

# The association between Parkinson's disease and anti-epilepsy drug carbamazepine: a case-control study using the UK General Practice Research Database

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## WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Parkinson's disease is associated with the intracellular accumulation of Lewy bodies, which are abnormal protein aggregations comprising misfolded  $\alpha$ -synuclein protein.
- Carbamazepine has been identified as a drug candidate that may enhance intracellular autophagy and the clearance of these mutant proteins.
- It is unknown whether use of this drug is associated with reduced risk of Parkinson's disease.

## WHAT THIS STUDY ADDS

- There is little evidence that use of carbamazepine is associated with reduced risk of Parkinson's disease, although a modest protective effect cannot be excluded.

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## AIMS

To investigate whether the use of carbamazepine is associated with reduced risk of Parkinson's disease.

## METHODS

We conducted a population-based, matched case-control study of patients randomly selected from the UK General Research Practice Database. We identified 8549 patients with Parkinson's disease using diagnosis criteria with a positive predictive value of 90%. These patients were compared with 42 160 control subjects matched for age, sex and general practice.

## RESULTS

Overall, 3.0% of cases (257 of 8549) had at least one recorded prescription for carbamazepine compared with 2.5% (1050 of 42 160) of controls. The crude odds ratio for the association between Parkinson's disease and carbamazepine was 1.22 (95% confidence interval 1.06–1.40), but this reduced to 0.93 (95% confidence interval 0.81–1.08,  $P = 0.34$ ) after adjusting for annual consultation rate. Further adjustment for body mass index, smoking status, alcohol consumption or use of calcium channel blockers did not affect results. There was no evidence that risk decreased with higher doses or longer duration of carbamazepine use.

## CONCLUSIONS

There was little to no evidence that use of carbamazepine is associated with reduced risk of Parkinson's disease. Although the study was underpowered, it does indicate that any effect of carbamazepine is likely to be small.

## Introduction

Parkinson's disease (PD) is a neurodegenerative disorder that is clinically characterized by symptoms of tremor, rigidity, bradykinesia and postural instability [1]. These abnormal motor functions are due to degeneration of dopaminergic neurons, which some have theorized is a result of intracellular accumulation of Lewy bodies [2, 3].

Lewy bodies are abnormal protein aggregations comprising misfolded  $\alpha$ -synuclein protein [3, 4]. The process which normally rids cells of these abnormal proteins is called autophagy, and its role in degrading toxic proteins has been recognized only recently [5]. Autophagy occurs when membranous structures called autophagosomes form around intracytosolic proteins or other structures and the contents are degraded by lysosomes [6]. Recent research has focused on identifying drugs which can modify autophagy, with the hope that drugs which stimulate the process could be used as treatments for neurodegenerative disorders. A number of autophagy-inducing compounds have been identified, one of which is the anti-epileptic drug carbamazepine [7].

Recent studies indicate that carbamazepine operates in a dose-dependent manner to increase autophagy in mice to amplify the degradation of mutant liver proteins [8]. The documented autophagy-enhancing properties of carbamazepine make it a prime candidate for treating or preventing PD. To date, no studies in humans have examined whether use of carbamazepine is associated with development of PD. We therefore used the UK General Practice Research Database (GPRD) to perform a large, matched case-control study to explore the risk of PD associated with exposure to carbamazepine.

## Methods

### *The General Practice Research Database*

The General Practice Research Database is the largest electronic database of general practice (GP) clinical records in the world and is a well-validated database for drug safety and effectiveness research [9, 10]. It contains information on demographic characteristics, diagnoses, prescriptions, clinical tests, immunizations and hospital referrals for nearly 9 million patients and has more than 50 million patient-years of follow-up [9]. Patients participating in the GPRD are representative of the UK with regard to age, sex and geographic distribution. The GPRD is held by the Clinical Practice Research Datalink, a research and data services provider, which is jointly funded by the Medicines and Healthcare products Regulatory Agency of the UK (MHRA) and the UK National Institute for Health Research [9]. The MHRA regularly monitors GPRD data [11], and several studies have found it to be of high quality [5]. To date, the GPRD has been the source of over 900 published studies.

### *Selection of participants*

This was a large-scale, matched case-control study of GPRD-registered patients. Cases were defined as all patients with at least one diagnostic record of PD, who were registered in the GPRD between 1990 and 2008, and who had at least 1 year of research-standard follow-up time before the first diagnosis. The index date for each case was the date of the first diagnosis of PD. A patient was excluded as a case if the date of diagnosis was unknown, if antipsychotic medications were prescribed less than 6 months prior to being diagnosed with PD (because they can induce PD-like symptoms [12]), if the case was a temporary resident of the UK or if secondary causes of PD were indicated. Patients with any of the following diagnoses were treated as having secondary causes of PD: syphilitic parkinsonism, postencephalitic parkinsonism, drug-induced parkinsonism, secondary parkinsonism due to other external agents, secondary parkinsonism, unspecified, or iatrogenic parkinsonism. Furthermore, cases were required to have at least two prescriptions for any PD therapies to increase the likelihood that the PD diagnosis was valid.

Controls were selected from patients registered in the GPRD and were matched in a 5:1 ratio to cases on age at index date ( $\pm 5$  years), sex and general practice. In order to be eligible, controls must have had at least 1 year of research-standard follow-up time prior to the index date of the corresponding case.

### *Data extraction and analysis*

All data management and statistical analyses were performed using Stata (version 11; StataCorp LP, College Station, TX, USA). Data were extracted from electronic records, and analyses were limited to drug exposures recorded before the index date. Drug exposure was defined as 'ever' or 'never' based on prescription histories prior to the index date. Patients with one or more prescriptions were included in the 'ever' exposure category. Median daily doses of carbamazepine were calculated for all exposed patients based on extracted daily dose information and were categorized as follows:  $\leq 200$  mg day<sup>-1</sup>;  $> 200$  to  $\leq 400$  mg day<sup>-1</sup>; and  $> 400$  mg day<sup>-1</sup>. The cumulative dose was also calculated for each exposed patient. The three levels of cumulative exposure to carbamazepine were as follows:  $< 30\ 000$  mg;  $\geq 30\ 000$  to  $< 300\ 000$  mg; and  $\geq 300\ 000$  mg. Notably, many exposed patients had missing daily dose values. These missing values were imputed in one of the following two ways: if possible, a patient's missing daily dose information was predicted from previous prescribing history; if this was not possible, the patient was treated as having the median daily dose associated with the specific drug prescribed (e.g. all subjects with missing daily dose values for Tegretol 100 mg tablets were assigned a daily dose of three tablets, the median daily dose for all individuals prescribed this drug). Lastly, prescription dates were extracted and used to

calculate the duration of treatment, which was categorized as <1 year,  $\geq 1$  to  $\leq 5$  years or >5 years.

Data were also extracted on the following potentially confounding variables, all of which were selected based on known or expected associations with Parkinson's disease: body mass index (BMI) [13]; smoking status [14, 15]; alcohol consumption [14]; use of calcium channel blockers [5]; and annual consultation rate (a measure of help-seeking behaviour defined as the number of times a patient initiated contact with a GP surgery in the 12 months prior to the index date). Consultation rate was considered for adjustment because patients who receive carbamazepine may have higher rates of consultation, which may also increase the opportunity for recording other diagnoses, such as PD.

Descriptive analyses were performed to tabulate the distribution of demographic characteristics and potentially confounding variables among cases and controls. Conditional logistic regression was used to assess exposure variables as confounders if they were associated with both carbamazepine exposure and PD. Conditional logistic regression models were built using a forward stepwise approach. Potentially confounding exposure variables were added to the model one by one, starting with the variable with the largest confounding effect. Confounding variables were kept in the model only if inclusion appreciably changed the effect of carbamazepine exposure on PD.

### Sensitivity analyses

Sensitivity analyses were conducted for the following reasons: (i) to assess the effect of imputing missing data; (ii) to explore the impact of treating patients with fewer than two prescriptions as 'unexposed'; (iii) to assess the effect of misclassification of the outcome by reclassifying some cases as controls and vice versa; and (iv) to assess the impact of misclassification of the duration of exposure by reclassifying patients with fewer than 5 years of carbamazepine exposure as 'unexposed.'

### Power

Power calculations were performed in Excel based on a formula by Schlesselman [16] and used the prevalence of the drug exposure among controls in this study and an  $\alpha$  level of 0.05. Calculations indicated that with five controls per case, this study had at least 80% power to detect a 20% reduction in PD due to use of carbamazepine.

Ethical approval was received from the London School of Hygiene and Tropical Medicine Research Ethics Committee and the Independent Scientific Advisory Committee for the MHRA.

## Results

A total of 8549 patients with PD were included in the study and matched with 42 160 control patients. Table 1 displays

the age and sex distribution of cases and controls, their BMI, smoking status, alcohol consumption status, use of calcium channel blockers and annual consultation rate. Smoking status, alcohol consumption and BMI were missing for some patients. Patients with missing data for covariates were analysed as separate strata. Sensitivity analyses in which missing data were imputed using multiple imputations by chained equations [17] showed no material differences in univariable estimates.

The majority (57.7%) of cases were male, and the median age of study patients was 75 years. The median BMI for all patients was 25.6 kg m<sup>-2</sup>, and cases had slightly lower median BMI than controls (25.2 vs. 25.8 kg m<sup>-2</sup>). There was strong evidence that current and ex-smokers had a lower risk of PD compared with nonsmokers [odds ratio (OR) for current smokers 0.46, 95% confidence interval (CI) 0.43–0.50], which is consistent with previous findings [14, 15]. Increasing alcohol consumption was also associated with reduced risk of diagnosis of PD (Table 1), but there was little evidence of an association between use of calcium channel blockers and PD (OR 1.02, 95% CI 0.96–1.08). As expected, cases had a substantially higher median annual consultation rate than controls (21 vs. 15 GP contacts year<sup>-1</sup>), and patients in the highest consultation rate quintile had almost eight times the odds of being diagnosed with PD as patients in the lowest quintile (OR 7.73, 95% CI 6.98–8.56). The median duration of follow-up time for cases and controls was nearly identical (7.58 vs. 7.61 years, respectively).

Table 2 displays the associations between diagnosis of PD and exposure to carbamazepine. Among cases, 3.0% (257 of 8549) had at least one recorded prescription for carbamazepine in comparison to 2.5% (1050 of 42 160) of controls.

The crude odds ratio for the association between 'ever' use of carbamazepine and a diagnosis of Parkinson's disease was 1.22 (95% CI 1.06–1.40). The association was diminished after adjusting for annual consultation rate, but it was not affected by further adjustment for BMI, smoking status, alcohol consumption or use of calcium channel blockers. After adjusting for annual consultation rate, the odds ratio for the association between carbamazepine use and PD diagnosis was 0.93 (95% CI 0.81–1.08,  $P = 0.34$ ). There was little evidence that the association differed by duration ( $P = 0.46$ ), cumulative dose ( $P = 0.38$ ) or daily dose of carbamazepine ( $P = 0.17$ ). Results from the sensitivity analysis that reclassified people with two or fewer carbamazepine prescriptions as unexposed were comparable to those of the primary analysis.

### Additional sensitivity analyses and model checking

The criteria we used for diagnosing patients with PD have a positive predictive value of 90% [5]. We therefore performed a sensitivity analysis in which we reclassified 10% of cases as controls, assuming that the misclassification

**Table 1**

Characteristics of cases and controls: univariable associations between exposures and Parkinson's disease

Characteristic	Cases (%) n = 8549	Controls (%) n = 42 160	Univariable odds ratio (95% confidence interval)
<b>Age*</b>			
<60 years	796 (9.3)	3967 (9.4)	–
60–69 years	1770 (20.7)	8751 (20.8)	–
70–79 years	3451 (40.4)	17 013 (40.4)	–
≥80 years	2532 (29.6)	12 429 (29.5)	–
<b>Sex*</b>			
Male	4940 (57.8)	24 292 (57.6)	–
Female	3609 (42.2)	17 868 (42.4)	–
<b>Body mass index (kg m<sup>-2</sup>)</b>			
<18.5	234 (2.7)	801 (1.9)	1
18.5–24.9	3044 (35.6)	13 720 (32.5)	0.76 (0.67–0.83)
25–29.9	2592 (30.3)	14 051 (33.3)	0.63 (0.57–0.70)
≥30	969 (11.3)	6271 (14.9)	0.53 (0.47–0.59)
Unknown	1710 (20.0)	7317 (17.4)	0.80 (0.75–0.93)
<b>Smoking status</b>			
Nonsmoker	4539 (53.1)	17 801 (42.2)	1
Current smoker	760 (8.9)	6153 (14.6)	0.46 (0.43–0.50)
Ex-smoker	2680 (31.4)	15 548 (36.9)	0.64 (0.61–0.68)
Unknown	570 (6.7)	2658 (6.3)	0.84 (0.76–0.93)
<b>Alcohol consumption</b>			
Nondrinker	1235 (14.5)	5708 (13.5)	1
Ex-drinker	158 (1.9)	583 (1.4)	1.25 (1.03–1.51)
Current drinker (unknown amount)	205 (2.4)	936 (2.2)	1.01 (0.86–1.20)
<2 units day <sup>-1</sup>	4891 (57.2)	24 307 (57.7)	0.92 (0.85–0.99)
3–6 units day <sup>-1</sup>	651 (7.6)	3904 (9.3)	0.74 (0.67–0.83)
>6 units day <sup>-1</sup>	68 (0.80)	452 (1.1)	0.67 (0.52–0.88)
Unknown	1341 (15.7)	6270 (14.9)	0.99 (0.90–1.08)
<b>Use of calcium channel blockers</b>			
Never	5740 (67.1)	28 751 (68.2)	1
Ever	2809 (32.9)	13 409 (31.8)	1.02 (0.96–1.08)
<b>Consultation rate</b>			
<6 contacts year <sup>-1</sup>	600 (7.0)	9497 (22.5)	1
6–12 contacts year <sup>-1</sup>	1373 (16.1)	8631 (20.5)	2.79 (2.52–3.09)
13–18 contacts year <sup>-1</sup>	1601 (18.7)	7768 (18.4)	3.98 (3.59–4.41)
19–27 contacts year <sup>-1</sup>	2194 (25.7)	8086 (19.2)	5.62 (5.08–6.22)
≥28 contacts year <sup>-1</sup>	2781 (32.5)	8178 (19.4)	7.73 (6.98–8.56)
Median annual consultation rate (interquartile range)	21 contacts year <sup>-1</sup> (13–31)	15 contacts year <sup>-1</sup> (6–24)	–
Median follow-up time prior to index date (interquartile range)	7.6 years (4.1–11.1)	7.6 years (4.1–11.1)	–

\*Matched variable.

would be nondifferential with respect to exposure status. We also performed a sensitivity analysis in which we reclassified 0.634% of controls as cases (the calculated mean European prevalence of PD [18]), assuming that the misclassification would be nondifferential with respect to exposure status. In both instances, the crude odds ratios were not materially different from primary analyses.

Given that the the onset of PD could occur several years before the onset of symptoms, we performed a sensitivity analysis in which we reclassified patients with fewer than 5 years of carbamazepine exposure as 'unexposed'. This analysis yielded results that were consistent with the primary analysis.

In primary analyses, adjusting for consultation rate reduced the association between carbamazepine use and

PD. We propose that this reduction occurred because consultation rate is a measure of help-seeking behaviour and current illness, and people who frequently contact or attend their GP surgery for either reason are likely to receive earlier diagnosis of PD by virtue of being seen by a clinician more often. However, it is also plausible that carbamazepine use itself increases the risk of PD, and as patients exposed to carbamazepine develop symptoms of PD they increase their rate of consultation with the GP. If this were the case, it would be inappropriate to adjust for consultation rate. To explore this, we examined the clinical records of a random sample of 20 PD cases with high consultation rates (top quintile), half whom were exposed to carbamazepine. We looked for consultations relating to neurological conditions, including conditions that are



**Table 2**

Associations between exposure to carbamazepine and diagnosis of Parkinson’s disease

Drug exposure	Cases (%) n = 8549	Controls (%) n = 42 160	Crude odds ratio (95% confidence interval)	Adjusted odds ratio * (95% confidence interval)	P value
<b>Carbamazepine</b>					
Never	8292 (97.0)	41 110 (97.5)	1	1	0.34
Ever	257 (3.0)	1050 (2.5)	1.22 (1.06–1.40)	0.93 (0.81–1.08)	
<b>Carbamazepine duration</b>					
Never	8292 (97.0)	41 110 (97.5)	1	1	0.46
<1 year	147 (1.7)	660 (1.6)	1.11 (0.93–1.33)	0.87 (0.72–1.04)	
1–5 years	56 (0.66)	204 (0.48)	1.36 (1.01–1.83)	0.99 (0.73–1.34)	
>5 years	54 (0.63)	186 (0.44)	1.44 (1.06–1.96)	1.09 (0.80–1.49)	
<b>Carbamazepine cumulative dose (mg × 10<sup>3</sup>)</b>					
Never	8292 (97.0)	41 110 (97.5)	1	1	0.38
<30	132 (1.5)	606 (1.4)	1.09 (0.99–1.32)	0.85 (0.70–1.04)	
30–299	66 (0.77)	244 (0.58)	1.34 (1.02–1.76)	1.02 (0.77–1.34)	
≥300	59 (0.69)	200 (0.47)	1.46 (1.09–1.96)	1.08 (0.80–1.45)	
<b>Carbamazepine median daily dose (mg × 10<sup>3</sup>)</b>					
Never	8292 (97.0)	41 110 (97.5)	1	1	0.17
≤200	116 (1.4)	548 (1.3)	1.05 (0.86–1.29)	0.81 (0.66–0.99)	
201–400	103 (1.2)	352 (0.83)	1.46 (1.17–1.82)	1.10 (0.86–1.38)	
>400	38 (0.44)	150 (0.36)	1.26 (0.88–1.80)	1.00 (0.69–1.45)	

\*Adjusted for consultation rate quintile.

indications for carbamazepine, such as epilepsy, pain and mood disturbances. These events accounted for 9.5% of consultations amongst unexposed cases and 8.4% of consultations amongst exposed cases. There was no excess of these events amongst exposed cases, which supports our theory that increased surveillance, rather than use of carbamazepine, better explains the higher rates of PD diagnosis that were observed among patients with high consultation rates.

## Discussion

We found little evidence that carbamazepine is associated with a reduced risk of Parkinson’s disease diagnosis. Despite this, our finding of a 7% reduction in odds of PD associated with use of carbamazepine, although not statistically significant, is consistent with the findings of Hidvegi *et al.* [8], who found that in a mouse model, carbamazepine promoted the reduction of mutant protein aggregations in the liver by increasing the rate of intracellular autophagy.

Adjusting for annual consultation rate reduced the crude odds ratio. We believe this adjustment was appropriate because the likelihood of receiving a prescription for carbamazepine and the diagnosis of PD were both related to the frequency of consultation. When compared with patients in the lowest consultation rate group, patients in the highest group had almost seven times the odds of receiving carbamazepine prescriptions. Moreover, the odds of a PD diagnosis were 7.73 times higher (95% CI 6.98–8.56) in these patients compared with those in the lowest consultation rate group. These results are logically

consistent with what probably occurs at the GP; people exposed to carbamazepine have serious medical conditions, which would require them to attend the GP more often than a healthy person. This frequent attendance is likely to result in earlier diagnosis of PD for these individuals. This early diagnosis explains why, after adjusting for annual consultation rate, the effect estimate for carbamazepine was reduced. Although sensitivity analyses provided support for this theory, we cannot rule out the possibility that the observed increase in consultation rates reflect an increased risk of Parkinson’s disease caused by carbamazepine use. This is an acknowledged limitation of our results.

This study is the first of its kind to examine the association between diagnosis of Parkinson’s disease and exposure to carbamazepine. Its strengths lie in its setting and design; it was a very large, population-based case–control study, with controls matched for age, sex and general practice. Additionally, because the geographic and demographic profile of patients enrolled in the GPRD are representative of the UK population, our findings should be generalizable to the UK as a whole.

Other strengths include the quality of exposure and outcome data. The GPRD contains very detailed drug exposure information, including drug name, dosage, dose frequency, prescription date and prescription duration, and the accuracy of these data collected in the GPRD has been validated [19]. The outcome data in this study are also reliable. The validity of GPRD diagnoses was recently examined by a systematic review, which found that 89% of all diagnoses were confirmed by additional review [10]. With respect to PD diagnoses in particular, among patients with

at least two prescriptions for PD, 90% of GPRD diagnoses of PD were confirmed by a review of medical records [5]. What we do not know, however, is the number of individuals with PD who were not picked up by our search criteria (e.g. false negatives); we are therefore unable to draw firm conclusions about the sensitivity of our case definition. However, sensitivity analyses indicated that minor misclassification would have little to no effect on our findings.

In spite of its size, the main weakness of our study was its inability to detect small reductions in risk. The 95% confidence intervals for the adjusted odds ratio for the association between 'ever' use of carbamazepine and PD diagnosis indicate that the data are consistent with an effect ranging from an odds ratio of 0.81 to 1.08. However, because so few study participants were exposed to carbamazepine, our study was underpowered to detect such small effects.

Another limitation is that because the symptoms of PD appear only after 50–70% of dopaminergic neurons are lost, it is possible that there are a number of undiagnosed, asymptomatic patients [20]. It is therefore plausible that some controls with early stage PD were not identified as cases. However, owing to the rarity of PD only a small number of controls would be affected by this, and there is no reason to suspect that this type of misclassification would have been differential with respect to exposure status. The scope of this type of misclassification was therefore likely to be minimal. Moreover, sensitivity analyses indicated that if this misclassification occurred, the effect would be negligible.

One of the limitations of examining drug effects using the GPRD is the uncertainty regarding drug exposure. Given that there are no assurances that patients took their prescribed medication, there is always the potential for misclassification of exposure. The potential for exposure misclassification in this study was amplified by the fact that 8.1% (2035 of 25 164) of carbamazepine daily dose values were missing and imputed. Our results showed that a higher proportion of cases than controls had at least one missing daily dose value for carbamazepine: 22.6 vs. 16.5% ( $P = 0.02$ ). If the imputed missing daily dose values did not reflect actual prescription information, then the estimates of effect in this study could be biased. Moreover, this study accounted only for drug received while patients were registered at a GPRD-participating clinic. It is therefore possible that some patients were exposed prior to registration and this information was not recorded. However, given that the majority of carbamazepine prescribing is through primary care in the UK, the scope for bias from such misclassification is likely to be low.

An additional limitation of using GPRD data is that the indication for use is not explicitly linked to each drug prescribed by a clinician. The likely indication can be inferred from the clinical diagnostic codes recorded around the time of the drug prescription, but the accuracy of these inferences cannot be guaranteed.

There is also a possibility that the variables estimating duration of treatment did not accurately reflect the length of time for which patients were exposed to a drug. Treatment duration was calculated by measuring the time elapsed between first and last prescriptions for a drug. This method was chosen over alternative methods in order to avoid generating biased estimates based on imputed daily dose data (alternative methods involve dividing the number of pills dispensed by the prescribed daily dose to achieve the number of days per prescription; then all prescription durations are summed to provide an overall duration of drug for each patient). However, our chosen method of measurement precludes the ability to take into account any gaps in treatment (i.e. periods of non-exposure). As a result, an inherent limitation of the duration exposure variable is that some individuals with long periods of time between only a few prescriptions will be misclassified as having a long period of exposure. This could impact results. For example, if the risk of PD does decrease with duration of treatment with carbamazepine, and if a portion of the patients in the longest duration group were actually exposed to the drug for only a short period of time, then the result would be to bias the odds ratio towards the null in the highest duration group. However, the data do not support an inference of misclassification among patients in the higher duration groups; of the 240 participants exposed to carbamazepine for more than 5 years, only 10 (4.2%) were in the lowest cumulative exposure group (<30 000 mg).

### Conclusion

Our analyses found little to no evidence that use of carbamazepine is associated with reduced risk of Parkinson's disease. Even though the observed 7% reduction in risk associated with carbamazepine use is not inconsistent with a protective effect given the limited power of our study, the lack of any association with either total or average dose suggests that a protective role for carbamazepine is unlikely. It is therefore infeasible to recommend carbamazepine as a preventive measure for PD. Our findings do not, however, preclude the possibility that other drugs have the potential to treat PD. Future studies should continue to examine the effects of autophagy-enhancing compounds on development of Parkinson's disease.

### Competing Interests

All authors have completed the Unified Competing Interest form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: L.S. had support from a Wellcome Trust Senior Research Fellowship in Clinical Science for the submitted work and I.D. had support from a Medical Research Council Methodology Fellowship for the submitted work; no

financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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