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Original Article

Risk of stroke associated with risperidone in dementia with and without comorbid cardiovascular disease: population-based matched cohort study

Joshua Choma, Alys Griffiths, William Henley, Christoph Mueller, Nefyn Williams, Clive Ballard, Rhian Hopkins, Katherine G. Young, John M. Dennis* and Byron Creese*

Background

Agitation and aggression occur in up to half of people living with dementia over the course of the disease. Although non-pharmacological interventions are used as first-line treatment strategies, antipsychotics may be indicated in severe cases. A major adverse effect of antipsychotics in dementia is stroke; the mechanism of action of atypical antipsychotic risperidone has been linked to cardiovascular disease (CVD) biological pathways in preclinical studies.

Aims

To evaluate the risk of stroke associated with risperidone across different patient subgroups defined by stroke and CVD history.

Method

Anonymised primary care data from the UK-based Clinical Practice Research Datalink were used to identify individuals diagnosed with dementia after the age of 65 years between 2004 and 2023. Risk of stroke over 1 year was compared between individuals initiating risperidone and propensity-score-matched controls across subgroups with and without history of stroke and any CVD.

Results

In the overall cohort (28 403 risperidone users and 136 324 mtatched controls), risperidone was associated with increased risk of stroke (adjusted hazard ratio: 1.28; 95% CI: 1.20–1.37). In the risperidone user group, the incidence rate of stroke was substantially higher in those with a prior history of stroke (incidence rate: 222 per 1000 person-years) and CVD (incidence rate: 94.1 per 1000 person-years) than in the overall cohort (incidence rate: 53.3 per 1000 person-years). Relative risks related to risperidone were similar across all CVD and stroke subgroup comparisons (hazard ratios between 1.23 and 1.44).

Conclusions

People with dementia with a prior history of CVD are at a significant increased risk of stroke, and risperidone further exacerbates this risk. Moreover, risperidone increases risk of stroke in patients without a prior history of CVD. This quantification of stroke risk across subgroups with and without history of CVD may help with communication of risk and aid more judicious prescribing.

Keywords

Risperidone; stroke; dementia; antipsychotic; Clinical Practice Research Datalink.

Agitation and aggression occur in up to half of people with dementia.[1,2] First-line approaches should be non-pharmacological; these include psychosocial interventions and assessment of unmet needs.[3] In instances where there is a significant risk of harm or severe distress and non-pharmacological options have not worked, antipsychotics may be indicated, but only for short term use.[4,5] In the UK and EU, risperidone is the only atypical antipsychotic licensed for severe aggression; others (namely quetiapine and olanzapine) are regularly used off-label, and risperidone is sometimes maintained beyond its licensed period (6 weeks in the UK). Risperidone is also approved for use in dementia in Australia, New Zealand and Canada; in the USA, it is not approved by the Food and Drug Administration but is used off label.[6] Randomised controlled trial (RCT) evidence indicates efficacy of risperidone for agitation, aggression and psychosis, but as for all antipsychotics, there is a risk of stroke.[7] Increased stroke risk has been observed in both real-world and RCT data, with estimates from RCTs typically being higher, creating a fine balance between risk and benefit in clinical decision-making.[8–11] However, although these estimates of risk are robust at the population level, they are of limited value in the clinic, where decisions are made at the patient level.[12]

Risperidone will continue to be prescribed while there is no safer or more effective alternative. Indeed, we have found in qualitative work accompanying this study that patients, carers and clinicians view it as a key last-resort treatment option.[13] It therefore follows that clinical decision-making could benefit from empirical evidence with respect to which patient subgroups are most at risk of adverse events if prescribed risperidone. A Danish health registry study found no differences in mortality risk between patients with and without comorbidities at antipsychotic prescription initiation.[14] However, all-cause mortality is a broad outcome and may not be specific to the mechanism of action of a given drug. Preclinical data in cell lines and animal models have directly linked risperidone to perturbations in cardiovascular disease (CVD)-related genes and proteins, suggesting that risperidone directly interacts with cardiovascular biology.[15,16] To our knowledge, few studies have examined whether risk of stroke differs in patients who are treated with antipsychotics relative to those who are not across subgroups. A small secondary analysis of risperidone RCT data suggested that there is evidence of heterogeneity in treatment outcomes

*Joint first authors.

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according to baseline clinical characteristics. Subgroups of patients based on the presence or absence of CVD showed marginally significant increased risks of treatment-emergent cerebrovascular adverse events in those with a history of CVD.[11] This suggests that there may be subgroups of patients at greater risk of stroke if prescribed risperidone; however, the subgroups were small ($n = 46$ for the CVD history subgroup), there was a relatively low rate of cerebrovascular adverse events (3%), and RCT data have the inherent limitation of being less representative than 'real-world' samples. Informed by these data, and aiming to address their limitations, we sought to determine whether risk of stroke following risperidone prescription differs across patient subgroups defined by CVD clinical history. We hypothesised that the relative risk of stroke in people treated with risperidone versus matched controls would be higher in those with a prior history of CVD than in those without a CVD history.

Method

Data sources

This study used the Clinical Practice Research Datalink (CPRD) Aurum,[17] a large population-representative UK database of electronic primary care health records, linked to Hospital Episode Statistics (HES), national deprivation data (Index of Multiple Deprivation) and Office of National Statistics death data.

Study population

The study population comprised people with dementia diagnosed at age 65 years or older with valid linked data available. We included individuals with any dementia diagnosis code recorded in primary care during the study period (1 January 2004 to and 30 November 2023). The date of dementia diagnosis was set to the date of the patient's first-ever dementia code. Dementia codes were reviewed and approved by two clinicians (N.W. and C.M.) and are available at https://github.com/Exeter-Diabetes/DementiaRisperidonePaper/tree/main. We excluded individuals with a record of risperidone prescription before dementia diagnosis or a history of either bipolar disorder or schizophrenia.

Study design

Exposure

We defined exposure as the first-ever initiation of risperidone after dementia diagnosis and during the study period. Patients who had received other antipsychotics (excluding prochlorperazine, because this is almost exclusively prescribed for nausea) within the 90 days before being prescribed risperidone were excluded, as these medications also increase stroke risk.[9] New risperidone users were followed up from the date of first prescription (index date) for 12 months or until the occurrence of stroke (see below), death, general practice deregistration, or the end of available primary care follow-up, whichever was earliest.

Prespecified subgroups of interest within the exposed population comprised (a) those with a history of stroke before risperidone initiation; (b) those with a history of any CVD, defined as the composite of heart failure, myocardial infarction, angina, ischaemic heart disease, peripheral arterial disease or stroke, before risperidone initiation. In an exploratory analysis, we examined the potential modifying effects on stroke risk of: (a) age at treatment initiation (categorised as 65–74, 75–84, or 85+ years) and (b) prior stroke recency (among those in the stroke history subgroup, categorised as less than 1 year, 1–5 years, or more than 5 years).

Outcomes

The primary outcome was stroke (ischaemic or haemorrhagic) recorded within 12 months of the index date in primary or secondary care data, or death with stroke as a cause in linked death data.

Covariates

Baseline covariates were organised into sociodemographic characteristics, clinical characteristics, comorbidities and family history, and biomarkers and clinical measurements (see Supplementary Table 1 available at https://doi.org/10.1192/bjp.2025.10419).

Sociodemographic characteristics (closest to index date) comprised age, sex, ethnicity (UK census classification: White, Asian, Black, mixed, other), care home status (i.e. living in care home or not), socioeconomic status as defined by the English Index of Multiple Deprivation quintile, and time between dementia code and index date (i.e. disease duration). Clinical characteristics were: (closest to index date) duration of dementia, alcohol use, smoking status, and history of other antipsychotics before risperidone initiation. Comorbidities and family history included angina, anxiety disorders, atrial fibrillation, heart failure, ischaemic heart disease, myocardial infarction, peripheral artery disease, family history of premature CVD, deep vein thrombosis, pulmonary embolism, venous thromboembolism, revascularisation, stroke, transient ischaemic attack, diabetes, family history of diabetes, falls, lower limb fracture, haematological cancer, solid cancer and anxiety disorders. Biomarkers and clinical measurements comprised body mass index, blood pressure and total cholesterol.

Matched controls

Each individual in the risperidone user group was matched with up to five people with dementia not prescribed risperidone or any other antipsychotic using a bespoke time-updated propensity matching approach. This approach meant that people with dementia who received risperidone during the study period were included in the potential control group until the date of risperidone initiation. For each calendar year of the study period, individuals initiating risperidone and matched controls were identified. Each matched control was then assigned a random index date during the calendar year of interest. Risperidone users were matched to controls using a combination of exact matching (for sex, current age (65–74, 75–84 or 85+ years), and history of stroke, transient ischaemic attack, heart failure, angina, ischaemic heart disease, peripheral artery disease or myocardial infarction) and nearest neighbour matching (using all other covariates listed in the above section). Matching was done with replacement (i.e. each matched control could be matched to more than one individual in the risperidone user group). Follow-up for matched controls was defined using the same approach as for risperidone users, with additional censoring applied if a matched control initiated risperidone during the follow-up period.

Statistical analysis

Risk of stroke was estimated in risperidone users versus matched controls. Incidence rates were calculated for each group and expressed as the number of strokes per 1000 person-years. One-year cumulative incidence of stroke was estimated using the Kaplan–Meier method, with proportional hazards assumptions confirmed. Adjusted Cox proportional hazards models stratified by matched set (risperidone users versus matched controls) were used to provide overall hazard ratios with cluster-robust standard errors.[18] Models were adjusted for the full set of baseline covariates described above in the multivariable analysis, with a category

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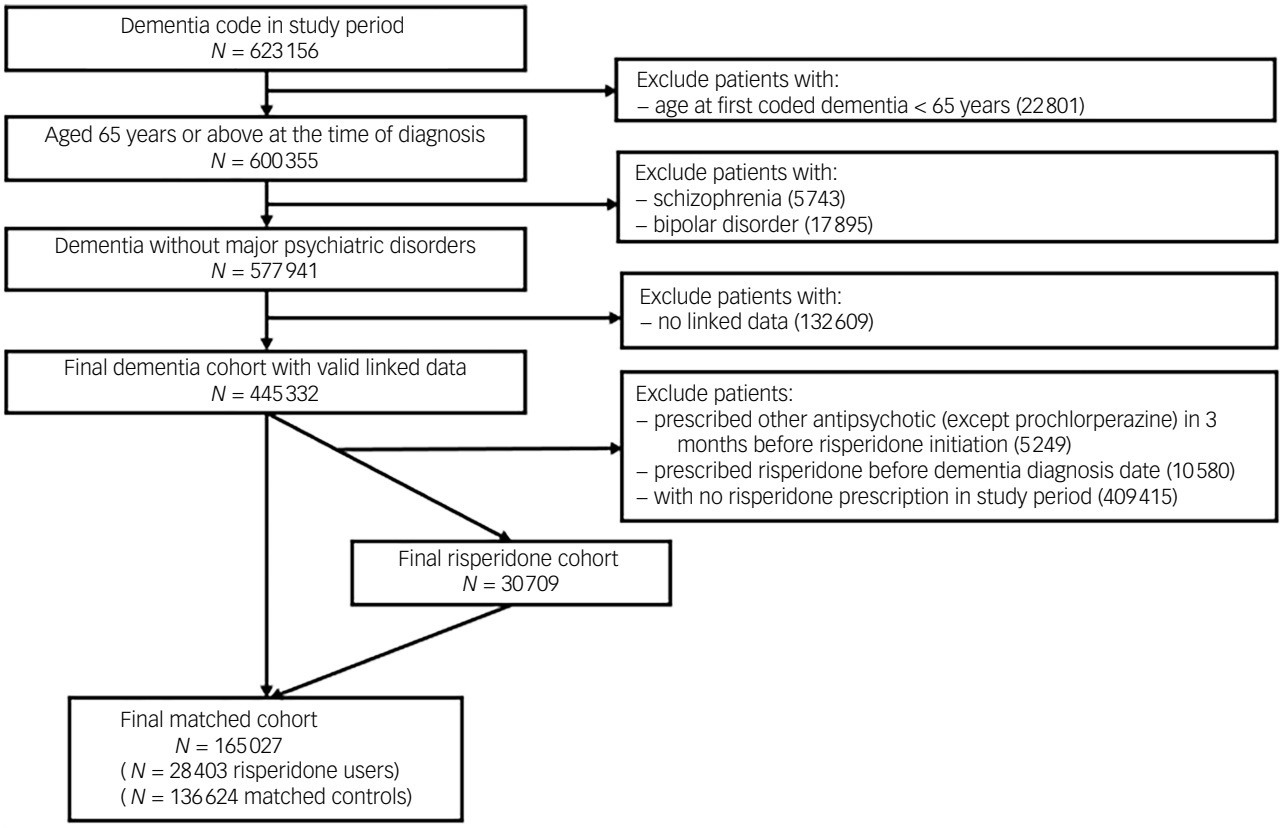

Fig. 1 Flow chart of the study and matched cohort.

assigned for missing data. The same approach was applied to subgroups with and without a history of stroke, and those with and without a history of CVD, and to the exploratory analysis examining prior stroke recency and age at initiation.

Sensitivity analysis

We performed the following sensitivity analyses to assess consistency of the results. (a) Adjustment for competing risk of death (all cause). (b) Definition of stroke outcomes on the basis of hospital admission data alone. (c) Censoring of individuals if there was a gap of 90 days or more between two consecutive risperidone prescriptions. This large gap was interpreted as a possible discontinuation of the medication. If such a gap (≥90 days) was detected, the follow-up time was censored 30 days after the date of the individual's last prescription before the gap. This 30-day window was based on the assumption that participants would collect their last prescription and adhere to it as normal for 30 days. (d) Restriction of the analysis to the pre-COVID period (adjusting the study end date to 1 February 2020) to eliminate potential pandemic-related biases. (e) Restriction of follow-up to 12 weeks to ensure that early increased stroke risk was captured and could be compared with longer-term effects.

Statistical analysis was performed using R version 4.4.0. The study was conducted and reported in line with the RECORD (reporting of studies conducted using observational routinely collected data) guidelines.[19]

Results

The final study cohort included 165 027 individuals, of whom 28 403 were in the risperidone user group and 136 624 were matched controls (Fig. 1). After matching, the risperidone user group was similar to the matched control group across all sociodemographic, clinical, comorbidity and family history, and biomarker variables. At index date, approximately 62% of each group were women, the mean age was 83 years, the average duration of dementia was approximately 2.7 years, ethnicity was coded as White in >90% of cases and 13% resided in a care home (see Supplementary Table 1 for full matching data).

Overall cohort: risk of stroke was increased in risperidone users compared to matched controls

During the study period, the unadjusted incidence rate of stroke was higher in the risperidone user group (53.2 [95% CI: 50.0, 56.4] stroke events per 1000 person-years) than among matched controls (40.6 [95% CI: 39.4, 41.8] per 1000 person-years). In multivariable adjusted Cox models, the risk of stroke was 28% higher in the risperidone user group relative to matched controls (adjusted hazard ratio: 1.28 [95% CI: 1.20, 1.37]; Table 1).

CVD subgroups: risk of stroke was consistently increased in risperidone users, irrespective of prior CVD or stroke history

Table 1 and Fig. 2 show the incidence of stroke (and associated hazard ratios) in risperidone users and matched controls according to CVD and stroke history subgroups. The incidence rates for stroke were higher in those with a prior history of stroke or CVD. There were 222 (95% CI: 203.7, 240.4) strokes per 1000 person-years in risperidone users with a history of stroke before prescription and 176.6 (95% CI: 169.6, 183.7) strokes per 1000 person-years in the matched control group with a history of stroke before prescription. For those without a history of stroke before

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Table 1 Adjusted hazard ratios for stroke associated with risperidone by subgroup

	Group	*N* total	*N* events	Person-years at risk	Incidence rate per 1000 person-years	Adjusted hazard ratio (95% CI)
Overall cohort	Matched controls	136 624	4534	111 742	40.6 (39.4, 41.8)	1.28 (1.20, 1.37)
	Risperidone users	28 403	1075	20 196	53.2 (50.0, 56.4)	
No stroke history	Matched controls	118 124	2111	98 024	21.5 (20.6, 22.5)	1.34 (1.22, 1.48)
	Risperidone users	24 462	512	17 660	29.0 (26.5, 31.5)	
Stroke history	Matched controls	18 500	2423	13 717	176.6 (169.6, 183.7)	1.23 (1.12, 1.35)
	Risperidone users	3941	563	2536	222.0 (203.7, 240.4)	
No CVD history	Matched controls	80 738	1278	67 724	18.9 (17.8, 19.9)	1.44 (1.27, 1.62)
	Risperidone users	16 717	334	12 319	27.1 (24.2, 30.0)	
CVD history	Matched controls	55 886	3256	44 017	74.0 (71.4, 76.5)	1.22 (1.13, 1.33)
	Risperidone users	11 686	741	7876	94.1 (87.3, 100.9)	

CVD, cardiovascular disease.

prescription, the incidence rates of stroke per 1000 person-years were 29.0 (95% CI: 26.5, 31.5) and 21.5 (95% CI: 20.6, 22.5) respectively. Similarly, for individuals with any CVD history, there were 94.1 (95% CI: 87.3, 100.9) strokes per 1000 person-years among risperidone users and 74 (95% CI: 71.4, 76.5) strokes per 1000 person-years in the matched control group. For those without a history of CVD before prescription, the incidence rates of stroke per 1000 person-years were 27.1 (95% CI: 24.2, 30.0) and 18.9 (95% CI: 17.8, 19.9) respectively.

Risperidone was associated with a higher relative risk of stroke across all subgroups (with and without stroke and CVD clinical history), with hazard ratios broadly similar to the 1.28 observed in the overall cohort. The differences in absolute incidence of stroke across subgroups were primarily driven by the presence of prior history of stroke and CVD, rather than exposure to risperidone (Table 1 and Fig. 2).

Recency of prior stroke and age at initiation

In those with a history of stroke, when the stroke had occurred <1 year before the index date, risperidone was not associated with an increased risk of stroke during follow-up. It should be noted that

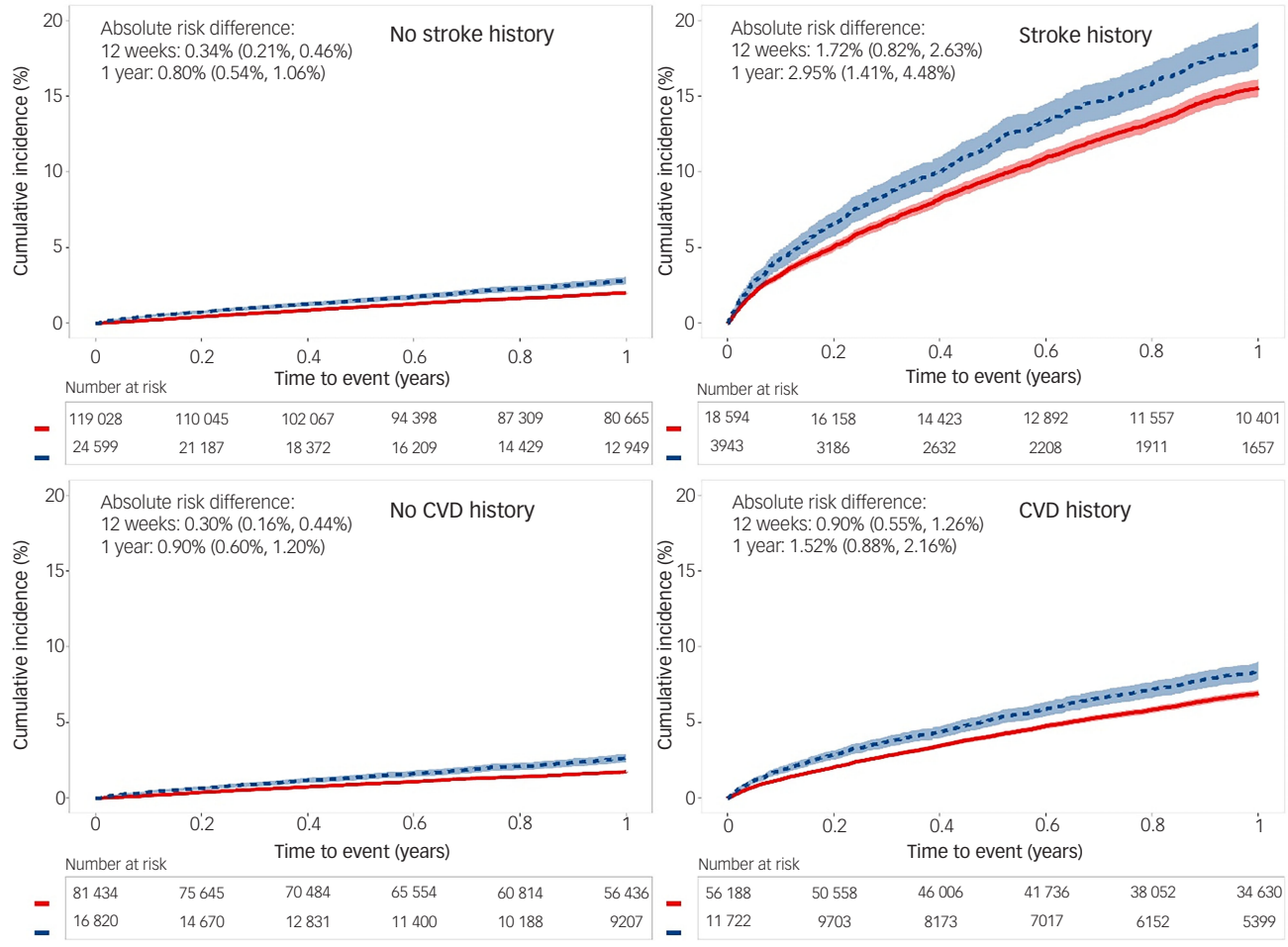

Fig. 2 Kaplan–Meier plots depicting the cumulative incidence of stroke in matched controls and risperidone users. Blue dashed line indicates risperidone users. Shading represents 95% confidence intervals. CVD, cardiovascular disease.

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in this group, the absolute incidence of stroke among both risperidone users and matched controls was very high, perhaps masking any more modest impact of risperidone (incidence per 1000 person-years at risk of 376.2 [95% CI: 301.4, 451.1] and 459.4 [95% CI: 390.6, 528.3], respectively). For strokes occurring 1–5 years before the index date and >5 years before the index date, the hazard ratios for a new stroke during follow-up were similar (1.22 [95% CI: 1.02, 1.46] and 1.31 [95% CI: 1.06, 1.62]). Hazard ratios for age at initiation were broadly similar for the 65–74, 75–84 and ≥85 year age groups (1.59 [95% CI: 1.29, 1.95], 1.23 [95% CI: 1.11, 1.36] and 1.27 [95% CI: 1.15, 1.41], respectively) (Supplementary Table 2).

Sensitivity analysis

Relative risk of stroke for risperidone users versus matched controls was similar across all sensitivity analyses. Adjustment for competing risk of death slightly attenuated the hazard ratios for the whole sample (1.21 [95% CI: 1.14, 1.33]) and for each of the subgroups (no stroke history: 1.26 [95% CI: 1.14, 1.38]; stroke history: 1.15 [95% CI: 1.05, 1.26]; no CVD history: 1.45 [95% CI: 1.20, 1.53]; CVD history: 1.16 [95% CI: 1.07, 1.25]). Results were also consistent when stroke outcomes were defined on the basis of hospital admission data alone, when individuals in the risperidone arm who were likely to have discontinued therapy were censored; and when only the pre-COVID period was analysed (Supplementary Table 3). The sensitivity analysis in which stroke outcome was defined on the basis of HES data alone was the only one in which the hazard ratio for stroke was (non-significantly) higher in the group with prior history of stroke than in the subgroup with no stroke history. Over a restricted 12-week follow-up period, the relative risk of stroke in risperidone users was higher than in matched controls across all subgroups: no stroke history, hazard ratio: 1.61 [95% CI: 1.37, 1.9]; stroke history, hazard ratio: 1.33 [95% CI: 1.16, 1.52]; no CVD history, hazard ratio: 1.69 [95% CI: 1.37, 2.08]; CVD history, hazard ratio: 1.37 [95% CI: 1.21, 1.54] (Supplementary Table 3).

Discussion

We compared the incidence of stroke in people living with dementia prescribed risperidone with that of a matched control group across subgroups of patients with and without a prior history of stroke and other CVD. Risperidone was associated with an increased risk of stroke in the overall cohort and in all subgroups over 1 year and in a 12-week sensitivity analysis. The principal new finding from this study was that relative risk of stroke was comparable across all subgroups. Although not in line with our *a priori* hypothesis, our findings are consistent with those of a recent Danish health registry study that implemented a similar design and noted no differences in mortality risk between patients with and without comorbidities at antipsychotic initiation.[14] Although all-cause mortality is a broad outcome and perhaps less likely to capture specific biological interactions with a drug, the consistency with our study, which was informed by preclinical work linking the mechanism of action of risperidone directly to cardiovascular biology, highlights an emerging finding that antipsychotics carry adverse effect risks for people with dementia irrespective of their comorbidities.

These findings have important clinical applications. For brevity, only the stroke-related subgroups are discussed, but the conclusions would be the same for the CVD subgroup comparisons shown in Table 1. For the stroke history subgroup, the overall 1-year incidence rate for stroke in those with history of stroke was 184 per 1000 person-years. For risperidone users and matched controls, the incidence rates were 222 and 177 per 1000 person-years, respectively. These data suggest that much of the incidence of stroke is attributable to past medical history rather than risperidone: of the 222 incident strokes during treatment with risperidone in patients with a history of stroke, 177 would have occurred irrespective of whether the drug was taken. To more closely align this finding with current guidance, the figures for a 12-week treatment duration would be 299 and 230 per 1000 person-years, respectively (Supplementary Table 3). Although the relative risk of 1.23 may appear modest, a baseline 1-year risk of 177 per 1000 person-years is significant, and clinicians should be mindful of prescribing a drug that increases stroke risk further in an already at-risk group.

The 1-year incidence rate for stroke was ~87% lower in the no stroke history subgroup than in the stroke history subgroup for each treatment group (risperidone users: 29 per 1000 person-years; matched controls: 22 per 1000 person-years). The 12-week incidence rates were 33 and 22 per 1000 person-years, respectively. The hazard ratio for risperidone in the no stroke history subgroup (1.34) was not statistically different to that of the stroke history subgroup (1.23). Therefore, on average, a patient with stroke history has about the same relative risk of stroke if prescribed risperidone as a patient with no stroke history. Despite the relatively low absolute incidence of stroke among both risperidone users and matched controls in the no stroke history subgroup, clinical decisions should not rely on population averages alone. Even modest absolute risks can be meaningful at a patient level when outcomes are serious and potentially preventable, as in the case of stroke.

Importantly, patient values and preferences must be central to decisions, particularly in populations with limited life expectancy or heightened vulnerability to adverse effects and possibly slower recovery from them. Although these findings may offer some reassurance regarding relative safety, they should not be interpreted as a justification for broader or more prolonged prescribing. Rather, they underscore the need for careful, individualised risk–benefit assessments and adherence to prescribing guidelines that emphasise short-term use only when non-pharmacological alternatives have been exhausted.

It is necessary to consider RCT findings to provide a balanced overview of risk, because RCTs generally report higher relative risk estimates than epidemiological studies.[8–10,20] This may be explained by both patient characteristics and study design. In the present study, the stroke incidence in the overall cohort control group (i.e. the baseline risk) over 12 weeks was 50 per 1000 person-years. This is comparable with a pooled estimate from four risperidone RCTs of approximately 40 per 1000 person-years (acknowledging that there were only five events across these four trials, so this estimate may be imprecise). By contrast, the estimated rate for the risperidone group was much lower in the present study than in these RCTs (70 per 1000 person-years in the present study and 182 per 1000 person-years according to the RCT data, although there were only 24 events in the RCTs).[8] The relatively similar control group rates between RCTs and the present study suggest that much of the discrepancy in risk may be attributed to who is prescribed risperidone in real-world clinical practice. This is further supported by a separate real-world study of secondary care data that found that patients prescribed antipsychotics for psychosis had higher risk of stroke (relative to patients receiving prescriptions for agitation).[20] In addition, differences in monitoring frequency and reliability of stroke reporting may contribute to the discrepancies between RCT results and real-world evidence.

In terms of study design, another explanation for the different estimates between epidemiological studies and RCTs is the follow-up period, with risk of stroke being higher over the short term.

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A recent study in CPRD estimated the 2-year hazard ratio for stroke to be 1.64, whereas RCTs of risperidone, which tend to be 6–12 weeks long, have reported relative risks in excess of 3.[8,9] Consistent with this, in the present study, the 12-week hazard ratios for the whole sample and all subgroups were modestly higher than 1-year estimates; this highlights the importance of short-term monitoring following prescription, which is discussed in more detail below.

Contextualising findings from secondary data analysis is vital. As such, we have completed a qualitative study to accompany this work, which provides important insights into future directions and applications.[13] Among relatives, carers and clinicians, there was a consistent theme around the importance of effective communication of risks. Moreover, although many participants understood the risks associated with risperidone and that it should be a last resort, they also understood its place in helping to alleviate severe symptoms. These qualitative data highlight the complex contexts in which risperidone prescription occurs and the careful balancing of risk and benefit that must be undertaken. Specifically, one clinician described personal guilt among relatives resulting from prescription of a drug known to cause stroke. In a hypothetical case of a patient with a history of stroke where there is no other option but to prescribe, using the present findings to communicate the patient's baseline risk and excess risk if prescribed risperidone may help relatives and clinicians to make more informed decisions and appraise the probable reasons for stroke, should there be one. Overall, this highlights a potential need for guidance to be updated to reflect the more nuanced estimates of subgroup absolute and relative risk reported here.

In terms of future directions, we see two key areas for development. The first is that stroke is not the only side-effect that is important to patients and caregivers; sedation and falls are also priorities (although they are not reliably coded in CPRD).[13] Although our study had an *a priori* focus on stroke owing to the putative biological targets of risperidone, using a similar subgroup design could uncover differential risks associated with other important outcomes and other drugs. As risperidone is still commonly prescribed, appropriate monitoring guidance remains a key pillar of harm reduction. However, there is wide variation in what monitoring is undertaken. This is reflected in the variety of guidance from health services and the charity sector, some of which is not dementia-specific but rather draws on the guidance for antipsychotic monitoring in patients with schizophrenia.[13,21,22] Therefore, a second avenue for future research will be to determine empirically which clinical parameters are more useful and feasible to monitor to minimise treatment-emergent stroke risk.

Strengths and limitations

This study focused on pre-specified evaluation of patient stratification using a large, representative data-set. This design meant the study could provide new insights into the effects of risperidone on people with dementia by moving from population-level estimates towards estimates for clinically relevant patient subgroups. The implementation of multivariable time-updated propensity score matching provides a means of controlling for measured confounding, including potential changes over time in the identification of dementia patients in UK primary care. In addition, this method minimises confounding resulting from temporal changes in recording and/or measurement of clinical characteristics and stroke outcomes over the study period. Several limitations should be noted. The severity of stroke was not considered, as this information was not available in the data-set. However, our analysis of only HES-recorded stroke data (which are likely to comprise more severe strokes that resulted in hospital admission) did not materially change the results. As with all UK studies using routine clinical data from primary care, we had information only on prescriptions being issued, not on whether the prescription was collected or the dosing regimen adhered to. Information about the severity of symptoms and the reason for the prescription (e.g. whether it was for agitation and aggression or psychosis) was not available. There are data that suggest that stroke risk associated with risperidone is highest when risperidone is prescribed to patients with psychosis but without concurrent agitation.[20] Therefore, not knowing the specific indication may have affected our hazard ratio estimates, although it is important to note that the direction of effect (increased risk associated with risperidone) is supported by numerous RCTs in which any confounding by indication was minimised by design. An inherent limitation of real-world data meant that it was possible that the risperidone user group and matched controls differed with respect to unmeasured clinical characteristics by virtue of the prescription of the drug. Several features of the study design mitigated this confounding, although they did not remove it altogether. First, we excluded patients with a history of schizophrenia or bipolar disorder and only considered exposure to risperidone after diagnosis of dementia to help ensure that the primary indication was dementia-related symptoms. Second, we used time-updated propensity score matching, meaning that every patient in the cohort was considered to be a control until they initiated risperidone. Although other approaches such as the prior event rate ratio method applied to self-controlled case series studies can reduce bias in estimates, studies employing these have reported findings consistent with those reported here.[10,23] Thus, although unmeasured confounding may still have existed, the findings were consistent with those of a wide range of other RCTs and epidemiological studies, suggesting that major unmeasured confounding was unlikely (in addition, the groups were also matched with respect to a wide range of other possible confounders). Finally, both groups were allowed a history of antipsychotic use >3 months before prescription and were matched on this variable. This helped to ensure that the matched control group did not simply comprise an atypical group with symptomology that had never warranted an antipsychotic. Twenty-six per cent and 27% of patients in the risperidone and control groups, respectively, had received an antipsychotic before the index date. It is also important to highlight that we could not reliably determine the aetiology of the dementia or the impact of any copathologies (e.g. vascular) in CPRD, so our conclusions are limited to all-cause dementia.

Clinical implications

The findings that risperidone increases the risk of stroke in subgroups of patients with a history of stroke or CVD, as well as in those without any prior history of CVD, indicates a need for close adherence to guidelines (ruling out other causes; trying non-pharmacological approaches first; and frequent and regular reviews of whether continuation of antipsychotic treatment is necessary), irrespective of patient CVD burden.

Joshua Choma, Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK; **Alys Griffiths**, Sheffield Institute for Translational Neuroscience (SITraN), Department of Neuroscience, University of Sheffield, Sheffield, UK; **William Henley**, Health Statistics Group, Institute of Health Research, University of Exeter Medical School, Exeter, UK; **Christoph Mueller**, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; **Nefyn Williams**, Department of Primary Care and Mental Health, University of Liverpool, Liverpool, UK; **Clive Ballard**, Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK; **Rhian Hopkins**, Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK; **Katherine G. Young**, Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK; **John M. Dennis**, Department of Clinical and Biomedical Sciences, University of Exeter, Exeter, UK; **Byron Creese**, Department of

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Psychology, College of Health Medicine and Life Sciences, Brunel University of London, London, UK

Correspondence: Byron Creese. Email: Byron.Creese@brunel.ac.uk

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Supplementary material

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Data availability

The data that support the findings of this study are available from CPRD. Restrictions apply to the availability of these data, which were used under licence for this study.

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Author contributions

J.C.: data preparation, data analysis, manuscript drafting; A.G., W.H., C.M. and N.W.: conception, design, interpretation, manuscript review; C.B.: interpretation, manuscript review; R.H. and K.G.Y.: data preparation; J.M.D. and B.C.: conception, design, interpretation, manuscript drafting, manuscript review.

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Declaration of interest

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Analytic code availability

Analytic code and codes used to define dementia diagnosis and study variables are available at https://github.com/Exeter-Diabetes/DementiaRisperidonePaper/tree/main.

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