RISK OF PROGRESSION TO DIABETES AND MORTALITY IN OLDER PEOPLE WITH PREDIABETES: THE ENGLISH LONGITUDINAL STUDY ON AGEING

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ABSTRACT

Aims: Prediabetes is used to identify people at increased risk for diabetes. However, the importance of prediabetes in older populations is still poorly explored. Therefore, we aimed to investigate the prevalence of prediabetes, based on either glycated haemoglobin (HbA1c) levels or fasting glucose (FG) levels, or both and the progression of prediabetes to diabetes or to mortality in older participants of the English Longitudinal Study on Ageing.

Materials and methods: Prediabetes was categorized based on HbA1c levels (5.7%-6.4%) and/or FG levels (5.6-7.0 mmol/L). Information regarding mortality and diabetes were recorded during follow-up period of ten years.

Results: In 2027 participants (mean age: 70.6 years, 55.2% females), the prevalence of prediabetes ranged between 5.9% to 31.1%. Over eight years of follow-up, 189 participants (5.4% of the initial population) developed diabetes and 606 (17.4%) died. Among 1403 people with HbA1c at the baseline <5.7%, 33 developed diabetes and 138 died; in contrast, among 479 participants with a diagnosis of prediabetes using a value of HbA1c between 5.7 and 6.4%, 62 developed diabetes and 56 died. Similarly, among 1657 people with normal values of FG at baseline 60 had a diagnosis of diabetes during follow-up and 163 died, compared to 225 with FG between 5.6 and 7.0 mmol/L in which 35 developed diabetes and 31 died.

Conclusion: The prevalence of prediabetes in older adults is high, but the progression from prediabetes to diabetes is uncommon, whilst the regression to normoglycemia or the progression to death was more frequent.

Keywords: prediabetes; diabetes; older people; ELSA.

KEY POINTS

- Pre-diabetes as a risk factor for diabetes in older people is still a prevalent topic.
- The prevalence of prediabetes in older adults is high, but the progression from prediabetes to diabetes is uncommon.
- The regression from prediabetes to normoglycemia or the progression to death was a more frequent finding.

INTRODUCTION

Diabetes and prediabetes, a condition that usually precedes diabetes, have high prevalence rates in older people: for example, some epidemiological data have shown that in the US about a quarter of older people have a diagnosis of diabetes and about 50% meet the necessary criteria for prediabetes.[1] Similar figures are present in Europe.[2]

However, despite the high epidemiological presence of diabetes and prediabetes in older people, the rate of progression from prediabetes to diabetes over time is poorly understood in the older population [3] and the prognostic implications of hyperglycemia among older adults is still being clarified.[4]

In addition, few studies have examined the prognostic implications of different definitions of prediabetes in older people.[5, 6]. More recently, data from large Atherosclerosis Risk in Communities (ARIC) Study found that prediabetes can be considered as a risk factor for diabetes in older people, whilst the association with mortality is still not clear.[7].

However, we feel that a better knowledge of the natural history and the prognostic importance of prediabetes in later life has relevant clinical and public health implications for screening, diagnosis, and management of prediabetes in older adults.[7].

Given this background, we aimed to investigate the prevalence of prediabetes, based on either glycated hemoglobin (HbA1c) levels or fasting glucose (FG) levels, or both and the progression of prediabetes to diabetes or to mortality in the English Longitudinal Study on Ageing, a large epidemiological study in older adults in the UK. [8]

MATERIALS AND METHODS

Study population

This study is based on data from the English Longitudinal Study on Ageing (ELSA) between wave 2 (2004–2005) until wave 7 (2014–2015). The ELSA is a prospective and nationally representative cohort of men and women living in England.[8] The ELSA was approved by the London Multicenter Research Ethics Committee (MREC/01/2/91). Informed consent was obtained from all participants. For the aims of our research we included people older than 60 years, of both genders; people with already a diagnosis of diabetes at baseline or with missing data during follow-up were excluded.

Prediabetes identification

Prediabetes was categorized according to the American Diabetes Association (ADA) criteria, based on HbA1c levels (5.7%-6.4%) and/or FG levels (5.6-7.0 mmol/L).[7, 9]

Outcomes: diabetes and mortality

At the baseline and during the follow-up, diabetes was defined as an HbA_1c level ≥47.5 mmol/mol (6.5%), a self-reported physician diagnosis of diabetes, the current use of glucose-lowering therapy or a value of fasting glucose (FG) $\geq$126 mg/dl ($\geq$ 7 mmol/L).[9, 10] Mortality was assessed during the follow-up period using administrative data. [8]

Covariates

We reported, as descriptive parameters, several clinical information available in the ELSA database and in particular: educational level, categorized as education >11 years of schooling vs. less; marital status; body mass index, categorized using the World Health Organization criteria; smoking status (present vs. other status); disability in one or more of five activities of daily living; physical activity level [11], categorized as sedentary, low,

moderate or high level; and depressive symptoms, using a value of the Center for Epidemiologic Studies Depression Scale ≥4.[11]

Statistical analyses

The data were weighted using the person-level longitudinal weight, core sample, wave 2 (http://www.ifs.org.uk/ELSA).

Means and standard deviations (SD) or median and quartiles (Q1, Q3) were used to describe quantitative measures, while percentages and counts were used for categorical variables. Normal distributions of continuous variables were tested using the Kolmogorov–Smirnov test. Characteristics of the study participants at the baseline (wave 2) were compared according to prediabetes status defined by HbA1c (<5.7 vs 5.7-6.4%) and by FG categories (<5.6 vs 5.6-7.0 mmol/L) considering the Chi-squared or Fisher exact tests for categorical variables, and Generalized linear models after testing for homoschedasticity (Levene test) or Wilcoxon rank sum test for the continuous variables.

Diabetes and mortality rates were estimated in terms of cumulative incidence proportion (%) and as incidence rates per 1,000 person-years, according to prediabetes status defined by HbA1c and FG categories. Sensitivity, specificity, positive predictive value and negative predictive value were calculated for each prediabetes definition in relation to diabetes incidence. Cox proportional hazard models for competing risks were considered to estimate hazard ratios (HR) and 95% confidence intervals (95% CI) for different prediabetes categories in relation to diabetes and death outcomes. Models were evaluated by duplicating the dataset, giving each participant a separate observation for each outcome, as described by Lunn and McNeil [12], and were adjusted for age and sex of the study participants.

All statistical tests were two-tailed, and a p-value < 0.05 was considered to be statistically significant. All analyses were performed using the SAS 9.4 software.

RESULTS

Sample selection

Of the 9432 participants of the wave 2 (baseline) of the ELSA study, 3186 were excluded because of age younger than 60 years, 3684 because data related to HbA1c or FG were missing, 442 had already a diagnosis of diabetes (or the criteria for diabetes diagnosis were met during the baseline assessment using FG and/or HbA1c levels). Finally, 93 had missing data during follow-up for diabetes or death. Therefore, our analytic study population included 2027 older individuals (**Figure 1**, unweighted data).

Baseline characteristics

The mean age of the 2027 participants was 70.6±7.7 years (range: 60-90), 55.2% were females. As shown in **Supplementary Figure 1**, the prevalence of prediabetes using a HbA1c between 5.7 and 6.4% was 25.5%, using an FG between 5.6 and 7.0 mmol/L was 12%, using one of the previous definitions was 31.1% and using the combination of elevated HbA1c and FG was 5.9%.

Table 1 shows the main descriptive findings of the participants included, according to HbA1c or FG categories. People having prediabetes with HbA1c values of 5.7-6.4% were significantly older, more frequently obese and present smokers, disabled, sedentary and with a higher median number of comorbidities than their counterparts with normal levels of HbA1c. Using FG parameters, people with a diagnosis of prediabetes (5.6-7.0 mmol/L) were more educated, obese, and with a higher median number of comorbidities than their counterparts, whilst no differences emerged for the other characteristics investigated.

Follow-up data

Over eight years of follow-up, 189 participants (5.4% of the initial population) developed diabetes and 606 (17.4%) died.

As shown in **Supplementary Figure 2**, among 1403 people with HbA1c at the baseline <5.7%, 33 developed diabetes and 138 died; on the contrary, among 479 participants with a diagnosis of prediabetes using a value of HbA1c between 5.7 and 6.4%, 62 developed diabetes and 56 died. Similarly, among 1657 people with normal values of FG at baseline 60 had a diagnosis of diabetes during follow-up and 163 died, compared to 225 with FG between 5.6 and 7.0 mmol/L in which 35 developed diabetes and 31 died.

Table 2 shows the incidence rates of diabetes and mortality, during the ten years of follow-up, according to HbA1c and/or FG levels at baseline. After adjusting for age and sex and using the definition of prediabetes of a HbA1c value between 5.7 and 6.4%, this condition led to a significant higher risk of diabetes (aHR=4.82; 95%CI: 2.91-7.99; p<0.0001), but not mortality (aHR=1.15; 95%CI: 0.85-1.55; p=0.3794). On the contrary, prediabetes using FG was able to predict both the onset of diabetes (aHR=2.94; 95%CI: 1.71-5.07; p=0.0001) and mortality (aHR=1.47; 95%CI: 1.02-2.13; p=0.0404). Among the combinations possible, only the presence of both elevated HbA1c levels (5.7-6.4%) and FG (5.6-7 mmol/L) led to an increased risk of diabetes (aHR=5.11; 95%CI: 2.83-9.23; p<0.0001) and mortality (aHR=1.65; 95%CI: 1.04-2.62; p=0.0351) (**Table 2**).

The performance of different definition of prediabetes in predicting incident diabetes is reported in **Supplementary Table 1**. The presence of one of either elevated HbA1c or FG had the best sensitivity in predicting diabetes (73.7%), whilst having both conditions had the

best specificity value (95.3%). Of importance, all the definitions used (singular or in combination) had a high negative predictive value (>95%).

DISCUSSION

In our study, we found that prediabetes is a common condition in older adults that participated in the ELSA study, affecting about one person out of three. During a period of ten years of follow-up, only 5% of the participants developed diabetes, whilst about 17% died. These findings confirm the fact that in older people affected by prediabetes, the regression to normal glycemic status or the progression to death is more common than progression to diabetes.

The adults participating to the ELSA are a 'young old' population, having a mean age of 70 years. Unfortunately, a consistent number of them are already comorbid, obese or overweight and/or disabled, delineating a population that is ageing more than expected. The concept of prediabetes is commonly used for identifying individuals at higher risk for developing diabetes and therefore also for the common consequences of this condition, such as cardiovascular diseases. As also shown in another recent paper [7], in the ELSA study, few individuals having prediabetes at baseline progressed to diabetes suggesting that the findings of previous studies undertaken in middle-aged population are poorly applicable to older subjects.[13-16]

Our findings are in agreement with the few studies documenting the progression from prediabetes to diabetes. For example, in one large Swedish study [5] including people of age 60 years and over, the authors found that the majority of the participants regressed to normal HbA1c levels than progressed to diabetes. [5] The ARIC study of approximately 3,500 older individuals, confirmed these findings, and indicated that the regression to normal metabolic values or the progression to death is paradoxically more common than the progression to diabetes. [7] Our sample is, however, younger than those represented in the ARIC study by about seven years, probably bridging the gap between the earlier studies

made in middle-age people and the ARIC's study and, consequently, having an ideal window for an intervention in this young-old population.

An important body of literature has shown that lifestyle interventions in prediabetes may reduce the risk of progression to diabetes.[17-19] In a populations of mean age 51 years. The Diabetes Prevention Program (DPP) trial [18] demonstrated the efficacy of an intensive lifestyle intervention in reducing the risk of diabetes. Therefore, recent ADA guidelines indicate that adults having a diagnosis of prediabetes should be referred to a lifestyle intervention, particularly if obese and sedentary. [9] Our findings are therefore in agreement with these indications, since lifestyle improvements are usually feasible and safe, even in frail older people.[20] At the same time, having in mind the low risk of the progression from prediabetes to diabetes, we believe that pharmacologic interventions, such as metformin, can give limited benefits and, on the contrary, may give harmful effects such as anxiety. [7] At the same time, we should not under-estimate the significance of discovering prediabetes in older people, since its presence may also indicate other detrimental consequences such increased arterial stiffness, with a consequent risk of cardiovascular conditions [21] and increased risk of hospitalizations.[22]

Another pertinent question is whether we should recommend a screening for prediabetes identification in older people. For example, the ADA recommends annual diabetes screening for adults who meet the criteria for prediabetes [9] and the Endocrine Society suggests that older adults with a diagnosis of prediabetes should be further screened using a 2-hour oral glucose tolerance test.[23] However, other research has found that the application of a 2-hour oral glucose tolerance test is unlikely to improve the detection of diabetes, again indicating the necessity of further studies to really understand the benefits of this test from a public health perspective.[24] Our study, in agreement with the findings of the ARIC study

[7], probably further indicates that aggressive diabetes screening in older people is not worthwhile, in view of the low progression rate to diabetes. Our findings also show that the presence of one of either elevated HbA1c or FG had a good sensitivity in predicting diabetes and an optimal negative predictive value.

The findings of our study should be interpreted within its limitations. First, we were able to include only a limited part of the people initially included in the wave 2 of the ELSA study, since several people had not available the determinations of the metabolic markers for prediabetes. This may introduce a selection bias, but in which direction this bias can modify our findings is hard to say. Second, being an observational study, we do not know if participants with a diagnosis of prediabetes may have been referred by their health care practitioner and advised on lifestyle modifications. Finally, 2-hour glucose testing was not conducted, even if, as mentioned previously, its importance is still discussed in older adults.

In conclusion, in our study including more than 2,000 older participants followed for ten years, the prevalence rates of prediabetes is extremely high. However, the progression from prediabetes to diabetes is uncommon, whilst the regression to normoglycemia or the progression to death was more frequent. Clinicians need to be informed that the classification ‘pre-diabetes’ does not help to identify those older adults at ‘high risk’ of developing diabetes, and that their focus of care in these individuals should be on lifestyle management which addresses obesity, smoking, avoiding frailty, and achieving satisfactory blood pressure control. These interventions should change the trajectory to improved survival.

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Data sharing: Data sharing The study protocol and statistical analysis plan for this project are available on request from the corresponding author. Data are available from the UK Data

Service for researchers who meet the criteria for access to confidential data. Data are from waves 2 to 7 of the ELSA study. Data and contact details may be obtained via the website **http://www.adls.ac.uk/find-administrative-data/linked-administrative-data/english-longitudinal-study-of-ageing/**

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Tables and Figures

Figure 1. Flow-chart of the study (not weighted data)

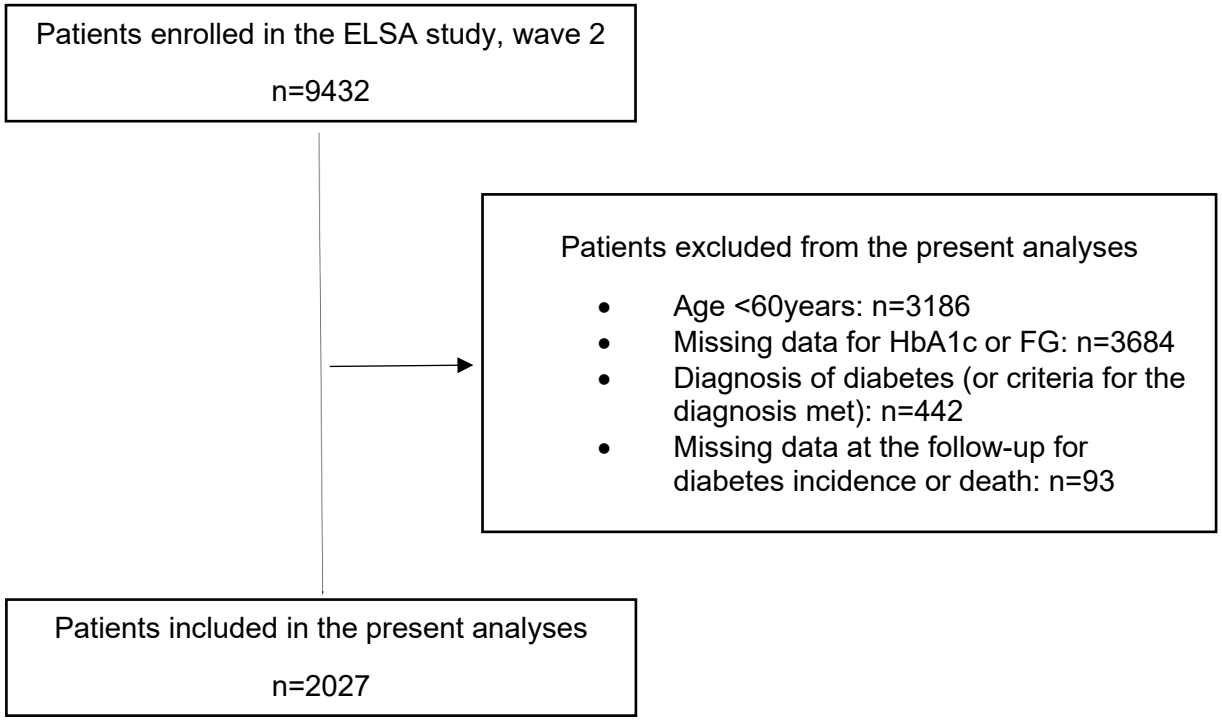

Table 1. Participants' characteristics at the baseline according to prediabetes status (weighted data)

	HbA1c categories			FG categories		
	Normoglycemia HbA1c<5.7% (n=1403)	**Prediabetes HbA1c 5.7-6.4% (n=479)**	**p-value**	**Normoglycemia FG<5.6 mmol/L (n=1657)**	**Prediabetes FG 5.6-7.0 mmol/L (n=225)**	**p-value**
Age, y, mean (SD)	67.6±5.3	68.1±5.3	0.0496	67.7±5.3	67.7±5.3	0.8144
Sex, male, n (%)	641 (45.7)	243 (50.7)	0.0607	888 (53.6)	109 (48.6)	0.1539
Education >11 years of schooling, n (%)	421 (31.3)	129 (28.4)	0.2446	467 (29.4)	83 (39.7)	0.0023
Marital status, married, n (%)	1028 (73.4)	343 (71.6)	0.4380	1203 (72.6)	170 (75.3)	0.3893
BMI, n (%)			<0.0001			<0.0001
<18.5 kg/m^2	13 (1.0)	4 (0.8)		16 (1.0)	1 (0.4)	
18.5-24.9 kg/m^2	441 (32.2)	86 (18.5)		494 (30.6)	33 (15.4)	
25.0-29.9 kg/m^2	630 (46.0)	202 (43.4)		736 (45.5)	96 (44.2)	
≥30 kg/m^2	285 (20.8)	173 (37.3)		371 (22.9)	87 (40.1)	
Present smoker, n (%)	155 (11.0)	83 (17.3)	0.0003	212 (12.8)	25 (11.2)	0.5088
Disability in 1 or more ADL, n (%)	194 (13.8)	94 (19.6)	0.0024	253 (15.3)	34 (15.2)	0.9836

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Physical activity level, n (%)			0.0185			0.0188
Sedentary	22 (1.6)	16 (3.4)		31 (1.9)	7 (3.1)	
Low	282 (20.1)	109 (22.8)		239 (19.9)	63 (27.8)	
Moderate	797 (56.8)	268 (56.0)		948 (57.3)	117 (51.9)	
High	302 (21.5)	85 (17.7)		348 (21.0)	39 (17.2)	
CES-D score ≥4	132 (9.5)	58 (12.2)	0.0854	166 (10.1)	24 (10.9)	0.7063
Comorbidities, median n (Q1, Q3)	1 (1, 2)	2 (1, 2)	<0.0001	1 (1, 2)	2 (1, 2)	0.0304
Comorbidities, 2+, n (%)	606 (43.2)	245 (51.1)	0.0027	737 (44.5)	114 (50.6)	0.0842
High blood pressure, ever diagnosed, n (%)	555 (39.6)	225 (47.1)	0.0041	666 (40.2)	115 (50.9)	0.0022
Angina, ever diagnosed, n (%)	117 (8.3)	61 (12.8)	0.0040	147 (8.9)	31 (13.6)	0.0249
Myocardial infarction, ever diagnosed, n (%)	58 (4.1)	42 (8.7)	0.0001	81 (4.9)	19 (8.3)	0.0307
Congestive heart failure, ever diagnosed, n (%)	8 (0.6)	4 (0.7)	0.7479	10 (0.6)	2 (0.9)	0.6620
Heat murmur, ever diagnosed, n (%)	53 (3.8)	20 (4.3)	0.6252	64 (3.9)	9 (4.0)	0.9122

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Arrhythmia, ever diagnosed, n (%)	92 (6.5)	37 (7.8)	0.3536	112 (6.7)	17 (7.6)	0.6188
Stroke, ever diagnosed, n (%)	43 (3.1)	21 (4.5)	0.1392	56 (3.4)	8 (3.6)	0.8746
Hedibonic lung disease, ever diagnosed, n (%)	84 (6.0)	52 (10.8)	0.0004	121 (7.3)	14 (6.4)	0.6092
Asthma, ever diagnosed, n (%)	184 (13.1)	73 (15.2)	0.2636	231 (14.0)	26 (11.4)	0.2952
Arthritis, ever diagnosed, n (%)	513 (36.6)	194 (40.5)	0.1312	622 (37.6)	85 (37.7)	0.9710
Osteoporosis, ever diagnosed, n (%)	95 (6.8)	33 (7.0)	0.9025	120 (7.3)	8 (3.7)	0.0441
Cancer, ever diagnosed, n (%)	125 (8.9)	38 (8.0)	0.5366	137 (8.3)	27 (12.0)	0.0590
Parkinson's Disease, ever diagnosed, n (%)	5 (0.4)	4 (0.9)	0.1245	8 (0.5)	2 (0.1)	0.6310
Psychiatric disorder, ever diagnosed, n (%)	111 (8.0)	34 (7.1)	0.5540	119 (7.2)	27 (11.9)	0.0144
Alzheimer's Disease, ever diagnosed, n (%)	0 (0.0)	0 (0.0)	--	0 (0.0)	0 (0.0)	--
Dementia or memory impairment, ever diagnosed, n (%)	4 (0.3)	1 (0.2)	1.0000	5 (0.3)	0 (0.0)	1.0000

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	Normoglycemia HbA1c<5.7% (n=1403)	**Prediabetes HbA1c 5.7-6.4% (n=479)**	**p-value**	**Normoglycemia FG<5.6 mmol/L (n=1657)**	**Prediabetes FG 5.6-7.0 mmol/L (n=225)**	**p-value**
HbA1c %, median (Q1, Q3)	5.3 (5.2, 5.5)	5.8 (5.7, 6.0)	<0.0001	5.4 (5.2, 5.6)	5.6 (5.3, 5.9)	<0.0001
<5.7%, n (%)	1403 (100.0)	0 (0.0)		1289 (77.8)	114 (50.6)	<0.0001
5.7-6.4%, n (%)	0 (0.0)	479 (100.0)		368 (22.2)	111 (49.4)	
FG mmol/L, median (Q1, Q3)	4.8 (4.6, 5.2)	5.0 (4.7, 5.5)	<0.0001	4.8 (4.5, 5.1)	5.8 (5.7, 6.1)	<0.0001
<5.6 mmol/L, n (%)	1289 (91.9)	368 (76.8)	<0.0001	1657 (100.0)	0 (0.0)	
5.6-7 mmol/L, n (%)	113 (8.1)	111 (23.2)		0 (0.0)	225 (100.0)	

Table 2. Incidence rates (per 1000 person years) and aHR* (95% CI) for diabetes and mortality, according to prediabetes status at the ELSA wave 2 (weighted data)

Prediabetes criteria	**Incident Diabetes**				**Death**			
	Events/ participants	**Incidence rate (95% CI)**	**aHR (95% CI)**	**p-value**	**Events/ participants**	**Incidence rate (95% CI)**	**aHR (95% CI)**	**p-value**
Normoglycemia (HbA1c<5.7%)	33/1403	3.5 (2.3-4.7)	ref		138/1403	13.7 (11.4-16.0)	ref	
Prediabetes (HbA1c 5.7-6.4%)	59/479	19.6 (14.6-24.6)	4.82 (2.91-7.99)	<0.0001	56/479	16.8 (12.4-21.2)	1.15 (0.85-1.55)	0.3794
Normoglycemia (FG<5.6 mmol/L)	60/1657	5.5 (4.1-6.9)	ref		163/1657	13.9 (11.7-16.0)	ref	
Prediabetes (FG 5.6-7 mmol/L)	35/225	23.8 (15.9-31.7)	2.94 (1.71-5.07)	0.0001	31/225	19.0 (12.3-25.6)	1.47 (1.02-2.13)	0.0404
Normoglycemia (HbA1c<5.7% and FG<5.6 mmol/L)	25/1288	2.9 (1.8-4.0)	ref		125/1288	13.6 (11.2-16.0)	ref	

Prediabetes criteria	Incident Diabetes				Death			
	Events/ participants	**Incidence rate (95% CI)**	**aHR (95% CI)**	**p-value**	**Events/ participants**	**Incidence rate (95% CI)**	**aHR (95% CI)**	**p-value**
Prediabetes (HbA1c 5.7-6.4% or FG 5.6-7 mmol/L)	70/592	18.3 (14.0-22.6)	4.55 (2.69-7.69)	<0.0001	69/592	16.4 (12.5-20.3)	1.18 (0.89-1.58)	0.2454
Normoglycemia (HbA1c<5.7% or FG<5.6 mmol/L)	68/1769	5.9 (4.5-7.2)	ref		176/1769	13.9 (11.9-16.0)	ref	
Prediabetes (HbA1c 5.7-6.4% and FG 5.6-7 mmol/L)	27/111	41.0 (25.6-56.5)	5.11 (2.83-9.23)	<0.0001	19/111	24.9 (13.7-36.1)	1.65 (1.04-2.62)	0.0351

95% CI: 95% Confidence interval; aHR: adjusted Hazard Ratio

Cox models with competing risks, adjusted for age and sex