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Evidence-based screening, clinical care and health education recommendations for Alaska Native peoples with prediabetes living in southcentral Alaska: findings from the Alaska EARTH follow-up study

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ABSTRACT

Pre-diabetes (pre-DM) is a strong predictor of diabetes (DM) over time. This study investigated how much of the recent increase in pre-DM identified among Alaska Native (AN) peoples living in urban southcentral Alaska may be due to changes in diagnostic methods. We used clinical and demographic data collected at baseline between 2004 and 2006 and at follow-up collected between 2015 and 2017 from the urban southcentral Alaska Education and Research Towards Health (EARTH) cohort. We used descriptive statistics and logistic regression to explore differences in demographic and clinical variables among the identified pre-DM groups. Of 388 participants in the follow-up study, 243 had A1c levels indicating pre-DM with only 20 demonstrating pre-DM also by fasting blood glucose (FBG). Current smoking was the sole predictor for pre-DM by A1c alone while abdominal obesity and elevated FBG-predicted pre-DM by A1c+FBG. No participants had an elevated FBG without an A1c elevation. A substantial portion of the rise in pre-DM found among urban southcentral AN peoples in the EARTH follow-up study was due to the addition of A1c testing. Pre-DM by A1c alone should be used to motivate behavioural changes that address modifiable risk factors, including smoking cessation, physical activity and weight management.

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Introduction

Development of pre-diabetes (pre-DM) is one of the strongest predictors of conversion to diabetes mellitus (DM) over time [1,2]; thus, prevention, diagnosis and treatment of pre-DM are paramount. Treatment of pre-DM can be preventive and unlike DM, pre-DM can be reversed [3], whereas treatment of DM is aimed at controlling the disease to reduce complications. In 2020, this investigative team published estimates of DM and pre-DM incidence among Alaska Native (AN) peoples living in the urban southcentral region of the state [4]. Using a subset of the Education and Research Towards Health (EARTH) Study baseline cohort established in 2004–2006, findings in a 10-year follow-up study indicated a much greater prevalence of DM and pre-DM than had previously been reported using data obtained through the statewide Alaska Native Diabetes Registry [5]. The EARTH cohort was established to explore risk factors for chronic disease development among Alaska Native people. While the study included three regions, the 10-year follow-up study was limited to the urban southcentral area. We noted several study limitations which reduced generalisability to all urban AN residents in the region. These limitations included a relatively small sample comprised mostly of women and limited to participants with relatively recent updated contact information [4]. We also noted two major changes instituted by the American Diabetes Association (ADA) that may have contributed to an artificial increase in pre-DM rates. In 2003, the ADA revised cut-points for pre-DM from a range of fasting blood glucose (FBG) of 110–125 mg/dL to a broader range of 100–125 mg/dL [6]. In 2010, the ADA implemented glycated haemoglobin testing (A1c) as a non-fasting blood test for diagnosing DM and pre-DM [7].

At baseline, EARTH study staff screened participants for dyslipidemia and hyperglycaemia using a finger

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stick blood droplet and portable analyser. No blood samples were collected for laboratory analysis [8]. The follow-up study added a venous blood sample for immediate portable testing of FBG by venous droplet as well as long-term storage based on participant consent. Blood collection provided the means for laboratory A1c testing in the follow-up study [9]. As reported by Koller et al. (2020) [4], results of portable FBG and laboratory A1c testing indicated that the prevalence of DM more than doubled and pre-DM prevalence rose sharply to 69% of the cohort in just 10 years since baseline. Restated, pre-DM prevalence among those who did not have DM or pre-DM at baseline or DM at follow-up rose to 90% among a convenience sample of the follow-up cohort. Importantly, a substantial portion of incident pre-DM was not confined to older age.

Concerned about the substantial rise in urban AN pre-DM in the follow-up study, we questioned how much of this rise was affected by the change in ADA definition of pre-DM. In other words, what would pre-DM prevalence be if based on pre-2003 ADA criteria versus 2003 ADA criteria? We were also interested in learning whether the ability to measure A1c in the follow-up study (but not at baseline) contributed to the rise in pre-DM diagnoses. Would the same individuals with pre-DM values indicated by their A1c also have been identified as having pre-DM by FBG and vice versa? Thus, this study aimed to investigate how much of the rise in pre-DM in the Alaska EARTH follow-up sample was due to changes in the ADA criteria and to determine if there were significant demographic or metabolic differences between those with incident pre-DM diagnosed by FBG or by A1c. The overarching goal was to consider how the findings might impact pre-DM prevention, diagnosis and treatment, and referral patterns among AN peoples within the southcentral Alaska region.

Materials and methods

Study population and setting

The Alaska EARTH baseline and southcentral Alaska follow-up studies are described in detail elsewhere [8,9]. Briefly, the original EARTH study enrolled approximately 1,300 AN adults in urban south central Alaska during 2004–2006. In 2015–2017, we contacted previous participants to complete a follow-up study visit. In both visits, participants consented to a medical chart review and a clinical exam in which study staff measured height, weight, blood pressure and waist circumference. Furthermore, we collected a finger stick measure of FBG and lipids after an 8-h fast using a Cholestech LDX portable analyser in both study visits. At follow-up, study staff additionally collected venous blood for laboratory testing (e.g. A1c). Observing Tribal policies, the Alaska Area IRB, Alaska Native Tribal Health Consortium (ANTHC), and Southcentral Foundation (SCF) reviewed and approved both baseline and follow-up EARTH study proposals. ANTHC and SCF research review committees reviewed and approved all draft manuscripts [10].

Variable definitions and study methods

The objective in the previous EARTH follow-up study [4] was to report past and current prevalence and 10-year incidence of DM and pre-DM by whatever means available to maximise the study sample size. Thus, we previously defined pre-DM by post-2003 ADA criteria (i.e. FBG 100–125 mg/dL or A1c 5.7–6.4%) [7]. This "either/or" definition allowed us to retain participants from whom only a finger stick FBG was available or a participant who may not have fasted a minimum of 400 min prior to blood draw, as well as those from whom study staff could obtain a venous sample for A1c testing. In this current study, we limited analysis to incident pre-DM to minimise potential confounding due to treatment among participants with diagnosed incident DM during the follow-up period and because the number of participants with undiagnosed incident DM was too small to detect significance.

Prevalence of pre-DM using pre- and post-2003 ADA guidelines for FBG

To determine the effect of the change in ADA definitions of pre-DM by FBG on the sample for the present study, we examined pre-DM prevalence at baseline using the pre-2003 ADA criteria (FBG 110–125 mg/dL) [6] and using the revised 2003 ADA criteria (FBG 100–125 mg/dL) [7]. All participants with FBG levels collected at baseline were included in this analysis providing they had fasted at least 400 min prior to blood sample collection. We then analysed the follow-up data for these individuals with pre-DM at baseline to determine DM outcomes for those with pre-DM at baseline using both the pre-2003 and 2003 ADA criteria.

Prevalence of pre-DM using A1c as diagnostic tool

We also aimed to determine the effect of A1c as a diagnostic tool on pre-DM prevalence at follow-up. Because we were interested in *how* the participants met these criteria, the categories for this analysis were defined as: "normal" range, FBG <100 mg/dL and A1c < 5.7%; "pre-

DM by A1c alone" (5.7–6.4%), "pre-DM by FBG alone" (100-125 mg/dL), and "pre-DM by A1c+FBG", carefully excluding participants with prevalent DM at baseline and those with diagnosed or undiagnosed DM during the period of follow-up. A clinical diagnosis of DM during the follow-up period was indicated by the presence of a DM diagnosis code using the *International Classification of Diseases Ninth and Tenth Editions with Clinical Modifications (ICD-9-CM and ICD-10-CM)* [11,12] or a prescription for DM medications located in the medical chart in the period between baseline and follow-up exam (Figure 1). Those without clinically diagnosed incident DM during the period of follow-up were considered to have undiagnosed incident DM if at least one blood test (A1c or FBG) was within the DM range at the follow-up study visit. Those with either A1c or FBG greater than normal, but less than DM range at the follow-up study visit we considered to have pre-DM.

Covariates

We examined whether specific covariates differed between individuals classified per the above-defined pre-DM categories at two time points: baseline (as predictors) and follow-up. Baseline covariates of interest included age, sex, smoking status, cardiometabolic risk factors, and whether participants were diagnosed with or prescribed medications for hypertension or hypercholesterolaemia. Smoking status was categorised as current, former or never smoked based on responses to three questions derived from national surveys [13,14]. Current smoking was defined as having smoked at least 100 cigarettes during one's lifetime and having smoked within the past 12 months; former smoking was defined as having smoked 100 cigarettes, but none within the past 12 months; never smoked was defined as never smoked 100 cigarettes. Cardiometabolic risk factors included those specified by the Third Report of the National Cholesterol Education Program expert panel on detection, evaluation and treatment of high blood cholesterol in adults (ATP III) for metabolic syndrome (MetS) [15]. Based on ATP III guidelines, we defined MetS as the presence of any three of the following five factors: abdominal adiposity (waist size >40 inches in men, >35 inches in women), elevated blood pressure (≥130/85), low HDL cholesterol (HDL-C <40 mg/dL in men, <50 mg/dL in women), elevated triglycerides (≥150 mg/dL), and elevated fasting glucose (≥100 mg/dL) or glycated haemoglobin (HgA1c ≥ 5.7%).

Follow-up covariates of interest included the above baseline covariates measured at the follow-up study visit. We additionally included measures of insulin resistance (using mean homoeostasis model assessment-estimated insulin resistance, HOMA-IR), and insulin sensitivity (using mean quantitative insulin-sensitivity check index, QUICKI) for each pre-DM group. HOMA-IR was estimated using the formula: fasting insulin (μU/mL) × fasting glucose

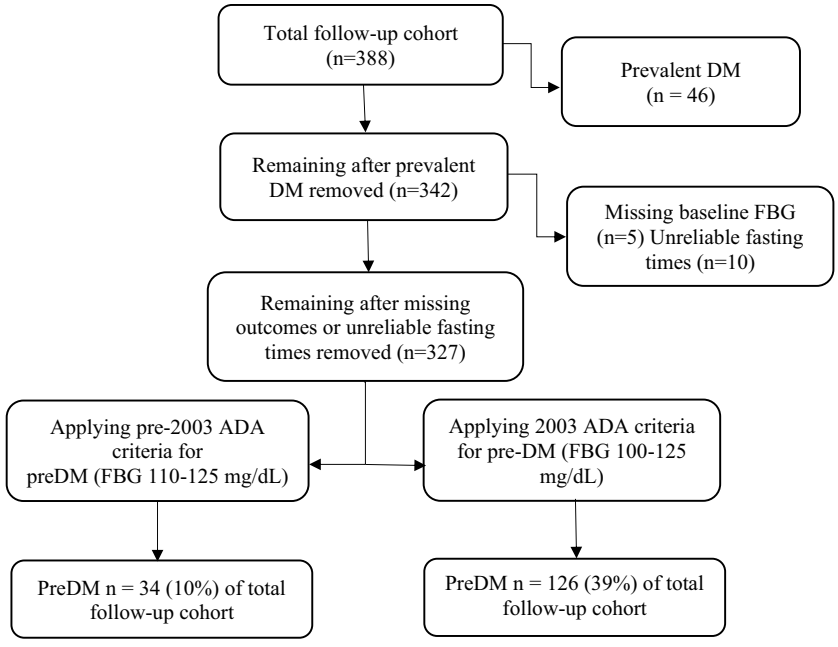

Figure 1. Flowchart of inclusions/exclusions used to compare baseline prevalence of pre-DM based on old and new ADA criteria for pre-DM by FBG.

Abbreviations/symbols: DM = diabetes based on fasting blood glucose ≥126 mg/dL or glycated haemoglobin ≥ 6.5% (48 mmol/mol), FBG = fasting blood glucose, ADA = American Diabetes Association, Pre-DM = prediabetes.

(mmol/L)/22.5 and QUICKI scores employed the formula: 1/Log (Fasting Insulin, μU/mL) + Log (Fasting Glucose, mg/dL) [16]. A HOMA-IR value > 2 suggests insulin resistance. A QUICKI value > 0.45 suggests healthy insulin sensitivity, while a value 0.30–0.45 indicates possible insulin resistance and value < 0.30 suggests DM. We calculated both values to provide insight into insulin resistance/sensitivity in participants with FBG and/or A1c in the pre-DM range at follow-up.

Statistical analysis

We calculated the baseline prevalence of pre-DM using both FBG cut points (pre- and post-2003 ADA criteria), determining significance by chi-square test ($p < 0.05$). Among only those with baseline pre-DM (by either pre-2003 and 2003 ADA criteria), we analysed diabetes outcomes to determine the direction in which each pre-DM level progressed by follow-up: normoglycemia, pre-DM by the pre-2003 criteria, pre-DM by 2003 ADA criteria or diabetes. As A1c was collected only at follow-up, we examined pre-DM outcomes by A1c alone at follow-up. We determined the number (*n*) and percent (%) of specific characteristics at baseline exam and again at follow-up in each diagnostic grouping (i.e. normoglycemia by both FBG and A1c; pre-DM by FBG alone, pre-DM by A1c alone, and pre-DM by both FBG and A1c). We used McNemar's test to determine significant differences in the prevalence of covariates between the two time points. We used median values with interquartile range to examine distributions for continuous data, determining significant differences by Kruskal–Wallis Rank Sum analysis. We selected medians, rather than means, to conserve data in the small sample size; medians are less susceptible to skew from extreme outliers and thus, no outliers were removed. As a final step, we conducted logistic regressions with multiple co-variables to determine significant baseline predictors for each outcome level as well as significant differences in associated characteristics at follow-up. Significance was based on $p < 0.05$.

Results

Pre-DM prevalence in the follow-up cohort at baseline

The follow-up cohort consisted of 388 participants from the baseline study (2004–2006) who participated in a follow-up visit ~10 years later (2015–2017). Of these 388, we removed 46 (12%) participants with prevalent DM (Figure 1). We also excluded five participants with no baseline FBG value and 10 additional participants with fewer than 400 min fasting time prior to blood testing. Of the final 327 in the follow-up cohort, 34 (10%) met criteria for pre-DM (or fasting impaired glucose, IFG) based on the pre-2003 ADA criteria (FBG = 110–125 mg/dL) at baseline. Applying 2003 ADA criteria (FBG = 100–125 mg/dL), another 92 participants met criteria for pre-DM, thus increasing the baseline prevalence of pre-DM in this cohort from 34 (10%) to 126 (39%) based on FBG alone.

Longitudinal outcomes in the follow-up cohort

We analysed participant outcomes at follow-up based on both pre-2003 and 2003 ADA pre-DM cut points for FBG and post-2003 for A1c. This analysis required both FBG and A1c results, and no participants with diagnosed DM up to the follow-up examination. Thus, in addition to removing the 46 participants with prevalent DM at baseline, we also excluded another 43 participants with one or more missing outcome data points, and another 31 participants diagnosed with and treated for DM within the 10-year follow-up period (diagnosed incident DM, Figure 2). Of the 268 participants without a clinical DM diagnosis by follow-up, an additional six participants met criteria for DM by FBG and/or A1c at the follow-up exam (undiagnosed incident DM) and were also excluded from this analysis so we could focus on baseline characteristics predictive of pre-DM at follow-up among the remaining 262 participants. Pre-DM outcomes were categorised by test type.

Analysis of these 262 participants produced 19 (7%) with normoglycemia at follow-up, while the vast majority ($n = 243/262$, 93%) met criteria for pre-DM at follow-up (Table 1). Of note, among the participants with normoglycemic values at follow-up, none reverted from pre-DM values of 110-125 mg/dL at baseline and fewer than 5 reverted to normal range with pre-DM values of 100–125 mg/dL at baseline. Of 243 participants with pre-DM at follow-up, 223 (92% of pre-DM) were identified by an elevated A1c alone (FBG within normoglycemic limits). The remaining 20 (8%) had both elevated A1c and FBG. None of the participants with pre-DM at follow-up had an elevated FBG without an elevated A1c.

Smoking status was the only baseline factor significantly different ($p = 0.02$) between the group with normoglycemia and the two pre-DM groups (Table 2). While 68% of the normoglycemic group reported that they had never smoked and only 11% reported they currently smoked, the percentage of persons with pre-DM by A1c only group who reported never smoking was 34% and current smoking was 27% (more than double the prevalence in the normoglycemic group, $p = 0.02$). Differences between the normoglycemic group and the group with pre-DM by A1c +FBG were even more substantial, with only 25% of the pre-DM by A1c+FBG group reporting never having smoked

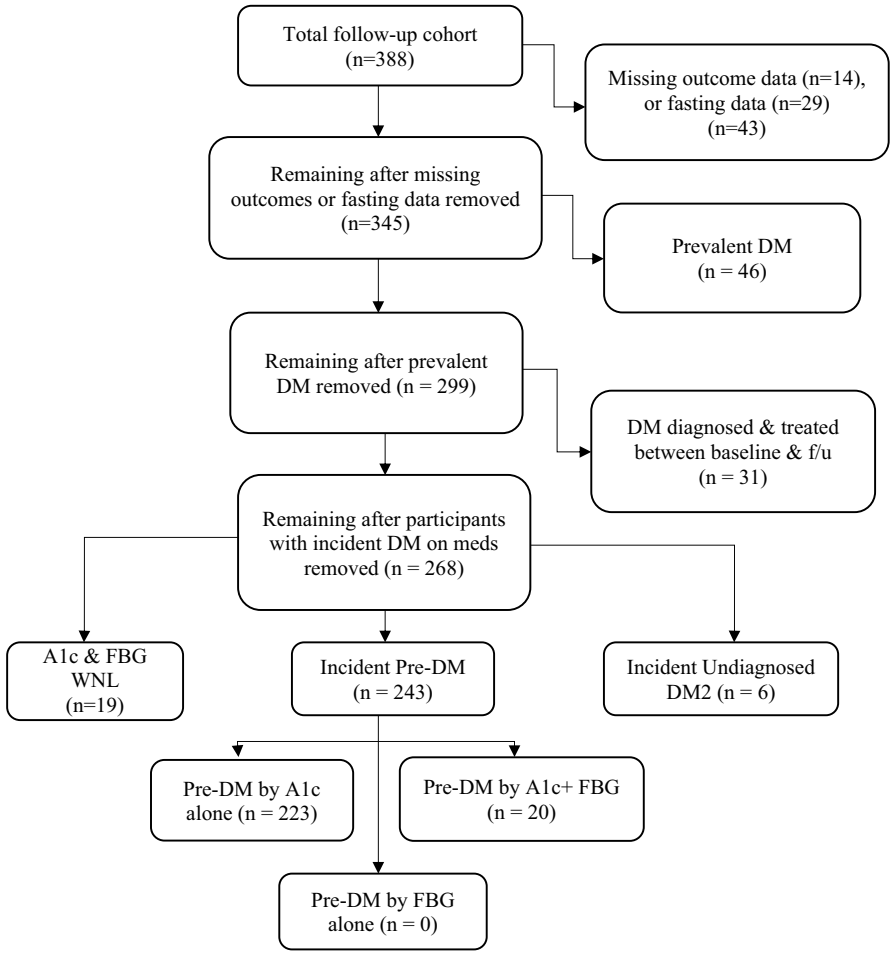

Figure 2. Flowchart of inclusion/exclusion criteria used for analysis of covariates at baseline and follow-up among participants with complete data (FBG at baseline and both A1c and FBG values at follow-up).

Abbreviations/symbols: DM=diabetes based on fasting blood glucose (FBG) ≥126 mg/dL or glycated hemoglobin (A1c) ≥6.5% (48 mmol/mol), WNL=within normal limits, Pre-DM=prediabetes based on FBG 100-125 mg/dL (39-47 mmol/mol) or A1c 5.7-6.4%.

and 50% reporting current smoking ($p = 0.01$). While the data suggest smoking may increase pre-DM risk diagnosed by A1c+FBG, differences between the two pre-DM groups were non-significant.

No significant differences in median cardiometabolic factor values were noted between the group with normoglycemic levels and the group with pre-DM by A1c, as noted in Table 2. However, we did note significant differences for baseline median waist circumference ($p < 0.004$) and FBG ($p < 0.001$) between the normoglycemic group (33.0 inches and 93 mg/dL, respectively) and the pre-DM by A1c+FBG (44.5 inches and 104 mg/dL, respectively). These differences were also significant ($p \leq 0.001$) between the pre-DM by A1c alone group (37.5 inches and 94.0 mg/dL, respectively) and the pre-DM by A1c+FBG group. Baseline body mass index (BMI) was significantly larger among those with pre-DM by A1c+FBG than the other two groups combined; when stratified, the only significant difference remained between the A1c+FBG and A1c alone groups ($p = 0.007$). Triglycerides appeared significantly greater among the two pre-DM groups combined, but no significant differences were found between any of the groups once stratified by testing method.

In multi-variable logistic regression models, smoking (OR 3.39, $p = 0.02$), larger waist size (OR 1.16, $p = 0.001$) and elevated FBG (OR 1.08, $p = 0.003$) at baseline significantly increased odds of pre-DM overall at follow-up. Excluding those with normoglycemic values at follow-up to include only those with pre-DM by either A1c or A1c+FBG ($n = 243$) in the model, baseline differences between the two pre-DM groups became apparent. In a full model controlling for age and sex, smoking, waist circumference, and FBG were significant independent predictors for pre-DM diagnosed by A1c+FBG elevations (Alt Table 3). Each 1-inch increase in waist circumference increased odds of pre-DM by 15% ($p = 0.01$), each 1 mg/dL increase in FBG increased odds by 8% ($p = 0.007$), and current smoking nearly tripled odds (OR 2.97, $p = 0.047$) for developing pre-DM by A1c+FBG.

Table 1. Descriptive statistics for demographic and clinical characteristics among participants with normoglycemia, pre-DM by A1c alone and pre-DM by A1c+FBG at follow-up.

	Normoglycemia at F/U ($n = 19$)		Pre-DM by A1c alone at F/U ($n = 223$)		Pre-DM by A1c+FBG at F/U ($n = 20$)	
	Baseline Mean (*sd*)	Follow-up Mean (*sd*)	Baseline Mean (*sd*)	Follow-up Mean (*sd*)	Baseline Mean (*sd*)	Follow-up Mean (*sd*)
Age (years)	35.2 (13.0)	46.5 (12.8)	39.0 (11.6)	49.9 (11.5)	40.3 (11.6)	48.1 (10.7)
	n (group %)	*n* (group %)	*n* (group %)	*n* (group %)	*n* (group %)	*n* (group %)
Sex (men)	3 (16)	3 (16)	66 (29)	66 (29)	7 (35)	7 (35)
Smoking						
Never (did not smoke 100 cigs in lifetime)	13 (68)	12 (67)	82 (37)	85 (40)	5 (25)	5 (25)
Former (no smoke in at least 1 year)	<25%	<25%	74 (33)	86 (39)	5 (25)	7 (35)
Current	<15%	<15%	66 (30)	44 (20)	10 (50)	8 (40)
Abdominal obesity 40 in. men, 35 in. women (102 cm men, 88 cm women)	7 (37)	9 (47)	115 (51)	145 (66)	15 (75)	18 (95)
BMI >25 kg/m^2	12 (63)	15 (79)	128 (57)	187 (84)	18 (90)	19 (95)
High trigs. ≥150 mg/dL (≥1.7 mmol/L)	5 (26)	<15%	55 (26)	41 (20)	9 (45)	10 (50)
Low HDL <40 mg/dL men, <50 mg/dL women (<1.03 mmol/L men, <1.29 mmol/L women)	<15%	5 (29)	52 (24)	55 (25)	8 (40)	9 (47)
High BP (>130/85 mmHg)	<15%	5 (26)	36 (16)	71 (32)	7 (35)	13 (65)
MetS	<25%	<15%	45 (20)	95 (43)	12 (60)	16 (80)
Total pre-DM (FBG 100-125 mg/dL)	<25%	0 (0)	59 (27)	0 (0)	14 (70)	20 (100)
FBG ≥110-125 mg/dL (6.1–6.9 mmol/L)	0 (0)	0 (0)	14 (6)	0 (0)	<25%	16 (80)
FBG ≥100-109 mg/dL (5.6–6.0 mmol/L)	<25%	0 (0)	45 (21)	0 (0)	10 (50)	<25%

Abbreviations: F/U = follow-up, pre-DM = prediabetes, A1c = glycated haemoglobin, FBG = fasting blood glucose, *n* = number, *sd* = standard deviation, Abd. = abdominal, in. = inches, cm = centimetres, BMI = body mass index, kg/m^2 = kilograms per metre squared, Trigs = triglycerides, mg/dL = milligrams per decilitre, mmol/L = millimoles per litre, HDL = high density lipoprotein cholesterol, BP = blood pressure, MetS = metabolic syndrome (3 or more of the following 5 factors present: abdominal obesity, high BP, high trigs., low HDL, elevated FBG.

Note: Cells with fewer than $n = 5$ participants reported in percentages < 25% or < 15% to protect participant confidentiality.

Importantly, after removing those with FBG elevations ($n = 20$) and including those with normoglycemia ($n = 242$) to examine baseline predictors for pre-DM by A1c alone, a history of smoking remained the only significant predictor: those with a history of smoking were 3.5 times more likely ($p = 0.02$) to develop pre-DM by A1c alone (Table 3).

Cross-sectional associations in the follow-up cohort

To analyse characteristics associated with each group at follow-up, we reviewed covariate data obtained at follow-up collected using identical methods as those collected at baseline (Table 4). At follow-up, only an elevated A1c appeared to significantly differentiate pre-DM by A1c alone from normoglycemia, while remaining significantly

Table 2. Average baseline values for age, clinical factors and smoking status among EARTH participants with normal A1c and FBG, pre-DM by A1c alone and preDM by A1c+ FBG at follow-up.

	Normoglycemia $n = 19$	PreDM by A1c only $n = 223$	PreDM by A1c +FBG $n = 20$	Kruskal-Wallis rank sum	Normo vs. Pre-DM by A1c alone	Normo vs. Pre-DM by A1c+FBG	Pre-DM by A1c alone vs. A1c +FBG
	Baseline Median (IQR)	Baseline Median (IQR)	Baseline Median (IQR)	*p*-value	*p*-values between groups (for significant differences only)		
Age (years)	35 (23.5)	38 (18)	34 (16.2)	0.47			
BMI (kg/m^2)	27.5 (9.1)	28 (8.2)	32.0 (9.8)	0.01*	0.71	0.13	0.007*
Waist Circumference (in.)	33 (8.5)	37.5 (8.5)	44.5 (8.5)	0.0005*	0.12	0.004*	0.001*
Systolic BP (mmHg)	116 (7)	115 (14)	120 (13)	0.29			
Diastolic BP (mmHg)	73 (10)	73 (11)	77.5 (17.5)	0.27			
HDL-C (mg/dL)	57.5 (13.2)	57 (21.8)	46.5 (20)	0.07			
Triglycerides (mg/dL)	100 (89)	111 (65.5)	141 (84.2)	0.046*	0.38	0.09	0.07
FBG (mg/dL)	93 (9.8)	94 (11.5)	104 (8.3)	0.0001*	0.34	0.0004*	0.0003*
	n (%)	*n* (%)	*n* (%)	*CS p-value*			
Sex, (men)	<25%	66 (29)	7 (35)	0.37			
Smoking							
Never	13 (68)	82 (34)	5 (25)	0.02*	0.02*	0.01*	0.17
Former	<25%	74 (31)	5 (25)				
Current	<15%	66 (27)	10 (50)				

Abbreviations: *n* = number, pre-DM = prediabetes, A1c = glycated haemoglobin, FBG = fasting blood glucose, normo = normoglycemia, IQR = interquartile range, BMI = body mass index, kg/m^2 = kilograms per metre squared, in. = inches, BP = blood pressure, mmHg = millimetres mercury, HDL-C = high density lipoprotein cholesterol, mg/dL = milligrams per decilitre, *n* = number, CS = chi-square.

Notes: Median used for continuous data to conserve sample size and minimise effect(s) of outliers. Cells with $n < 5$ participants reported in percentages < 25% or < 15% to protect participant confidentiality.

*Denotes significance at $p < 0.05$.

Table 3. Baseline predictors for pre-DM by A1c+FBG among participants with pre-DM by any test at follow-up ($n = 243$).

Full Model	OR	95% CI (lower, upper)		p-value
Sex (ref = women)	1.50	0.43,	5.83	0.54
Age (years)	0.98	0.94,	1.03	0.54
Triglycerides (mg/dL)	1.00	1.00,	1.01	0.51
Waist circumference (inches)	1.15	1.04,	1.29	0.01*
Systolic BP (mm Hg)	1.03	0.96,	1.10	0.41
Diastolic BP (mm Hg)	0.99	0.92,	1.06	0.73
HDL (mg/dL)	0.99	0.95,	1.03	0.64
FBG (mg/dL)	1.08	1.02,	1.14	0.007*
Current smoking (ref never)	2.97	1.01,	8.99	0.047*

Abbreviations: OR = odds ratio, CI = confidence interval, ref = referent, mg/dL = milligrams per decilitre, mmHg = millimetres mercury, HDL-C = high density lipoprotein cholesterol, FBG = fasting blood glucose.

*Significant based on p-value ≤0.05.

Note: Among those with pre-DM, smoking at baseline increased odds of pre-DM by A1c+FBG at follow-up nearly 3-fold; odds for pre-DM by A1c+FBG increased 8% for every mg/dL increase in FBG and 15% for everyone inch increase in waist circumference at baseline.

Table 4. Average follow-up values for age, clinical measures and smoking status among EARTH participants with normoglycemia, pre-DM by A1c alone and PreDM by A1c+FBG at follow-up.

	Normoglycemia n = 19	Pre-DM by A1c alone n = 223	PreDM by A1c+FBG n = 20
	Median (IQR)	Median (IQR)	Median (IQR)
Age	47 (23)	50 (18)	45.5 (17.8)
BMI (kg/m^2)	28 (7.2)	29.4 (5.0)	34.9 (11.1)
Waist Circumference (in.)	35 (7.3)	39 (7.3)	43.8 (6.0)
Systolic BP (mmHg)	114 (15.5)	118 (20.0)	124 (15.0)
Diastolic BP (mmHg)	74 (16.0)	76 (16.0)	86 (8.0)
HDL-C (mg/dL)	61 (30.0)	58 (28.3)	48 (30.5)
Trigs (mg/dL)	94 (69.0)	89 (71.5)	141 (122.6)
FBG (mg/dL)	82 (9.5)	85 (11.0)	106 (5.2)
A1c (%)	5.6 (0.2)	6.0 (0.2)	6.2 (0.15)
Fasting Insulin (μU/mL)	4.0 (4.4)	3.0 (3.0)	2.9 (3.6)
Insulin Resistance (HOMA-IR)	0.6 (0.5)	0.6 (0.7)	1.8 (1.4)
	Mean (*sd*)	**Mean (*sd*)**	**Mean (*sd*)**
Insulin Sensitivity (QUICKI)	0.45 (0.08)	0.43 (0.07)	0.36 (0.04)
Smoking Status	***n* (%)**	***n* (%)**	***n* (%)**
Never	10 (56)	74 (34)	5 (25)
Former	6 (33)	97 (45)	7 (35)
Current	<15%	44 (20)	8 (40)

Abbreviations: Pre-DM = prediabetes, A1c = glycated haemoglobin, FBG = fasting blood glucose, n = number, IQR = interquartile range, BMI = body mass index, HDL-C = high density lipoprotein cholesterol, Trigs = triglycerides, mg/dL = milligrams per decilitre, μU/mL = micro-units per millilitre, HOMA-IR = Homeostatic Model Assessment for Insulin Resistance, *sd* = standard deviation, QUICKI = Quantitative Insulin-sensitivity Check Index.

Note: Cells with $n < 5$ participants reported in percentages < 25% or < 15% to protect participant confidentiality.

different between pre-DM by A1c alone and by A1c+FBG. However, we detected significant differences between those with normoglycemia and pre-DM by A1c+FBG that were also evident between pre-DM by A1c alone and pre-DM by A1c+FBG. Compared to those with normoglycemia and pre-DM by A1c alone, median BMI, waist circumference, diastolic blood pressure and triglycerides were significantly higher among those with pre-DM by A1c+FBG. In addition, median FBG and A1c were also significantly different. Fortunately, no significant increases in insulin resistance (by HOMA-IR) or decreases in insulin sensitivity (by QUICKI) were noted between any of the groups.

Discussion

Previously, the EARTH follow-up study conducted among a convenience sampling of urban-dwelling AN cohort documented an unexpected and sharp rise in pre-DM prevalence from 39% at baseline to 69% within 10 years [4]. The present findings demonstrate that while a portion of this rise in prevalence could reflect "true" increases in pre-DM, a considerable portion was due to use of the A1c as a diagnostic tool in the follow-up study, which was not available at the baseline assessment. Indeed, as many as 223 of the 243 (92%) with pre-DM at follow-up were detected by an elevated A1c level alone, while FBG levels remained within the normoglycemic range. The present data demonstrate that if FBG alone was used as the diagnostic tool, pre-DM (or fasting impaired glucose by current ADA criteria) prevalence would be much lower (5% of the total follow-up cohort [20/388] or 8% of the cohort without diagnosed diabetes at follow-up [20/262]), far less than the 39% pre-DM prevalence observed at baseline using current ADA criteria for pre-DM. We also note that 108 participants (27% of the follow-up cohort) would have

been missed completely, as their non-fasting status would have excluded them from analysis. Together, these findings indicate several take-home messages relevant to the health care for AN peoples: the importance of consistency in application of pre-DM criteria and the prevalence and important metabolic differences between those diagnosed with pre-DM by A1c alone versus by A1c+FBG.

A major benefit of A1c testing is that it does not require a pre-draw fasting state. A major barrier to testing removed, one may surmise that increases in screening rates could produce short-term artifactual increases in diagnoses. However, we can rule this out in this longitudinal cohort study, as the same study participants were tested at both time points. Instead, the use of the A1c test at follow-up (but not available at baseline) was the primary reason for nearly 30% more pre-DM at follow-up than would have been detected using only FBG. This stark difference in prevalence contrasts to recent findings from Meijnikman et.al (2017) [17], who observed underdiagnosis of pre-DM using A1c alone in a Caucasian population. Conversely, one study of urban-dwelling Vietnamese adults [18] and another using the Korean National Health and Nutrition Examination Survey (NHANES) data [19] demonstrated substantially higher pre-DM prevalence when using A1c values compared to FBG. The mixed nature of these findings is reflected in the literature more broadly in the past 10 years [20–28]. Recent findings from the U.S. NHANES support that, compared to the oral glucose tolerance test (the gold standard), both FBG and A1c have lower sensitivity as diagnostic tests for pre-DM and DM [29]. However, NHANES data are cross-sectional national level data, not longitudinal or population-specific, and thus diagnostic differences in small populations, such as AN peoples, can be masked.

These findings have important clinical implications; specifically, they highlight a potential for pre-DM overdiagnosis if clinicians use A1c alone as a diagnostic tool and/or for inconsistent diagnosis if clinicians are differentially utilising A1c versus FBG. However, pre-DM by A1c may afford an earlier opportunity to intervene to delay or prevent DM and/or its complications, which begin to manifest before DM conversion and well before actual DM diagnosis [30]. Clinicians and healthcare systems providing care to AN people may wish to consider the guidance put forth by Tucker (2020) to rely on neither the A1c or FBG as a replacement for the oral glucose tolerance test in diagnosing DM or pre-DM unless both tests agree [29]. Alternatively, based on the findings of greater MetS risk in those with pre-DM by A1c+FBG, clinicians may consider FBG with A1c to assess DM risk. Importantly, whether A1c is relied upon alone or in concert with FBG to diagnose pre-DM, clinicians must follow ADA guidelines to screen and treat pre-DM. These data also highlight the need for consistency in measurements over time in longitudinal cohort studies.

These analyses were also intended to discern whether those with pre-DM by A1c alone were significantly different from those with pre-DM by A1c+FBG. Identifying characteristic differences at baseline and/or follow-up could help providers identify those at greatest DM risk for closer monitoring while identifying and referring all at risk to appropriate interventions to prevent disease progression and complications. Few studies in recent literature report longitudinal outcomes. Anjana et al. (2015) [31] reported that while baseline modifiable risk factors for pre-DM among Asian Indian people were similar to those identified among AN participants in this study, they did not test for differences by testing methods. Results reported by Wang et al. (2010) [32] demonstrated most instances of pre-DM found among American Indian people in the Strong Heart Study were based on an elevated FBG, rather than elevations in 2-h oral glucose values. Strong Heart Study authors also noted that elevated A1c increased risk for DM conversion from pre-DM; however, risks predicting A1c elevations in the pre-DM range were not reported.

Based on the literature, this study is the first to demonstrate smoking as a sole independent predictor for pre-DM by A1c alone in urban-dwelling AN people. We also demonstrated that in addition to smoking, those with abdominal obesity or pre-DM FBG levels at baseline were more likely to fall into the pre-DM by A1c + FBG than the A1c alone category at follow-up. As A1c measurements were not included at baseline, we could not assess whether A1c had any impact on risk for DM conversion.

We observed cross-sectional differences in covariates at follow-up between the two groups, with those diagnosed pre-DM by A1c alone having a significantly smaller waist circumference ($p = 0.003$) and lower FBG ($p = 0.004$) than those diagnosed with pre-DM by A1c + FBG. Again, the literature in the past 10 years produces mostly population-specific cross-sectional studies with mixed results. While several studies examined differences in covariates by testing methods, most concentrated on diabetes as the outcome, not pre-DM. A few studies examined associations between pre-DM testing methods and associated cardiovascular risk factors. Zhang et al. (2012) [33] reported that although southern Chinese participants with pre-DM appeared to be more sensitive to A1c testing, they also appeared to have more serious cardiovascular risk (older age, larger

waist, higher BP and poorer lipid levels) than those with elevated FBG. While this study also supplied evidence that AN people may also be more sensitive to A1c than FBG testing, these findings differ in that those with pre-DM by A1c+FBG had greater prevalence of MetS factors at follow-up than those with pre-DM by A1c alone. Using Korean NHANES data, Kim et al. (2015) reported a larger proportion of individuals with pre-DM by A1c (55%) than A1c+FBG (29%), but unlike findings in this study, also detected 16% with pre-DM by FBG without A1c elevation [19]. Comparing only A1c alone and FBG alone groups, those with pre-DM by A1c alone tended to be older age and women, while those with pre-DM by FBG had significantly higher blood pressure and waist circumference than the A1c alone group. These findings compare closely to this study.

Based on these data, a smoking history significantly increases risk for pre-DM ($p = 0.02$ by A1c alone, $p = 0.01$ by A1c+FBG), which clearly accentuates the need for smoking cessation – at any age. Overall, current smoking increased odds for pre-DM at follow-up more than threefold (OR 3.39, $p = 0.02$). Recent data show that smoking prevalence in Alaska is greater than that of the overall U.S. and that AN adults statewide exhibit more than double the prevalence of smoking of non-Native adults living in Alaska [34]. Despite these data, studies exploring tobacco cessation interventions have documented that AN people seeking care in the Tribal health system are receptive to acting upon the advice of their healthcare providers [35]. If not already doing so, primary-care providers must consistently assess smoking status and refer to cessation treatment programs using techniques such as the 5As (ask, advise, assess, assist, and arrange) [36] at the earliest opportunity. Nicotine replacement therapy is available through most Tribal health programs and the State of Alaska Tobacco Quitline [37]. Tribal tobacco cessation treatment programs, such as those already offered in the southcentral region by SCF and ANTHC [38,39], can assume an important role in pre-DM prevention, given findings in this study.

These data affirm waist circumference is an independent predictor for pre-DM by A1c+FBG, but not for pre-DM by A1c alone. Waist circumference is recommended by the National Cholesterol Education Program's ATP III guidelines to determine abdominal obesity when assessing risk for MetS, a known precursor for DM [15,40,41]. While BMI estimates total body mass, it does not account for differences in sex, race or stature (e.g. height or muscle vs. fat mass) and is not an indicator of abdominal obesity, per se. Waist circumference is measured directly and guidelines for determining abdominal obesity are sex-specific. Additionally, monitoring individual weight change is a necessary part of diabetes prevention programs because even relatively small reductions in weight over time can decrease DM and cardiovascular disease risk. In a study assessing long-term outcomes among American Indian and Alaska Native adults enrolled in the Special Diabetes Program for Indians Diabetes Prevention Program lifestyle intervention, Jiang et al. (2018) reported those who lost 5% or more of their initial weight reduced their risk for DM by 64% during the first 6 years of follow-up [42]. Importantly, whereas weight may not change substantially with the addition of physical activity, abdominal circumference will change as body mass is redistributed away from the abdomen. Observing this change in waist size may motivate individuals to remain physically active to manage their waist size, which has been shown to not only decrease diabetes risk but also decrease risks for heart disease and stroke [36].

A FBG in the pre-DM range at baseline also predicted pre-DM by A1c+FBG at follow-up. One might assume that participants with both tests elevated may have been older and possibly exposed to hyperglycaemia longer or at greater levels than those with elevated A1c alone. However, the median age among those with pre-DM by A1c alone was slightly (but not significantly) older than the group with pre-DM by both tests. These findings suggest that those with elevated A1c+FBG are at greater risk for DM conversion despite age. Median A1c level at follow-up was the only significant ($p < 0.001$) factor distinguishing those with pre-DM by A1c alone (6.0%) from those with normoglycemia (5.6%). In contrast, multiple factors at follow-up differed significantly between those with normoglycemia and pre-DM by A1c+FBG, including BMI ($p = 0.010$), waist circumference, diastolic blood pressure, triglycerides, FBG and A1c. These data support the need for follow-up of those with an elevated A1c to determine if they also have elevated FBG and expedite treatment and referral for those with both tests elevated.

Several health education opportunities for pre-DM prevention are available to AN people living in the urban southcentral Alaska region. It is important for clinicians within the Alaska Tribal Health System to provide referrals to these programs for people diagnosed with pre-DM to delay or prevent DM2 and its complications. The fact that regular primary care received at SCF by AN people with DM is associated with 177% increase in glycaemic control is noteworthy [43] and should prompt primary providers to encourage regular visits for those with pre-DM, since this condition is reversible and can prevent or delay DM, heart disease and stroke.

Despite the important findings, this study has several limitations that warrant consideration in interpreting the findings. The primary limitation is its small sample size due to the small proportion of original (baseline) study participants completing the follow-up visit 10 years later (29%). Small sample size may have restricted our ability to detect additional differences between groups. The lack of A1c measurements in the initial (baseline) study is also a limitation inherent to the Alaska EARTH study design; without this information, we are unable to determine whether the prevalence of pre-DM diagnosed via A1c changed over time or whether baseline A1c alone was predictive of conversion to DM2 over follow-up duration. Another limitation is the greater proportion of women than men. While central obesity was the primary predictor for pre-DM incidence in the follow-up cohort, the data imply women were more likely to have larger waist size than men. It is possible that abdominal obesity is tied to sex and that this interrelationship increases pre-DM risk; however, after controlling for sex, increased waist size at baseline remained significant. Study strengths are also important to note. This study is the first to use longitudinal data to investigate predictive factors for pre-DM in this urban AN population. The data confirm anecdotal observations made by those working closely with Alaska Native Diabetes Registry and the documented changes in DM2 and pre-DM incidence cited by the Alaska Native Diabetes Program – that incidence of both conditions has drastically risen in the past 15 years [5].

In conclusion, we aimed to determine how much of the rise in pre-DM in the Alaska EARTH follow-up sample was due to changes in the ADA diagnostic criteria and to assess demographic or metabolic differences between those with incident pre-DM diagnosed by A1c alone or by A1c and/or FBG testing. We found a substantial portion of the previously reported rise in pre-DM among southcentral AN peoples was an artifact of changes in the way we measured and defined pre-DM; specifically, the addition of A1c as a diagnostic criterion at follow-up which was not readily available for the baseline measurements. Further, we highlighted differences in measures of obesity and cardiometabolic health between those diagnosed with pre-DM using A1c alone versus A1c in combination with FBG.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

Data are not readily available due to Tribal research data restrictions. Researchers interested in these data may contact the corresponding author for more information on the process for requesting access to these Tribal data.

Informed Consent

Informed consent was obtained from all participants involved in the study.

Geolocation Information

This study pertains to Alaska Native EARTH Study participants living in the southcentral (Anchorage) region of the U.S. state of Alaska.

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