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ARTICLE

Prediabetes, intervening diabetes and subsequent risk of dementia: the Atherosclerosis Risk in Communities (ARIC) study

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Abstract

Aims/hypothesis The aim of this work was to evaluate whether the association of prediabetes with dementia is explained by the intervening onset of diabetes.

Methods Among participants of the Atherosclerosis Risk in Communities (ARIC) study we defined baseline prediabetes as HbA_{1c} 39–46 mmol/mol (5.7–6.4%) and subsequent incident diabetes as a self-reported physician diagnosis or use of diabetes medication. Incident dementia was ascertained via active surveillance and adjudicated. We quantified the association of prediabetes with dementia risk before and after accounting for the subsequent development of diabetes among ARIC participants without diabetes at baseline (1990–1992; participants aged 46–70 years). We also evaluated whether age at diabetes diagnosis modified the risk of dementia.

Results Among 11,656 participants without diabetes at baseline, 2330 (20.0%) had prediabetes. Before accounting for incident diabetes, prediabetes was significantly associated with the risk of dementia (HR 1.12 [95% CI 1.01, 1.24]). After accounting for incident diabetes, the association was attenuated and non-significant (HR 1.05 [95% CI 0.94, 1.16]). Earlier age of onset of diabetes had the strongest association with dementia: HR 2.92 (95% CI 2.06, 4.14) for onset before 60 years; HR 1.73 (95% CI 1.47, 2.04) for onset at 60–69 years; and HR 1.23 (95% CI 1.08, 1.40) for onset at 70–79 years.

Conclusions/interpretation Prediabetes is associated with dementia risk but this risk is explained by the subsequent development of diabetes. Earlier age of onset of diabetes substantially increases dementia risk. Preventing or delaying progression of prediabetes to diabetes will reduce dementia burden.

Keywords Age at diabetes onset · Dementia · Prediabetes · Survival analysis

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Research in context

What is already known about this subject?

- Approximately 70% of people with prediabetes will develop diabetes during their lifetime
- Prediabetes may be a risk factor for dementia incidence
- Few studies of prediabetes with dementia have accounted for the intervening development of diabetes

What is the key question?

- Is the association between prediabetes and dementia explained by the intervening onset of diabetes?

What are the new findings?

- Prediabetes is associated with dementia risk but this risk is explained by the subsequent development of diabetes
- Earlier age of onset of diabetes substantially increases dementia risk

How might this impact on clinical practice in the foreseeable future?

- Improving early detection and engagement in people with prediabetes to prevent or delay the progression to diabetes may have long-term population benefits for dementia prevention

Abbreviations

ARIC Atherosclerosis Risk in Communities
FG Fasting glucose

Introduction

Diabetes is strongly linked to dementia risk [1–3]. Prediabetes is an intermediate stage of hyperglycaemia that confers a high risk of progression to diabetes but is also independently associated with other clinical outcomes [4]. Prior studies have shown that prediabetes is a risk factor for neurocognitive outcomes including cognitive decline and dementia [5–7]. The risk of progression to diabetes among people with prediabetes is substantial; among middle-aged adults with prediabetes, 5–10% per year will develop diabetes for a total of 70% during their lifetime [8, 9]. Few studies of dementia have accounted for the transition from prediabetes to diabetes. Thus, it is unclear to what extent the intervening development of diabetes explains the excess risk of dementia in people with prediabetes.

There is also substantial heterogeneity in risk of diabetes complications according to age at diabetes onset [10–13]. Earlier onset of diabetes is associated with a more severe presentation and confers a higher life-long risk of clinical outcomes compared with later-onset diabetes [10–13]. Considering the age at diabetes onset is critical to evaluating risk of long-term outcomes such as dementia.

In this study, we used data from a large population-based cohort to characterise the association of prediabetes with dementia risk and examine the extent to which this association is explained by the intervening development of clinical diabetes. We also characterised the association between dementia risk and incident diabetes according to age at diabetes onset.

Methods

Study population The Atherosclerosis Study population-Risk in Communities (ARIC) study is a prospective cohort that originally recruited 15,792 participants aged 45–64 years in 1987–1989 from four US counties: Forsyth County, North Carolina; Jackson, Mississippi; suburbs of Minneapolis, Minnesota; and Washington County, Maryland. Baseline for our analysis was visit 2 (1990–1992), the first visit where HbA_{1c} and cognitive function were measured in the ARIC study. Among 14,348 participants who attended visit 2, we excluded participants according to the following criteria: missing HbA_{1c} measurements (n=279); missing covariates (n=589); prevalent dementia (n=7); died before age 50 years (n=7); or diabetes at baseline based on self-reported physician diagnosis, diabetes medication use or HbA_{1c}≥47 mmol/mol (6.5%) (n=1810). There were 11,656 adults included in our final analytical sample.

Baseline prediabetes and incident diabetes definitions In our primary analysis, we defined prediabetes based on HbA_{1c} criteria (39–46 mmol/mol [5.7–6.4%]) [14]. Participants without prediabetes (HbA_{1c}<39 mmol/mol [5.7%]) served as the reference group. We also conducted secondary

analyses of the association of prediabetes with dementia based on three additional definitions of prediabetes: fasting glucose (FG) 5.55–6.94 mmol/l; elevated HbA_{1c} (39–46 mmol/mol [5.7–6.4%]) or elevated FG (5.55–6.94 mmol/l); and elevated HbA_{1c} (39–46 mmol/mol [5.7–6.4%]) and elevated FG (5.55–6.94 mmol/l) [14].

Incident diabetes was defined as either self-reported physician diagnosis or diabetes medication use reported by participants during in-person visits or annual telephone calls (semi-annually beginning in 2012). The date of incident diabetes was defined as the date on which diabetes was first reported during an in-person visit or telephone call. This definition of diabetes has been shown to be highly reliable and specific [15]. We categorised age at diabetes diagnosis as <60, 60–69, 70–79 or 80–93 years.

Dementia ascertainment Dementia was defined by expert committee review of cognitive function assessments, informant reports and hospitalisation codes as detailed previously [16]. The cognitive function assessments incorporated data from a three-test cognitive battery administered at visits 2 (1990–1992) and 4 (1996–1998), the expanded neuropsychological ten-test battery [17] administered from visit 5 (2011–2013) onwards and informant interview (Clinical Dementia Rating [CDR] scale [18] and the Functional Activities Questionnaire [FAQ]). The Mini-Mental State Examination (MMSE) was also administered [19]. A computer algorithm generated preliminary diagnoses based on low scores in these tests. Dementia diagnoses were then verified by an expert panel of clinicians and neuropsychologists. For participants who did not return for an in-person follow-up evaluation, the expert panel used information from the Telephone Interview for Cognitive Status-Modified (TICSm) or Six-Item Cognitive Screener administered to the participant and an Ascertain Dementia Eight-Item Informant Questionnaire administered to an informant. Dementia was also identified by discharge hospitalisation ICD-9 (http://www.icd9data.com/2007/Volume1/default.htm) or death certificate dementia codes. Follow-up time for dementia was measured from visit 2 (1990–1992) to the first diagnosis of dementia or censoring due to death, loss to follow-up, or administrative censoring on 31 December 2019.

Demographic and genetic risk factors All baseline data were collected at visit 2 (1990–1992) unless otherwise stated. Date of birth was self-reported at visit 1 and was used to calculate age at baseline (visit 2). Sex and education level were also self-reported at visit 1. Education level was further categorised into three groups: less than high school; high school graduate or equivalent; and college or above. Race was self-selected from four fixed categories (Asian, Black, American Indian/Alaskan Indian, or White) at visit 1. We modelled race as Black vs White participants, including the small number of Asian and American Indian (n=34) participants in the White category (n=9149). ARIC field centres (Forsyth County, Jackson, Minneapolis Suburbs and Washington County) were included. *APOE* ε4 genotype was performed using the TaqMan assay (Applied Biosystems, Foster City, CA, USA) and defined based on the number of ε4 alleles (0, 1 or 2 alleles) at visit 2.

Lifestyle factors BMI was calculated from weight (kg) divided by height (m^2) at visit 2. BMI was categorised into four groups: normal weight <25 kg/m^2; overweight 25–29.9 kg/m^2; obesity 30–39.9 kg/m^2; and morbid obesity ≥40 kg/m^2. Smoking history and alcohol use were self-reported as current, former or never smokers and alcohol users at visit 2. Physical activity was assessed at visit 1 using a modified Baecke questionnaire and categorised according to American Heart Association guidelines into recommended, intermediate or poor [20].

Clinical factors All clinical factors were assessed at visit 2. Hypertension was defined as systolic BP ≥140 mmHg, diastolic BP ≥90 mmHg, or use of BP-lowering medication. Plasma total cholesterol (mmol/l) was measured using enzymatic methods. HDL-cholesterol (mmol/l) was measured after dextran magnesium precipitation. Prevalent stroke was ascertained from self-report during visits 1 and 2, or hospitalisation or death related to stroke prior to visit 2. Prevalent atrial fibrillation was based on self-report and ECG at visit 2.

Statistical analysis We compared baseline characteristics of the participants according to prediabetes status at baseline using proportions and mean (SD). We used age 50 years as the time origin for survival analysis. We conducted a Kaplan–Meier analysis to evaluate dementia survival by baseline prediabetes status and by age of onset of incident diabetes. Each curve in the incident diabetes age of onset Kaplan–Meier was conditional on being dementia and death free at the starting point. We used Cox proportional hazards regression models to characterise the association of prediabetes with incident dementia. To examine the degree to which incident diabetes explained the association between baseline prediabetes and incident dementia, we added incident diabetes during follow-up as a time-varying covariate to our models. The incident diabetes variable was also evaluated by diagnosis age categories <60, 60–69, 70–79 and ≥80 years. Demographic and genetic factors were adjusted in Model 1 and lifestyle and clinical factors were additionally adjusted in Model 2. We evaluated the assumption of proportionality using log–log plots.

As a sensitivity analysis, we compared the HRs (95% CIs) of dementia according to the four different definitions of prediabetes, with and without adjusting for incident

diabetes as a time-varying variable for both Model 1 and Model 2. Since stroke is a major risk factor for dementia, we also performed a sensitivity analysis excluding prevalent stroke. All analyses were done using Stata/SE 17.0 (StataCorp, College Station, TX, USA). p values <0.05 were considered statistically significant.

Results

Among 11,656 participants without diabetes at baseline, the mean age was 56.8 (SD 5.7) years, 55.3% were female, and 20.0% had prediabetes (HbA_{1c} 39–46 mmol/mol [5.7–6.4%]). Participants with prediabetes (vs without) were

Table 1 Characteristics of participants without diabetes in the ARIC study according to prediabetes status at baseline (Visit 2, 1990–1992)

Characteristic	No prediabetes (HbA_{1c} <39 mmol/mol [5.7%]) (*N*=9326)	Prediabetes (HbA_{1c} 39–46 mmol/mol [5.7–6.4%]) (*N*=2330)
Age at baseline, years, mean (SD)	56.5 (5.7)	58.0 (5.7)
Female sex	5212 (55.9)	1221 (52.4)
Black race	1553 (16.7)	920 (39.5)
ARIC field centre		
Forsyth County	2543 (27.3)	532 (22.8)
Jackson	1349 (14.5)	813 (34.9)
Minneapolis Suburbs	2855 (30.6)	477 (20.5)
Washington County	2579 (27.7)	508 (21.8)
Education		
Less than high school	1588 (17.0)	704 (30.2)
High school graduate or equivalent	4005 (42.9)	908 (39.0)
College or above	3733 (40.0)	718 (30.8)
APOE alleles		
0	6502 (69.7)	1559 (66.9)
1	2586 (27.7)	705 (30.3)
2	238 (2.6)	66 (2.8)
BMI, kg/m^2, mean (SD)	27.0 (4.8)	29.1 (5.8)
BMI category		
Normal and underweight ≤25 kg/m^2	3430 (36.8)	527 (22.6)
Overweight 25 to <30 kg/m^2	3841 (41.2)	935 (40.1)
Obesity 30 to <40 kg/m^2	1895 (20.3)	751 (32.2)
Morbid obesity ≥40 kg/m^2	160 (1.7)	117 (5.0)
Smoking status		
Current	1947 (20.9)	703 (30.2)
Former	3577 (38.4)	832 (35.7)
Never	3802 (40.8)	795 (34.1)
Alcohol use		
Current	5778 (62.0)	1156 (49.6)
Former	1613 (17.3)	610 (26.2)
Never	1935 (20.7)	564 (24.2)
Physical activity category		
Poor	3110 (33.3)	1032 (44.3)
Intermediate	2388 (25.6)	506 (21.7)
Recommended	3828 (41.0)	792 (34.0)
Total cholesterol, mmol/l, mean (SD)	5.38 (0.99)	5.52 (1.02)
HDL-cholesterol, mmol/l, mean (SD)	1.33 (0.44)	1.21 (0.39)
Hypertension	2763 (29.6)	1019 (43.7)
Stroke	120 (1.3)	52 (2.2)
Atrial fibrillation	58 (0.6)	22 (0.9)

Data are presented as n (%) unless otherwise noted

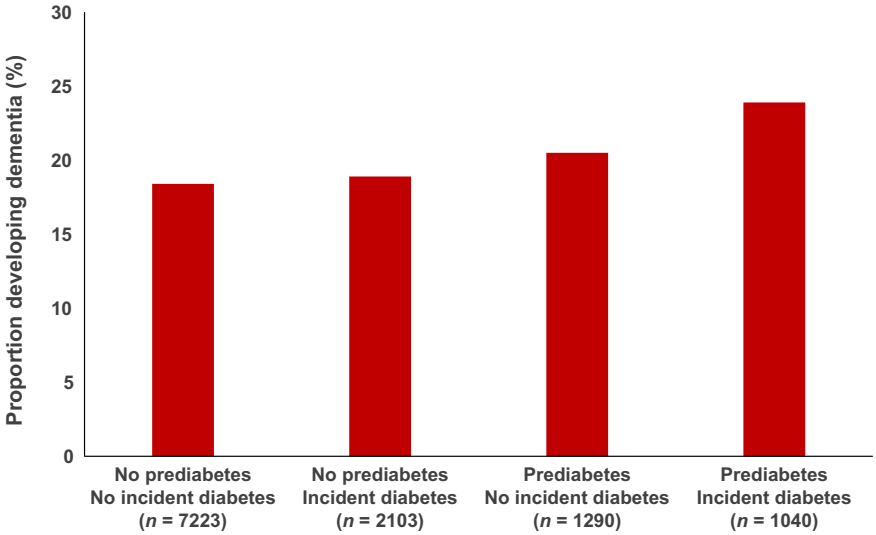

Fig. 1 Proportion of participants developing dementia by baseline prediabetes and incident diabetes status: follow-up from 1987–1989 to 2019

more likely to self-report Black race (39.5% vs 16.7%) and were more likely to have lower than a high school education (30.2% vs 17.0%). Participants with prediabetes had a higher burden of lifestyle and clinical risk factors (Table 1).

Overall, there were 3143 participants who developed diabetes during a median of 15.9 (p25–p75: 10.0–21.0) years of follow-up. The mean age of incident diabetes was similar for those with and without prediabetes at baseline (~71.6 years). However, those with (vs without) prediabetes were more likely to develop diabetes (44.6% vs 22.5%) (ESM Table 1).

A total of 2247 participants developed dementia over a median of 24.7 (p25–p75: 17.9–27.1) years of follow-up. The development of dementia varied by prediabetes and incident diabetes status (Fig. 1). For instance, among those with prediabetes, the cumulative incidence of dementia was 16.6% higher in those who developed vs did not develop diabetes (23.9% vs 20.5%).

The cumulative incidence of dementia in people with prediabetes was 15% (vs 10% in those without prediabetes) by age 80 years and 63% (vs 53%) by age 90 years (Fig. 2a). Prediabetes was significantly associated with incident dementia (HR 1.19 [95% CI 1.07, 1.31]) after adjusting for demographics and *APOE* (Table 2, Model 1A). After adjusting for incident diabetes as a time-varying variable,

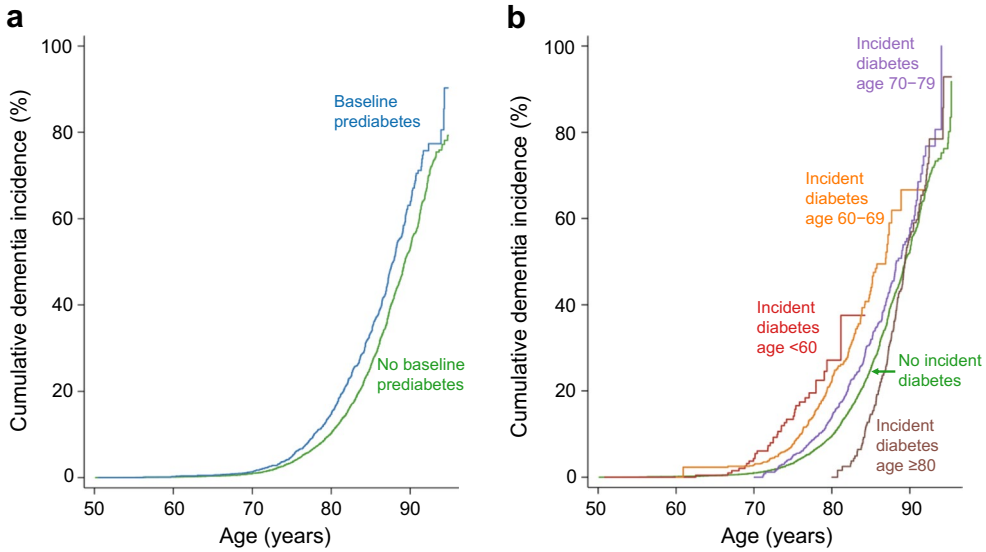

Fig. 2 Risk (cumulative incidence) of dementia (Kaplan–Meier curves) according to baseline prediabetes status (**a**) and by age at onset of incident diabetes during follow-up (**b**). For each curve in (**a**), there were *n*=9326 participants without prediabetes and *n*=2330 with prediabetes at the time origin. At the beginning time for each curve in (**b**), there were *n*=11,656 participants with no incident diabetes, *n*=237 with diabetes onset at age <60 years, *n*=971 with diabetes onset at age 60–69 years, *n*=1534 with diabetes onset at 70–79 years and *n*=401 with diabetes onset at 80–93 years

the association of prediabetes and dementia was strongly attenuated and was no longer statistically significant (HR 1.09 [95% CI 0.98, 1.21]) (Model 1B). Results were similar in models that adjusted for other lifestyle and clinical risk factors (HR 1.12 [95% CI 1.01, 1.24] before and HR 1.05 [95% CI 0.94, 1.16] after adjusting for incident diabetes) (Models 2A and 2B).

The cumulative incidence of dementia was highest among those who developed diabetes at an earlier age (Fig. 2b). Participants who developed diabetes at age 70–79 or ≥80 years had roughly similar cumulative dementia incidence to those without incident diabetes. In multivariable adjusted models, the strength of the association between incident diabetes and dementia decreased with older age at diabetes onset (Table 2). Individuals who were diagnosed with diabetes at younger than 60 years of age were at the highest risk of dementia (HR 2.92 [95% CI 2.06, 4.14]) (Model 2B). Those diagnosed with diabetes when aged 80 years or older did not have a statistically significantly elevated risk of dementia (HR 1.13 [95% CI 0.94, 1.35]). The HRs were 1.73 (95% CI 1.47, 2.04) for onset at 60–69 years and 1.23 (95% CI 1.08, 1.40) for onset at 70–79 years.

When we compared different definitions of prediabetes, stronger associations with dementia were observed for prediabetes based on HbA_{1c} (ESM Table 2). For all definitions of prediabetes, prediabetes was no longer significantly associated with risk of dementia after adjusting for incident diabetes. Due to the small number of participants with stroke at baseline (*N*=172 [1.5%]), the results were essentially unchanged after excluding these individuals from analysis.

Discussion

In this community-based study, we found that prediabetes in midlife was modestly associated with dementia risk. After adjusting for the intervening onset of diabetes, however, prediabetes was no longer independently associated with dementia. Results were similar across different definitions of prediabetes. Earlier age at diabetes onset was also associated with substantially greater risk of dementia. Taken together, our findings suggest that preventing prediabetes progression, especially in younger individuals, may be an important way to reduce the dementia burden.

Our study suggests that prediabetes is associated with dementia but this association is primarily explained by the development of clinical diabetes. Prior studies have demonstrated small to moderate relative risks of prediabetes with dementia, ranging from 1.01 to 1.20 [2, 7, 12]. In a meta-analysis, the RR for the association of prediabetes with dementia was 1.18, consistent with our findings [2]. However, no prior studies have formally considered the progression of prediabetes to diabetes in analyses of dementia risk. Our results provide a fuller picture of the association and suggest that prediabetes is not a robust risk factor for dementia in the absence of a subsequent diagnosis of diabetes.

In the USA, up to 96 million adults have prediabetes, accounting for 38% of the adult population [21]. Structured lifestyle intervention programmes (such as the CDC-led National Diabetes Prevention Program) [22] can effectively prevent diabetes progression. However, fewer than 5% of adults with prediabetes receive referrals to these programmes from their healthcare providers [23]. More than 80% of adults with prediabetes are also unaware that they have the condition [22]. Improving early detection and

Table 2 Adjusted HR (95% CI) for the association of prediabetes at baseline with dementia before (Models 1A and 2A) and after (Models 1B and 2B) accounting for incident diabetes during follow-up by age of diabetes onset

Diabetes status	Model 1A[a]	Model 1B[b]	Model 2A[a]	Model 2B[b]
Baseline diabetes status				
No prediabetes (*N*=9326)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Prediabetes (*N*=2330)	1.19 (1.07, 1.31)**	1.09 (0.98, 1.21)	1.12 (1.01, 1.24)*	1.05 (0.94, 1.16)
Incident diabetes				
No incident diabetes (*N*=11,656)		1 (reference)		1 (reference)
Diabetes onset at age <60 years (*N*=237)		2.97 (2.10, 4.20)***		2.92 (2.06, 4.14)***
Diabetes onset at age 60–69 years (*N*=971)		1.82 (1.55, 2.14)***		1.73 (1.47, 2.04)***
Diabetes onset at age 70–79 years (*N*=1534)		1.26 (1.11, 1.43)***		1.23 (1.08, 1.40)***
Diabetes onset at age 80–93 years (*N*=401)		1.14 (0.95, 1.37)		1.13 (0.94, 1.35)

[a] Models 1A and 1B adjusted for sex, race, ARIC field centre, education and *APOE*

[b] Models 2A and 2B adjusted for sex, race, ARIC field centre, education, *APOE*, BMI, smoking status, alcohol use, physical activity, total cholesterol, HDL-cholesterol, hypertension, stroke and atrial fibrillation

*p<0.05, **p<0.01, ***p<0.001

engagement in prediabetes progression to diabetes may have long-term population benefits for dementia prevention, particularly since earlier age of onset of diabetes is associated with the most dramatic risk of dementia.

Our study confirms the strong link between diabetes and dementia risk [1–3] but we found strong modification of this association depending on the age of onset of diabetes. Diabetes that was diagnosed earlier in adulthood (age <60 years) was strongly associated with dementia risk whereas old-age-onset diabetes (age >80 years) did not contribute to an excess risk of dementia. There are a few studies regarding dementia risk with diabetes age of onset and our results are in line with the current evidence. The Whitehall II study showed every 5 year earlier onset of diabetes was significantly associated with higher hazard of dementia (HR 1.24 [95% CI 1.06, 1.46]) [12]. The Swedish Twin Registry study reported greater odds of dementia among people whose diabetes age of onset was less than 65 years (OR 2.41 [95% CI 1.05, 5.51]) but not more than 65 years. Our finding suggests the elevated dementia hazard is non-linear. They also suggest that sustained exposure to hyperglycaemia is critical for dementia development. Prevention efforts in people with diabetes diagnosed younger than 65 years should be a high priority [24].

Studies of prediabetes as a risk factor have proposed similar mechanisms to those with diabetes as a risk factor for dementia. Putative mechanisms include acute and chronic hyperglycaemia, glucose toxicity, insulin resistance and microvascular dysfunction of the central nervous system [25–30]. Increased peripheral insulin in people with hyperglycaemia results in neuronal insulin receptor desensitisation, which may lead to a decrease in Aβ clearance [25, 28, 29] and an increase in prephosphorylation of τ protein [25, 26, 30]. Glucose toxicity and microvascular dysfunction are associated with increased inflammatory and oxidative stress, leading to increased blood–brain permeability [30–33]. The combination of these mechanisms has been proposed to explain the link between diabetes and vascular and Alzheimer's dementia.

Strengths of our study include the large, community-based cohort and long duration of follow-up. We were able to adjust for important confounding factors including *APOE* and other major dementia risk factors, which were measured by trained personnel using standardised protocols. We identified over 3000 incident cases of diabetes after baseline, and we were able to account for diabetes as a time-varying risk factor in the association between prediabetes and dementia. Our study also benefited from the rigorous ascertainment and adjudication of dementia in the ARIC study.

There are several important limitations of our study. First, we only considered single baseline measurement of HbA_{1c} and fasting glucose. However, we compared different prediabetes definitions with the combination of elevated HbA_{1c} and elevated fasting glucose. Second, we did not have information to differentiate dementia subtypes. Prior studies have shown a higher RR of prediabetes with vascular dementia than with Alzheimer's disease. Third, the duration of prediabetes at baseline was unknown; we were not able to account for duration of prediabetes in our analyses. Last, we are not able to rule out residual confounding due the observational nature of our study.

In conclusion, prediabetes was associated with dementia risk but this association was explained by the intervening development of diabetes. Earlier age of onset of diabetes was associated with a substantially greater risk of dementia. Among people with prediabetes, preventing and delaying the progression to diabetes is likely to reduce dementia burden.

Supplementary Information The online version of this article (https://doi.org/10.1007/s00125-023-05930-7) contains peer-reviewed but unedited supplementary material.

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Data availability The ARIC data are not publicly available due to confidentiality issues. Investigators can access data from the ARIC study by submitting a manuscript proposal to aricpub@unc.edu.

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Authors' relationships and activities ES is on the advisory board for *Diabetologia* and had no role in peer-review of the manuscript. All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement JH, MF, JC and ES designed the study, researched the data and contributed to discussion. JH conducted the analyses and wrote the initial manuscript. All authors provided substantial contributions to the interpretation of data, made critical revisions to the manuscript and approved the final manuscript. JH is the guarantor of this work and, as such, had full access to all the data in the study, controlled the decision to publish and takes responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author, ES, attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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