Received: 26 January 2023 | Revised: 26 April 2023 | Accepted: 19 May 2023

DOI: 10.1002/alz.13349

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

RESEARCH ARTICLE

Dementia risk in patients with type 2 diabetes: Comparing metformin with no pharmacological treatment

Bang Zheng[1,2] | **Bowen Su**[3] | **Sara Ahmadi-Abhari**[1] | **Dimitrios Kapogiannis**[4] | **Ioanna Tzoulaki**[3] | **Elio Riboli**[3,5] | **Lefkos Middleton**[1,5]

[1]Ageing Epidemiology Research Unit, School of Public Health, Imperial College London, London, UK

[2]Department of Non-communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK

[3]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

[4]Laboratory of Clinical Investigation, Intramural Research Program, National Institute on Aging, Baltimore, USA

[5]Public Health Directorate, Imperial College NHS Healthcare Trust, London, UK

Correspondence
Lefkos Middleton, Ageing Epidemiology Research Unit, School of Public Health, Imperial College London, London W6 8RP, UK.
Email: l.middleton@imperial.ac.uk

Funding information
Imperial College London – China Scholarship Council

Abstract

INTRODUCTION: Metformin has been suggested as a therapeutic agent for dementia, but the relevant evidence has been partial and inconsistent.

METHODS: We established a national cohort of 210,237 type 2 diabetes patients in the UK Clinical Practice Research Datalink. Risks of incident dementia were compared between metformin initiators and those who were not prescribed any anti-diabetes medication during follow-up.

RESULTS: Compared with metformin initiators (n = 114,628), patients who received no anti-diabetes medication (n = 95,609) had lower HbA1c and better cardiovascular health at baseline. Both Cox regression and propensity score weighting analysis showed metformin initiators had lower risk of dementia compared to those non-users (adjusted hazard ratio = 0.88 [95% confidence interval: 0.84–0.92] and 0.90 [0.84–0.96]). Patients on long-term metformin treatment had an even lower risk of dementia.

DISCUSSION: Metformin may act beyond its glycemic effect and reduce dementia risk to an even lower level than that of patients with milder diabetes and better health profiles.

KEYWORDS
cohort, dementia, drug repurposing, metformin, type 2 diabetes

Highlights

- Metformin initiators had a significantly lower risk of dementia compared with patients not receiving anti-diabetes medication.
- Compared with metformin initiators, diabetes patients not receiving pharmacological treatment had better glycemic profiles at baseline and during follow-up.
- Patients on long-term metformin treatment had an even lower risk of subsequent dementia incidence.
- Metformin may act beyond its effect on hyperglycemia and has the potential of being repurposed for dementia prevention.

1 | BACKGROUND

Alzheimer's disease and related dementias (ADRD) have become a major global healthcare and socioeconomic challenge,[1,2] yet there are still no efficacious disease-modifying therapies.[3] Dementia is known to be multi-factorial, resulting from complex interactions of non-modifiable and modifiable risk factors and/or comorbidities, over time.[4] Type 2 diabetes (T2D) and insulin resistance are established risk factors for dementia,[4–6] hence implying the potential of repurposing anti-diabetes drugs for dementia prevention and treatment.[7]

Emerging evidence suggests that metformin, the most commonly prescribed first-line anti-diabetes drug, could delay the onset of ADRD.[7–9] Several in vitro and animal studies have shown that metformin has neuroprotective effects by reducing the generation and accumulation of phosphorylated tau and β-amyloid proteins and improving neuronal insulin signaling.[10–13] However, results from several population-based studies on the metformin-dementia association have been variable and somewhat controversial.[14–16]

Leveraging the large-scale longitudinal electronic health records (EHR) data from the UK Clinical Practice Research Datalink (CPRD),[17] this study aimed to examine the association between metformin and dementia risk and explore whether such an association goes beyond its glycemic effect by comparing T2D patients initially prescribed metformin versus T2D patients with milder disease, receiving no anti-diabetes medication during follow-up.

RESEARCH IN CONTEXT

1. **Systematic Review**: The relevant literature was reviewed using PubMed. Metformin has been proposed as a therapeutic agent for dementia. Several in vitro and animal studies revealed neuroprotective effects of metformin, and two pilot clinical trials in patients with mild cognitive impairment showed some supportive evidence. However, results from population-based longitudinal studies have been controversial.
2. **Interpretation**: In this national population-based cohort study that included 210,237 patients with type 2 diabetes, metformin initiators were at a significantly lower risk of developing dementia compared with patients not prescribed anti-diabetes medication, despite that those non-users had better glycemic profiles and cardiovascular health at baseline. Patients on long-term metformin treatment had even lower risk of subsequent dementia incidence compared with non-users.
3. **Future Directions**: Metformin may act beyond its effect on hyperglycemia and has the potential of being repurposed for dementia prevention. Future well-powered clinical trials in at-risk older adults are needed to confirm our findings.

2 | METHODS

2.1 | Data sources

The UK CPRD GOLD database is a longitudinal primary care database that includes data on symptoms, diagnoses, investigations, prescriptions, secondary, and tertiary care referrals of over 17 million individuals.[17] Data are systematically collected from EHR systems in general practitioners (GP) practices across 13 regions in the UK, since 1987. The demographic profile of patient population of CPRD has been shown to be representative of the UK general population.[17] CPRD has also been linked to secondary care data from Hospital Episode Statistics (HES), mortality data from Office for National Statistics (ONS), and small-area measures of social deprivation. Since the coding and data quality in CPRD have been improved over time, and to account for the change of clinical practice and guidelines for diabetes management,[18] we opted to use data from 2001 to 2018, for this study.

2.2 | Study population and exposure assessment

To establish the cohort of metformin initiators, we included T2D patients initially treated with metformin between 2001 and 2018 and aged over 50 years at the first metformin prescription date. Presence of T2D was based on relevant CPRD Medcodes (excluding Medcodes for Type 1 diabetes) and prescriptions (British National Formulary codes) (Table S1). In this study, metformin initiators were defined as T2D patients, whose initial anti-diabetes drug treatment was metformin monotherapy for 12 months. Eligible patients should have at least 1-year registration in CPRD practices prior to the first prescription of metformin, to ensure that they are new users and allow time for baseline information to be recorded; have at least two metformin prescriptions and no other anti-diabetics prescription during the initial 12-month treatment period; and have no dementia record before the metformin treatment.

For the non-user cohort, we included T2D patients aged over 50 years at any point during their CPRD registration period who had no anti-diabetes drug prescription records, throughout the entire CPRD observation period. According to the UK National Institute for Health and Care Excellence (NICE) guideline for T2D management,[19] these patients were most likely to have been successfully managed through diet and lifestyle intervention, not requiring anti-diabetes medication. Patients entered the cohort at age 50, the date of diabetes diagnosis or January 1, 2001, whichever was the latest. In addition, eligible participants were required to have been registered in CPRD for at least 1 year prior to cohort entry and have no dementia record before cohort entry.

A total of 114,628 metformin initiators and 95,609 T2D patients with no anti-diabetes drug treatment during their CPRD registration were included in the analyses.

2.3 | Assessment of dementia incidence

Patients were considered to have dementia if they met one of the following criteria: (1) had a dementia diagnosis based on Medcodes in CPRD; (2) had a dementia diagnosis based on International Classification of Diseases (ICD) codes in linked HES or ONS database; or (3) had at least one dementia-specific drug prescription (donepezil, galantamine, rivastigmine, or memantine) (Table S2). We did not distinguish specific types of dementia, as such granularity of data is variably registered in CPRD and the precision of health data recording varies over time. Moreover, it is acknowledged that most cases of late-onset dementia harbor mixed cerebral pathologies.[20,21] Dementia patients with diagnoses of specific etiologies unrelated to ageing, such as HIV infection, Creutzfeldt-Jakob disease, alcoholic and drug-induced, were excluded.

The outcome event date was defined as the first dementia diagnosis date or the first prescription date of dementia-specific drugs, whichever occurred earlier.

2.4 | Covariates

Information on the following covariates before or at cohort entry was also extracted: age, sex, calendar year of the cohort entry, region in the UK, index of multiple deprivation (IMD, a proxy of socioeconomic status), body mass index (BMI), smoking status, level of glycosylated hemoglobin (HbA1c, the most recent record within 2 years before cohort entry) and comorbidities including cardiovascular diseases (atrial fibrillation, coronary heart disease, stroke, heart failure, peripheral vascular disease), hypertension, chronic kidney disease, chronic obstructive pulmonary disease, and cancer, as well as prescription records of anti-hypertensive medications and statins. In addition, HbA1c records during the follow-up period were extracted to evaluate treatment response and diabetic disease progression, both in the metformin and the non-user groups.

2.5 | Statistical analyses

Distributions of baseline characteristics were compared between metformin initiators and non-users. Follow-up time of individual patient was calculated from the date of the first metformin prescription for the metformin cohort or the latest date of age 50, diabetes diagnosis or January 1, 2001, for non-users, until the date of dementia incidence, death, patient transfer-out date, last data collection date of the GP practice, or May 1, 2018, whichever occurred first.

Risks of dementia incidence were compared between metformin initiators and non-users using the Cox proportional hazards model, with age as the underlying time scale. To account for confounding bias, we used both conventional adjustment for the above-mentioned covariates (i.e., conventional Cox model) and the propensity score weighting (PSW) method.[22] Distributions of potential confounding factors were balanced between the two groups in the PSW analysis. The propensity score was the conditional probability of being initially treated with metformin, estimated with a binary logistic regression of the actual group variable on baseline covariates. The average treatment effects on the treated (ATT) weighting scheme was then applied to the Cox model.[23] Balance check of baseline covariates, after weighting, was conducted using Somers' D statistics. Robust variance estimators were used in weighted Cox models.

We created four models to account for missing values in covariates for both conventional Cox regression and PSW analysis: Model 1 adjusted for baseline age, sex, calendar year of cohort entry,[18] and region (which had no missing values); Model 2 was a fully-adjusted model using complete-case analysis, also adjusted for IMD (in quintile), smoking status (non-smoker, current smoker, or ex-smoker), BMI category (< 25, 25- < 30, or ≥30 kg/m^2), HbA1c category (< 7%, 7%–10%, or > 10%), and comorbidities; Model 3 was a fully-adjusted model treating missing values as a separate category for each covariate with missing values; Model 4 was a fully-adjusted model with Multiple Imputation by Chained Equations.

We further evaluated whether the difference in dementia risk between metformin and non-user groups was due to differences in diabetes control. Longitudinal changes in HbA1c levels during follow-up were compared between the two groups using multilevel linear regression, with repeated measurements of HbA1c as dependent variable and patient-level intercept as random-effect. Independent variables (fixed-effects) included follow-up time, group variable (metformin vs. non-user), and their interaction term, adjusting for age, sex, calendar year of cohort entry, and region.

To account for the continued prescription or discontinuation of metformin therapy and explore the effect of long-term metformin usage on dementia risk, we conducted further analysis according to the duration of treatment. Among the metformin initiators, we identified patients who followed the metformin monotherapy for at least 2 years (operationalized as not receiving other anti-diabetes drugs during months 1–24, with at least one metformin record during months 18–24); and metformin initiators who received combination therapy, including metformin, for at least 2 years (operationalized as having received other anti-diabetes drugs during months 1–24, with at least one metformin record during months 18–24). These two subgroups were compared with non-users separately in terms of subsequent dementia risk (i.e., dementia incidence after the first 2 years follow-up). Similarly, we repeated the above analysis with a 5-year (instead of a 2-year) cutoff point.

We also conducted subgroup analyses by sex and age at baseline (< 70 or ≥70 years) and tested their possible effect modifications on the metformin-dementia association. The following sensitivity analyses were performed to assess the robustness of main findings: (1) creating a 2-year lag of cohort entry (i.e., exclude the first 2 years of follow-up for all patients) to reduce the possibility of reverse causality and to ensure sufficient time for possible neuroprotective effects of metformin to act biologically; (2) creating a 5-year lag of cohort entry to further account for reverse causality; (3) additionally adjusting for the average number of GP consultations per year during follow-up of each patient; (4) additionally adjusting for the prescriptions of

five classes of anti-hypertensive medications[24] (angiotensin II receptor blockers [ARBs], calcium channel blockers [CCBs], angiotensin converting enzyme inhibitors [ACE inhibitors], beta blockers, and diuretics), and statins[25] which could also be associated with dementia risk. Finally, to account for the influence of duration of diabetes, we (5) additionally adjusted for the duration of diabetes at cohort entry, and (6) restricting the non-user cohort to patients with initial diabetes diagnosis after age 50 (i.e., incident diabetes cases), who were also required to have been registered in CPRD for at least 1 year prior to diabetes diagnosis to ensure that they were not prevalent cases.

The statistical analyses were performed using Stata (version 15, Stata). All statistical tests were two-sided, and the significance level was defined as $p < 0.05$.

3 | RESULTS

3.1 | Baseline characteristics of study population

The baseline characteristics of 114,628 metformin initiators and 95,609 T2D patients with no anti-diabetics treatment are presented in Table 1. Compared with the non-users, metformin initiators were slightly younger, had higher BMI, and were more likely to have cardiovascular diseases, hypertension, and prescriptions of anti-hypertensive medications and statins at baseline ($p < 0.05$). They also had significantly higher HbA1c levels on average than non-users before cohort entry (8.3% vs. 6.5%; $p < 0.05$). Overall, the non-user group had relatively milder diabetes, better glycemic profiles, and better cardiovascular health than metformin initiators.

Given the differences between the two groups, we further used logistic regression to examine baseline predictors for the clinical decision of metformin prescription and estimated the odds ratio (OR) of being treated (Table S3). The following factors were strong independent predictors of metformin prescription: high HbA1c (odds ratio [OR] = 19.5 [95% confidence interval [CI]: 19.0–20.0] and 85.3 [95% CI: 78.7–92.4] for the 7%–10% and > 10% categories, respectively), high BMI (OR = 1.77 [95% CI: 1.71–1.84] for being overweight and 2.40 [95% CI: 2.31–2.49] for obesity), and hypertension (OR = 1.89, 95% CI: 1.80–1.97).

3.2 | Dementia risk in metformin initiators versus non-users

During a median of 5 years follow-up (ranging from 0 to 17 years) of the 210,237 T2D patients, 15,005 (7.1%) incident dementia cases were recorded (6839 [6.0%] in the metformin group and 8166 [8.5%] in the non-user group). Consistent results were obtained from conventional Cox regression and propensity score weighting analysis (Figure 1). Metformin initiators had lower risk of dementia incidence than non-users, with the estimated hazard ratios (HRs) of Models 1–4 ranging from 0.77 to 0.91 in conventional Cox regressions and 0.84–0.92 in PSW analyses ($p < 0.05$). We considered Model 3 as the optimal model because the missing patterns in these CPRD covariates were not likely to fulfil the missing-at-random assumption, the HRs of which were 0.88 (95% CI: 0.84–0.92) and 0.90 (95% CI: 0.84–0.96), respectively. For example, it is not unusual for a primary care physician to only record smoking status or BMI for active smokers or patients requiring weight management. The balance check in PSW analysis showed that all covariates were well-balanced between groups after weighting (Somers' D < 0.10; Figure S1).

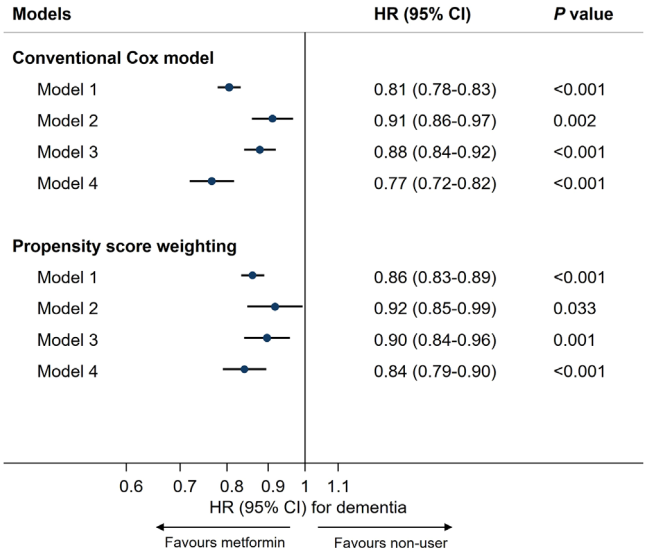

FIGURE 1 Comparing risks of dementia incidence between 114,628 metformin initiators and 95,609 non-users. Note: HR, hazard ratio; CI, confidence interval. Reference group in all models: non-users. Model 1 adjusted for age, sex, region, and year of cohort entry; Model 2 is a fully-adjusted model using complete-case analysis with further adjustment of IMD, smoking status, BMI, HbA1c, and comorbidities; Model 3 is a fully-adjusted model treating missing values as a separate category for those variables with missing values; Model 4 is a fully-adjusted model in which we used Multiple Imputation by Chained Equations to impute missing values

3.3 | Longitudinal HbA1c levels in metformin initiators versus non-users

A total of 184,427 participants had HbA1c records during follow-up. Results of multilevel linear regression showed that, in both groups, HbA1c levels dropped significantly during the initial 1–2 years of follow-up (due to metformin treatment or possible lifestyle intervention following diabetes diagnosis, respectively), and then increased slowly thereafter (Figure 2). Although the magnitude of the initial HbA1c reduction was much larger in metformin initiators, marginal analysis showed that HbA1c levels remained significantly higher on average in metformin initiators than non-users at all time-points ($p < 0.001$, Figure 2), implying that the metformin group continued to have a worse glycemic profile, whilst on medication.

TABLE 1 Baseline characteristics of metformin initiators and non-users.

Covariates	Metformin initiators ($n = 114,628$)	Non-users ($n = 95,609$)
Baseline age (year), mean (SE)	65.7 (0.029)	68.6 (0.036)
Sex (male), *n* (%)	64,826 (56.6)	49,852 (52.1)
Year of the cohort entry, median (IQR)	2009 (7)	2009 (8)
IMD (quintile), *n* (%)		
Q1 (least deprived)	21,246 (19.9)	20,264 (22.6)
Q2	19,688 (18.5)	17,433 (19.4)
Q3	22,788 (21.4)	18,763 (20.9)
Q4	22,880 (21.5)	18,142 (20.2)
Q5 (most deprived)	19,973 (18.7)	15,099 (16.8)
Baseline HbA1c level (%), mean (SE)*	8.3 (0.005)	6.5 (0.003)
Baseline BMI (kg/m^2), mean (SE)	31.9 (0.018)	30.0 (0.021)
Smoking status, *n* (%)		
Current smoker	18,742 (16.5)	12,688 (14.3)
Ex-smoker	41,834 (37.0)	30,708 (34.6)
Non-smoker	52,624 (46.5)	45,412 (51.1)
Comorbidities, *n* (%)		
CVD	64,245 (56.1)	52,511 (54.9)
Hypertension	109,168 (95.2)	84,887 (88.8)
CKD	10,092 (8.8)	10,138 (10.6)
COPD	6042 (5.3)	5124 (5.4)
Cancer	12,416 (10.8)	12,466 (13.0)
Non-diabetes medications, *n* (%)		
ARBs	17,148 (15.0)	12,176 (12.7)
ACE inhibitors	57,147 (49.9)	36,050 (37.7)
CCBs	44,572 (38.9)	34,577 (36.2)
Beta blockers	39,486 (34.5)	30,888 (32.3)
Diuretics	37,789 (33.0)	28,995 (30.3)
Statins	63,380 (55.3)	34,839 (36.4)

Note: IMD, BMI, HbA1c, and smoking status had 6%, 8%, 19%, and 4% missing values, respectively. The statistics presented in this table for these variables are based on complete cases. All covariates were significantly different between groups ($p < 1 \times 10^{-4}$), except for COPD ($p > 0.05$). * Baseline HbA1c level was based on the most recent HbA1c record of each patient within 2 years before cohort entry.

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; BMI, body mass index; CCB, calcium channel blockers; CKD, chronic kidney disease; CVD, cardiovascular disease; COPD, chronic obstructive pulmonary disease; HbA1c, glycosylated hemoglobin A1c; IMD, index of multiple deprivation; IQR, interquartile range; SE, standard error.

3.4 | Analyses of dementia risk by duration of metformin treatment

Among the 89,116 metformin initiators with at least 2 years of follow-up, 72,173 (81.0%) continued receiving metformin monotherapy during the first 2 years and 9963 (11.2%) received combination therapy (metformin plus other antidiabetics), whilst treatment was discontinued in 7.8% of patients within 2 years. Compared to non-users with at least 2 years of follow-up, those on metformin monotherapy (for at least 2 years) had lower risk of subsequent dementia; the HRs were 0.82 (95% CI: 0.77–0.86) in conventional Cox regression and 0.82 (95% CI: 0.75–0.89) in PSW analysis (Table 2). There was no suggestion that receiving combination therapy for at least 2 years further decreased the risk of dementia; similar magnitudes of association with dementia risk were observed for metformin monotherapy and combination therapy (Table 2).

Among the 55,707 metformin initiators with at least 5 years of follow-up, 29,275 (52.6%) received metformin monotherapy during the first 5 years; 18,730 (33.6%) received a combination therapy (including metformin); and metformin was discontinued in 13.8% of patients. An even stronger effect of metformin on subsequent dementia risk was observed among patients with at least 5 years of metformin monotherapy or combination therapy, with the estimated HRs being 0.75 (95% CI: 0.69–0.81) for monotherapy and 0.70 (95% CI: 0.63–0.78) for

TABLE 2 Analysis of dementia risk by duration of metformin treatment using conventional Cox regression and propensity score weighting method.

Subgroups	No. of metformin initiators	HR (95% CI)	
		Conventional Cox	PSW
Metformin monotherapy users during the initial 2-year treatment	72,173	0.82 (0.77–0.86)	0.82 (0.75–0.89)
Metformin combination therapy users during the initial 2-year treatment	9963	0.79 (0.70–0.89)	0.83 (0.70–0.99)
Metformin monotherapy users during the initial 5-year treatment	29,275	0.75 (0.69–0.81)	0.71 (0.63–0.80)
Metformin combination therapy users during the initial 5-year treatment	18,730	0.70 (0.63–0.78)	0.64 (0.52–0.78)

Note: Results were estimated based on Model 3, a fully-adjusted model treating missing values as a separate category, with diabetes patients receiving no anti-diabetes drug treatment as reference group. .
Abbreviations: CI, confidence interval; HR, hazard ratio; PSW, propensity score weighting analysis.

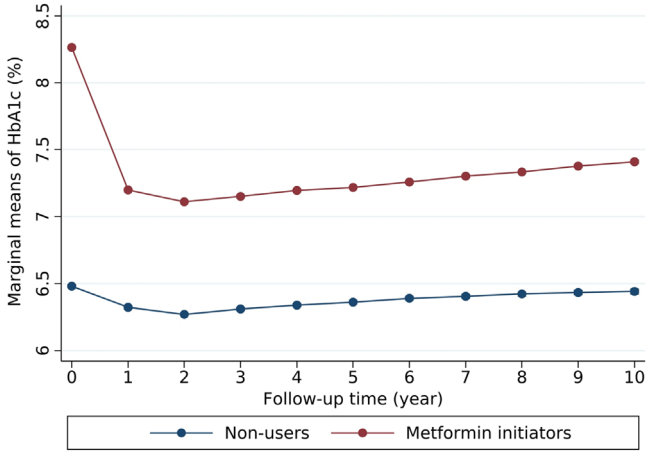

FIGURE 2 Longitudinal changes of HbA1c levels during follow-up in metformin initiators versus non-users. Note: Estimates of marginal means of HbA1c were based on multilevel linear regression, adjusted for age, sex, calendar year, and region. Each point represents a marginal mean at the corresponding time-point. The 95% confidence interval of marginal mean was not displayable here due to its small scale (standard errors of HbA1c marginal means ranged from 0.003%–0.009%). Baseline HbA1c level (Time 0) was extracted from the most recent record within 2 years before cohort entry

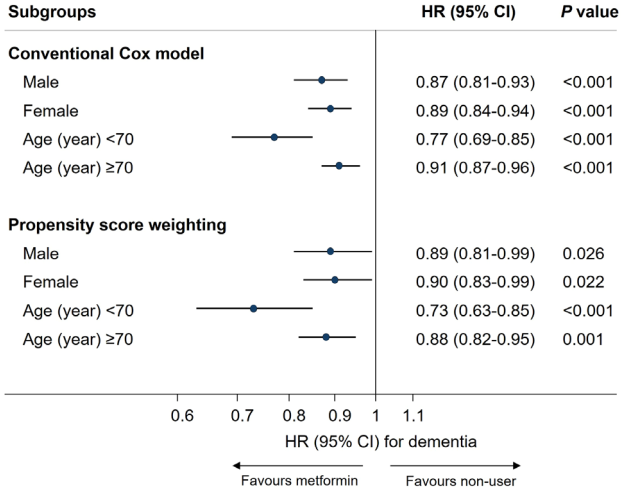

FIGURE 3 Subgroup analyses by sex and baseline age using conventional Cox regression and propensity score weighting method Note: HR, hazard ratio; CI, confidence interval. Results were estimated based on Model 3, a fully-adjusted model treating missing values as a separate category, with diabetes patients receiving no anti-diabetes drug treatment as reference group

combination therapy in conventional Cox regressions and 0.71 (95% CI: 0.63–0.80) and 0.64 (95% CI: 0.52–0.78), respectively, in PSW analyses (Table 2).

3.5 | Subgroup and sensitivity analyses

The subgroup analysis by age showed a stronger effect of metformin on dementia risk among T2D patients aged < 70 years at cohort entry than those aged ≥70 years, with the HRs being 0.77 (95% CI: 0.69–0.85) versus 0.91 (95% CI: 0.87–0.96) in conventional Cox regression ($P_{interaction}$ < 0.001) and 0.73 (95% CI: 0.63–0.85) versus 0.88 (95% CI: 0.82–0.95) in PSW analysis (Figure 3). The sex-specific analysis revealed consistent results between men and women ($P_{interaction}$ = 0.691; Figure 3). The sensitivity analyses yielded similar results as in the main analysis (Table S4).

4 | DISCUSSION

This study is one of the largest cohort studies to investigate the association between metformin usage and risk of incident dementia in T2D patients. We applied both conventional Cox regression and propensity score methodologies to address confounding bias, and also used four different models to deal with missing values in covariates. Our results consistently indicated that initial and long-term treatment with metformin was robustly associated with lower risk of dementia compared with no anti-diabetes medication, among T2D patients.

Our results are in line with a previous cohort study in 25,393 T2D patients showing that, compared to patients with no pharmaceutical

treatment during follow-up, those treated with metformin monotherapy and combination therapy of metformin and sulfonylureas had lower risks of dementia incidence (HR = 0.76 [95% CI: 0.58–0.98] and 0.65 [95% CI: 0.56–0.74], respectively).[16] In contrast, two cohort studies comparing metformin initiators with non-metformin initiators[26] or metformin users with non-metformin users[27] did not find any significant differences in dementia risk between groups, possibly due to the heterogeneous definitions of exposure and reference groups and/or insufficient sample size or length of follow-up.

In addition, results from two cohort studies of US veterans with T2D showed that new users of metformin had lower risk of dementia than new users of sulfonylureas (another first-line anti-diabetes drug) among those aged < 75 years.[15,28] However, it was not possible to determine whether the difference could be attributed to a beneficial neuroprotective effect of metformin or a potential neurotoxicity of sulfonylureas, a common limitation in comparative effectiveness studies. A recent US/UK collaborative study, including our group, found that metformin initiators had lower all-cause mortality and lower dementia risk than sulfonylureas initiators in both the UK CPRD and the US RPDR databases (HR = 0.86 [95% CI: 0.77–0.96] and 0.81 [95% CI: 0.69–0.94] for dementia, respectively).[29] Parallel in vitro system pharmacology analysis also showed reduced brain expression of AD-related proteins (apolipoprotein E [APOE] and SPP1) by pharmacologic concentrations of metformin, indicative of an independent biological effect of metformin on dementia risk.[29] In the current study, our analysis comparing metformin initiators with a "clean control group", defined as T2D patients not requiring anti-diabetes medication, who had lower mean HbA1c level both prior to baseline and throughout the follow-up period than the metformin group, provides further evidence of a neuroprotective effect of metformin, going beyond the glycemic control. Patients in this control group were also less likely to be current smokers or have obesity, hypertension, or cardiovascular diseases at baseline. Given that hyperglycemia, smoking, hypertension, and cardiovascular diseases are established risk factors for dementia,[4,30] their higher prevalence in the metformin group would be expected to affect results by obscuring a possible beneficial effect of metformin. Therefore, the observed lower dementia risk in the metformin group adds credence to a true pharmacological effect of metformin on reducing dementia incidence. The fact that the metformin-treated group continued to show higher HbA1c levels than the control group despite treatment further suggests that metformin may act beyond its effect on hyperglycemia and "reverse" the elevated dementia risk due to diabetes and other risk factors in this group of treated patients.

Our study also explored continued prescription during follow-up and the effect of long-term metformin usage. Results implied that longer treatment of metformin (e.g., over five years) in diabetic patients had a stronger effect on reducing dementia risk. This observation reinforces the case of repurposing this low-cost, generic medicine for the prevention of dementia. Although we did not detect substantial difference between the associations of metformin monotherapy versus combination therapy with dementia risk, several previous studies suggested that the combination of anti-diabetes medications might be superior to monotherapy in terms of reducing neuropathological burden[31,32] or the risk of dementia incidence,[33] which warrants further research. In addition, our observation of a stronger metformin effect in T2D patients aged < 70 years was in line with the two afore-mentioned cohort studies in the US veterans,[15,28] where the metformin-dementia association was only detected in patients aged < 75 years but not in those aged ≥75 years. This could be due to the presence of additional factors related to brain ageing, further complicating the multi-factorial aetiological puzzle of dementia in the older old population,[34] in which metformin's effect may not be sufficient to alter the trajectory or delay disease onset.

Several potential mechanisms have been proposed for the effect of metformin on dementia risk, including its role on diabetic/vascular pathways[35] and/or independent neuroprotective mechanisms. On the one hand, metformin could reduce dementia risk via improved glycemic control and fewer vascular complications in T2D patients,[36] given that long-term glycaemia, HbA1c variability and diabetic complications have been linked to dementia risk.[6,37,38] On the other hand, metformin can rapidly cross the blood-brain-barrier and may have direct intra-cerebral neuroprotective effects including, and going beyond, combatting brain insulin resistance and its effect on brain ageing and AD pathology.[39,40] Experimental studies have suggested that metformin could also reduce the burden of phosphorylated tau and β-amyloid,[10–13] and a potential preventative effect has been shown on brain cell dysfunction and death, through activation of longevity-promoting signaling molecules (e.g., AMPK).[41,42] In fact, metformin has been reported to have wide pleiotropic anti-ageing effects through modulation of inflammation, oxidation, autophagy, and DNA repair,[41–43] and a meta-analysis of observational studies showed that metformin reduces all-cause mortality, independent of its effect on diabetic control[44].

The potential of metformin being repurposed for dementia has been supported by two small-scale randomized controlled trials (RCTs) in non-diabetic patients with mild cognitive impairment (MCI). A Phase 2 RCT (n = 80) showed efficacy in improving memory performance (although not global cognitive function) after 1-year treatment versus placebo among amnestic MCI patients ($p < 0.05$).[45] Another crossover designed RCT (n = 20) showed that 8-week metformin treatment had beneficial effects on executive functions, compared to placebo ($p < 0.05$).[46] The ongoing multi-center Phase II/III RCT "Metformin in Alzheimer's Dementia Prevention" (MAP, NCT04098666) is testing long-acting metformin versus placebo for 24 months in patients with amnestic MCI, with memory performance as the primary outcome. The "Targeting Aging with Metformin" (TAME) RCT will test whether metformin modulates a variety of ageing-related diseases (including dementia) and mortality beyond its impact on diabetes among ~3000 subjects.[41] Given the long preclinical stages of accumulating neuropathology in ADRD, there is increasing interest in conducting dementia prevention trials in *at-risk* cognitively unimpaired individuals. The newly launched phase IIb MET-FINGER trial[47] (NCT05109169) will examine the effect of a combination of personalized multi-domain lifestyle intervention and metformin treatment on change of cognition in an *APOE-ε4* enriched sample of *at-risk* population.

This study has several limitations. First, dementia cases could be underreported or underdiagnosed in CPRD. Although we maximized the number of dementia cases by using the linkage data from HES

and ONS databases and dementia-specific drug records, the remaining misclassification in outcome events may have led to bias. However, assuming that the remaining misclassification was independent of the exposure variable, our estimates of HRs would have likely been biased toward the null hypothesis.[48] In addition, two CPRD-based studies on dementia by the same group of authors validated a small subset of extracted dementia cases (n = 100 and 150) by writing to their GP for detailed medical history; they found that the rates of confirmation by GPs (i.e., positive predictive value of CPRD-based diagnosis) were 83%[49] and 100%.[50] Another large-scale validation study found that 88% of dementia cases identified in CPRD had corroborating evidence for their dementia diagnosis in relevant clinical records.[51] Second, our non-user comparison group, based on CPRD T2D clinical codelist, may have included prediabetes individuals together with T2D patients with mild disease. Nevertheless, this reinforces our key finding of a beneficial effect of metformin in reducing the dementia risk in T2D patients to an even lower level than in those with milder or prodromal disease. Moreover, the possibility of residual confounding bias cannot be ruled out due to, for instance, the paucity of data regarding educational attainment and physical activity.[4,52] The presence of missing data is a common limitation of large-scale EHR analyses. We employed multiple statistical methodologies to mitigate this risk, all showing consistent results. Finally, causality cannot be established in an observational study. Results of the above and other future well-designed large-scale RCTs are required to confirm the role of metformin in dementia prevention or treatment, in both diabetic and non-diabetic individuals.

In conclusion, this population-based cohort study provides strong epidemiological evidence of a beneficial role of metformin on dementia risk in T2D patients, going beyond its glycemic effect. Our results add credence to the potential generalizability and repurposing of metformin for primary and secondary dementia prevention.

AUTHOR CONTRIBUTIONS

Concept and design: Middleton, Zheng, Tzoulaki. *Acquisition, analysis, or interpretation of data*: Zheng, Su, Tzoulaki, Middleton, Ahmadi-Abhari, Kapogiannis, Riboli. *Drafting of the manuscript*: Zheng, Middleton. *Critical revision of the manuscript for important intellectual content*: All authors. *Statistical analysis*: Zheng, Su. *Administrative, technical, or material support*: Zheng, Middleton. *Supervision*: Middleton.

ACKNOWLEDGMENTS

B. Zheng was supported for his PhD program by the Imperial College London – China Scholarship Council.

CONFLICT OF INTEREST STATEMENT

D. Kapogiannis was supported by the Intramural Research Program of the National Institute on Aging, National Institutes of Health (NIH); I. Tzoulaki and L. Middleton were supported by Imperial College NHS Heathcare Trust BRC Programme and the NIH; and L. Middleton was supported by Janssen, Merck, Astra Zeneca, Eli Lilly, Novartis, Takeda, Eisai, Gates Ventures and the European Institute of Innovation and Technology for Health (EIT-Health). All other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

This study is based on data from the Clinical Practice Research Datalink extracted under license from the UK Medicines and Healthcare Products Regulatory Agency (No. 19_065R). Data extracts can be requested by applying to the Clinical Practice Research Datalink (https://www.cprd.com).

CONSENT STATEMENT

This study is based on anonymized electronic health record data from the Clinical Practice Research Datalink, and consent was not necessary for this study.

REFERENCES

1. Imfeld P, Brauchli Pernus YB, Jick SS, Meier CR. Epidemiology, co-morbidities, and medication use of patients with Alzheimer's disease or vascular dementia in the UK. *J Alzheimers Dis*. 2013;35(3):565-573.
2. Winblad B, Amouyel P, Andrieu S, et al. Defeating Alzheimer's disease and other dementias: a priority for European science and society. *Lancet Neurol*. 2016;15(5):455-532.
3. Gauthier S, Albert M, Fox N, et al. Why has therapy development for dementia failed in the last two decades? *Alzheimers Dement*. 2016;12(1):60-64.
4. Livingston G, Huntley J, Sommerlad A, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*. 2020;396(10248):413-446.
5. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. *J Diabetes Investig*. 2013;4(6):640-650.
6. Zheng B, Su B, Price G, Tzoulaki I, Ahmadi-Abhari S, Middleton L. Glycemic control, diabetic complications, and risk of dementia in patients with diabetes: results from a large U.K. cohort study. *Diabetes Care*. 2021;44(7):1556-1563.
7. Corbett A, Pickett J, Burns A, et al. Drug repositioning for Alzheimer's disease. *Nat Rev Drug Discov*. 2012;11(11):833-846.
8. Ye F, Luo YJ, Xiao J, Yu NW, Yi G. Impact of insulin sensitizers on the incidence of dementia: a meta-analysis. *Dement Geriatr Cogn Disord*. 2016;41(5-6):251-260.
9. Pomilio C, Perez NG, Calandri I, et al. Diabetic patients treated with metformin during early stages of Alzheimer's disease show a better integral performance: data from ADNI study. *Geroscience*. 2022;44(3):1791-1805.
10. Gupta A, Bisht B, Dey CS. Peripheral insulin-sensitizer drug metformin ameliorates neuronal insulin resistance and Alzheimer's-like changes. *Neuropharmacology*. 2011;60(6):910-920.
11. Kickstein E, Krauss S, Thornhill P, et al. Biguanide metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling. *Proc Natl Acad Sci U S A*. 2010;107(50):21830-21835.
12. Xu X, Sun Y, Cen X, et al. Metformin activates chaperone-mediated autophagy and improves disease pathologies in an Alzheimer disease mouse model. *Protein Cell*. 2021;12(10):769-787.
13. Chen Y, Zhao S, Fan Z, et al. Metformin attenuates plaque-associated tau pathology and reduces amyloid-beta burden in APP/PS1 mice. *Alzheimers Res Ther*. 2021;13(1):40.
14. Imfeld P, Bodmer M, Jick SS, Meier CR. Metformin, other antidiabetic drugs, and risk of Alzheimer's disease: a population-based case-control study. *J Am Geriatr Soc*. 2012;60(5):916-921.
15. Orkaby AR, Cho K, Cormack J, Gagnon DR, Driver JA. Metformin vs sulfonylurea use and risk of dementia in US veterans aged ≥65 years with diabetes. *Neurology*. 2017;89(18):1877-1885.
16. Hsu CC, Wahlqvist ML, Lee MS, Tsai HN. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. *J Alzheimers Dis*. 2011;24(3):485-493.

17. Herrett E, Gallagher AM, Bhaskaran K, et al. Data resource profile: clinical practice research datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836.
18. Wilkinson S, Douglas I, Stirnadel-Farrant H, et al. Changing use of antidiabetic drugs in the UK: trends in prescribing 2000-2017. *BMJ Open*. 2018;8(7):e022768.
19. NICE. *Type 2 diabetes in adults: management*. NICE. Accessed January 24, 2023. https://www.nice.org.uk/guidance/ng28
20. Schneider JA, Arvanitakis Z, Bang W, Bennett DA. Mixed brain pathologies account for most dementia cases in community-dwelling older persons. *Neurology*. 2007;69(24):2197-2204.
21. Toledo JB, Arnold SE, Raible K, et al. Contribution of cerebrovascular disease in autopsy confirmed neurodegenerative disease cases in the National Alzheimer's Coordinating Centre. *Brain*. 2013;136(9):2697-2706. Pt.
22. Curtis LH, Hammill BG, Eisenstein EL, Kramer JM, Anstrom KJ. Using inverse probability-weighted estimators in comparative effectiveness analyses with observational databases. *Med Care*. 2007;45(10 Supl 2):S103-107.
23. Abdia Y, Kulasekera KB, Datta S, Boakye M, Kong MY. Propensity scores based methods for estimating average treatment effect and average treatment effect among treated: a comparative study. *Biometrical J*. 2017;59(5):967-985.
24. Levi Marpillat N, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens*. 2013;31(6):1073-1082.
25. Olmastroni E, Molari G, De Beni N, et al. Statin use and risk of dementia or Alzheimer's disease: a systematic review and meta-analysis of observational studies. *Eur J Prev Cardiol*. 2022;29(5):804-814.
26. Huang CC, Chung CM, Leu HB, et al. Diabetes mellitus and the risk of Alzheimer's disease: a nationwide population-based study. *PLoS One*. 2014;9(1):e87095.
27. Heneka MT, Fink A, Doblhammer G. Effect of pioglitazone medication on the incidence of dementia. *Ann Neurol*. 2015;78(2):284-294.
28. Scherrer JF, Salas J, Floyd JS, Farr SA, Morley JE, Dublin S. Metformin and sulfonylurea use and risk of incident dementia. *Mayo Clin Proc*. 2019;94(8):1444-1456.
29. Charpignon M, Vakulenko-Lagun B, Zheng B, Magdamo C, Su B. Causal inference in medical records and complementary systems pharmacology for metformin drug repurposing towards dementia. *Nat Commun*. 2022;13:7652.
30. Zheng B, Su B, Udeh-Momoh C, et al. Associations of cardiovascular and non-cardiovascular comorbidities with dementia risk in patients with diabetes: results from a large UK cohort study. *J Prev Alzheimers Dis*. 2022;9(1):86-91.
31. Beeri MS, Schmeidler J, Silverman JM, et al. Insulin in combination with other diabetes medication is associated with less Alzheimer neuropathology. *Neurology*. 2008;71(10):750-757.
32. Robinson A, Lubitz I, Atrakchi-Baranes D, et al. Combination of Insulin with a GLP1 agonist is associated with better memory and normal expression of insulin receptor pathway genes in a mouse model of Alzheimer's disease. *J Mol Neurosci*. 2019;67(4):504-510.
33. Kim JY, Ku YS, Kim HJ, et al. Oral diabetes medication and risk of dementia in elderly patients with type 2 diabetes. *Diabetes Res Clin Pract*. 2019;154:116-123.
34. Gardner RC, Valcour V, Yaffe K. Dementia in the oldest old: a multi-factorial and growing public health issue. *Alzheimers Res Ther*. 2013;5(4):27.
35. Dearborn JL, Schneider AL, Sharrett AR, et al. Obesity, insulin resistance, and incident small vessel disease on magnetic resonance imaging: atherosclerosis risk in communities study. *Stroke*. 2015;46(11):3131-3136.
36. Turner RC, Holman RR, Stratton IM, et al. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*. 1998;352(9131):854-865.
37. Crane PK, Walker R, Hubbard RA, et al. Glucose levels and risk of dementia. *N Engl J Med*. 2013;369(6):540-548.
38. Exalto LG, Biessels GJ, Karter AJ, et al. Risk score for prediction of 10 year dementia risk in individuals with type 2 diabetes: a cohort study. *Lancet Diabetes Endocrinol*. 2013;1(3):183-190.
39. Farris W, Mansourian S, Chang Y, et al. Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci U S A*. 2003;100(7):4162-4167.
40. Arnold SE, Arvanitakis Z, Macauley-Rambach SL, et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums. *Nat Rev Neurol*. 2018;14(3):168-181.
41. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a Tool to Target Aging. *Cell Metab*. 2016;23(6):1060-1065.
42. Kulkarni AS, Gubbi S, Barzilai N. Benefits of Metformin in Attenuating the Hallmarks of Aging. *Cell Metab*. 2020;32(1):15-30.
43. Martin-Montalvo A, Mercken EM, Mitchell SJ, et al. Metformin improves healthspan and lifespan in mice. *Nat Commun*. 2013;4:2192.
44. Campbell JM, Bellman SM, Stephenson MD, Lisy K. Metformin reduces all-cause mortality and diseases of ageing independent of its effect on diabetes control: a systematic review and meta-analysis. *Ageing Res Rev*. 2017;40:31-44.
45. Luchsinger JA, Perez T, Chang H, et al. Metformin in amnestic mild cognitive impairment: results of a pilot randomized placebo controlled clinical trial. *J Alzheimers Dis*. 2016;51(2):501-514.
46. Koenig AM, Mechanic-Hamilton D, Xie SX, et al. Effects of the insulin sensitizer metformin in alzheimer disease: pilot data from a randomized placebo-controlled crossover study. *Alzheimer Dis Assoc Disord*. 2017;31(2):107-113.
47. Kivipelto M, Mangialasche F, Snyder HM, et al. World-Wide FINGERS Network: a global approach to risk reduction and prevention of dementia. *Alzheimers Dement*. 2020;16(7):1078-1094.
48. Wang L, Hubbard RA, Walker RL, Lee EB, Larson EB, Crane PK. Assessing robustness of hazard ratio estimates to outcome misclassification in longitudinal panel studies with application to Alzheimer's disease. *PLoS One*. 2017;12(12):e0190107.
49. Dunn N, Mullee M, Perry VH, Holmes C. Association between dementia and infectious disease: evidence from a case-control study. *Alzheimer Dis Assoc Disord*. 2005;19(2):91-94.
50. Dunn N, Holmes C, Mullee M. Does lithium therapy protect against the onset of dementia? *Alzheimer Dis Assoc Disord*. 2005;19(1):20-22.
51. Pujades-Rodriguez M, Assi V, Gonzalez-Izquierdo A, et al. The diagnosis, burden and prognosis of dementia: a record-linkage cohort study in England. *PLoS One*. 2018;13(6):e0199026.
52. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014;13(8):788-794.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zheng B, Su B, Ahmadi-Abhari S, et al. Dementia risk in patients with type 2 diabetes: Comparing metformin with no pharmacological treatment. *Alzheimer's Dement*. 2023;1-9. https://doi.org/10.1002/alz.13349