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Natural history of prediabetes in older adults from a population-based longitudinal study

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Abstract. Shang Y, Marseglia A, Fratiglioni L, Welmer A-K, Wang R, Wang H-X, Xu W (Karolinska Institutet; Stockholm Gerontology Research Center; Karolinska University Hospital; Stockholm University; Stockholm, Sweden; and Tianjin Medical University, Tianjin, China) Natural history of prediabetes in older adults from a population-based longitudinal study. *J Intern Med* 2019; **286**: 326–340.

Background. The natural history of prediabetes in older adults remains unknown.

Objectives. To assess the rate at which prediabetes progresses to diabetes, leads to death or reverts to normoglycaemia in older adults and to identify prognostic factors related to different outcomes of prediabetes.

Methods. In the Swedish National Study on Aging and Care-Kungsholmen, 2575 diabetes-free participants aged ≥60 years were examined at baseline and followed for up to 12 years. At each wave, diabetes was diagnosed via medical examination, antidiabetic drug use, medical records or glycated haemoglobin (HbA1c) ≥6.5%. Prediabetes was defined as HbA1c ≥5.7% and normoglycaemia as HbA1c <5.7% in diabetes-free participants. Data were analysed with multinomial logistic regression.

Results. At baseline, 918 (36%) individuals had prediabetes. Of them, 204 (22%) reverted to normoglycaemia (3.4/100 person-years, 95% CI 5.6–12.3), 119 (13%) developed diabetes (2.0/100 person-years, 95% CI 1.7–2.4) and 215 (23%) died (13.0/100 person-years, 95% CI 11.4–14.9) during the 12-year follow-up. The rates of reversion, progression and mortality were higher in the first 6-year than in the second 6-year follow-up, albeit not statistically significant. Lower systolic blood pressure (SBP), absence of heart diseases and weight loss promoted the reversion from prediabetes to normoglycaemia, whilst obesity accelerated its progression to diabetes.

Conclusions. During a 12-year follow-up, most of older adults with prediabetes remained stable or reverted to normoglycaemia, whereas only one-third developed diabetes or died. Lower SBP, no heart diseases and weight management may promote reversion to normoglycaemia, suggesting possible strategies for achieving normoglycaemia in older adults with prediabetes.

Keywords: older adults, prediabetes, prognostic factors, progression, reversion.

Introduction

In 2017, 352 (7.3%) million adults were living with prediabetes worldwide, and this number is expected to increase to 587 million (8.3%) by 2045 [1]. Prediabetes is an asymptomatic condition preceding type 2 diabetes (hereafter, diabetes). It is characterized by hyperglycaemia, which is defined as a blood glucose level that is higher than normal but below the level for a clinical diagnosis of diabetes [2]. Prediabetes is more common in older than younger people; about 48% of U.S. adults aged ≥65 years had this condition in 2010 [3,4].

Prediabetes is a high-risk state for diabetes; about 5–10% of prediabetes may convert to diabetes annually. According to American Diabetes Association expert panel, 70% of individuals with prediabetes may eventually develop diabetes [5]. On the other hand, prediabetes may also convert back to normoglycaemia. Several studies have shown that about 3% of adults aged 25–52 years reverted to normoglycaemia annually [6]. In addition,

prediabetes is linked to high mortality rate in older adults [7,8]. Although the progression of prediabetes is often described in working-age adults, the evidence on the progression, reversion and mortality of prediabetes in older adults is limited. Given the high prevalence and heterogeneous outcomes of prediabetes in old age, it is pivotal to investigate the natural course of prediabetes amongst older adults.

Glycaemic control can be improved by lifestyle modification in working-age adults [9,10]. Clinical trials have demonstrated reduction in the risk of developing diabetes amongst people with prediabetes followed by lifestyle interventions (such as weight loss) [11]. However, other trials showed that lifestyle interventions are associated with a reduced risk of progression to diabetes only amongst adults aged 45–60 with prediabetes, and suggested that benefit from low glycaemic level may be confined to younger patients [12]. Indeed, glycated haemoglobin A1c (HbA1c) values increase with age amongst diabetes-free subjects, and low glucose level may increase mortality in old age [13,14]. Questions remain on which factors are related to the reversion from prediabetes to normoglycaemia, independently of mortality amongst the older population.

In the present study, we aimed to estimate the rate at which prediabetes reverts to normoglycaemia, progresses to diabetes or leads to death in older adults and to identify prognostic factors related to the reversion of prediabetes using 12-year follow-up data from a population-based longitudinal study of Swedish older adults.

Materials and methods

Study population

Data were derived from the Swedish National Study on Aging and Care in Kungsholmen (SNAC-K), an ongoing population-based longitudinal study on ageing [15]. A random sample of all registered inhabitants aged ≥60 years living at home or in nursing homes in Kungsholmen in central Stockholm were invited to the baseline assessment (2001–2004). Because health conditions change more rapidly and attrition rates increase as people grow older, sampling was stratified by 11 age cohorts. The younger age cohorts (60, 66 and 72 years) were followed up every 6 years, and the older age cohorts (78, 81, 84, 87, 90, 93, 96, and ≥99 years) were followed up every 3 years. Of the 4590 people who were alive and eligible, 3363 (73.3%) agreed to participate. In the current study, we excluded people with baseline type 1 ($n = 21$) or type 2 ($n = 292$) diabetes, resulting in a total of 3050 diabetes-free participants. Further, 475 participants refused follow-up examinations or were no longer contactable, leading to the analytical sample of 2575 diabetes-free participants who were followed for up to 12 years (Fig. 1). Those who dropped out were older and more likely to be female, to have less than an elementary school education, physically inactive, consume less alcohol and have lower Mini-Mental State Examination (MMSE) score than those included in the study ($P < 0.01$ for all; Table A1 in Appendix).

Written informed consent was obtained from all participants or from a proxy of those with cognitive impairment. SNAC-K was approved by the Ethics Committee at Karolinska Institutet and by the Regional Ethical Review Board in Stockholm, Sweden.

Data collection

Data on demographic and lifestyle factors, current medication use, and medical history were collected through structured interviews and clinical examinations carried out by trained nurses and physicians (protocol available from http://www.snac-k.se). Peripheral blood samples were taken for laboratory testing.

Education was measured as the number of years of formal schooling and dichotomized into elementary school versus above elementary school. Smoking was dichotomized into current smoking versus never or former smoked. Alcohol consumption was categorized as 'no or occasional', 'light-to-moderate' or 'heavy' based on the frequency and amount of drinks [16]. Physically active was dichotomized as being physically inactive (never engaged, engaged ≤2–3 times per month in light- or/and moderate-to-intense exercise) versus active (performing weekly moderate-to-vigorous exercise) [17].

Weight and height were measured without shoes and heavy clothes at each wave. Body mass index (BMI) was calculated as body weight divided by the square of height and categorized as underweight (<20), normal weight (20–24.9), overweight (25–29.9) and obesity (≥30 kg m^{-2}). Weight change was calculated as the weight at the visit when glycaemic

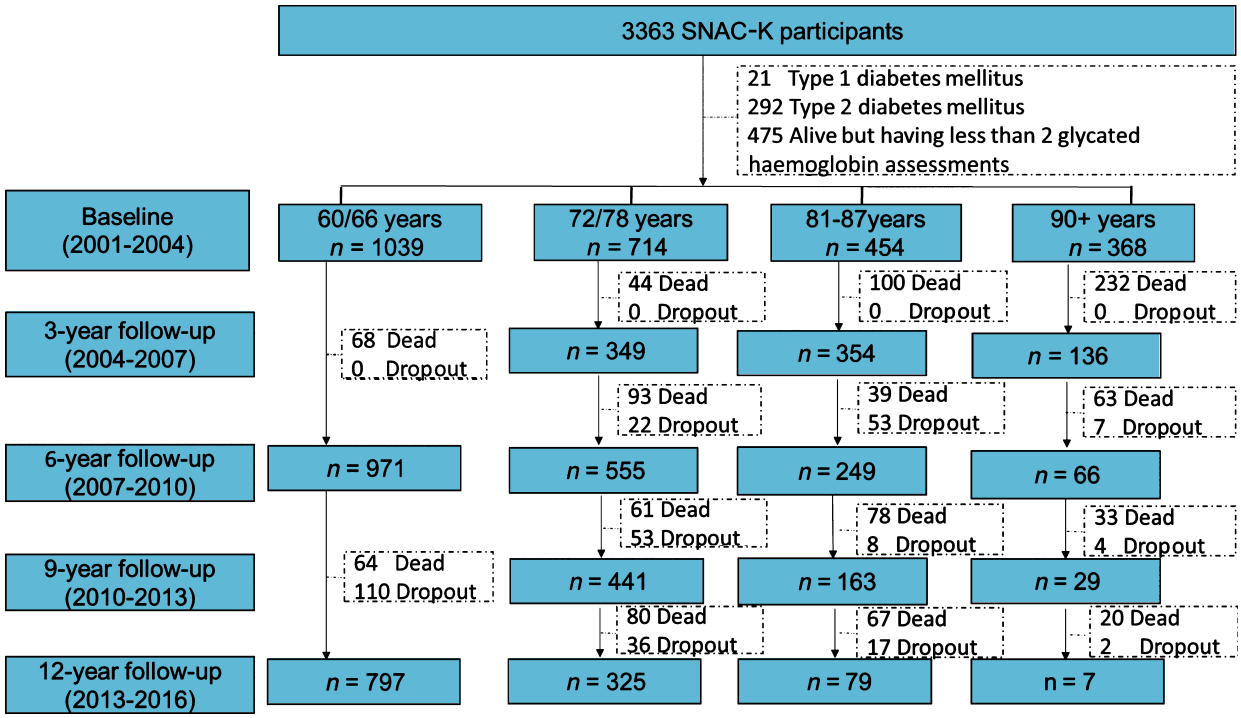

Fig. 1 *Flow chart of study population.*

status (i.e. prediabetes, normoglycaemia) was identified minus baseline weight. To avoid possible reverse causality, for those who developed diabetes, weight change was calculated as the weight at the follow-up prior to diabetes occurrence minus baseline weight. We divided weight change into tertiles based on its distribution and further interpreted the tertiles as 'loss' (−33 to −5), 'stable' (−4 to 0) and 'gain' (+1 to +17 kg).

Arterial blood pressure was measured on the right arm using sphygmomanometer when participants were seated. It was measured twice with a 5-min interval, and the average of the two readings was used to determine systolic and diastolic blood pressure (SBP and DBP [mm Hg]). High total cholesterol was defined as nonfasting total cholesterol of ≥6.22 mmol L^{-1} or use of cholesterol-lowering agents (Anatomical Therapeutic Chemical [ATC] code C10). MMSE was used to evaluate global cognitive function [18].

Data on chronic medical conditions included self-reports and medication use, SNAC-K clinical examination results, and information from the Swedish National Inpatient/Outpatient Registers. International Classification of Disease (ICD 10) was used to identify medical conditions [19]. Cerebrovascular diseases and heart diseases (atrial fibrillation, cardiac valve disease, heart failure, bradycardias, conduction diseases, ischaemic heart disease) were identified. Data on the total number of medications used were obtained through visual inspection.

For participants who died during follow-up, information on the cause of death was extracted from the Swedish Cause of Death Registry (Jun 2001–December 2016). It was also used to obtain information on the vital status of participants who dropped out.

Assessment of prediabetes, diabetes and normoglycaemia

HbA1c was collected at each wave. Until December 2010, HbA1c was assessed with Swedish Mono-S filament High Performance Liquid Chromatography, and 1.1% was added to the individual's values to render them equal to international values in accordance with National Glycohemoglobin Standardization Program (NGSP; HbA1c in %) [20]. Since 1 January 2011, HbA1c has been assessed

with the International Federation of Clinical Chemistry (IFCC) reference method. A standard equation (NGSP = [0.9148 * IFCC] + 2.152; available at: http://www.ngsp.org/ifccngsp.asp) was applied to convert IFCC HbA1c (in mmol mol^{-1}) to NGSP value (in %), to render HbA1c results from all waves comparable [21].

At each wave, diabetes was identified by combining information from different sources: medical examination, antidiabetic drug use, diagnoses from the National Patient Register (ICD-9: code 250; ICD-10: code E11), from the Swedish Cause of Death Registry (any cause of death = diabetes) or HbA1c ≥6.5% (48 mmol mol^{-1}) [2]. In diabetes-free participants, prediabetes was defined as HbA1c of ≥5.7% to 6.4% (39–46 mmol mol^{-1}), and normoglycaemia was defined as HbA1c <5.7% (39 mmol mol^{-1}) [2].

Statistical analysis

Baseline characteristics in participants with normoglycaemia and prediabetes were compared with the chi-square test for categorical variables and the *t*-test or Mann–Whitney test for continuous variables. Evolution rates from prediabetes to each outcome were calculated as the number of events divided by the follow-up time (sum of person-years at risk). For participants who developed diabetes, follow-up time was calculated as full time during which participants were diabetes-free plus half of the time during which diabetes developed. If no diabetes occurred, follow-up time was calculated as the time from baseline until last examination. Similar methods were applied to calculate mortality rate and reversion rate in prediabetes, except that the follow-up time was the full interval between baseline examination and date of death, or the follow-up examinations when normoglycaemia was first identified. All estimates from baseline to the 12-year follow-up and every 6 years were reported. Furthermore, the corresponding evolution rates of incident prediabetes identified during first 6-year follow-up were calculated.

Multinomial logistic regression was used to calculate the odds ratios and 95% confidence intervals of the factors associated with reversion to normoglycaemia, progression to diabetes or death in prediabetes, with stable prediabetes during 12-year follow-up as the reference group. The selection procedure followed a forward stepwise approach. All analyses were first adjusted for age, sex, education and follow-up time (model 1). Alcohol consumption, physical activity, baseline BMI, SBP, MMSE, heart diseases and total number of medications used were included as covariates. We additionally included weight change in the analysis (model 2). Potential interactions between prognostic factors were investigated. Stratified analysis was performed if a significant interaction was present.

Multiple imputation was performed to handle missing data at baseline (<8.5%). $P < 0.05$ was considered statistically significant, and all analyses were performed using STATA 15.0 (StataCorp, College Station, TX, USA).

Results

Baseline characteristics of the study population

At baseline, the mean age of the 2575 participants was 74.4 ± 11.3 years. A total of 1684 (65.4%) were women, 1656 (64.3%) had normoglycaemia, and 918 (35.6%) had prediabetes. Baseline characteristics of participants according to glycaemic status are summarized in Table 1. People with prediabetes were older than those with normoglycaemia. They were also more likely to consume less alcohol, to be overweight or obese, to have higher SBP and MMSE score, to have heart diseases and to use more medications.

Natural history of prediabetes

The total follow-up time for reversal to normoglycaemia was 5675 person-years [median: 8.7 years, interquartile range (IQR): 6.0 years], for incident diabetes, 5339 person-years (median: 8.6 years, IQR: 8.4 years) and for death, 1627 person-years (median: 4.3 years, IQR: 4.54 years). The transition of glycaemic status and death over 12 years is shown in Fig. 2.

Of the 918 people with prediabetes, 380 (41.3%) had prediabetes at the 12-year follow-up, 204 [22.2%; 3.4/100 person-years (95% CI: 3.1–4.1)] reverted to normoglycaemia, 119 [11.0%; 2.3/100 person-years (95% CI: 1.9–2.7)] progressed to diabetes and 215 [23.4%; 13.0/100 person-years (95% CI: 11.4–14.9)] died. The results remain similar after adjusting for sex [reversion rate = 3.6/100 person-years (95% CI: 3.1–4.1); progression rate = 2.2/100 person-years (95% CI: 1.8–2.6); mortality rate = 12.9/100 person-years (95% CI: 11.2–14.7)]. We observed an age-related

Table 1 *Baseline characteristics of the SNAC-K participants by glycaemic status (*n = *2575)*

Characteristics	Normoglycaemia *n* = 1656	Prediabetes *n* = 918	*P*
Age group			
60/66	734 (44.3)	305 (33.2)	<0.001
72/78	438 (26.4)	276 (30.1)	
81–87	256 (15.6)	198 (21.6)	
90+	229 (13.8)	139 (15.1)	
Female sex	1081 (65.2)	603 (65.7)	0.819
Education above elementary school	1381 (84.2)	756 (82.4)	0.225
Current smoker[a]	208 (13.0)	146 (16.0)	0.073
Alcohol consumption			
No/occasional	507 (31.7)	357 (39.3)	0.001
Light-to-moderate	818 (51.1)	409 (45.0)	
Heavy	277 (17.3)	142 (15.6)	
Physically active, *n* (%)	1131 (68.3)	613 (66.8)	0.442
Body mass index			
<20	110 (7.1)	61 (6.9)	0.002
20–24.9	692 (44.8)	346 (38.9)	
25–29.9	594 (38.5)	357 (40.1)	
≥30	149 (9.6)	126 (14.2)	
SBP[a], mm Hg	141 (±20.7)	143 (±20.2)	0.018
DBP[a], mm Hg	81 (±11.3)	80 (±10.9)	0.194
MMSE score	27 (±6.5)	28 (±3.2)	<0.001
High total cholesterol	718 (48.4)	475 (52.0)	0.080
Cerebrovascular diseases	117 (7.1)	73 (7.9)	0.407
Heart diseases	331 (20.0)	248 (27.0)	<0.001
Total no. of medication use	3.7 (±3.2)	4.0 (±3.4)	0.003

DBP, diastolic blood pressure; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure.
Data are presented as mean ± standard deviation, number (%).
[a]Missing data: 17 were missing data on education, 69 on smoking, 65 on alcohol consumption, 218 on body mass index and 177 on total cholesterol.

gradient in the reversion (*P* for trend <0.001) and progression rates (*P* for trend = 0.63). Highest mortality rate was observed in those ≥90 years (Table 2).

Table 3 presents factors related to the natural history of prediabetes over the 12 years of follow-up. After controlling for individual follow-up time, demographic factors, lifestyle factors, baseline BMI, SBP, MMSE, heart diseases and total number of medications (model 2), weight loss significantly increased the odds of reverting to normoglycaemia [odd ratios (OR) = 2.0, 95% CI: 1.1–3.2]. The association appears to be more evident in participants who were overweight (*P* for interaction: 0.03) or obese (*P* for interaction: 0.06) at baseline than in those who were not. In stratified analysis, we combined overweight and obese into one group due to the same direction of association and the small number of people with obesity. The odds ratios were 2.9 (95% CI 1.4–6.2) for weight loss on reversal to normoglycaemia in those who were overweight or obese at baseline. Apart from this, reversion to normoglycaemia was also inversely associated with higher SBP (OR = 0.9, 95% CI: 0.8–0.9) and heart diseases (OR = 0.5, 95% CI: 0.3–0.9; model 2).

Participants with baseline obesity had a higher probability of progressing to diabetes than those who were underweight or of normal weight at

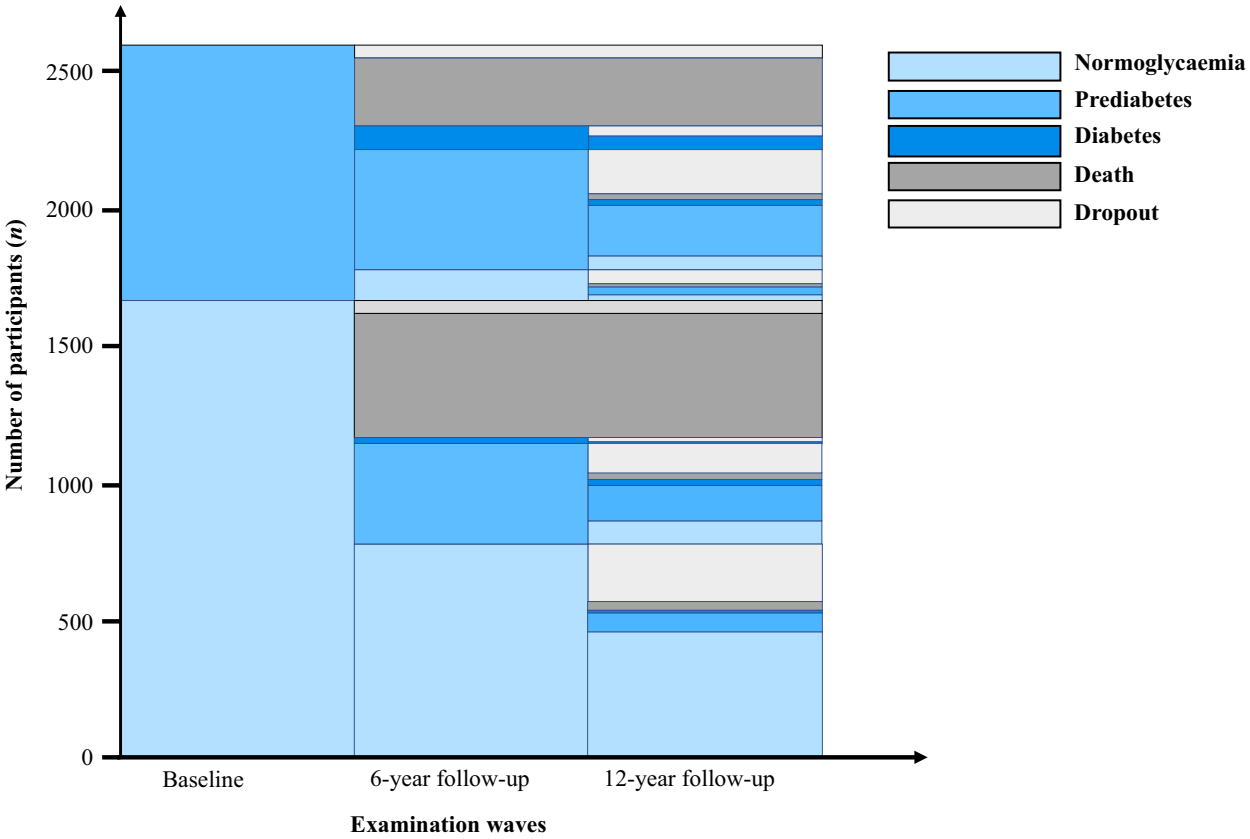

Fig. 2 *Transition of glycaemic status and death over the examination waves.*

baseline (OR = 2.8, 95% CI: 1.3–6.6). After controlling for demographic factors and follow-up time (model 1), higher SBP increased the odds of progressing to diabetes, but the association was not statistically significant after full adjustment (model 2).

Participants who were physically active were associated with reduced mortality (OR = 0.6, 95% CI: 0.3–0.8) adjusting for demographic factors, alcohol consumption, MMSE score, baseline BMI, SBP, heart diseases and total number of medication use (table not shown), but was not statistically significant after taking into account weight change (model 2).

Supplementary analysis

Because of the higher attrition rate in those ≥78 years and the frequent transitions between normoglycaemia and prediabetes, we also estimated occurrence of each outcome during the two follow-up periods: from baseline (2001–2004) to the 6-year follow-up (2007–2010) and from the 6-year follow-up (2007–2010) to the 12-year follow-up (2013–2016). In general, the evolution rates of prediabetes slowed down: the reversion rate to normoglycaemia decreased from 16.0% (reversion rate = 3.7/100 person-years, 95% CI: 3.1–4.3) to 13.1% (3.3/100 person-years, 95% CI 2.5–4.3), the progression rate to diabetes decreased from 10.1% (progression rate = 2.5/100 person-years, 95% CI: 2.0–3.0) to 6.0% (1.6/100 person-years, 95% CI: 1.0–2.3), and the mortality rate declined from 17.6% (mortality rate = 14.2/100 person-years, 95% CI: 12.2–16.6) to 12.2% (8.8/100 person-years, 95% CI: 6.7–27.3; Table A2 in Appendix). During the first 6-year follow-up, 363 incident prediabetes was identified, and corresponding evolution showed generally similar patterns to those from the initial analysis (Table A3 in Appendix).

Table 2 *Reversion, progression and mortality rates (100 person-years, [95% confidence interval]) by age group during 12 years amongst people with prediabetes*

Reversion from prediabetes to normoglycaemia

Age group	Prediabetes (*n*)	Normoglycaemia (*n*)/person-years	Reversion rate (95% CI)
60/66	305	74/2597	2.8 (2.3–3.6)
72/78	276	62/1860	3.3 (2.5–4.3)
81–87	198	43/938	4.6 (3.4–6.2)
90+	139	25/279	8.9 (6.1–13.3)
Total	918	204/5674	3.4 (3.1–4.1)

Progression from prediabetes to diabetes

Age group	Prediabetes (*n*)	Diabetes (*n*)/ person-years	Progression rate (95% CI)
60/66	305	49/2457	2.0 (1.5–2.6)
72/78	276	38/1718	2.2 (1.6–3.0)
81–87	198	25/900	2.7 (1.9–4.1)
90+	139	7/263	2.7 (1.3–5.6)
Total	918	119/5339	2.3 (1.9–2.7)

Death

Age group	Prediabetes (*n*)	Death (*n*)/ person-years	Mortality rate (95% CI)
60/66	305	35/254	13.7 (9.8–19.2)
72/78	276	58/474	12.0 (0.3–15.6)
81–87	198	46/503	8.9 (6.7–11.9)
90+	139	76/394	18.9 (15.1–23.8)
Total	918	215/1627	13.0 (11.4–14.9)

Discussion

In this population-based cohort study that followed Swedish older adults aged ≥60 for 12 years, the overall reversion rate from prediabetes to normoglycaemia was 3.4/100 person-years (about 22%), progression rate to diabetes was 2.0/100 person-years (13%), and mortality rate was 13.0/100 person-years (23%). Lower SBP, no heart diseases and weight loss were associated with reversion to normoglycaemia, and obesity anticipated the progression from prediabetes to diabetes. Physical activity also reduced mortality rate related to prediabetes.

Previous studies focused either on the reversion from prediabetes to normoglycaemia, the progression from prediabetes to diabetes, or the mortality rate related to prediabetes; however, these three outcomes have not been assessed simultaneously in older population. A study on the evolution of prediabetes in middle-aged adults showed a reversion rate of normoglycaemia of around 23% and a progression rate to diabetes of about 30% [22]. In a Swedish middle-aged population, the reversion rate was 36% during 8–10 years [23]. We observed an approximately 22% reversion rate in older adults over 12 years. The only other longitudinal population-based study of older adults to examine the reversion rate to normoglycaemia, the KORA S4/F4 study of 55- to 74-year-olds in Germany, found a reversion rate of 16.3% over 7 years of follow-up, using oral glucose tolerance test (OGTT) as diagnostic criterion [24]. We reported a slightly higher reversion rate of 16% during the first 6-year follow-up, which may be explained by a larger proportion of prediabetes diagnosed by HbA1c, as the sensitivity of HbA1c test in diagnosing prediabetes is inferior to the OGTT [25].

In our study, the incidence of diabetes (2.0/100 person-years) was slightly higher than that found in studies of people of the same age range carried out in other regions of Europe, where it varied from 0.7 to 1.2/100 person-years in people with normoglycaemia or prediabetes [26]. One study in a Dutch population aged 55 to 75 years reported much higher rates of progression from prediabetes to diabetes; specifically, 5.2/100 person-years (33%) from impaired fasting glucose (IFG) to diabetes and 5.8/100 person-years (34%) from impaired glucose tolerance (IGT) to diabetes [27]. The higher estimates from the Dutch study are probably due to different methods used to assess prediabetes and the younger population with a higher prevalence of prediabetes (64.5% in the Dutch study and 35.3% in SNAC-K).

The mortality rate of prediabetes in our study was slightly higher than in a few previous studies that used HbA1c as prediabetes assessment. In participants with mean age of 52 years without diabetes treatment in the NIPPON DATA90, the mortality rate was 23.7% during 10 years of observation [8]. A Danish study reported a 10-year mortality rate of around 15.7% in those with mean age of 56 years with prediabetes [28]. The higher rates observed in our study could be explained by older age, higher level of average HbA1c, blood pressure, more preexisting diseases and longer follow-up compared to other studies.

Table 3 *Prognostic factors associated with reversion, progression and death in prediabetes over 12 years of follow-up. Odds ratios and 95% confidence intervals (OR; 95% CI) from multinomial logistic regression with the 380 participants with stable prediabetes as reference group*

	Reverted to normoglycaemia (n = 204)			Progressed to diabetes (n = 119)			Death (n = 215)		
Characteristics	n	Model 1 OR (95% CI)	Model 2 OR (95% CI)	n	Model 1 OR (95% CI)	Model 2 OR (95% CI)	n	Model 1 OR (95% CI)	Model 2 OR (95% CI)
Body mass index									
<25	89	Ref.	Ref.	38	Ref.	Ref.	104	Ref.	Ref.
25–30	85	1.0 (0.7–1.5)	1.3 (0.8–2.2)	53	1.6 (0.9–2.8)	1.5 (0.8–2.9)	59	0.8 (0.5–1.3)	1.1 (0.5–2.2)
≥30	19	0.7 (0.4–1.2)	0.7 (0.3–1.5)	27	2.5 (1.2–5.1)	2.8 (1.3–6.6)	22	0.9 (0.5–1.8)	0.9 (0.3–2.0)
Weight change over 12 years, kg									
Loss (−33 to −5)	80	1.6 (1.0–2.6)[a]	2.0 (1.1–3.2)	24	0.8 (0.4–1.7)	0.7 (0.4–1.5)	23	1.2 (0.6–2.5)	1.1 (0.5–2.5)
Stable (−4 to 0)	59	Ref.	Ref.	45	Ref.	Ref.	19	Ref.	Ref.
Gain (1 to 17)	51	1.2 (0.7–2.1)	1.1 (0.6–2.0)	48	1.7 (1.0–3.3)[a]	1.7 (0.8–3.4)	10	0.8 (0.3–2.0)	0.8 (0.3–2.0)
Physically active	147	1.0 (0.6–1.6)	0.9 (0.5–1.8)	83	1.1 (0.6–2.0)	0.9 (0.5–1.8)	99	0.5 (0.3–0.7)	0.6 (0.3–1.2)
Alcohol consumption									
No/occasional	66	0.7 (0.5–1.1)	0.5 (0.3–1.1)	39	0.8 (0.5–1.4)	0.6 (0.3–1.1)	107	0.9 (0.6–1.7)	1.1 (0.7–1.8)
Light-to-moderate	97	Ref.	Ref.	56	Ref.	Ref.	79	Ref.	Ref.
Heavy	40	1.3 (0.8–2.1)	1.1 (0.6–2.0)	23	1.3 (0.6–2.6)	1.2 (0.5–3.5)	24	1.4 (0.7–2.6)	1.5 (0.7–2.8)
SBP	203	0.9 (0.9–1.0)	0.9 (0.8–0.9)	117	1.1 (1.1–1.2)	1.0 (0.9–1.0)	213	1.0 (0.9–1.0)	0.9 (0.8–1.0)
Heart diseases	31	0.6 (0.4–0.9)	0.5 (0.3–0.9)	38	1.3 (0.8–2.4)	1.2 (0.6–2.5)	99	1.6 (0.9–2.3)	1.2 (0.7–1.9)

BMI, body mass index; OR, odds ratio; SBP, systolic blood pressure.
Model 1 adjusted for age, sex, education and follow-up time. Model 2 adjusted for variables in Model 1 and alcohol consumption, physical activity, body mass index, weight change, SBP, heart diseases, Mini-Mental State Examination score and total medication use.
[a]P = 0.049.

To our knowledge, only one observational study in older adults has investigated the association between weight change and normalization of glycaemia [24]. This study showed that weight loss, but not initial BMI, strongly increased the likelihood of reverting from prediabetes to normoglycaemia. Previous studies also show that lower SBP could decrease insulin resistance [29], which is crucial in the aetiology and progression of prediabetes. Our results were consistent with these findings. Additionally, in the stratified analysis, the association between weight loss and reversion to normoglycaemia was present only amongst individuals who were overweight or obese at baseline, suggesting that lifestyle modifications, promoting weight loss, can help restore the normoglycaemia in adults with adiposity [30]. Currently, the guidelines for prevention of diabetes emphasize the management of blood pressure, through lowering SBP, as a potential strategy to improve the glycaemic control in diabetes [31]. Based on this, we believe that even at the prediabetic stage, lowering the SBP levels might improve glycaemia, thus promoting normoglycaemia restoration. However, reduction of blood pressure should not be excessively strict in very old people in order to avoid, for example, possible falls due to hypotension. Furthermore, preexisting heart diseases might hamper the reversion to normoglycaemia, as impaired vascular endothelial function and oxidative stress generated by atherosclerosis may further worsen insulin resistance [32].

Apart from overweight and obesity, weight gain may also increase the risk of progression from prediabetes to diabetes through increased insulin resistance [12,33]. Weight gain, particularly accumulation of visceral fat, could increase inflammation around liver and impair insulin signalling, which in turn worsens insulin sensitivity [34]. Indeed, we found this association was independent of baseline BMI, albeit statistically insignificant.

Physical activity was found to be associated with reduced mortality, which was consistent with previous studies [35]. However, the significance was diminished after additional adjustment for weight change, indicating that weight change might mediate the physical activity–mortality association. We further performed analysis in people without heart diseases to rule out potential reverse causality and the results remained similar.

Although the factors that promoted normoglycaemia differed to some extent from those that predicted progression to diabetes, the impact of weight change appears to be consistent. This result suggests that weight management may be an effective strategy for preventing prediabetes and its progression to diabetes, possibly by improving insulin sensitivity. For example, weight loss, which can be achieved through regular physical activity, could be recommended to older adults with overweight or obesity, as possible effective strategy to restore normoglycaemia. Another reason to emphasize weight management in people with prediabetes is that more cardiovascular benefits can be obtained if an effective weight management is achieved during the prediabetic stage [36].

The main strengths of our study included the population-based longitudinal study design, identifying diabetes from multiple sources, the repeated measurements of health-related conditions, repeated blood sampling and the long follow-up time. However, some limitations need to be acknowledged. First, we could not differentiate prediabetes phenotypes. IFG, IGT and the combination of IFG and IGT represent multiple pathophysiological abnormalities, which are likely to differ in their rates of evolution and clinical relevance [5]. Moreover, the recommended HbA1c cutoffs to identify diabetes (≥6.5%) might have lower sensitivity compared to OGTT [25]. Therefore, the number of people with diabetes and the magnitude of observed associations may have been underestimated. Nevertheless, ascertaining prediabetes and diabetes with the HbA1c test has substantial advantages particularly in older populations: it does not require fasting status and can be measured regardless of the time of day, and it reflects hyperglycaemia over the past three months. As HbA1c was likely to be influenced by the presence of anaemia, we further conducted sensitivity analysis to exclude those with anaemia and the results remain similar. Secondly, selection bias may be present, as those who completed the follow-ups were generally younger and more educated, more physically active and have higher MMSE score at baseline than those lost to follow-up. Hence, this may have led to overestimation of the reversion rate to normoglycaemia and an underestimation of incident diabetes. However, this should have relatively small impact of the results, as the number of those dropped out was relatively small and the probability of participation was independently of HbA1c level. The limitations of a potential selection bias and

small sample size may still account for the lack of association between some lifestyle factors and evolution of prediabetes. For the missing information of covariates at baseline, analyses using multiple imputation yields estimates with similar magnitude and direction for most prognostic factors. Finally, since there is no conventional definition of weight loss, stable or gain in older adults, we conducted the analysis based on data distribution. As the range of values in weight change is wide and our results might be potentially driven by the extreme values, we excluded outliers and the association between weight loss and normoglycaemia remained similar. The major findings of this study can be generalized to populations with characteristics similar to those of our study population.

In conclusion, our findings provide evidence on the natural history of prediabetes: during a 12-year follow-up, 42% older adults affected by prediabetes remain stable, 22% reverted to normoglycaemia, whereas 13% progressed to diabetes or 23% died. We found that baseline BMI, weight changes, SBP and preexisting heart diseases could influence the natural history of prediabetes. The latter finding may help to identify people at high risk of progressing to diabetes and suggests possible strategies for achieving normoglycaemia in older adults with prediabetes.

Conflict of interest statement

No potential conflicts of interest relevant to this article were reported.

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Availability of data and material

The data that support the findings of this study are available from the SNAC-K but restrictions apply to the availability of these data, which were used under licence for the current study, and so are not publicly available. The data are, however, available from the authors upon reasonable request and with permission of the SNAC-K study.

Ethics approval and consent to participate

Written informed consent was obtained from all participants or from a proxy of those with cognitive impairment. SNAC-K was approved by the Ethics Committee at Karolinska Institutet and by the Regional Ethical Review Board in Stockholm, Sweden (Dnrs: KI 01-114, 04-929/3, Ö26-2007, 2009/595-32, 2010/447-31/2, 2013/828-31/3 and 2016/730-31/1).

Authors' contributions

Y.S. and W.X. conceptualized and designed the study. Y.S. performed the literature search; analysed the data; interpreted the findings; and wrote, reviewed and edited the manuscript. L.F. designed, initiated and directed SNAC-K. All authors contributed to the data interpretation and revision of the manuscript and approved the final draft. Y.S. 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.

Consent for publication

Not applicable.

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APPENDIX

Table A1 *Baseline characteristics of those included in the study sample and those not*

Characteristics	Study sample (n = 2575)	Excluded from study sample (n = 475)	P value
Age group			
60/66	1039 (40.3)	167 (35.2)	0.003
72/78	714 (27.7)	115 (24.2)	
81–87	454 (17.6)	112 (23.6)	
90+	368 (14.3)	81 (17.1)	
Female sex	1684 (65.4)	341 (71.8)	0.007
Education above elementary school	2137 (83.5)	363 (78.9)	0.015
Current smoker	354 (14.1)	74 (16.4)	0.198
Alcohol consumption			
No/occasional	864 (34.4)	216 (48.0)	<0.001
Light-to-moderate	1227 (48.9)	172 (38.2)	
Heavy	419 (16.7)	62 (13.8)	
Physically active	1744 (67.7)	282 (60.0)	<0.001
Body mass index, kg m^{-2}			
<20	153 (6.5)	40 (10.1)	0.065
20–24.9	1005 (42.6)	159 (40.3)	
25–29.9	933 (39.6)	149 (37.7)	
≥30	266 (11.3)	47 (11.9)	
HbA1C, %	5.5 (±0.3)	5.5 (±0.4)	0.376
SBP, mm Hg	142 (±20.5)	144 (±20.6)	0.099
DBP, mm Hg	81 (±11.1)	81 (±11.4)	0.844
High total cholesterol	1193 (49.8)	191 (47.5)	0.406
MMSE score	27.4 (±5.8)	26.2 (±7.0)	<0.001
Cerebrovascular diseases	190 (7.4)	40 (8.5)	0.429
Heart diseases	579 (22.5)	112 (23.6)	0.601
Total no. of medications use	3.8 (±3.2)	4.0 (±3.2)	0.074

DBP, diastolic blood pressure; HbA1C, glycated haemoglobin A1C; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure.
Data are presented as mean ± standard deviation, number (%).

Table A2 *Evolution rate (100 person-years [95% confidence interval]) of baseline prediabetes during two periods of follow-up*

	First 6-year follow-up (2001–2004 to 2007–2010)			Second 6-year follow-up (2007–2010 to 2013–2016)		
Reversion from prediabetes to normoglycaemia						
Age group	Prediabetes (*n*)	Normoglycaemia (*n*)/ person-years	Reversion rate (95% CI)	Prediabetes (*n*)	Normoglycaemia (*n*)/person-years	Reversion rate (95% CI)
60/66	305	46/1627	2.9 (2.1–3.8)	197	28/899	3.1 (2.1–4.5)
72/78	276	38/1305	2.9 (2.1–4.0)	158	24/600	3.9 (2.6–5.9)
81–87	198	39/796	4.9 (3.6–6.7)	66	4/179	2.2 (0.8–5.9)
90+	139	24/264	9.1 (6.1–13.5)	13	1/23	4.2 (0.6–30.3)
Total	918	147/3994	3.7 (3.1–4.3)	434	57/1702	3.3 (2.5–4.3)
Progression from prediabetes to diabetes						
Age group	Prediabetes (*n*)	Diabetes (*n*)/ person-years	Progression rate (95% CI)	Prediabetes (*n*)	Diabetes (*n*)/ person-years	Progression rate (95% CI)
60/66	305	41/1513	2.7 (2.0–3.7)	197	8/859	0.9 (0.2–1.6)
72/78	276	24/1249	1.9 (1.3–2.9)	158	14/576	2.6 (1.2–3.9)
81–87	198	22/750	2.9 (1.9–4.5)	66	3/173	2.1 (0.6–5.4)
90+	139	6/255	2.3 (1.1–5.2)	13	1/21	4.6 (0.6–32.3)
Total	918	93/3769	2.5 (2.0–3.0)	434	26/1649	1.7 (1.1–2.4)
Death						
Age group	Prediabetes (*n*)	Death (*n*)/ person-years	Mortality rate (95% CI)	Prediabetes (*n*)	Death (*n*)/ person-years	Mortality rate (95% CI)
60/66	305	21/115	18.1 (11.8–27.9)	197	14/74	18.9 (11.2–32.0)
72/78	276	36/258	13.5 (9.7–18.8)	158	22/310	7.1 (4.6–10.7)
81–87	198	32/377	8.2 (5.8–11.7)	66	14/182	7.6 (4.5–12.9)
90+	139	73/365	19.7 (15.6–24.8)	13	3/34	10.0 (2.8–27.4)
Total	918	162/1117	14.2 (12.2–16.6)	434	53/600	9.0 (6.6–11.5)

Table A3 *Evolution rate (100 person-years, [95% confidence interval]) of incident prediabetes at first 6-year follow-up (2007–2010)*

Reversion from prediabetes to normoglycaemia

Age group	Prediabetes (*n*)	Normoglycaemia (*n*)/person-years	Reversion rate (95% CI)
60/66	216	79/1015	7.8 (6.2–9.7)
72/78	95	20/410	5.3 (2.9–7.6)
81–87	41	4/100	4.5 (1.5–10.7)
90+	11	1/18	5.6 (0.8–39.9)
Total	363	104/1543	6.7 (5.6–8.2)

Progression from prediabetes to diabetes

Age group	Prediabetes (*n*)	Diabetes (*n*)/ person-years	Progression rate (95% CI)
60/66	216	10/986	1.0 (0.3–1.5)
72/78	95	4/402	1.4 (0.01–2.7)
81–87	41	0/100	–
90+	11	0/17	–
Total	363	14/1506	0.9 (0.4–1.5)

Death

Age group	Prediabetes (*n*)	Death (*n*)/ person-years	Mortality rate (95% CI)
60/66	216	10/113	8.8 (4.7–16.4)
72/78	95	9/169	5.3 (2.8–10.2)
81–87	41	8/143	5.6 (2.7–11.2)
90+	11	1/39	2.6 (0.4–18.1)
Total	363	28/465	6.0 (4.2–8.7)

Table A4 *Baseline characteristics of participants with prediabetes (*n *= 918) by glycaemic status and death at 12-year follow-up*

Characteristics	Reverted to normoglycaemia (*n* = 204)	Remained as prediabetes (*n* = 380)	Progressed to diabetes (*n* = 119)	Death (*n* = 215)	*P* value
Age group					
60/66	74 (36.3)	147 (38.7)	49 (41.2)	35 (16.3)	<0.001
72/78	63 (30.4)	118 (31.1)	38 (31.9)	58 (27.9)	
81–87	43 (21.1)	84 (22.1)	25 (21.0)	46 (21.4)	
90+	25 (12.3)	31 (8.2)	7 (5.9)	76 (35.4)	
Female sex	147 (72.1)	266 (70.0)	66 (55.5)	124 (57.7)	<0.001
Education above elementary school	175 (85.8)	316 (83.2)	101 (84.9)	164 (76.3)	0.050
Current smoker	32 (15.8)	61 (16.1)	12 (10.2)	41 (19.3)	0.192
Alcohol consumption					
Occasional or no	66 (32.5)	145 (38.5)	39 (33.1)	107 (50.9)	0.003
Light-to-moderate	97 (47.8)	177 (46.9)	56 (47.5)	79 (37.6)	
Heavy	40 (19.7)	55 (14.6)	23 (19.5)	24 (11.4)	

Table A4 (*Continued*)

Characteristics	Reverted to normoglycaemia (n = 204)	Remained as prediabetes (n = 380)	Progressed to diabetes (n = 119)	Death (n = 215)	P value
Physically active	147 (72.1)	284 (74.7)	83 (69.7)	99 (46.1)	<0.001
Body mass index, kg m^{-2}					
<20	7 (3.6)	11 (2.9)	5 (4.2)	33 (17.8)	<0.001
20–24.9	82 (42.3)	151 (40.9)	33 (27.9)	71 (38.4)	
25–29.9	85 (44.3)	153 (41.5)	53 (44.9)	59 (31.9)	
≥30	19 (9.8)	54 (14.6)	27 (22.9)	22 (11.9)	
SBP, mm Hg	142 (±18.1)	144 (±18.7)	149 (±20.5)	140 (±22.7)	<0.001
DBP, mm Hg	81 (±10.4)	81 (±9.9)	83 (±12.1)	77 (±12.4)	<0.001
HbA1c (%)	5.8 (±0.1)	5.9 (± 0.2)	6.0 (±0.2)	5.9 (±0.2)	<0.001
High total cholesterol	113 (55.6)	209 (55.0)	65 (55.6)	88 (41.5)	0.007
MMSE score	28 (±2.2)	27 (± 2.1)	28 (±1.8)	27 (±5.0)	<0.001
Cerebrovascular diseases	9 (4.4)	25 (6.6)	10 (8.4)	29 (13.5)	0.004
Heart diseases	31 (15.2)	80 (21.1)	38 (31.9)	99 (46.1)	<0.001
No. of medications use	3.6 (±3.2)	3.6 (±3.4)	3.9 (±2.9)	5.1 (±3.6)	<0.001

DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; MMSE, Mini-Mental State Examination; SBP, systolic blood pressure.
Data are presented as mean ± standard deviation, number (%).
Pairwise comparison using Bonferroni correction; P-value < 0.05; reference group: participants who still had prediabetes during follow-up.

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