. We additionally extracted individuals’ height, BMI and smoking status from the GPD where available.

For comparison, we extracted lifetime diagnoses and estimated crude rates, as well as age- and gender-standardised rates, of health outcomes for the whole population and those diagnosed with schizophrenia between the ages of 17 and 84 years (as at 30 June 2016). For estimating standardised rates from SAIL, crude rates were first computed for five age groups (17–34, 35–44, 45–54, 55–64 and 65–84 years) for both genders. Standardised rates were then estimated based on the age and gender distribution in the clinical cohort. Linked data in SAIL were interrogated using structured query language (SQL DB2).

Genetic data
Genotyping and CNV calling
Samples were genotyped on OmniCombi or OmniExpress arrays (Illumina). After standard quality control, imputation was performed using IMPUTE2 and the 1000 genomes (phase 3) and UK10K reference panels.28 Best-guess genotypes were generated with the following thresholds: minimal genotypic confidence >90%, INFO-score >0.9, minor allele frequency (MAF) >1%, and Hardy-Weinberg equilibrium P-value <1 × 10−8.

Full details of the CNV calling methods and quality controls measures used have been published elsewhere.29 Illumina Genome Studio (version 2011.1) was used to process raw intensity data into log R ratios (LRR) and B allele frequencies. PennCNV (version 1.0.3.18) was then used to call CNVs based on 666,868 probes common to all Illumina arrays used.30 CNVs were joined if separated by less than 50% of their combined length. CNVs were excluded if they were (a) called with fewer than ten probes, (b) overlapped low copy repeats by more than 50% of their length, (c) had a probe density of less than 1 probe/20 kb, or (d) had a frequency of >1%.31

CNVs
To examine for enrichment of rare, pathogenic CNVs in physical health comorbidity, we analysed the presence of 12 CNVs robustly associated with the risk of schizophrenia.16,29 and 54 CNVs nominally associated (P < 0.05) with intellectual disability, autism spectrum disorder or schizophrenia (‘neurodevelopmental CNVs’).32 Following the approach taken in our previous work, 15q11.2 duplications were excluded because of their high frequency.33 CNV burden analyses were carried out using PLINK on regions of variable copy number at two size thresholds (a) ≥500 KB and (b) ≥1 MB and converted into carrier status for the purpose of regression analyses.
Polygenic risk scores

Polygenic risk scores were calculated using the largest published schizophrenia genome-wide association study meta-analysis (39 915 individuals with schizophrenia, 64 639 controls) as a training set and using the established method described by Wray et al.34,35 All study individuals were excluded from the training set. scores were generated using the –score function in PLINK53 for Single nucleotide polymorphisms with MAF >10%, INFO score >0.9, a low linkage disequilibrium to each other and excluding indels and the extended major histocompatibility complex region. Polygenic risk scores were calculated at nine P-value thresholds; 1 \times 10^{-1}, 1 \times 10^{-2}, 1 \times 10^{-3}, 1 \times 10^{-4}, 0.01, 0.05, 0.1, 0.2 and 0.5.

Analysis

Rates of physical illness

Linked data in SAIL were interrogated using structured query language (SQL DB2). All crude rates and standardised rates of health outcomes were expressed as a percentage of population affected (lifetime prevalence). All standardised rate ratios (SRRs) and their 95% confidence intervals were calculated as previously described.36–38

Ascertainment rates of behaviours and diagnoses

We evaluated the agreement on diagnoses between the clinical and electronic cohorts for each health outcome by constructing two \times two contingency tables based on the paired responses from the interview and SAIL. Level of agreement was then assessed by unweighted Cohen’s kappa coefficient39 and Gwet’s AC1.40 The 95% confidence intervals of Cohen’s kappa and Gwet’s AC1 were estimated as described in Fleiss, Cohen & Everitt41 and Gwet,40 respectively. Strength of agreement metrics was categorised according to previously described criteria.82

CNV analyses

Association analyses were carried out using linear regression for average BMI (normalised using log_{10} transformation) and average height, and Firth logistic regression for all binary traits (type 2 diabetes mellitus, smoking, ischaemic heart disease, congenital disorders, epilepsy, intellectual disability). Firth logistic regression allows for the analysis of low numbers in addition to the inclusion of covariates. All analyses included age and gender as covariates.83

Polygenic risk analyses

We regressed a model for each polygenic risk score created from various training P-value thresholds against a base model including age, gender, the first five principal components and any additional principal components from the first 20 that were nominally associated with the phenotype of interest. We repeated these analyses with the addition of covariates reflecting symptom severity, non-response to antipsychotics, antipsychotic exposure, smoking status and genotyping platform (defined in supplementary Table 2). All statistical analyses were carried out in R and results were subject to Bonferroni correction for the eight phenotype examinations (P-value threshold 0.0063).

Table 1

Rates of physical health phenotypes in Cardiff Cognition in Schizophrenia (CardiffCOGS) sample compared with the population rates in Secure Anonymised Information Linkage (SAIL)*

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>CardiffCOGS rate, % (n)</th>
<th>SAIL schizophrenia population rate, % (n)</th>
<th>SAIL population rate, % (n)</th>
<th>SRR_{gen, sch} (95% CI)</th>
<th>SRR_{sch, gen} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital disorder</td>
<td>1.34 (12)</td>
<td>0.93 (326)</td>
<td>0.53 (21745)</td>
<td>1.44 (0.81–2.57)</td>
<td>1.77 (1.57–1.99)</td>
</tr>
<tr>
<td>Intellectual disability</td>
<td>1.56 (14)</td>
<td>1.80 (623)</td>
<td>0.38 (22142)</td>
<td>0.87 (0.51–1.48)</td>
<td>3.11 (2.06–3.11)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>6.93 (62)</td>
<td>6.97 (3649)</td>
<td>4.46 (207197)</td>
<td>0.99 (0.77–1.28)</td>
<td>1.57 (1.51–1.63)</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>4.69 (62)</td>
<td>7.49 (2628)</td>
<td>1.40 (52208)</td>
<td>0.63 (0.46–0.85)</td>
<td>5.34 (3.11–5.57)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>17.43 (156)</td>
<td>13.50 (5293)</td>
<td>5.51 (216187)</td>
<td>1.29 (1.01–1.52)</td>
<td>2.45 (2.38–2.53)</td>
</tr>
<tr>
<td>Smoking (current/ex)</td>
<td>86.99 (689)</td>
<td>83.87 (22120)</td>
<td>58.38 (1649589)</td>
<td>1.04 (0.97–1.11)</td>
<td>1.44 (1.42–1.46)</td>
</tr>
</tbody>
</table>

- = sample (CardiffCOGS), sch = schizophrenia, gen = general population.

a. SRR_{gen, sch} represents the standardised rate ratio (SRR) of the clinical cohort to the schizophrenia population ascertained in SAIL. SRR_{sch, gen} represents the standardised rate ratio of the schizophrenia population ascertained in SAIL to the general population ascertained in SAIL. SRRs were standardised using the age and gender distribution from the clinical cohort as reference. Crude unadjusted population rates are given in supplementary Table 3. Numbers stated are out of 895 for the CardiffCOGs sample (except for smoking which was out of 792).

Results

A total of 896 (93.5%) study individuals from CardiffCOGS were linked to health records held in the SAIL databank. Linked study individuals had an age range of 17–84 years (mean 44 years), 371 (41%) were female and 724 (81%) had genetic data available.

Physical health outcomes in CardiffCOGS and SAIL

Table 1 and Fig. 1 outlines the frequencies of the physical health outcomes in the CardiffCOGS sample and SAIL. Within the SAIL population, individuals with schizophrenia had increased rates of epilepsy (SRR = 5.34, 95% CI 5.11–5.57), intellectual disability (SRR = 3.11, 95% CI 3.06–3.11), type 2 diabetes (SRR = 2.45, 95% CI 2.38–2.53), congenital disorders (SRR = 1.77, 95% CI 1.57–1.99), ischaemic heart disease (SRR = 1.57, 95% CI 1.51–1.63) and smoking (SRR = 1.44, 95% CI 1.42–1.46). Individuals within CardiffCOGS had higher rates of type 2 diabetes (SRR = 1.29, 95% CI 1.10–1.52) compared with the population with schizophrenia in SAIL. Crude unadjusted population rates are given in supplementary Table 3.

Comparison of ascertainment rates of behaviours and diagnoses in CardiffCOGS and SAIL

For physical health outcomes that were also reported at interview (smoking, type 2 diabetes mellitus, ischaemic heart disease, and epilepsy), we compared agreement with their health records (Table 2). Both Cohen’s κ and Gwet’s AC1 for all physical conditions ranged from 0.502 to 0.936. These show that the agreement of the rates ascertained from the interview and health records were moderate to high.83 The highest agreements were observed for ischaemic heart disease and epilepsy. The strength of agreement was lowest for smoking behaviour (Cohen’s κ = 0.380 and Gwet’s AC1 = 0.621), reflecting only fair to substantial agreement.

CVN

A total of 2.1% (n = 15) of the CardiffCOGS sample carried a schizophrenia-associated CNV, 4.9% (n = 32) carried a...
neurodevelopmental CNV, 9.5% carried a chromosomal duplication or deletion $\geq 500$ KB (19 deletions, 52 duplications, 2 both) and 3.2% carried a duplication or deletion $\geq 1$ MB (6 deletions, 17 duplications). We found no evidence that CNV carriers had increased rates of poor physical health outcomes (Table 3). However, average height was nominally associated with carrier status for CNVs associated with schizophrenia (beta = $-0.075$, 95% CI $-0.14$ to $-0.01$, $P = 0.017$) and neurodevelopmental disorders (beta = $-0.077$, 95% CI $-0.64$ to $-0.07$, $P = 0.015$) (Table 3). CNV carriers were on average 7.5–7.7 cm shorter than non-carriers.

There was no evidence for association between rare CNVs of 500 KB or greater and any of the phenotypes examined (supplementary Table 4).

**Polygenic risk for schizophrenia**

We found no evidence for an association between polygenic risk scores for schizophrenia and the physical health outcomes studied (Fig. 2, supplementary Table 5), although there was weak evidence for an association with ischaemic heart disease at the genome-wide $P$-value threshold (odds ratio (OR) = 1.65, 95% CI 1.22–2.24; adjusted $R^2 = 0.035$, $P = 0.001$). The lack of

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Interrater agreement of the rates of ascertainment between the Cardiff Cognition in Schizophrenia (CardiffCOG) interview and linkage to National Health Service records.</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAIL</td>
<td>CardifCOGS interview</td>
</tr>
<tr>
<td>---------</td>
<td>----------------------</td>
</tr>
<tr>
<td>T2DM</td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>75</td>
</tr>
<tr>
<td>Unaffected</td>
<td>14</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>Affected</td>
</tr>
<tr>
<td>Unaffected</td>
<td>18</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Affected</td>
</tr>
<tr>
<td>Unaffected</td>
<td>28</td>
</tr>
<tr>
<td>Smoking</td>
<td>Affected</td>
</tr>
<tr>
<td>Unaffected</td>
<td>74</td>
</tr>
</tbody>
</table>

SAIL, Secure Anonymised Information Linkage.

a. The smoking variable compares results for current/ex smoking status in SAIL and ever a regular smoker at interview. Cohen’s $\kappa$ refers to Cohen’s kappa statistic. Gwet’s AC1 refers to the first order agreement coefficient. Both values range between 0 (chance, or no agreement) and 1 (perfect agreement). Values below 0.4 indicate poor agreement, values of 0.4–0.59 indicate moderate agreement and values above 0.6 indicate substantial agreement.
The association between schizophrenia polygenic risk scores and physical health outcomes remained in sensitivity analyses covarying for symptom severity, non-response to antipsychotics, antipsychotic exposure, smoking status and genotyping array (supplementary Table 6). However, we did identify significant associations between non-response to antipsychotics and type 2 diabetes (OR = 2.94, 95% CI 1.79–4.85, P ≤ 0.0001) and an association between symptom severity and intellectual disability (OR = 1.24, 95% CI 1.05–1.46, P = 0.0012). There were additional nominal associations (P < 0.05) between non-response to antipsychotics and epilepsy, and smoking and ischaemic heart disease (supplementary Table 6).

**Discussion**

In this study, we report the linkage of genetic data from a clinically ascertained sample of individuals with schizophrenia to

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**Table 3** Association analysis results for physical health phenotypes and two groups of copy number variants (CNVs, 12 schizophrenia CNVs and 53 neurodevelopmental CNVs)

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Schizophrenia CNVs</th>
<th>Neurodevelopmental CNVs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Carriers</td>
<td>Non-carriers</td>
</tr>
<tr>
<td>Average height (GP)</td>
<td>13</td>
<td>611</td>
</tr>
<tr>
<td>Average BMI log10 (GP)</td>
<td>13</td>
<td>604</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus (both)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>&lt;5</td>
<td>126</td>
</tr>
<tr>
<td>Unaffected</td>
<td>11</td>
<td>576</td>
</tr>
<tr>
<td>Smoking – current or ex-smoker (GP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>9</td>
<td>552</td>
</tr>
<tr>
<td>Unaffected</td>
<td>&lt;5</td>
<td>78</td>
</tr>
<tr>
<td>Ischaemic heart disease (both)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>0</td>
<td>53</td>
</tr>
<tr>
<td>Unaffected</td>
<td>15</td>
<td>656</td>
</tr>
<tr>
<td>Congenital disorders (both)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>&lt;5</td>
<td>8</td>
</tr>
<tr>
<td>Unaffected</td>
<td>14</td>
<td>701</td>
</tr>
<tr>
<td>Epilepsy (both)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>&lt;5</td>
<td>36</td>
</tr>
<tr>
<td>Unaffected</td>
<td>13</td>
<td>673</td>
</tr>
<tr>
<td>Intellectual disability (both)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected</td>
<td>&lt;5</td>
<td>8</td>
</tr>
<tr>
<td>Unaffected</td>
<td>14</td>
<td>701</td>
</tr>
</tbody>
</table>

P, uncorrected P-value; GP, general practice.

a. General practice/hospital/both in parentheses in the phenotype column refers to the source of diagnostic information used. Effect size refers to odds ratio in all cases except average height and average body mass index for which the effect size is standardised beta. Counts below five are masked to preserve participant anonymity.

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**Fig. 2** Graphs of the results from regression models for the association between polygenic risk for schizophrenia and physical health outcomes.

(a) Odds ratio; (b) Beta. Odds ratios are shown for the P-value thresholds at which markers were selected.
anonymised NHS health records in the SAIL databank. Consistent with data collected at interview, we found that individuals with schizophrenia in Wales had increased rates of neurodevelopmental disorders (epilepsy, intellectual disability and congenital disorders), smoking, type 2 diabetes mellitus and ischaemic heart disease compared with the general population. However, the results of our genetic analyses suggest that these increased rates are not because of genetic liability to schizophrenia; we found no evidence for an association between genetic risk for schizophrenia indexed by CNVs or polygenic risk scores and physical health outcomes.

These findings are supported by a recent population-based study that linked genetic and health record data for 106 160 individuals and found an inverse association between increased schizophrenia polygenic risk scores and obesity and an inverse association with diabetes when controlling for schizophrenia diagnosis or for antipsychotic medication history.43 No association was found between schizophrenia polygenic risk scores and the other physical health outcomes found in this study.44 Thus, the evidence available indicates that increased rates of poor physical health observed in patients with schizophrenia is unlikely to be driven by the genetic liability for the disorder.

There may be many other factors contributing to an increased rate of the physical health outcomes examined. For the non-neurodevelopmental outcomes, these include, but are not limited to, medication side-effects and lifestyle choices such as smoking and diet. For example, weight gain caused by antipsychotic medication, poor diet and smoking may all contribute to the risk of type 2 diabetes mellitus and ischaemic heart disease. This is supported by our study; we found significant associations between non-response to antipsychotics and type 2 diabetes mellitus and nominal associations between non-response to antipsychotics and epilepsy, and smoking and ischaemic heart disease. The associations with non-response to antipsychotics may reflect the frequent use of clozapine in this patient group, an antipsychotic known to cause weight gain and increase the risk of type 2 diabetes mellitus. Our additional analyses also found that intellectual disability was significantly associated with a greater symptom severity. The reasons for this association are not yet clear. Importantly, several of these non-genetic factors are amenable to targeted intervention, which may reduce the risk of their consequent physical health outcomes.

Our finding that carriers of rare neurodevelopmental CNVs tend to be shorter than CNV non-carriers is in keeping with previous work on CNV associations with anthropometric traits in a sample of 191 161 adults.44 Macé et al report associations between both total CNV length and CNV count with small effect sizes. However, it can still be concluded that genetic liability to schizophrenia does not have a large or significant impact on the occurrence of physical comorbidity. Nonetheless, our plan for future work is to link genetic data for a far greater number of individuals to their health records. This study does provide an important exemplar for the value of linking genetic data to routinely collected health-related data. Such an approach has great potential to generate a wealth of evidence, which can be translated into improved health outcomes for patients.

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Supplementary material
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Data availability
All data requests should be submitted to the corresponding authors for consideration.

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Author contributions
K.K., A.J., S.C.L., S.E.L. and I.T.R.W. made substantial contributions to the conception and design of the study. All authors contributed either to the acquisition or analysis of the data. K.K., S.C.L. and S.L.L. carried out the data analysis. K.K., A.J., S.C.L., S.E.L. and I.T.R.W. drafted the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content and gave final approval of the version to be published.

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Declaration of interest
The authors declare no conflicts of interest.
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