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RESEARCH ARTICLE

Risk of progression from pre-diabetes to type 2 diabetes in a large UK adult cohort

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Abstract

Aims: People with pre-diabetes are at high risk of progressing to type 2 diabetes. This progression is not well characterised by ethnicity, deprivation and age, which we describe in a large cohort of individuals with pre-diabetes.

Methods: A retrospective cohort study with The Health Improvement Network (THIN) database was conducted. Patients aged 18 years and over and diagnosed with pre-diabetes [HbA1c 42 mmol/mol (6.0%) to 48 mmol/mol (6.5%) were included]. Cox proportional hazards regression was used to calculate adjusted hazard rate ratios (aHR) for the risk of progression from pre-diabetes to type 2 diabetes for each of the exposure categories [ethnicity, deprivation (Townsend), age and body mass index (BMI)] separately.

Results: Of the baseline population with pre-diabetes (n = 397,853), South Asian (aHR 1.31; 95% CI 1.26–1.37) or Mixed-Race individuals (aHR 1.22; 95% CI 1.11–1.33) had an increased risk of progression to type 2 diabetes compared with those of white European ethnicity. Likewise, deprivation (aHR 1.17; 95% CI 1.14–1.20; most vs. least deprived) was associated with an increased risk of progression. Both younger (aHR 0.63; 95% CI 0.58–0.69; 18 to <30 years) and older individuals (aHR 0.85; 95% CI 0.84–0.87; ≥65 years) had a slower risk of progression from pre-diabetes to type 2 diabetes, than middle-aged (40 to <65 years) individuals.

Conclusions: South Asian or Mixed-Race individuals and people with social deprivation had an increased risk of progression from pre-diabetes to type 2 diabetes. Clinicians need to recognise the differing risk across their patient populations to implement appropriate prevention strategies.

KEYWORDS

epidemiology, incidence, pre-diabetes, progression, type 2 diabetes

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1 | INTRODUCTION

Whilst all ethnic groups are affected by type 2 diabetes,[1] certain ethnic groups such as South Asians have a greater susceptibility to type 2 diabetes.[1] Furthermore, high levels of deprivation have been associated with the risk of developing type 2 diabetes[2] and older age is associated with an increased prevalence of type 2 diabetes.[3]

However, data on determinants of the transition from pre-diabetes to type 2 diabetes are less clear, though high BMI and poor beta cell function are key determinants.[4] There is inconsistency in the results of studies assessing the association of age and the risk of progression from pre-diabetes to type 2 diabetes.[4–6] While some studies have shown that younger age of diagnosis with pre-diabetes is associated with an increased risk of progression[4,6] others have reported that progression from pre diabetes to type 2 diabetes may actually be slower in younger age groups.[5]

Two studies have compared the risk of progression from pre-diabetes to type 2 diabetes for a broad range of ethnicities.[5,7] Retrospective cohort studies from both Canada[7] and the United States[5] found that Asian and South-East Asian individuals with pre-diabetes had a higher risk of progressing to type 2 diabetes compared with white Europeans. However, these studies have limitations including a lack of adjustment for BMI in the Canadian study and a lack of ethnic diversity in the American study, where the majority of the cohort were white individuals in the Midwestern Region of the United States. Similarly, although high levels of social deprivation have been associated with increased risk of developing pre-diabetes[2] and type 2 diabetes,[2,8] no study has examined the association between social deprivation and risk of progression from pre-diabetes to type 2 diabetes. Furthermore, type 2 diabetes disproportionally affects those with high levels of social deprivation.[9] Hence, social deprivation is a potential contributor to the risk of conversion from pre-diabetes to type 2 diabetes. Knowledge of the risk of patients, enables triaging and signposting of individuals to appropriate interventions such as lifestyle modification which has been shown to be very effective in slowing the transition to type 2 diabetes.

The primary aims of this study were to examine if the risk of progression from pre-diabetes to type 2 diabetes differed by (1): ethnicity and (2) deprivation. The secondary aim of the study was to determine if the risk of progression from pre-diabetes to type 2 diabetes was different across different age groups. We hypothesised that (1): South Asian, Mixed-Race or Black individuals would have an increased risk of progression from pre-diabetes to type 2 diabetes compared with white Europeans and that (2) individuals with social deprivation would have a higher risk of converting to type 2 diabetes compared with individuals from the least deprived areas.

What's new?

- People with pre-diabetes are at high risk of progressing to type 2 diabetes. However, this progression is not well characterised by ethnicity, deprivation and age.
- South Asian, or Mixed-Race individuals had an increased risk of progression from pre-diabetes to type 2 diabetes compared with white European individuals. Deprivation was associated with an increased risk of progression from pre-diabetes to type 2 diabetes, particularly in white European individuals.
- Our findings emphasise that clinicians need to recognise the differing risk across their patient populations to implement appropriate prevention strategies.

2 | METHODS

We report our study following the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.[10] Ethical approval was received by The Health Improvement Network (THIN) Scientific Review Committee on 7 August 2019 (SRC reference number: 19THIN003).

2.1 | Study design

We conducted a retrospective cohort study of patients registered with THIN database, a primary care database in the United Kingdom (UK).[11] The study period was between 01 January 2005 and 31 December 2017.

2.2 | Data source

THIN is a primary care database that includes anonymised longitudinal data from over 787 general practices across the UK.[11] THIN captures about 6% of the total registered population[11] and is generalisable to the UK population. The database includes patient demographic information, their co-morbidities and treatments. The THIN database is representative of the age structure of the UK population.[12] Patient information uses Read code data.[13]

2.3 | Participants

To ensure adequate data quality, general practices were eligible for inclusion in the study after a minimum of 12 months' usage of electronic medical records and 12 months after achieving acceptable mortality reporting.

2.3.1 | Selection criteria

All patients aged 18 years and over from eligible general practices and with a diagnosis of pre-diabetes between 01 January 2005 and 31 December 2017 were included in the study. Pre-diabetes was defined by any of the following three criteria: (1) with a Read code of pre-diabetes; (2) with a record of fasting blood glucose between 6 mmoL/L and 7 mmoL/L (or between 110 mg/dl and 126 mg/dl), or (3) with an HbA1c between 42 mmol/mol (6.0%) and 48 mmol/mol (6.5%).[14] Patients with a Read code record of type 1 diabetes, at any point in time, were excluded. Patients taking glucose-lowering drugs other than metformin at baseline were excluded. We excluded patients with both type 1 and type 2 diabetes.

2.4 | Exposure

The primary exposures were (i) ethnicity and (ii) deprivation. Ethnicity was stratified into five groups based on read codes: white European (reference group), South Asian, Black, Mixed-Race and other. Deprivation was recorded as quintiles of the Townsend score with a score of 1 representing the least deprived (reference group) and a score of 5 representing the most deprived.[15] Townsend score is an Individual-level deprivation index and is a measure of social deprivation, calculated based on employment, overcrowding, car ownership and house ownership. Adult age (18 years and over) and BMI were secondary exposures. Patients were stratified into four age groups: 18 to <30 years; 30 to <40 years; 40 to <65 years (the reference group) and ≥65 years. BMI measurements were the latest recorded prior to the index date (or diagnosis date of pre-diabetes) and we used ethnic-specific cut-offs for BMI.[16] Underweight/normal weight was the reference group.

2.5 | Outcome

A diagnosis of type 2 diabetes was defined as a record of a relevant Read code. The Read code was taken from the clinical diagnosis directly, to ensure accuracy. According to NICE, care is needed when using single laboratory measures (either plasma glucose or HbA1c) to diagnose type 2 diabetes.[17]

2.6 | Statistics

2.6.1 | Follow-up

This was from the date of diagnosis of pre-diabetes (index date) until the earliest of the following end points: (1) death date; (2) date the patient left the practice; (3) date the practice ceased contributing to THIN; (4) outcome (type 2 diabetes) and (5) study end date.

2.6.2 | Covariates

In analyses of each of the exposures of interest (ethnicity, deprivation, age and BMI), the other exposures were included as covariates in the model. The following covariates age,[4,5] gender,[18] BMI,[4–6] ethnicity,[5] deprivation,[2,8] smoking status,[19] baseline cardiovascular disease (CVD) events,[20] baseline hypertension events[4] and diabetes mellitus drugs (metformin) at baseline[21] were selected from the literature and included in all adjusted models.

2.6.3 | Missing data

Patients with missing data for ethnicity, BMI and deprivation (Townsend) were assigned to a separate category for those variables. As these were exposure variables in this study, multiple imputation is not the appropriate method for these variables. Indeed, ethnicity, BMI and deprivation were not missing randomly (especially for ethnicity, with over 40% missing data). Regarding missingness for smoking status, we have used multiple imputation and this method is now applied in all analyses. We also undertook subgroup analyses in participants with and without missing ethnicity records and looked at the effect on the risk of progression by age, BMI and deprivation categories.

2.6.4 | Analyses

Baseline exposures and covariates were summarised using appropriate descriptive statistics. Categorical variables were presented as numbers and percentages and continuous variables were presented as mean and standard deviation (SD). Crude progression (incidence) rates (IR) for the development of type 2 diabetes from prediabetes were calculated for each of ethnicity, Townsend (deprivation), age and BMI exposure categories separately. Cox proportional hazards regression was used to conduct time-to-event analysis. Deaths and participants transferred out of practice are potential competing events in this setting and

might introduce some informative censoring. Hence, we have also undertaken competing risk Cox regression for these events. Unadjusted, and then adjusted hazard rate ratios (HR) with 95% confidence intervals (CIs) were calculated for the risk of progression from pre-diabetes to type 2 diabetes for each of the exposure categories (ethnicity, deprivation, age and BMI) separately. In adjusted analyses of each exposure of interest, the other exposures were included as covariates in the model, as well as smoking status, gender, baseline CVD events (peripheral vascular disease, stroke, ischaemic heart disease and heart failure), baseline hypertension and metformin prescription at baseline. The Schoenfeld Residuals test was applied to check the proportional hazards assumption by visually inspecting the Schoenfeld residual plots over time for exposures ethnicity, deprivation, age and BMI.

2.6.5 | Subgroup analyses

We stratified by white European, South Asian, Black and Mixed-Race individuals and assessed the effect of deprivation, age and BMI exposure categories separately on the risk of progression from pre-diabetes to type 2 diabetes. Subgroup analyses stratified by deprivation, age and BMI, respectively, were also undertaken. We calculated unadjusted and adjusted hazard rate ratios (HR) and for each exposure of interest, the other exposures were included as covariates in the model, as well as gender, smoking status, baseline CVD events, baseline hypertension and metformin prescription at baseline.

2.6.6 | Sensitivity analyses

To check whether taking metformin medication at baseline had an effect on the risk of progression from pre-diabetes to type 2 diabetes, we repeated the main analyses but excluded patients taking metformin at baseline.

All analyses were conducted using STATA 14.0[22] and two sided p-value <0.05 were considered to be statistically significant.

3 | RESULTS

3.1 | Baseline Characteristics

Table 1 includes baseline characteristics by age group. The number of individuals meeting the pre-diabetes criteria at baseline was 397,853, of whom 45.1% were white, 3.1% of individuals were South Asian, 1.6% of participants were Black, 0.7% were Mixed-Race and 49.1% with missing ethnicity data. Mean (SD) age at baseline was 63.7 (13.9) years. Mean (SD) BMI at baseline was 29.7 (6.3) kg/m^2.

3.2 | Unadjusted incidence rates (IR) of progression

Diabetes incident rate for the whole population with pre-diabetes (n = 397,853) was 53.5 per 1000 person-years. Unadjusted incidence rates (IR) of type 2 diabetes are detailed in Table 2. The median follow-up time was 2.6 years (IQR 1.1 to 5.1 years). The number of competing events (deaths and number of participants transferred out of practice) are detailed in Table S1.

3.3 | Adjusted Hazard rate ratios (aHR)

Proportional hazards assumption was not violated in this study as the Schoenfeld residual plots were constant over time for each of ethnicity, deprivation, age and BMI (Figure S1).

The risk of progression from pre-diabetes to type 2 diabetes are detailed in Table 2. South Asian (aHR 1.31; 95% CI 1.26–1.37) or Mixed-Race (aHR 1.22; 95% CI 1.11–1.33), but not Black (aHR 0.98; 95% CI 0.92–1.04) individuals had an increased risk of progression from pre-diabetes to type 2 diabetes compared with white European individuals, after adjusting for age, gender, BMI, ethnicity, deprivation, smoking status, baseline CVD events, baseline metformin and baseline hypertension.

Individuals with social deprivation had an increased risk of progression from pre-diabetes to type 2 diabetes (aHR 1.17; 95% CI 1.14–1.20; most vs least deprived) and the relationship was linear (p trend <0.0001).

Both younger age (aHR 0.63; 95% CI 0.58–0.69; 18 to <30 years vs. 40 to <65 years) and older age (aHR 0.85; 95% CI 0.84–0.87; ≥65 years vs. 40 to <65 years) of pre-diabetes diagnosis were associated with a reduced risk of progression from pre-diabetes to type 2 diabetes.

Greater BMI (aHR 1.58; 95% CI 1.54–1.62; overweight vs. underweight/normal weight), as expected, was associated with an increased risk of progression from pre-diabetes to type 2 diabetes (linear; p trend <0.0001).

3.4 | Subgroup analyses

Adjusted Hazard rate ratios (aHR) of type 2 diabetes stratified by white European, South Asian, Black and Mixed-Race individuals are detailed in Table 3. There

TABLE 1 Baseline characteristics by age groups for individuals with pre-diabetes.

	18 to <30 years	30 to <40 years	40 to <65 years	≥65 years	Overall
n	1659	18,027	186,676	191,491	397,853
Mean Age, years (SD)	25.7 (3.2)	35.91 (2.80)	55.0 (6.7)	75.4 (7.2)	63.7 (13.9)
Male (%)	1624 (36.5)	7231 (47.5)	102,631 (55.0)	88,971 (46.5)	200,457 (50.4)
Mean BMI, kg/m^2 (SD)	31.9 (9.4)	32.3 (8.2)	31.0 (6.6)	28.2 (5.3)	29.7 (6.3)
BMI categories (%)					
Underweight/Normal weight	1010 (22.7)	2500 (16.4)	27,816 (14.9)	49,658 (25.9)	80,984 (20.4)
Overweight	681 (15.3)	3614 (23.7)	58,489 (31.3)	72,336 (37.8)	135,120 (34.0)
Obesity	1983 (44.6)	7670 (50.3)	87,894 (47.1)	57,551 (30.1)	155,098 (39.0)
Missing	773 (17.4)	1455 (9.5)	12,477 (6.7)	11,946 (6.2)	26,651 (6.7)
Ethnicity (%)					
White	1754 (39.4)	5894 (38.7)	85,755 (45.9)	86,222 (45.0)	179,625 (45.1)
South Asian	489 (11.0)	1978 (13.0)	7621 (4.1)	2341 (1.2)	12,429 (3.1)
Black	146 (3.3)	668 (4.4)	4298 (2.3)	1188 (0.6)	6300 (1.6)
Mixed-Race	53 (1.2)	291 (1.9)	1871 (1.0)	554 (0.3)	2769 (0.7)
Others	38 (0.9)	133 (0.9)	791 (0.4)	239 (0.1)	1201 (0.3)
Missing	1967 (44.2)	6275 (41.2)	86,340 (46.3)	100,947 (52.7)	195,529 (49.1)
Townsend (%)					
1st (least deprived)	472 (10.6)	1895 (12.4)	37,898 (20.3)	43,131 (22.5)	83,396 (21.0)
2nd	567 (12.8)	2011 (13.2)	33,543 (18.0)	39,756 (20.8)	75,877 (19.1)
3rd	802 (18.0)	2918 (19.1)	35,307 (18.9)	36,346 (19.0)	75,373 (18.9)
4th	933 (21.0)	3192 (20.9)	31,470 (16.9)	29,875 (15.6)	65,470 (16.5)
5th (most deprived)	914 (20.6)	2697 (17.7)	23,039 (12.3)	19,113 (10.0)	45,763 (11.5)
Missing	759 (17.1)	2526 (16.6)	25,419 (13.6)	23,270 (12.2)	51,974 (13.1)
Smoker (%)					
Non-smokers	2442 (54.9)	8032 (52.7)	89,579 (48.0)	96,831 (50.6)	196,884 (49.5)
Discontinued smokers	546 (12.3)	2767 (18.2)	53,037 (28.4)	71,500 (37.3)	127,850 (32.1)
Current smokers	1343 (30.2)	4227 (27.7)	42,497 (22.8)	21,528 (11.2)	69,595 (17.5)
Missing	116 (2.6)	213 (1.4)	1563 (0.8)	1632 (0.9)	3524 (0.9)
Metformin (%)	226 (5.1)	654 (4.3)	983 (0.5)	380 (0.2)	2243 (0.6)
Hypertension (%)	133 (3.0)	1754 (11.5)	69,565 (37.3)	114,104 (59.6)	185,556 (46.6)
CVD events (%)	27 (0.6)	266 (1.7)	24,781 (13.3)	69,850 (36.5)	94,924 (23.9)

Note: *n* is the number of participants. Continuous variables present mean and standard deviation (SD). Categorical variables presented as numbers (percentages).

was evidence that white European individuals (aHR 1.16; 95% CI 1.12–1.21; most deprived vs. least deprived) but not South Asian (aHR 1.04; 95% CI 0.89–1.21; most deprived vs. least deprived), Black (aHR 0.93; 95% CI 0.70–1.23; most deprived vs. least deprived), nor Mixed-Race (aHR 1.18; 95% CI 0.84–1.66; most deprived vs. least deprived) individuals with social deprivation had an increased risk of progression from pre-diabetes to type 2 diabetes. Younger and older individuals in both white Europeans and South Asians had a reduced risk of progression from pre-diabetes to type 2 diabetes than middle-aged individuals (Table 3). Greater BMI was associated with an increased risk of progression from pre-diabetes to type 2 diabetes in white European, South Asian, Black and Mixed-Race individuals (Table 3). Subgroup analyses for deprivation (Table S2), age (Table S3) and BMI (Table S4) categories are detailed in the Appendices. For the differences in age, BMI and deprivation, we found little effect on the analyses when we undertook subgroup analyses in individuals with and without missing ethnicity records (data not shown).

TABLE 2 Incident rates (IR) per 1000 person-years and adjusted Hazard rate ratios (aHR) by ethnicity, deprivation, age and BMI exposure categories for risk of progression from pre-diabetes to type 2 diabetes.

Type 2 diabetes	*n*	Events	Person-years	IR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Overall	397,853	74,827	1,399,298	53.5 (53.1-53.9)	N/A	N/A
Age categories						
18 to <30 years	4447	543	15,027.6	36.1	0.60 (0.55–0.65)	0.63 (0.58–0.69)
30 to <40 years	15,239	2,820	52,482.0	53.7	0.90 (0.86–0.93)	0.89 (0.85–0.92)
40 to <65 years	186,676	40,975	691,423.2	59.3	Reference	Reference
≥65 years	191,491	30,489	640,365.4	47.6	0.79 (0.78–0.80)	0.85 (0.84–0.87)
BMI categories						
Underweight/ Normal weight	80,984	8,083	281,082.6	28.8	Reference	Reference
Overweight	135,120	22,824	492,918.9	46.3	1.62 (1.58–1.66)	1.58 (1.54–1.62)
Obesity	155,098	38,939	520,879.8	74.8	2.59 (2.52–2.65)	2.49 (2.43–2.55)
Missing	26,651	4,981	104,416.9	47.7	1.70 (1.64–1.76)	1.65 (1.59–1.71)
Ethnicity						
White	179,625	33,770	633,038.9	53.3	Reference	Reference
South Asian	12,429	2,455	38,430.3	63.9	1.17 (1.12–1.22)	1.31 (1.26–1.37)
Black	6,300	1,040	18,373.7	56.6	1.02 (0.96–1.09)	0.98 (0.92–1.04)
Mixed-Race	2,769	472	8,042.1	58.7	1.06 (0.97–1.16)	1.22 (1.11–1.33)
Others	1,201	177	3,459.2	51.2	0.93 (0.80–1.07)	0.96 (0.83–1.12)
Missing	195,529	36,913	697,954.2	52.9	0.99 (0.98–1.01)	1.01 (1.00–1.03)
Townsend						
1st, least deprived	83,396	14,765	301,053.9	49.0	Reference	Reference
2nd	75,877	13,897	274,500.1	50.6	1.03 (1.01–1.06)	1.01 (0.99–1.04)
3rd	75,373	14,317	265,020.7	54.0	1.10 (1.07–1.12)	1.05 (1.03–1.08)
4th	65,470	13,386	223,373.4	59.9	1.21 (1.18–1.24)	1.15 (1.12–1.17)
5th, most deprived	45,763	9,544	152,892.0	62.4	1.26 (1.23–1.29)	1.17 (1.14–1.20)
Missing	51,974	8,918	182,458.1	48.9	0.99 (0.97–1.02)	0.96 (0.93–0.98)

[a]Cox proportional hazard models adjusted for age, gender, BMI, ethnicity, Townsend index, smoking status, baseline CVD events, baseline hypertension events and metformin drugs at baseline.

3.5 | Sensitivity analyses

We found little effect on the analyses when we compared conventional cox regression (Table 2) with competing risk cox regression (Table S5). Hence conventional Cox regression was used in the primary analysis and subgroup analysis. We found little effect on the analyses when we excluded patients taking metformin at baseline (data not shown).

4 | DISCUSSION

In this retrospective cohort study utilising a large primary care database of 400,000 individuals with pre-diabetes we examined if the risk of progression to type 2 diabetes varied by ethnicity, deprivation and by age group. The results of the analyses showed that South Asian or Mixed-Race, but not Black, individuals had an increased risk of progression from pre-diabetes to type 2 diabetes compared with white European individuals. Similarly, social deprivation was associated with an increased risk of progression from pre-diabetes to type 2 diabetes, particularly in white European individuals, but not in South Asians. Both younger age and older age were associated with a reduced risk of progression to type 2 diabetes (compared with middle-aged). Greater BMI was associated with an increased risk of progression from pre-diabetes to type 2 diabetes.

Being South Asian has previously been shown to be associated with an increased risk of progression to type 2 diabetes, in studies from both the US[5] and Canada.[7] The Canadian study also reported an increased risk in Sub-Saharan African/Caribbean individuals with pre-diabetes, who had a higher risk of progressing to type 2 diabetes

TABLE 3 Adjusted hazard rate ratios (aHR) by deprivation, age and BMI categories, stratified by white European, South Asian, Black and Mixed-Race individuals, for risk of progression from pre-diabetes to type 2 diabetes.

HR (95% CI)[a]	White European ($n = 179,625$)	South Asian ($n = 12,429$)	Black ($n = 6300$)	Mixed-race ($n = 2769$)	Missing ($n = 19,5529$)
Age categories					
18 to <30 years	0.69 (0.61–0.79)	0.43 (0.32–0.59)	0.60 (0.34–1.07)	0.67 (0.29–1.51)	0.63 (0.56–0.72)
30 to <40 years	0.89 (0.84–0.95)	0.88 (0.78–1.00)	0.66 (0.51–0.85)	0.93 (0.68–1.29)	0.91 (0.86–0.96)
40 to <65 years	Reference	Reference	Reference	Reference	Reference
≥65 years	0.87 (0.85–0.89)	0.81 (0.73–0.91)	0.82 (0.70–0.97)	0.77 (0.60–1.00)	0.84 (0.82–0.86)
BMI categories					
Underweight/Normal weight	Reference	Reference	Reference	Reference	Reference
Overweight	1.63 (1.57–1.69)	1.34 (1.20–1.50)	1.42 (1.13–1.77)	1.51 (1.19–1.93)	1.58 (1.52–1.64)
Obesity	2.64 (2.55–2.74)	1.93 (1.72–2.17)	1.94 (1.57–2.41)	1.80 (1.40–2.33)	2.45 (2.36–2.53)
Missing	1.74 (1.65–1.85)	1.39 (1.15–1.68)	1.70 (1.23–3.36)	1.28 (0.86–1.91)	1.62 (1.54–1.70)
Townsend					
1st, least deprived	Reference	Reference	Reference	Reference	Reference
2nd	1.02 (0.98–1.05)	0.92 (0.77–1.09)	1.12 (0.80–1.57)	1.10 (0.75–1.61)	1.01 (0.98–1.05)
3rd	1.06 (1.02–1.09)	1.05 (0.91–1.22)	0.96 (0.71–1.29)	1.28 (0.91–1.81)	1.04 (1.01–1.08)
4th	1.17 (1.13–1.22)	1.22 (1.05–1.41)	0.95 (0.72–1.27)	1.08 (0.77–1.53)	1.11 (1.08–1.15)
5th, most deprived	1.16 (1.12–1.21)	1.04 (0.89–1.21)	0.93 (0.70–1.23)	1.18 (0.84–1.66)	1.20 (1.16–1.25)
Missing	0.89 (0.86–0.93)	1.00 (0.86–1.17)	0.89 (0.67–1.18)	0.97 (0.69–1.35)	1.01 (0.97–1.05)

[a]Cox proportional hazard models adjusted for age, gender, BMI, ethnicity, Townsend index, smoking status, baseline CVD events, baseline hypertension events and metformin drugs at baseline.

compared with white European individuals, though importantly they failed to adjust for BMI in their analyses.

A higher risk of progression from pre-diabetes to type 2 diabetes in South Asian individuals compared with whites Europeans might be due to biological susceptibility.[5] South Asian individuals develop type 2 diabetes at a younger age than white European individuals, are more insulin resistant and experience earlier decline in beta cell function.[1] For similar levels of BMI, there is evidence that South Asians have higher levels of abdominal and visceral fat compared with white Europeans.[1] Greater visceral fat is associated with an increase in C-reactive protein (CRP) levels and an increased risk for type 2 diabetes.[1]

An increased risk of progression to type 2 diabetes in South Asian individuals might be influenced by lifestyle behaviours.[1,23] South Asians appear to be less physically active than local white Europeans and have diets richer in carbohydrates and saturated fats.[1,23] Reduced physical activity and higher intake of carbohydrates and saturated fats increase the risk of type 2 diabetes in all ethnic groups.[1,23]

Unhealthy lifestyle factors such as low physical activity and poor diet are commonly associated with higher levels of social deprivation.[24] However, no study has examined the association between deprivation and the risk of progression from pre-diabetes to type 2 diabetes. According to the English indices of deprivation 2019,[25] South Asian people as a whole were the most likely group to live in the most deprived neighbourhoods. In our study, a greater percentage of Black (28%) and South Asian (18%) individuals were from the most socially deprived groups, compared with just 12% for white European individuals. In a retrospective cohort study in Canada, a significant number of immigrants to Canada lived in lower income neighbourhoods.[7] In our subgroup analyses, social deprivation was associated with an increased risk of progression in white European individuals, but not for South Asians. This may have been because many South Asian individuals were categorised as having low socioeconomic status and hence the gradient was poor. There are several plausible mechanisms potentially explaining the link between social deprivation and the risk of progression from pre-diabetes to type 2 diabetes.[26] As well as behavioural factors, the physical and social environments such as poor living conditions, and unemployment, might exacerbate the risk of progressing to type 2 diabetes.[26] Unemployment might lead to chronic stress, anxiety, unhealthy food choices and hence an increased risk of type 2 diabetes.[26,27] Poorer neighbourhoods might have less availability of healthy food options and physical activity amenities, hence an increased risk for obesity and type 2 diabetes.[28]

Compared with middle-aged people, we found that both younger age and older age of pre-diabetes diagnosis were associated with a reduced risk of progression from pre-diabetes to type 2 diabetes. In cohort studies in the United States, both younger[6] and older[5] age of pre-diabetes diagnosis have been associated with an increased risk of progression from pre-diabetes to type 2 diabetes. Physiological studies in younger individuals with type 2 diabetes have shown that there is accelerated loss of beta cell function in younger age groups compared to older adults.[29,30] The primary cause of disease progression to type 2 diabetes is beta cell function decline.[4] This effect may be exacerbated if pre-diabetes at a younger age, results in greater insulin resistance.[4] We therefore would have expected that younger adults had an increased risk of progression from pre-diabetes to type 2 diabetes compared to older adults. We did find this to be the case. However, older age was also associated with a higher risk of progression to type 2 diabetes compared with middle-aged people. A note of caution with these physiological studies is that they were limited by a low sample size.[29] Furthermore, there may be interactions between age, ethnicity, deprivation and BMI which might explain these associations, but we were likely underpowered in our sub-group analyses to detect these effects by age.

There is consistent evidence from the literature that being overweight, or having obesity, increases the risk of progression from pre-diabetes to type 2 diabetes.[4,6] As expected, we found an increased risk of progression in individuals who had overweight or obesity in all ethnicities.

These findings are key to improving referral for highest risk individuals to appropriate interventions. In a systematic review investigating the impact of lifestyle interventions on the incidence of type 2 diabetes in adults 18 or over with pre-diabetes, manipulation of dietary intake and physical activity levels were the main approaches taken.[31] The Diabetes Prevention Program (DPP) in the United States,[31,32] demonstrated the effectiveness of intensive lifestyle interventions (healthy diet and physical activity) at reducing the risk of type 2 diabetes progression in high-risk groups. In 2016, the NHS Diabetes Prevention Programme (NHS DPP) was developed to prevent or delay the onset of type 2 diabetes in high-risk adults by supporting people to adopt a healthy diet, increase physical activity and lose weight.[33] The high-risk group included people of South Asian descent aged 25 years and over, with a BMI greater than 23 Kg/m^{2}.[14]

Individuals of South Asian descent, experience an increased risk of conversion to type 2 diabetes, at a lower BMI and younger age.[14] Furthermore, deprivation is associated with an increased risk of progression from pre-diabetes to type 2 diabetes. Knowledge of the risk of patients enables triaging of individuals to appropriate resources such as lifestyle modification, which has been shown to be effective in slowing the transition to type 2 diabetes. In the NHS DPP, Asian and Mixed-Race groups had lower completion rates than white European groups, as did participants from more deprived backgrounds.[33] These under-served groups should be actively targeted when designing diabetes prevention programmes. For example, including payment schedule incentives[33] and allocated programme places.[32]

This large-scale retrospective cohort study used THIN, which captured about 6% of the registered UK population, included 399,219 individuals with pre-diabetes. This study has several limitations. There was 49% missing ethnicity data in THIN. Reassuringly, BMI and deprivation were consistent in individuals with and without missing ethnicity data. In the UK, a blood test followed by a risk assessment (based on the patient's health records) is implemented to identify people at high risk of type 2 diabetes by General Practitioners and other health professionals.[34] People at high risk of type 2 diabetes (e.g. individuals with obesity) might receive more intensive surveillance or screening compared with those at low risk. Since only individuals with pre-diabetes (by definition already at high risk of type 2 diabetes) were included in this study, the difference by surveillance/screening across different groups should be minimal.

In conclusion, the results showed South Asian or Mixed-Race individuals and people with social deprivation were associated with a higher risk of progression from pre-diabetes to type 2 diabetes. Clinicians need to recognise the differing risk across their patient populations.

AUTHORS' CONTRIBUTIONS

Srikanth Bellary, Neil Thomas and Krishnarajah Nirantharakumar designed the initial study. Michael P. Gardner wrote the manuscript. Jingya Wang performed the statistical analysis. Jingya Wang, Michael P. Gardner, Neil Thomas, Krishnarajah Nirantharakumar and Srikanth Bellary interpreted the results. Michael P. Gardner, Jingya Wang, Jonathan M. Hazlehurst, Chris Sainsbury, Jacqueline Blissett, Krishnarajah Nirantharakumar, Neil Thomas and Srikanth Bellary all reviewed and revised the manuscript and agreed to the submission of the final manuscript. Krishnarajah Nirantharakumar is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

SB received honoraria and speaker fees from AstraZeneca, Boehringer Ingelheim, NAPP, Sanofi-Aventis, Merck Sharpe and Dohme, Eli Lilly and research grants and speaker fees from NovoNordisk Ltd. The remaining authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

DATA AVAILABILITY STATEMENT

THIN data governance does not allow us to share individual patient data and therefore, where possible metadata are presented. Researchers may apply for individual patient data access at https://www.iqvia.com/contact.

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SUPPORTING INFORMATION

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

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