Dementia risk in a diverse population: A single-region nested case-control study in the East End of London

Phazha L.K. Bothongo,1,2 Mark Jitlal,3,4 Eve Parry,5 Sheena Waters,6 Isabelle F. Foote,6 Cameron J. Watson,6 Jack Cuzick,6
Gavin Giovannoni,6,7 Ruth Dobson,6,7 Alastair J. Noyce,6,7 Naaheed Mukadam,8 Jonathan P. Bestwick,6 and
Charles R. Marshall6,8,9

1Preventive Neurology Unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London, London EC1M 6BQ, UK
2Department of Neurology, Barts Health NHS Trust, London, UK
3Division of Psychiatry, University College London, London, UK
4Tower Hamlets Diagnostic Memory Clinic, East London NHS Foundation Trust, London, UK

Summary

Background Most evidence about dementia risk comes from relatively affluent people of White European ancestry. We aimed to determine the association between ethnicity, area level socioeconomic deprivation and dementia risk, and the extent to which variation in risk might be attributable to known modifiable clinical risk factors and health behaviours.

Methods In this nested case-control study, we analysed data from primary care medical records of a population of 1,016,277 from four inner East London boroughs, United Kingdom, collected between 2009 and 2018. The outcome measures were odds ratios for dementia according to ethnicity and deprivation, before and after the addition of major modifiable risk factors for dementia; and weighted population attributable risk for comparison between individual risk factors.

Findings We identified 4137 dementia cases and 15,754 matched controls (mean age for cases and controls were 80±7 years, (SD 8±7); 81±3 years, (SD 8±9) respectively, range 27–103). Black and South Asian ethnicity were both associated with increased risk of dementia relative to White (odds ratios [95% CI]: Black 1.43 [1.31–1.56]; South Asian 1.17 [1.06–1.29]). Area-level deprivation was independently associated with an increased risk of dementia in a dose-dependent manner. Black and South Asian ethnicity were both associated with a younger age at dementia diagnosis (odds ratios [95%CI]: 0.70 [0.61–0.80] and 0.55 [0.47–0.65], respectively). Population attributable risk was higher for ethnicity (9.7%) and deprivation (11.7%) than for any established modifiable risk factor in this population.

Interpretation Ethnicity and area-level deprivation are independently associated with dementia risk in East London. This effect may not be attributable to the effect of known risk factors.

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Introduction

As the number of global dementia cases approaches 50 million,1 there is increasing emphasis placed on risk factors that might be useful targets for efforts to prevent or delay the onset of dementia.2,3 However, complex diseases like dementia have mostly been explored in affluent people of White European ancestry.4,5 An increased understanding of variation in dementia risk by ethnicity and socioeconomic status is needed for the development of effective preventive interventions across geographical, cultural and socioeconomic boundaries.6

Several studies have shown increased dementia risk in Black ethnic groups,7–12 while evidence in Asian ethnic groups is sparser and more conflicting.13,14 South Asian communities, in particular, have rarely been studied.9 Underrepresentation in dementia research cohorts has made it difficult to definitively establish

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*Corresponding author at: Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University of London, London EC1M 6BQ, UK.
E-mail address: charles.marshall@qmul.ac.uk (C.R. Marshall).

1 These authors contributed equally to this work.
the mechanisms responsible for variation by ethnicity, but it has been hypothesised that ethnicity acts as a proxy for other risk factors (including access to health services, differential burden of vascular risk factors, racism and socioeconomic deprivation). However, pooled evidence does not clearly demonstrate that these factors are sufficient to account for differences in dementia risk. Improving our understanding of the role of ethnicity in dementia, and diversifying representation in dementia research cohorts are urgent unmet needs.  

We sought to evaluate the relationships between ethnicity, area level socioeconomic deprivation and dementia risk in the diverse and deprived population of the East End of London. We hypothesised that dementia risk would vary by ethnicity and that this would be independent of socioeconomic status and modifiable risk factors. We further hypothesised that age at dementia diagnosis would vary by ethnicity. Finally, we aimed to demonstrate the relative impact of dementia risk factors in this population, expressed as weighted population attributable risk.

Methods

Study design and data sources

We performed a nested case-control study using data extracted from EMIS electronic health care records for the SHARE project (Secure Health Analysis and Research in East London) on 6th February 2018. The data included demographic information, diagnoses, important comorbidities, free text, and clinical measurements, all with dates. Health records are of 1,016,277 adults from 170 primary care practices across 4 Clinical Commissioning Groups (CCGs) in East London: Hackney & City of London, Newham, Tower Hamlets, and Waltham Forest. 98% of all adult patients registered with a primary care provider in the region are included in this dataset.

Selection of cases and controls

Due to the cross-sectional retrospective nature of our dataset, we chose a nested case-control design. We were able to define exposures as those measured prior to the outcome occurring, thus allowing matching between cases and controls at the time of the outcome event (i.e. age at dementia diagnosis).

Patients with a recorded and dated diagnosis on their GP record of all-cause dementia, made between July 2009 and January 2018, were selected as cases. A diagnosis of dementia was defined as the presence in the patient’s record of any Read codes for dementia as a diagnosis, symptom, or referral (see Supplementary Table 1 for Read codes). We excluded those with undated diagnoses of dementia due to concerns about the reliability of these data, and because we required a date of diagnosis to define exposures occurring prior to diagnosis. We did not have an age cut-off for selecting cases and controls, due to concerns about introducing bias if younger onset dementia was disproportionately represented in some ethnicities or strata of deprivation. The youngest age at which a case was diagnosed was 27 years, with 87 cases below 60 years old (% of cases = 2.1), and the oldest at 103 years. We defined all-cause
dementia collectively because accuracy for all-cause dementia coding in UK primary care records is high (around 87%), whereas the accuracy for specific dementia diagnoses is much lower, and because most evidence on modifiable risk factors comes from all-cause dementia studies. In total, 4138 cases were identified but one female case (aged 105 years) had no matching controls and was dropped, leaving 4137 cases in the matched case-control analysis.

Individual matching was done whereby each case was randomly matched to a maximum of four controls, selected from the same dataset, based on gender and year of birth. Patients that had an undated dementia diagnosis or a diagnosis of any other chronic neurological condition (see Supplementary Table 2 for Read codes) were excluded as controls (we did not exclude chronic neurological conditions from cases since many of these diseases are causes of dementia). 3746 dementia cases were successfully matched to four controls, 379 to 2 controls, and 12 to 1 control giving a total of 15,754 controls. Cases with fewer controls were primarily older (≥90 years), female and more deprived (IMD 1-2).

Definition of factors of interest. Age. As the relationship between age and dementia risk is highly nonlinear, we treated age as a categorical variable using the following age groups: <65, 65–69, 70–74, 75–79, 80–84, 85–89, ≥90

Ethnicity. Ethnicity was defined by self-report according to UK census categories: White (including English, Welsh, Scottish, Northern Irish, British, Irish, Gypsy or Irish Traveller, any other White background); Black (including African, Caribbean and any other Black, African or Caribbean Background); South Asian (including Indian, Pakistani, and Bangladeshi); Other (any other specified ethnicity including mixed ethnicities); and Unknown.

Index of Multiple Deprivation (IMD). Area level deprivation was defined using IMD, the official measure of relative deprivation for small areas in England. It ranks every Lower Layer Super Output Area (LSOA; a geographical area comprising approximately 1500 residents and 650 households), incorporating seven aspects of deprivation: income (22.5%), employment (22.5%), health and disability (13.5%), education, skills and training (13.5%), barriers to housing and services (9.3%), living environment (9.3%), and crime (9.3%). This ranking was used to assign each participant to a national IMD decile. Further information can be found at: https://www.gov.uk/government/statistics/english-indices-of-deprivation-2019.

Major modifiable risk factors. We selected modifiable risk factors identified by the Lancet Commission. Data were not available for four of these (less education, less physical activity, social isolation, and air pollution). The remaining eight risk factors (obesity, depression, diabetes, head injury, hearing loss, high alcohol intake, hypertension, and smoking) were categorised as (1) never recorded, (2) first recorded at any life stage prior to dementia diagnosis (or for controls prior to the date of diagnosis of their matched case), (3) first recorded after dementia diagnosis, or (4) unknown (Table 1). The Unknown category was used where data were missing, where there was no date of recording, or when the age at which the risk factor was measured fell below a clinically relevant or meaningful threshold (BMI ≤18 years, smoking <12 years; hypertension, diabetes, depression, hearing loss, alcohol, and head injury all aged < 0 years). For all analyses, the comparison of interest was between the risk factor never having been recorded and having been recorded prior to dementia diagnosis; the other two categories were treated as covariates of no interest.

Modifiable risk factors were defined as follows: type II diabetes, depression, hypertension, high alcohol intake, head injury, and hearing loss were defined by the presence of a recorded diagnosis (see Supplementary Tables 3–8 for Read codes), hearing loss was also defined by a referral for assessment of reported hearing difficulty. Smoking status was defined as current, previous, or never having smoked. Body mass index (BMI) was calculated using height and weight measurements and participants were categorised as Overweight/Obese (BMI 25.0–50.0 kg/m²), Normal weight (BMI 20.0–24.9 kg/m²), or Underweight (10.0–19.9 kg/m²). Where height was outside the range of 155–230 cm, weight was outside the range of 9–250 kg, or BMI was outside the range of 10–50 kg/m², these data were deemed likely to be spurious and were reclassified as Unknown.

We used a chi squared test to compare the proportion of subjects with exposure to each risk factor between ethnic groups.

Missing data. Of the 19,896 participants in the matched analysis, the only completed observed variables were age and gender, other variables had missingness that fell below ten percent (Table 1). Missing data in were categorised as unknown and treated as a separate level in all analyses. As a sensitivity analysis, we repeated the analyses with multiple imputation (MI), using the “mice” R package, following confirmation that data were missing at random (MAR). MI creates m > 1 complete datasets, in our case five, where the distribution of observed data/variables is used to estimate plausible values for missing data. Logistic regression models were then fitted to each complete dataset. The m results were pooled into a final estimate with
computation of the total variance over the repeated analyses by using Rubin’s Rule (1987).  

Statistical modelling

Logistic regression models. We used conditional logistic regression analysis to estimate odds ratios for dementia for each factor of interest (Table 2). We modelled the association of ethnic group and deprivation decile with odds of dementia, adjusting for age and gender (Matched Model 1). We then added modifiable risk factors to the model as covariates (Matched Model 2). As a sensitivity analysis, we built a multivariable model fully adjusted for all covariates (age, gender, and modifiable risk factors) using the entire population of potential controls (Unmatched Model).

Interaction testing. Within the matched case-control analysis, we explored pairwise multiplicative interactions of ethnicity and deprivation with each other, and with each modifiable risk factor found to have a significant effect in the preceding models, correcting for multiple comparisons. The fit of the model with the addition of each interaction term was assessed using the Akaike information criterion. We used the Benjamini-Hochberg test, to correct for pairwise interaction tests, with a pre-specified alpha of 0.05 (Supplementary Table 9). Where significant interactions were identified, post hoc testing was used to identify which subject group(s) were responsible for the effect.

We also examined for an additive interaction of ethnicity and deprivation in the matched-case control analysis, using a binarized deprivation classification (IMD deciles 1-2 vs IMD deciles 3-10) where the relative excess risk due to interaction (RERI) was estimated.

Association of ethnicity and deprivation with age at dementia diagnosis. To determine the effects of ethnicity and deprivation on age group at diagnosis of dementia we built a cumulative model, with age group at diagnosis as the response variable and gender, ethnicity and deprivation decile as explanatory variables (Table 4).

Calculation of population attributable risk. To allow comparison of the importance of individual risk factors within previous work in less diverse populations, we estimated the weighted population attributable risk (PAR) for each factor of interest (Table 3). Individual unweighted PARs were initially calculated for each variable in turn, using Levin’s formula and their ORs adjusted for all covariates in the unmatched population (which approximates risk ratio for the rare outcome of dementia). All the factors of interest were dichotomised as follows: (1) ethnicity: White vs. Minoritized Ethnicity (Black, South Asian, and Other); (2) deprivation: remainder of quintiles vs. most deprived quintile; 3) modifiable risk factors: never present vs. present prior to diagnosis.

To calculate PAR estimates for interrelated risk factors, we weighted the PAR by factor communality. We calculated a tetrachoric correlation matrix for the factors of interest, which was used to conduct a principal component analysis. Communality for each measured variable was calculated as the square of the loadings of the first principal component, which had eigenvalue ≥ 1. We then calculated weighted PAR as follows:

\[ Weight \ (w) = 1 - communality \]

\[ Overall \ PAR_{\text{weighted}} = 1 - \left( \prod_{i=1}^{n} \frac{1}{1 - PAR_i} \right) \]

\[ Individual \ PAR_{\text{weighted}} = \frac{Individual \ PAR_{\text{unweighted}}}{\sum(individual \ PAR_{\text{unweighted}})} \times Overall \ PAR_{\text{weighted}} \]

Software

All statistical analyses were performed in R (v3.6.0). This research was supported by the High-Performance Cluster computing network hosted by Queen Mary University of London.

Role of the funding source

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Results

Population demographics

Demographic and modifiable risk factor characteristics are summarised in Table 1. Dementia cases and controls were well-matched for age (mean age for cases: 80.7 years, (SD) 8.7; controls: 81.3 years, (SD) 8.9), and gender (female cases: 60.3%, n = 2494; female controls: 59.4%, n = 9354). The ethnic composition of the entire population was consistent with UK census estimates for the region (White: 43.7%, n = 440,812; Black: 13.3%, n = 134,297; South Asian: 21.5%, n = 216,408). There were low levels of missing ethnicity data for matched analysis (cases: 6.4%, n = 265; controls: 5.4%, n = 845). There were high levels of deprivation, with 45%
# Table 1 (Continued)

| Characteristics | Factors | Dementia Cases, n = 4,137, n (%) | Matched Controls, n = 15,754, n (%) | Entire Population, n = 1,016,277, n (%) |
|-----------------|---------|-----------------------------------|-------------------------------------|----------------------------------------|
| Age, mean (SD)  | 80-78   | 80.7 (8.7)                        | 81.3 (8.9)                          | 40.5 (15.4)                            |
| Age             | <65     | 95.4 (7.7)                        | 78.0 (5.3)                          | 926,867 (91.2)                         |
|                 | 65-69   | 208 (5.0)                         | 332 (5.3)                           | 29,544 (2.9)                           |
|                 | 70-74   | 328 (8.0)                         | 1,316 (8.4)                         | 21,246 (2.1)                           |
|                 | 75-79   | 749 (18.3)                        | 2,996 (19.0)                        | 16,421 (1.6)                           |
|                 | 80-84   | 1,021 (24.7)                      | 4,084 (25.9)                        | 11,916 (1.2)                           |
|                 | 85-89   | 981 (23.7)                        | 3,924 (24.9)                        | 6,831 (0.7)                            |
|                 | 90+     | 654 (15.8)                        | 1,822 (11.6)                        | 3,452 (0.3)                            |
| Gender          | Female  | 2,494 (60.3)                      | 9,354 (59.4)                        | 496,577 (48.9)                         |
|                 | Male    | 1,643 (39.7)                      | 6,400 (40.6)                        | 519,686 (51.1)                         |
|                 | Unknown | -                                 | -                                   | 14 (0.1)                               |
| Ethnicity       | White   | 1,965 (47.5)                      | 8,336 (52.9)                        | 444,931 (43.8)                         |
|                 | Black   | 941 (22.7)                        | 2,828 (18.0)                        | 135,971 (13.4)                         |
|                 | South Asian | 685 (16.6)            | 2,547 (16.2)                        | 217,803 (21.4)                         |
|                 | Other   | 281 (6.8)                         | 1,198 (7.6)                         | 114,995 (11.3)                         |
|                 | Unknown | 265 (6.4)                         | 845 (5.4)                           | 102,577 (10.1)                         |
| IMD Decile      | Most deprived-1 | 735 (17.8)   | 2,210 (14.0)                        | 137,992 (13.6)                         |
|                 | 2       | 1,380 (33.4)                      | 4,881 (31.0)                        | 319,069 (31.4)                         |
|                 | 3       | 1,039 (25.1)                      | 4,557 (28.9)                        | 305,722 (30.1)                         |
|                 | 4       | 308 (7.4)                         | 1,795 (11.4)                        | 121,600 (12.0)                         |
|                 | 5       | 133 (3.2)                         | 914 (5.8)                           | 56,163 (5.5)                           |
|                 | 6       | 57 (1.4)                          | 326 (2.1)                           | 21,000 (2.1)                           |
|                 | 7       | 48 (1.2)                          | 194 (1.2)                           | 13,147 (1.3)                           |
|                 | 8-10    | 37 (0.9)                          | 233 (1.5)                           | 13,193 (1.3)                           |
|                 | Unknown | 400 (9.7)                         | 644 (4.1)                           | 28,391 (2.8)                           |
| Modifiable Risk Factors | - | -                                 | -                                   | -                                      |
| Depression:     | Never   | 3,393 (82.0)                      | 14,169 (89.9)                       | 938,056 (92.3)                         |
|                 | Prior-Dem | 627 (15.2)             | 1,387 (8.8)                         | 75,219 (7.4)                           |
|                 | Post-Dem | 98 (2.4)                          | 169 (1.1)                           | 355 (<0.1)                             |
|                 | Unknown  | 19 (0.5)                          | 29 (0.2)                            | 2,647 (0.3)                            |
| Head Injury:    | Never   | 3,810 (92.1)                      | 15,115 (95.9)                       | 983,035 (96.7)                         |
|                 | Prior-Dem | 195 (4.7)               | 423 (2.7)                           | 32,622 (3.2)                           |
|                 | Post-Dem | 131 (3.2)                        | 214 (1.4)                           | 518 (0.1)                              |
|                 | Unknown  | 1 (<0.1)                          | 2 (<0.1)                            | 102 (<0.1)                             |
| Type II Diabetes: | Never | 2,664 (64.4)                      | 11,155 (70.8)                       | 947,329 (93.2)                         |
|                 | Prior-Dem | 1,257 (30.4)           | 3,859 (24.5)                        | 65,470 (6.4)                           |
|                 | Post-Dem | 168 (4.1)                        | 640 (4.1)                           | 1,293 (0.1)                            |
|                 | Unknown  | 48 (1.2)                          | 100 (0.6)                           | 2,185 (0.2)                            |
| Underweight:    | Never   | 3,660 (88.5)                      | 14,676 (93.2)                       | 774,203 (76.2)                         |
|                 | Prior-Dem | 195 (4.7)               | 579 (3.7)                           | 98,121 (9.7)                           |
|                 | Post-Dem | 69 (1.7)                          | 81 (0.5)                            | 241 (<0.1)                             |
|                 | Unknown  | 213 (5.1)                         | 418 (2.7)                           | 143,712 (14.1)                         |
| Hearing Loss:   | Never   | 3,207 (77.5)                      | 12,406 (78.7)                       | 973,348 (95.8)                         |
|                 | Prior-Dem | 681 (16.5)             | 2,289 (14.5)                        | 39,488 (3.9)                           |
|                 | Post-Dem | 245 (5.9)                        | 1,048 (6.7)                         | 2,539 (0.2)                            |
|                 | Unknown  | 4 (0.1)                           | 11 (0.1)                            | 902 (0.1)                              |
| Hypertension:   | Never   | 657 (15.9)                        | 2,810 (17.8)                        | 815,185 (80.2)                         |
|                 | Prior-Dem | 3,114 (75.3)           | 11,596 (73.6)                       | 195,228 (19.2)                         |
|                 | Post-Dem | 328 (7.9)                        | 1,228 (7.8)                         | 2,582 (0.3)                            |
|                 | Unknown  | 38 (0.9)                          | 120 (0.8)                           | 3,282 (0.3)                            |
| Smoking:        | Never   | 2,396 (57.9)                      | 9,054 (57.5)                        | 616,858 (60.7)                         |
|                 | Ex      | 1,015 (24.5)                      | 3,967 (25.2)                        | 116,318 (11.4)                         |

**Notes:**
- Male = 1,965 (47.8%); Female = 1,643 (39.7%); Unknown = 144 (0.3%)
- White = 1,965 (47.8%); Black = 941 (22.7%); South Asian = 685 (16.6%); Other = 281 (6.8%); Unknown = 40 (10.0%)
- IMD Decile: 0-9+ = 654 (15.8%); 10-14 = 1,021 (24.7%); 15-19 = 981 (23.7%); 20-24 = 208 (5.0%); 25-29 = 328 (7.9%); 30+ = 1,015 (24.5%); Unknown = 4 (0.1%)
- Post-Dem = 69 (1.7%); Prior-Dem = 195 (4.7%); Unknown = 19 (0.5%)
- Underweight: 80-84 = 3,810 (92.1%); 85-89 = 981 (23.7%); 90+ = 654 (15.8%); Unknown = 19 (0.5%)
- Hypertension: Never = 657 (15.9%); Prior-Dem = 3,114 (75.3%); Post-Dem = 328 (7.9%); Unknown = 38 (0.9%)
- Smoking: Never = 2,396 (57.9%); Ex = 1,015 (24.5%); Unknown = 4 (0.1%)
Association of ethnicity and deprivation with risk of dementia

ORs for ethnicity and deprivation are shown in Table 2 and Figure 1. In Matched Model 1 (incorporating ethnicity and deprivation, adjusting for age and gender), dementia risk was increased in Black (OR 1.43, 95% CI 1.31–1.56) and South Asian ethnicities (OR 1.17, 95% CI 1.06–1.29) relative to White. Dementia risk decreased with decreasing deprivation (p value for trend <0.001), suggesting a dose-response relationship through the most deprived five deciles (ORs 95%CI relative to 1st decile: 2nd 0.85 (0.77–0.94), 3rd 0.69 (0.62–0.76), 4th 0.52 (0.45–0.60), 5th 0.44 (0.36–0.53)). Results for deciles 6–10 suggested a protective effect of decreasing deprivation, but the estimates were imprecise.

Association of ethnicity and deprivation with age at dementia diagnosis

The effect of ethnicity and deprivation on age at dementia diagnosis is shown in Table 4 and Figure 2. The cumulative odds of being in an older age group at diagnosis revealed that Black (OR 0.70, 95% CI 0.61–0.80), South Asian (OR 0.55, 95% CI 0.47–0.65) and Other (OR 0.72, 95% CI 0.57–0.90) ethnic groups had lower odds of being in an older age group at diagnosis (i.e. were on average younger at diagnosis) than White subjects (all p < 0.001). There was no significant association of deprivation with age at dementia diagnosis (all p > 0.200).

Effects of modifiable risk factors

ORs for modifiable risk factors are shown in Table 2 and Figure 1. After adjusting for all covariates, risk factors found to have an effect on an increased risk of dementia were depression (OR 1.90, 95%CI 1.70–2.11), head injury (OR 1.77, 95%CI 1.48–2.11), underweight (OR 1.43, 95%CI 1.20–1.69), diabetes (OR 1.34, 95%CI 1.24–1.46), hearing loss (OR 1.17, 95%CI 1.06–1.29) and hypertension (OR 1.07, 95%CI 0.97–1.19). High alcohol intake was strongly partitioned by ethnicity (due to cultural/religious influences on alcohol consumption patterns) and made the models unstable. It was therefore removed from subsequent analyses. The effects of ethnicity and deprivation were largely unchanged after the inclusion of modifiable risk factors in Matched Model 2.

Comparison of the proportion of subjects with dementia having exposure to each risk factor prior to dementia diagnosis revealed that prevalence of all risk factors varied between groups (all p < 0.004) except head injury (p=0.277) (Table 6). Exposure to type II diabetes prior to a dementia diagnosis had the most clinically meaningful variation in prevalence by ethnic group (Blacks 40.3% and South Asians 53.7% compared to Whites 19.3%).

Sensitivity analyses

The results of the unmatched model are shown in Table 2. The OR estimates for factors that were not used in the matching process were similar, suggesting that there was no substantial bias introduced by the case-control matching process. The results of the models with multiple imputation for missing data are shown in Table 2. The effect estimates for ethnicity and deprivation were not materially altered, suggesting the missingness was not a major source of bias.

Interaction testing

Results of multiplicative interaction testing are shown in Supplementary Table 9 and additive interaction testing in Table 3.

Where statistically significant multiplicative interactions were identified, post hoc analysis showed in all cases that these were driven by small numbers of subjects in the “Unknown” category, with only trends towards significance in the categories that did not represent missing data. Thus, overall, no clinically meaningful interactions were identified for the pairwise multiplicative interactions of ethnicity and deprivation.

| Characteristics | Factors | Dementia Cases, n=4,137, n (%) | Matched Controls, n=15,754, n (%) | Entire Population, n=1,016,277, n (%) |
|-----------------|---------|-------------------------------|-----------------------------------|--------------------------------------|
| Current         | 634 (15.3) | 2,487 (15.8) | 228,677 (22.5) |
| Unknown         | 92 (2.2)   | 246 (1.6)   | 54,424 (5.4)   |

Table 1: Demographic and modifiable risk factor characteristics of dementia cases, matched controls, and entire population.

Abbreviations: IMD, Index of Multiple Deprivation; SD, standard deviation.
Here we show in a diverse population that those who (weighted PAR 11)

Weighted PARs are shown in Table 5. The most important risk factors in this population were deprivation (weighted PAR 11.7%) and minority ethnicity (weighted PAR 9.7%).

**Discussion**

Here we show in a diverse population that those who identify as Black or South Asian are at an increased risk of dementia relative to those who identify as White. This disparity was not accounted for by area-level socioeconomic deprivation or modifiable risk factors. Ethnicity and deprivation had higher population attributable fractions than any of the more established modifiable clinical risk factors and health behaviours in this study, suggesting that they are important independent associations of dementia risk.

Research cohorts tend to be over-representative of relatively affluent White participants.54–56 The roles of ethnicity and deprivation in determining dementia risk have therefore often been overlooked, and this is a major knowledge gap in dementia research.57 By leveraging National Health Service data infrastructure to create a population study of one of the most diverse and deprived regions of the United Kingdom,58 we show that those who are less likely to be represented in dementia research are more likely to suffer from dementia. This highlights that improving representation in research is urgently needed.
| Ethnicity | N cases/controls | OR (95%CI) | N cases/controls | OR (95%CI) | N cases/controls | OR (95%CI) | ORs (95%CI) for IMD 1-2 within strata of ethnicity | ORs (95%CI) for Unknown IMD within strata of ethnicity |
|-----------|-----------------|------------|-----------------|------------|-----------------|------------|-----------------------------------------------|-----------------------------------------------|
| White     | 677/4188        | 1.00       | 1055/3758       | 1.64 (1.47–1.82); P < 0.00 | 233/390 | 3.43 (2.85–4.13); P < 0.00 | 1.65 (1.48–1.84); P < 0.00 | 3.46 (2.87–4.17); P < 0.00 |
| Black     | 373/1272        | 1.83 (1.58–2.12); P < 0.00 | 497/1475       | 2.08 (1.81–2.38); P < 0.00 | 71/81 | 5.26 (3.75–7.37); P < 0.00 | 1.14 (0.98–1.34); P < 0.00 | 2.90 (2.04–4.11); P < 0.00 |
| S.Asian   | 315/1416        | 1.35 (1.15–1.57); P < 0.00 | 337/1081       | 1.81 (1.55–2.10); P < 0.00 | 33/50 | 3.92 (2.47–6.16); P < 0.00 | 1.32 (1.10–1.58); P < 0.00 | 3.01 (1.87–4.80); P < 0.00 |
| Other     | 138/665         | 1.30 (1.06–1.59); P = 0.01 | 123/492        | 1.54 (1.23–1.91); P < 0.00 | 20/41 | 3.12 (1.77–5.33); P < 0.00 | 1.21 (0.91–1.60); P = 0.19 | 2.52 (1.38–4.48); P < 0.00 |
| Unknown   | 119/478         | 1.38 (1.10–1.72); P < 0.00 | 103/285        | 1.89 (1.47–2.43); P < 0.00 | 43/82 | 2.51 (1.68–3.69); P < 0.00 | 1.39 (1.01–1.92); P = 0.04 | 1.76 (1.11–2.75); P = 0.01 |

ORs (95%CI) for Black ethnicity within strata of IMD
- 1.83 (1.57–2.13); P < 0.00
- 1.25 (1.09–1.43); P < 0.00
- 1.48 (1.00–2.19); P = 0.05

ORs (95%CI) for S.Asian ethnicity within strata of IMD
- 1.35 (1.15–1.58); P < 0.00
- 1.09 (0.94–1.27); P = 0.25
- 1.08 (0.65–1.80); P = 0.75

ORs (95%CI) for Other ethnicity within strata of IMD
- 1.32 (1.07–1.62); P = 0.01
- 0.92 (0.74–1.14); P = 0.46
- 0.86 (0.47–1.52); P = 0.61

ORs (95%CI) for Unknown ethnicity within strata of IMD
- 1.54 (1.22–1.93); P < 0.00
- 1.00 (0.77–1.29); P = 1.00
- 0.82 (0.52–1.26); P = 0.36

Table 3: Additive interaction between ethnicity and deprivation on the risk of a dementia diagnosis.
Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; MI, Multiple Imputation Model; OR, odds ratio.
Measure of interaction on additive scale: RERI (95%CI) = -2.24 (-2.49 to -1.95).
ORs are adjusted for age (categorised), gender, and modifiable risk factors (depression, head injury, diabetes, underweight, hearing loss, hypertension and smoking.
Reference group.

ORs are adjusted for age (categorised), gender, and modifiable risk factors (depression, head injury, diabetes, underweight, hearing loss, hypertension and smoking.
Reference group.
This work is the first dementia study to adequately represent a large UK South Asian population and demonstrates that dementia risk is higher in this group than in the White population within the same region. The finding of increased risk in the Black population is consistent with previous evidence.\textsuperscript{7-10,21} Whereas this increase in risk has sometimes been ascribed to deprivation or vascular risk factors,\textsuperscript{10} adjusting for these did not materially alter the effect estimates in our study, suggesting that the association is likely to be mediated by other unobserved factors. There was no meaningful multiplicative interaction between ethnicity, deprivation

| Coefficients for parameters | Dementia Cases, n = 4,137, n (%) | OR for age at diagnosis (95%CI) | P value |
|-----------------------------|----------------------------------|---------------------------------|---------|
| **Gender:**                 |                                  |                                 |         |
| Female\textsuperscript{1}   | 2,494 (60 3)                     | 1.00                            | -       |
| Male                        | 1,643 (39 7)                     | 0.70 (0.63-0.78)                | < 0.001 |
| **Ethnicity:**              |                                  |                                 |         |
| White\textsuperscript{1}    | 1,965 (47 5)                     | 1.00                            | -       |
| Black                       | 941 (22 7)                       | 0.70 (0.61-0.80)                | < 0.001 |
| S. Asian                    | 685 (16 6)                       | 0.55 (0.47-0.65)                | < 0.001 |
| Other                       | 281 (6 8)                        | 0.72 (0.57-0.90)                | < 0.001 |
| Unknown                     | 265 (6 4)                        | 1.06 (0.84-1.34)                | 0.823   |
| **IMD Decile:**             |                                  |                                 |         |
| Most Deprived 1\textsuperscript{1} | 735 (17 8) | 1.00                            | -       |
| 2                           | 1,380 (33 4)                     | 0.99 (0.85-1.17)                | 0.880   |
| 3                           | 1,039 (25 1)                     | 1.04 (0.88-1.23)                | 0.500   |
| 4                           | 308 (7 4)                        | 0.99 (0.78-1.25)                | 0.667   |
| 5                           | 133 (3 2)                        | 0.97 (0.70-1.34)                | 0.885   |
| 6                           | 57 (1 4)                         | 1.43 (0.90-2.30)                | 0.211   |
| 7                           | 48 (1 2)                         | 1.19 (0.69-2.05)                | 0.691   |
| 8-10                        | 10 (0 2)                         | 1.38 (0.75-2.54)                | 0.322   |
| Unknown                     | 400 (9 7)                        | 1.63 (1.31-2.02)                | < 0.001 |

Table 4: Cumulative model of age at dementia diagnosis by ethnicity, deprivation and gender.
Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; MI, Multiple Imputation Model; OR odds ratio.
Age at dementia diagnosis (years): < 65 (reference), 65-69, 70-74, 75-79, 80+.
OR represent the cumulative odds of being in an older age group at death (OR below 1 estimates a younger age at diagnosis, and OR above 1 estimates an increased age at diagnosis compared to reference group).
\textsuperscript{1}Reference group.

| Factor | Dementia Cases, n = 4,137, n (%) | Unmatched Controls, n = 1,007,94, n (%) | Adjusted OR (95%CI) | Population Prevalence | Unweighted PAR | Communality | Weighted PAR |
|--------|----------------------------------|----------------------------------------|---------------------|-----------------------|-----------------|-------------|--------------|
| Ethnic Minority\textsuperscript{a} | 1,908 (46 1) | 465,104 (46 1) | 1.31 (1.21-1.41) | 51.3% | 13.7% | 1.7% | 9.7% |
| Deprived (IMD deciles 1 and 2) | 2,117 (51 1) | 452,940 (44 9) | 1.43 (1.33-1.53) | 46.3% | 16.6% | 1.9% | 11.7% |
| Depression\textsuperscript{b} | 627 (15 1) | 74,592 (7 4) | 1.98 (1.80-2.18) | 7.4% | 6.8% | 18.6% | 4.8% |
| Head injury\textsuperscript{b} | 195 (4 7) | 32,095 (3 2) | 1.76 (1.50-2.05) | 3.2% | 2.4% | 1.8% | 1.1% |
| Type II diabetes\textsuperscript{b} | 1,257 (6 4) | 64,213 (30 4) | 1.36 (1.26-1.47) | 6.5% | 2.3% | 72.4% | 1.6% |
| Underweight\textsuperscript{b} | 195 (4 7) | 97,926 (9 7) | 1.38 (1.17-1.61) | 11.2% | 4.1% | 25.1% | 2.9% |
| Hearing loss\textsuperscript{b} | 681 (16 5) | 38,807 (3 9) | 1.35 (1.24-1.48) | 3.9% | 1.3% | 24.0% | 1.0% |
| Hypertension\textsuperscript{b} | 3,114 (75 2) | 192,114 (19 1) | 1.30 (1.18-1.44) | 19.3% | 5.5% | 73.7% | 3.9% |
| Ex Smoking\textsuperscript{b} | 1,015 (24 5) | 114,411 (11 4) | 1.01 (0.93-1.10) | 12.1% | 0.1% | 7.9% | 0.1% |

Table 5: Population attributable risk of ethnicity, deprivation, and modifiable risk factors.
Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation; MI, Multiple Imputation Model; OR Odds Ratio; PAR, population attributable risk.
The table shows adjusted ORs from the unmatched model incorporating all risk factors (age, gender, ethnicity, deprivation, modifiable risk factors), together with population risk factor prevalence, unweighted PAR, communality of each risk factor and weighted PAR estimate after adjusting for communality.
\textsuperscript{a}Ethnic Minority group consists of: Black, South Asian, and Other.
\textsuperscript{b}The comparison of interest was between the risk factor never having been recorded and having been recorded prior to dementia diagnosis, or being an ex-smoker.
and modifiable risk factors, implying that the effect of each risk factor is similar across ethnic and socioeconomic groups (with the caveat that there may be inadequate power to detect small interaction effects in this study). Despite the absence of interaction, the variation in prevalence of risk factors by ethnic group may still account for some of the variation in dementia risk. In particular, the increased prevalence of diabetes among Black and South Asian subjects with dementia may account for some of the excess risk in these groups, and this is reflected in the relatively high PAR for diabetes in the population as a whole.

These findings have implications for prioritising dementia prevention strategies in diverse and deprived populations, in whom the importance of modifiable risk factors have previously been emphasised. The population attributable risk estimates we show indicate that targeting established modifiable risk factors may be of relatively modest benefit within East London, whereas targeting any modifiable factors underlying the increased risk attributable to ethnicity and deprivation could potentially prevent a greater proportion of cases.

Ethnicity and area-level deprivation are complex social constructs, and there are many possible factors that could mediate the observed increase in dementia risk. Stressful and traumatic life events are increasingly recognised to influence risk of dementia, and it is possible that certain adverse events across the life course are more common in specific demographic groups. In particular, experience of both daily and institutional racism might determine some of the racial differences in the burden of stressful life events, and thereby affect later life cognitive function and risk of dementia. Similarly, stress induced by poverty has been shown to directly influence cognitive function. The finding that dementia risk declined through the most deprived four deciles and was relatively static thereafter is consistent with an effect of poverty in those who are most deprived, without a clear linear effect among the less deprived deciles. The negative additive interaction we identified (where ethnicity had a relatively greater effect among those who are less deprived) could also be consistent with an effect of chronic stressors.

Although ethnicity cannot be defined in genetic terms, it is possible that there is a degree of genetic stratification within ethnoracial groups. Most current knowledge concerning genetic risk for dementia is derived from participants of White European ancestry. Evaluating genetic risk in other populations will require new genome-wide association studies in those populations. Some evidence has suggested that APOE ε4 genotype may have a smaller effect on dementia risk in populations with African ancestry, and that gene-environment interactions could also vary by ethnicity.

The setting for this study has important strengths. The use of a single geographical region is likely to have reduced confounding by environmental factors such as air pollution, while the comprehensive analysis of almost all adults registered with a primary care provider

**Figure 1.** The figure shows odds ratios for factors of interest in the matched case-control analysis with all risk factors included (Matched Model 2). Error bars represent 95% CI. Abbreviations: CI, confidence interval; IMD, Index of Multiple Deprivation.
may have mitigated to some extent against selection and ascertainment biases. Where ascertainment bias exists in our study, it is likely to relate to factors that influence access to memory clinic services and diagnostic accuracy within those services.\textsuperscript{35} In other studies, these have tended to result in underestimating dementia risk in ethnic minority and deprived groups, suggesting that they would bias our results towards the null.\textsuperscript{9} Our data may have suffered less from this bias than other studies because healthcare provision in East London is designed to try to address some of these inequities, including community dementia awareness-raising, bilingual staff in memory clinics, and the use of bespoke culturally fair assessment tools. This drive to recognise and mitigate health inequalities in East London is also reflected by the near universal ascertainment of ethnicity at primary care registration, reflected here by low rates of missing ethnicity data in comparison to other studies.\textsuperscript{9}

A major limitation of this study is the lack of data on some dementia risk factors, particularly education and air pollution. It is possible that the associations between ethnicity, deprivation and dementia risk are partly confounded by such factors. It is unlikely that education could account for all of the effect, particularly as the large effect of education on dementia risk estimated by the Lancet Commission is based on having no secondary education at all.\textsuperscript{2} We would anticipate this to be rare in our population: only 0.2% of UK adults have no secondary education.\textsuperscript{16} Moreover, recent evidence suggests that socioeconomic status may in fact mediate the association between education and dementia risk.\textsuperscript{37} A further important limitation is an inability with these data to account for migration, and therefore to establish how much of dementia risk might be attributable to place of residence at different times of life. This may be particularly problematic for those with dementia who have moved into residential care away from their earlier life exposures. There are inherent limitations in the ascertainment of dementia cases through primary care recording: and we were unable here to meaningfully analyse variations in risk for specific dementia syndromes.\textsuperscript{18} We are also unable to establish whether variations in the accuracy of recorded diagnosis by ethnicity could be a source of bias in this study. There are potential limitations in the type of analysis employed here. A nested case-control study is known to reduce statistical power, compared to the parent cohort due to smaller sample size, and is also limited in its potential for causal inference. The fully adjusted models in the logistic regression also risk overadjustment, and hence attenuation of the effects of modifiable risk factors.

Dementia risk factors have varying effects across the life course.\textsuperscript{2} While most of the modifiable risk factors here had effects broadly consistent with previous evidence, these data are unable to fully take account of the timing and duration of the risk factors. This may go some way to explaining the attenuated effect of smoking in this population, and the inverse association with body mass index. There is growing interest in the link between nutritional factors and dementia risk.\textsuperscript{38} Dietary patterns vary according to ethnicity and deprivation, and our finding that the association between BMI and dementia risk is dominated by underweight rather than overweight goes some way to suggesting that poor nutrition could be of particular importance in this population, although declining BMI is also recognised as a prodromal feature of dementia.\textsuperscript{39} Patterns of risk factor treatment might also alter the effect of risk factors (e.g. through undertreatment, delayed treatment or the use of
of particular medications), and this warrants further exploration.

Future work should emphasise the value of adequately representative longitudinal cohort studies, which reflect the ethnicity and area-level socioeconomic status of the population from which they are drawn. This would support more detailed analysis to uncover the biological underpinnings of variation in dementia.

Table 6: Demographic and risk factor characteristics in dementia cases, stratified by ethnicity.

| Characteristics          | Factors                  | Dementia Cases, n = 4,137, n (%) | X^2 Test | P value |
|--------------------------|--------------------------|----------------------------------|----------|---------|
|                          | White n = 1,965 (47.5)   | Black n = 941 (22.7)             |          |         |
|                          | S Asian n = 685 (16)     | Other n = 281 (6.8)              |          |         |
| Age, mean (SD)           |                          |                                  |          |         |
| <65                      | 82.3 (8.8)               | 80.7 (8.3)                       | 78.9 (8.7)| 80.4 (9.8)| 0.001 |
| 65-69                    | 102 (5.2)                | 50 (5.3)                         | 47 (6.9) | 17 (6.0) | <0.001|
| 70-74                    | 148 (7.5)                | 74 (7.9)                         | 54 (7.9) | 32 (11.4)| <0.001|
| 75-79                    | 320 (16.3)               | 185 (19.7)                       | 164 (23.9)| 48 (17.1)| <0.001|
| 80-84                    | 346 (22.2)               | 282 (30.0)                       | 185 (27.0)| 62 (22.1)| <0.001|
| 85-89                    | 497 (25.3)               | 212 (22.5)                       | 138 (20.1)| 67 (23.8)| <0.001|
| 90+                      | 390 (19.8)               | 105 (11.2)                       | 48 (7.0) | 41 (14.6)| <0.001|
| Gender ^1               |                          |                                  |          |         |
| Female                   | 1260 (64.1)              | 558 (59.3)                       | 345 (50.4)| 160 (56.9)| <0.001|
| Male                     | 705 (35.9)               | 383 (40.7)                       | 340 (49.6)| 121 (43.1)|         |
| IMD Binary               |                          |                                  |          |         |
| 1-2                      | 1055 (53.7)              | 497 (52.8)                       | 337 (49.2)| 123 (43.8)| <0.001|
| 3-10                     | 677 (34.5)               | 373 (39.6)                       | 315 (46.0)| 138 (49.1)|         |
| Unknown ^4              | 233 (11.9)               | 71 (7.5)                         | 33 (4.8) | 20 (7.1) |         |
| Depression:              |                          |                                  |          |         |
| Never ^4                 | 1,547 (78.7)             | 817 (86.4)                       | 568 (82.9)| 236 (84.0)| <0.001|
| Prior-Dem ^b             | 355 (18.1)               | 100 (10.6)                       | 98 (14.3) | 40 (14.2) |         |
| Post-Dem ^c              | 53 (2.7)                 | 18 (1.9)                         | 17 (2.5) | 5 (1.8) |         |
| Unknown ^d               | 10 (0.5)                 | 6 (0.6)                          | 2 (0.3) | 0 (0.0) |         |
| Head Injury:             |                          |                                  |          |         |
| Never ^4                 | 1785 (90.8)              | 875 (93.0)                       | 646 (94.3)| 257 (91.5)| 0.277 |
| Prior-Dem ^b             | 108 (5.5)                | 44 (4.7)                         | 20 (2.9) | 12 (4.3) |         |
| Post-Dem ^c              | 71 (3.6)                 | 22 (2.3)                         | 19 (2.8) | 12 (4.3) |         |
| Unknown ^d               | 1 (0.1)                  | 0 (0.0)                          | 0 (0.0) | 0 (0.0) |         |
| Type II Diabetes:        |                          |                                  |          |         |
| Never ^4                 | 1,524 (77.6)             | 495 (52.6)                       | 262 (38.2)| 179 (63.7)| <0.001|
| Prior-Dem ^b             | 380 (19.3)               | 379 (40.3)                       | 368 (53.7)| 87 (31.0) |         |
| Post-Dem ^c              | 52 (2.6)                 | 46 (4.9)                         | 45 (6.6) | 12 (4.3) |         |
| Unknown ^d               | 9 (0.5)                  | 21 (2.2)                         | 10 (1.5) | 3 (1.1) |         |
| Underweight:             |                          |                                  |          |         |
| Never ^4                 | 1,738 (88.4)             | 873 (92.8)                       | 615 (89.8)| 264 (64.2)| <0.001|
| Prior-Dem ^b             | 91 (4.6)                 | 30 (3.2)                         | 51 (7.4) | 11 (4.5) |         |
| Post-Dem ^c              | 33 (1.7)                 | 14 (1.5)                         | 5 (0.7) | 1 (0.6) |         |
| Unknown ^d               | 103 (5.2)                | 24 (2.6)                         | 14 (2.0) | 5 (25.3) |         |
| Hearing Loss:            |                          |                                  |          |         |
| Never ^4                 | 1483 (75.5)              | 769 (81.7)                       | 522 (76.2)| 214 (76.2)| 0.004 |
| Prior-Dem ^b             | 369 (18.8)               | 118 (12.5)                       | 117 (17.1)| 45 (16.0) |         |
| Post-Dem ^c              | 112 (5.7)                | 53 (5.6)                         | 44 (6.4) | 22 (8.7) |         |
| Unknown ^d               | 1 (0.1)                  | 1 (0.1)                          | 2 (0.3) | 0 (0.0) |         |
| Hypertension:            |                          |                                  |          |         |
| Never ^4                 | 374 (19.0)               | 97 (10.3)                        | 75 (10.9)| 41 (14.6)| <0.001|
| Prior-Dem ^b             | 1,408 (71.7)             | 776 (82.5)                       | 554 (80.9)| 217 (77.2)|         |
| Post-Dem ^c              | 164 (8.3)                | 58 (6.2)                         | 49 (7.2) | 21 (7.5) |         |
| Unknown ^d               | 19 (1.0)                 | 10 (1.1)                         | 7 (1.0) | 2 (0.7) |         |
| Smoking:                 |                          |                                  |          |         |
| Never ^4                 | 939 (47.8)               | 674 (71.6)                       | 441 (64.4)| 187 (66.5)| <0.001|
| Ex- ^e                   | 605 (30.8)               | 171 (18.2)                       | 122 (17.8)| 54 (19.2) |         |
| Current ^f               | 381 (19.4)               | 80 (8.5)                         | 111 (16.2)| 35 (12.5) |         |
| Unknown ^g               | 40 (2.0)                 | 16 (1.7)                         | 11 (1.6) | 5 (1.8) |         |

Abbreviations: IMD, Index of Multiple Deprivation; SD, standard deviation.

^1 Never recorded.

^2 First recorded prior to dementia diagnosis (or for controls prior to the date of diagnosis of their matched case).

^3 First recorded after dementia diagnosis.

^4 The Unknown category was used where data were missing, where there was no date of recording, or when the age at which the risk factor was measured fell below a clinically relevant or meaningful threshold (BMI <18 years, smoking <12 years, hypertension, diabetes, depression, hearing loss, and head injury all aged <0 years).
risk by these demographic factors, paving the way for more inclusive therapeutic trials, and ultimately for more equitable prevention and treatment of dementia.

Conclusions
Ethnicity and area-level deprivation are independently associated with dementia risk in this deprived multiracial urban population. Understanding the underlying mechanisms by which ethnicity and deprivation confer this increased risk of dementia could enhance dementia prevention efforts, making them applicable across ethnORacial and socioeconomic boundaries.

Author contributions
Conceptualization and design: PLKB, MJ, JPB, and CRM.
Data curation: PLKB, MJ, SH, JC, GG, RD, AJN, JPB, and CRM.
Formal analysis: PLKB, MJ, JPB, CRM.
Investigation: PLKB, MJ, AJN, RD, JPB, CRM.
Methodology: PLKB, MJ, NM, CRM.
Code lists: PLKB, MJ.
Project administration: PLKB, MJ, AJN, RD, JPB, CRM.
Software: PLKB, MJ, JPB.
Visualisation: PLKB, MJ, SW, CRM.
Writing – original draft: PLKB, MJ, CRM.
Writing- review & editing: All.
Guarantor: PLKB and CRM.
The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Ethics approval
Ethical approval was not required as patient-level data are anonymised and aggregated patient data are reported in this study. All GPs in the participating east London practices consented to the use of their anonymised patient data for research and development for patient benefit.

Transparency statement
The manuscript’s guarantor affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Data sharing statement
In accordance with NHS Digital’s Information Governance requirements, the study data cannot be shared.

Declaration of interests
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