Experience of Point-of-Care HbA1c testing in the English National Health Service Diabetes Prevention Programme: an observational study

Short title: Experience of Point-of-care testing in the NHS DPP

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Abstract

Introduction

To report the observations of point-of-care (POC) HbA1c testing in people with non-diabetic hyperglycaemia (NDH; HbA1c 42-47mmol/mol (6.0-6.4%)), applied in community settings, within the English National Health Service Diabetes Prevention Programme (NHS DPP).

Research Design and Methods

A service evaluation assessing prospectively collected national service-level data from the NHS DPP, using data from the first referral received in June 2016 to October 2018. Individuals were referred to the NHS DPP with a laboratory measured HbA1c in the NDH range and had a repeat HbA1c measured at first attendance of the programme using one of three POC devices; DCA Vantage, Afinion or A1C Now+. Differences between the referral and POC HbA1c and the standard deviation (SD) of the POC HbA1c were calculated. The factors associated with the difference in HbA1c and the association between POC HbA1c result and subsequent attendance of the NHS DPP were also evaluated.

Results

Data from 73,703 participants demonstrated a significant mean difference between the referral and POC HbA1c of -2.48mmol/mol (-0.23%) ($t=157, p<0.001$) with significant differences in the mean difference between devices ($F(2, 73,700)=738, p<0.001$). The SD of POC HbA1c was 4.46mmol/mol (0.41%) with significant differences in SDs between devices ($F(2, 73,700)=1,542, p<0.001$). Participants who were older, from more deprived areas and from Asian, black and mixed ethnic groups were associated with smaller HbA1c differences. Normoglycaemic POC HbA1c vs. NDH POC HbA1c values were associated with lower subsequent attendance at behavioural interventions (58% vs. 67%, $p<0.001$).

Conclusions

POC HbA1c testing in community settings was associated with significantly lower HbA1c values when compared to laboratory-measured referrals. Acknowledging effects of regression to the mean, these differences were also associated with POC method, location, individual patient-factors and time between measurements. Compared to POC HbA1c values in the NDH range, normoglycaemic POC HbA1c values were associated with lower subsequent intervention attendance.

What is already known about this subject?

Point-of-care (POC) HbA1c devices are increasingly used in community settings and may vary in performance.

What are the new findings?

POC HbA1c measurements within the NHS DPP were significantly lower when compared to referral HbA1c measurements. These differences were associated with the POC assay, it's location of use, individual patient-factors (including deprivation status, age and ethnicity) and the time between measurements.

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

Practitioners using POC HbA1c devices to assess people with NDH should be aware of factors associated with differences in HbA1c values but crucially the impact of these values on interpretation and on subsequent attendance at behavioural interventions.

- POC HbA1c measurements within the National Health Service Diabetes Prevention Programme were significantly lower when compared to referral venous laboratory HbA1c measurements.
- Acknowledging the effects of regression to the mean, the differences observed were also associated with the POC device used, individual patient factors and time between measurements.
- The decrease moved a proportion of people into the normoglycaemic range, who were then less likely to attend behavioural interventions.

Introduction

In 2016, the Healthier You: National Health Service Diabetes Prevention Programme (NHS DPP) was developed to prevent or delay onset of type 2 diabetes in adults in England identified with non-diabetic hyperglycaemia (NDH) (glycated haemoglobin (HbA1c) 42-47mmol/mol (6.0-6.4%) or fasting plasma glucose (FPG) 5.5–6.9mmol/l).[1] The NHS DPP delivers behavioural interventions based on guidance from the National Institute for Health and Care Excellence (NICE) via Provider organisations who used serial point-of-care (POC) HbA1c testing to track responses to interventions.[2]

Routine internal monitoring of the programme indicated a significant mean difference between laboratory measured HbA1c values obtained on referral to the programme (undertaken by referring general practices) and values obtained on first attendance of the programme, where HbA1c was re-measured using a POC device.

Differences in an HbA1c level measured at two time points may reflect regression to the mean, a genuine biological change, or variation in the testing methodology used. The demographic, individual patient or assay-related factors that affect change in HbA1c outside of the diabetes range are not well-studied. This knowledge is vital however, if serial measurements are used in people with NDH, which represents a narrow clinical range of interest, and where small changes in HbA1c have the potential to diagnose type 2 diabetes at one extreme or declassify NDH status at the other.

Using data from the first 28 months of the NHS DPP, we aimed to

1) Determine if there were significant differences between laboratory measured HbA1c and subsequent POC HbA1c measurements across all devices and testing pathways in the NHS DPP
2) Identify modifiable and non-modifiable factors associated with observed differences between laboratory measured HbA1c and POC measured HbA1c in the NHS DPP
3) Assess the association between POC re-measurements of HbA1c and subsequent attendance of the NHS DPP .

The study does not attempt to assess the performance of POC devices in the measurement of HbA1c but rather to examine the implications of their use in a community setting as a follow up to a laboratory HbA1c measurement.

Research Designs and Methods

Study design

A service evaluation in England assessing prospectively collected national service-level data from the NHS DPP using data from the first referral received in June 2016 to October 2018.

Intervention

The NHS DPP delivers behavioural interventions encouraging weight loss in those overweight or obese, increased physical activity and healthier diets, through a minimum of 13 face-to-face group-based sessions, over at least 9 months, constituting at least 16 hours of contact-time. Over this time period, interventions were delivered by one of four service Providers selected as part of a national competitive procurement process: Reed Momenta Ltd (London, UK), ICS Health and Wellbeing (Leeds, UK), Ingeus UK Ltd (London, UK), and Living Well Taking Control LLP (Birmingham, UK).

Participants

Individuals with a test result indicating NDH within the previous 12 months, aged 18 years or over, not pregnant and not previously diagnosed with Type 2 diabetes were identified from NHS Health Checks,[3] general practice records or routine clinical practice. The majority of referrals included HbA1c results from laboratory testing, rather than FPG, although testing methodology was not stipulated. Individuals referred to the programme were invited to attend an Initial Assessment (IA) during which further details of the programme were provided, and participants were assigned to a group for intervention delivery.

Data collection

Programme providers were contractually required to collect a minimum dataset; age, sex, post-code, the referral HbA1c/FPG and optionally, weight, were recorded on referral; ethnicity, weight and height at IA. Providers were contractually required to assess HbA1c at IA if the referral HbA1c or FPG was assessed more than 3 months previously. This service evaluation involved assessment of anonymised data collected during routine service delivery; NHS England has published an information governance framework setting out the legal basis for data collection and data flows, ensuring that the service and its evaluation are delivered in compliance with data protection legislation.[4]

Sex was recorded as male, female or indeterminate. Recorded ages were grouped (to align with both NHS health checks and retirement age) into <40, 40-64, 65-74 and 75+ years and self-reported ethnicity as white, Asian, black, mixed or other. Deprivation scores were obtained using Lower Super Output Area (derived from participant postcode) linked to the deprivation quintile from the Index of Multiple Deprivation. BMI was calculated for participants who had weight and height recorded at IA. All variables also include an unknown category where either the participant declined to give the relevant information, or where a value was not recorded.

POC Devices

An expert working group was established to advise on internationally stipulated minimum performance criteria for HbA1c within the programme and provided more specific guidance around use of POC devices,[5] including calibration to the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) reference measurement procedure (RMP); and that Medicines and Healthcare products Regulatory Authority (MHRA) guidance around the provision of a quality framework, including internal quality control and external quality assessment (EQA) to support POC delivery, be followed.[6]

EQA, a process by which individual analytical devices can be compared to a reference or other devices, captures device bias and, with serial assessment, changes in analytical performance over time for any single device. Deviation in EQA performance can be investigated and resolved.

The four Providers used HbA1c POC devices: DCA Vantage (Siemens Healthcare Ltd, Guildford, UK), Afinion (Abbott Diagnostics, Maidenhead, UK) or A1C Now+ (BHR Pharmaceutical Ltd, Nuneaton, UK). A 'POC pathway' was defined as the combination of the device used and the location where testing was performed - either a Lloyds pharmacy (subcontracting arrangements used by two Providers) or "in-house" (a community venue where a Provider delivered the intervention). Pathways are listed in Table 1. Providers used the same device and pathway for each participant. Though not contractually required, in some individuals Providers undertook POC HbA1c within 3 months of the referral HbA1c.

Table 1: Provider pathways and devices used by the NHS Diabetes Prevention Programme

Provider Pathway	**Device**
Living Well Taking Control - Provider 1	Afinion
ICS Health and Wellbeing - Provider 2	DCA Vantage
Reed via Lloyds Pharmacy - Provider 3	A1c Now+
Reed in-house pathway - Provider 3	A1c Now+
Ingeus via Lloyds Pharmacy - Provider 4	A1c Now+
Ingeus in-house pathway - Provider 4	DCA Vantage

Outcomes

The primary outcomes were the difference in HbA1c between laboratory measured HbA1c and subsequent POC measured HbA1c and standard deviation (SD) of POC measured HbA1c. The factors associated with the difference in HbA1c and the association between IA POC HbA1c and subsequent attendance were also evaluated.

The HbA1c difference between referral and IA and the SD of IA POC HbA1c were calculated for participants with a valid HbA1c recorded at both referral and IA. For a subgroup of participants with available data, the relationship between recorded HbA1c difference and weight change was examined. In those who had had sufficient time to attend, the relationship between IA POC HbA1c results and subsequent attendance at the group-based behavioural intervention sessions was studied, by grouping individuals according to IA POC HbA1c values as normoglycaemic (<42 mmol/mol), NDH (42-47.9mmol/mol) and Type 2 diabetes range ($\geq$48 mmol/mol).

Statistical Analysis

A paired t-test was used to test for differences between the mean referral and mean IA HbA1c and a one-way analysis of variance was used to determine differences in the mean HbA1c change at IA. Where the null hypothesis for Bartlett's test for equality of variances was rejected, Kruskal-Wallis

equality of population rank test was also undertaken. Levene's test was used to test equality of SDs between pathways.

Mixed effects linear regression models were used to identify factors associated with differences in HbA1c. In Model One, pathway, referral HbA1c, time (days) between referral HbA1c and IA HbA1c, and participant characteristics (age, sex, ethnicity and deprivation) were considered as fixed effects and local referral area as a random effect with the contribution of the random effect quantified using the Intraclass Correlation Coefficient (ICC). Local referral areas are only associated with a single provider and therefore incorporate the same facilities and facilitators used by that provider. Variation between the four providers was directly accounted for by a fixed effect in the model. Model Two substituted pathway for device, with other variables remaining the same. Model three included weight change between referral and IA. A mixed-effects logistic regression model was used to identify factors associated with attendance of at least one intervention session following IA and was applied to the subgroup who had had at least 6 months to attend an intervention session. Pathway, participant characteristics (including BMI at IA) and POC HbA1c grouping at IA were considered as fixed factors and local referral area as a random effect. Only participants from the given subgroup for whom all data fields were complete were included in the regression analyses.

Sensitivity analyses were conducted on the regression models using multiple imputation, employing the Multivariate Chained Equations approach to impute missing data and then comparing the results to the primary analyses.[7] We used the Fraction of Missing Information as a rule of thumb to estimate the number of imputations needed and imputed missing values for age, deprivation, sex, ethnicity and BMI. All participants had recorded data for pathway, local referral area, referral HbA1c and IA HbA1c.

Statistical significance was defined as p-value<0.05. Where there were multiple comparisons, a post-hoc Bonferroni correction was applied. Confidence Intervals (Cis) were set at 95%. All data were analysed using Stata version 15.

Results

HbA1c at referral

Overall 73,703 participants had an HbA1c measurement at both referral and IA. Characteristics of participants are provided in Table 2; 44% of participants were male, the mean (SD) age was 64 (12) years and 20% were of black, Asian, mixed or other (BAME) ethnicity, 65% white and 16% unknown. There was broadly equal representation from all deprivation quintiles. The mean (SD) HbA1c at referral was 43.7(1.5) mmol/mol (6.1(0.14)%). Though statistically significant differences, there were no clinically meaningful differences in the mean (SD) referral HbA1c by pathway, ranging from 43.6 (1.5) mmol/mol (6.1 (0.14) %) to 43.8 (1.5) mmol/mol (6.2 (0.14) %). Data were missing for; age (<0.01%), sex (0.6%), ethnicity (15.7%) and deprivation (0.4%). There were no missing data for referral HbA1c, IA HbA1c and pathway and device.

HbA1c at Initial Assessment

The mean (SD) number of days between HbA1c measurements was 203 (120) days. The mean (SD) IA HbA1c was 41.2 (4.46) mmol/mol (5.9 (0.41) %), a significant difference of -2.48mmol/mol (-0.23%) from the mean referral HbA1c (t=157,p<0.001). Significant differences were observed for all pathways and for all devices (Table 2). Mean differences were significantly different between pathways (F(5, 73,697)=374,p<0.001) and between devices (F(2, 73,700)=738, p<0.001), with significant differences for 11 of the 15 pairwise combinations of pathways and all pairwise combinations of devices (Supplementary Tables S1 and S2).There were significant differences in the SD of the HbA1c at IA between pathways (F(5, 73,697)=598.9, p<0.001) and devices (F(2, 73,700)=1541.8, p<0.001) (Table 2). There were no significant differences in the SD between pathways using the same device. There were significant differences between the DCA Vantage and A1c Now+ devices (F(1, 62,133)=2186.6,p<0.001), Afinion and A1c Now+ devices F(1, 42,832)=1548.4,p<0.001) and Afinion and DCA Vantage devices F(1, 42,502)=68.0, p<0.001).

Factors associated with the change in HbA1c from referral to IA

Univariate analyses of outcomes are provided in Table 2. HbA1c differences between referral and IA measurements became larger as the number of days between measurements increased from the <28 days category up to the 84-111 days category, then reduced as the number of days increased further (Figure 1, panel A). The SD of the HbA1c at IA increased as the number of days between measurements increased (Figure 1, panel B). Regression analysis indicated that for each 1.0mmol/mol higher value of referral HbA1c, there was a corresponding 0.2mmol/mol greater difference between referral and IA POC HbA1c (Table 3). POC pathway had a significant association with observed HbA1c difference; using the ICS Health and Wellbeing (DCA Vantage) pathway (which had the greatest number of participants) as a reference, no difference in the magnitude of reduction was observed for the Ingeus (DCA Vantage) pathway, however all other pathways were associated with a greater HbA1c difference. Measurements from participants who were older or from more deprived areas were associated with smaller HbA1c differences, but there was no effect of sex. Relative to white groups, Asian, black and mixed ethnic groups had a smaller HbA1c difference. Clustering by local referral area made a proportionally small contribution to the outcomes (ICC 3.7(2.6-5.4)%). In Model Two, device was found to be significantly associated with HbA1c difference; Afinion and A1C Now+ devices were both associated with larger differences compared to the DCA Vantage device (supplementary Table S3).

Table 2: Mean HbA1c laboratory measurement at Referral, point-of-care (POC) re-measurement at Initial Assessment (IA), change in HbA1c between referral and IA and Standard deviation (SD) of IA HbA1c by device, pathway and participant characteristics

		N	%	Mean referral HbA1c mmol/mol	SD of referral HbA1c mmol/mol	Mean IA POC HbA1c mmol/mol	Mean change in HbA1c (95% CI) mmol/mol	P value (paired t-test)	P value (one-way ANOVA)**	SD of IA POC HbA1c (95% CI) mmol/mol
Overall		73,703		43.7	1.5	41.2	-2.48 (-2.51 to -2.45)	<0.001	n/a	4.46 (4.44 to 4.48)
Device	A1c Now+	31,230	42%	43.6	1.5	40.6	-3.04 (-3.10 to -2.99)	<0.001	<0.001	5.28 (5.24 to 5.33)
	Afinion	11,586	16%	43.7	1.5	40.8	-2.85 (-2.91 to -2.79)	<0.001		3.35 (3.30 to 3.39)
	DCA Vantage	30,887	42%	43.7	1.5	41.9	-1.78 (-1.82 to -1.74)	<0.001		3.75 (3.72 to 3.78)
Pathway	ICS Health and Wellbeing (DCA Vantage)	29,422	40%	43.7	1.5	42.0	-1.76 (-1.80 to -1.72)	<0.001	<0.001	3.74 (3.71 to 3.77)
	Ingeus Inhouse (DCA Vantage)	1,465	2%	43.6	1.5	41.4	-2.18 (-2.37 to -2.00)	<0.001		3.89 (3.76 to 4.04)
	Ingeus Lloyds (A1c Now+)	4,108	6%	43.6	1.5	39.4	-4.23 (-4.38 to -4.08)	<0.001		5.06 (4.95 to 5.17)
	Living Well Taking Control (Afinion)	11,586	16%	43.7	1.5	40.8	-2.85 (-2.91 to -2.79)	<0.001		3.35 (3.30 to 3.39)
	Reed Inhouse (A1c Now+)	26,767	26%	43.6	1.5	40.8	-2.86 (-2.93 to -2.80)	<0.001		5.30 (5.25 to 5.34)
	Reed Lloyds (A1c Now+)	355	0%	43.8	1.5	40.9	-2.86 (-3.34 to -2.39)	<0.001		4.86 (4.53 to 5.25)
Sex	Male	32,561	44%	43.7	1.5	41.2	-2.51 (-2.56 to -2.47)	<0.001	0.2259**	4.62 (4.59 to 4.66)
	Female	40,684	55%	43.7	1.5	41.2	-2.46 (-2.50 to -2.42)	<0.001		4.33 (4.30 to 4.36)
	Indeterminate	49	0%	43.6	1.4	41.4	-2.25 (-3.81 to -0.69)	0.01		5.53 (4.61 to 6.91)
	Unknown	409	1%	43.7	1.5	41.5	-2.27 (-2.61 to -1.93)	<0.001		3.62 (3.38 to 3.88)
Age	<40	*	*	43.6	1.5	41.2	-2.41 (-2.62 to -2.21)	<0.001	<0.001	5.53 (5.38 to 5.68)
	40-64	30,483	41%	43.7	1.5	41.4	-2.33 (-2.38 to -2.28)	<0.001		4.74 (4.70 to 4.78)

		N	%	Mean referral HbA1c mmol/mol	SD of referral HbA1c mmol/mol	Mean IA POC HbA1c mmol/mol	Mean change in HbA1c (95% CI) mmol/mol	P value (paired t-test)	P value (one-way ANOVA)**	SD of IA POC HbA1c (95% CI) mmol/mol
	65-74	25,228	34%	43.7	1.5	41.1	-2.60 (-2.65 to -2.55)	<0.001		4.21 (4.17 to 4.25)
	75+	15,388	21%	43.7	1.5	41.1	-2.60 (-2.66 to -2.54)	<0.001		4.05 (4.01 to 4.10)
	Unknown	*	*	*	*	*	*	*	*	*
Ethnicity	Asian	7,998	11%	43.8	1,6	41.8	-2.06 (-2.15 to -1.97)	<0.001	<0.001	4.21 (4.15 to 4.28)
	Black	4,917	7%	43.8	1.5	42.3	-1.48 (-1.63 to -1.33)	<0.001		5.36 (5.26 to 5.47)
	Mixed	1,009	1%	43.6	1.5	42.0	-1.65 (-1.90 to -1.40)	<0.001		4.12 (3.95 to 4.31)
	Other	624	1%	43.7	1.5	40.8	-2.84 (-3.21 to -2.46)	<0.001		4.96 (4.70 to 5.25)
	White	47,610	65%	43.6	1.5	41.1	-2.55 (-2.59 to -2.52)	<0.001		4.12 (4.09 to 4.14)
	Unknown	11,545	16%	43.7	1.5	40.7	-2.97 (-3.06 to -2.88)	<0.001		5.36 (5.29 to 5.43)
Deprivation	IMD 1 (most deprived)	15,031	20%	43.7	1.5	41.6	-2.12 (-2.19 to -2.05)	<0.001	<0.001	4.82 (4.77 to 4.88)
	IMD 2	14,700	20%	43.7	1.5	41.4	-2.31 (-2.38 to -2.24)	<0.001		4.59 (4.54 to 4.64)
	IMD 3	15,098	20%	43.7	1.5	41.2	-2.47 (-2.53 to -2.40)	<0.001		4.33 (4.28 to 4.38)
	IMD 4	14,389	20%	43.7	1.5	40.9	-2.71 (-2.77 to -2.64)	<0.001		4.23 (4.18 to 4.28)
	IMD 5 (least deprived)	14,163	19%	43.6	1.5	40.8	-2.83 (-2.90 to -2.76)	<0.001		4.25 (4.20 to 4.30)
	Unknown	322	0%	43.6	1.5	40.7	-2.97 (-3.38 to -2.56)	<0.001		3.86 (3.59 to 4.19)

* Suppressed due to small numbers

**The Bartlett's test for equality of variances was rejected in all cases. The K-wallis test gave the same result as the ANOVA in term of significance with the exception of Sex where it indicated a significant difference ($p < 0.0055$).

Association of HbA1c change with weight

A subset of 20,576 participants had available weight measurements at referral and IA. At referral, the mean (SD) weight was 81.7(18.3) kg and mean (SD) HbA1c, 43.6 (1.5) mmol/mol (6.1 (0.14) %). The mean weight change between referral and IA was +1.4kg (t= 39.8,p<0.001)) with 56% of participants gaining weight, 17% remaining the same and 27% losing weight. The mean HbA1c difference between referral and IA for those with recorded weight measures was -3.13mmol/mol (-0.29%) (t=95,p<0.001). A reduction in the mean HbA1c was observed across all weight change categories (gaining weight/remaining the same/losing weight). Incorporating weight into the regression model (Model Three) showed that change in the referral weight had a small, but significant positive association with the change in HbA1c; for each 1kg increase in weight there was 0.06 mmol/mol smaller decrease in HbA1c (supplementary Table S4). The ICC was 1.8 (0.9-3.7)%.

Association between POC HbA1c result and attendance at subsequent intervention session

Studying only those who had sufficient time to attend an intervention session (46,894), 48% of HbA1c measurements were in the normoglycaemic range, 46% in the NDH range and 6% in the type 2 diabetes range. Participants with an IA POC HbA1c in the normoglycaemic range had significantly lower subsequent attendance at an intervention session compared to those in the NDH range (58% vs. 67%; p<0.001). Logistic regression analysis indicated that participants who were older, up to 74 years, female, from less deprived areas and with a higher BMI, were more likely to attend a subsequent intervention session. It also confirmed lower attendance for those with IA POC HbA1c in the normoglycaemic range, even after adjusting for other factors (Table4). The ICC was 26.1(18.3-35.8)%.

Sensitivity analyses conducted by re-running the regression models using imputed data showed no changes in direction and magnitude of the associations (supplementary Tables S5-8).

Table 3: Difference between laboratory measured HbA1c at Referral and Point-of-Care re-measurement at Initial Assessment by pathway (N=61,623), mixed effects linear regression

		Coefficient	95% lower CI	95% upper CI	Standard error	P value
	Referral HbA1c Reading	-0.20	-0.22	-0.18	0.01	<0.001
Pathway	ICS Health and Wellbeing (DCA Vantage)					
	Ingeus Inhouse (DCA Vantage)	-0.34	-0.93	0.24	0.30	0.25
	Ingeus Lloyds (A1c Now+)	-2.18	-2.77	-1.60	0.30	<0.001
	Living Well Taking Control (Afinion)	-0.85	-1.37	-0.32	0.27	<0.001
	Reed Inhouse (A1c Now+)	-0.98	-1.58	-0.39	0.30	<0.001
	Reed Lloyds (A1c Now+)	-1.83	-2.57	-1.09	0.38	<0.001
Sex	Male					

		Coefficient	95% lower CI	95% upper CI	Standard error	P value
	Female	0.00	-0.06	0.07	0.03	0.993
	Indeterminate	0.82	-0.37	2.01	0.60	0.18
Age group	<40					
	40-64	0.34	0.16	0.52	0.09	<0.001
	65-74	0.38	0.19	0.56	0.10	<0.001
	75+	0.41	0.22	0.61	0.10	<0.001
Ethnicity	White					
	Asian	0.36	0.25	0.47	0.06	<0.001
	Black	0.93	0.80	1.07	0.07	<0.001
	Mixed	0.63	0.38	0.88	0.13	<0.001
	Other	0.15	-0.17	0.47	0.16	0.35
Deprivation	IMD 1 (most deprived)					
	IMD 2	-0.11	-0.22	-0.01	0.05	0.03
	IMD 3	-0.19	-0.29	-0.09	0.05	<0.001
	IMD 4	-0.28	-0.39	-0.17	0.05	<0.001
	IMD 5 (least deprived)	-0.34	-0.45	-0.23	0.06	<0.001
Number of days between referral and IA HbA1c	<28 days					
	28-55 days	-0.72	-1.06	-0.38	0.17	<0.001
	56-83 days	-0.98	-1.31	-0.65	0.17	<0.001
	84-111 days	-1.51	-1.83	-1.20	0.16	<0.001
	112-139 days	-1.31	-1.63	-0.99	0.16	<0.001
	140-167 days	-1.31	-1.63	-0.99	0.16	<0.001
	168-195 days	-1.17	-1.50	-0.85	0.17	<0.001
	196-223 days	-1.09	-1.41	-0.76	0.17	<0.001
	224-251 days	-1.12	-1.45	-0.79	0.17	<0.001
	252-279 days	-1.06	-1.39	-0.73	0.17	<0.001
	280-307 days	-0.99	-1.33	-0.66	0.17	<0.001
	308-335 days	-0.89	-1.23	-0.55	0.17	<0.001
	336-363 days	-0.67	-1.01	-0.33	0.17	<0.001
	363-739 days	-0.81	-1.13	-0.49	0.16	<0.001
	>730 days	-0.84	-1.72	0.03	0.45	0.06
	Constant	7.63	6.61	8.65	0.52	<0.001

Random-effects Parameters	Estimate	Std. Err.	95% lower	95% upper
Local referral area: Identity				
var(_cons)	0.61	0.12	0.42	0.89
var(Residual)	15.68	0.09	15.51	15.86

LR test vs. linear model: chibar2(01) = 1619.49 Prob>=chibar2=<0.001

Table 4: Attendance of at least one Intevention Session in the NHS Diabetes Prevention Programme after Initial Assessment (N=33,544), mixed effects logistic regression

		Odds ratio	95% lower CI	95% upper CI	P value
Pathway**	ICS Health and Wellbeing (DCA Vantage)				
	Living Well Taking Control (Afinion)	2.17	0.99	4.75	0.05
	Reed Inhouse (A1c Now+)	1.67	0.72	3.86	0.23
	Reed Lloyds (A1c Now+)	1.62	0.65	4.05	0.3
Sex	Male				
	Female	1.07	1.02	1.12	0.01
	Indeterminate	0.76	0.34	1.67	0.49
Age	<40				
	40-64	1.64	1.43	1.88	<0.001
	65-74	2.37	2.06	2.73	<0.001
	75+	1.90	1.64	2.20	<0.001
Ethnicity	White				
	Asian	1.09	1.00	1.18	0.05
	black	1.30	1.18	1.44	<0.001
	mixed	1.17	0.97	1.41	0.1
	other	1.28	0.95	1.71	0.1
Deprivation	IMD 1 (most deprived)				
	IMD 2	1.17	1.09	1.26	<0.001
	IMD 3	1.29	1.20	1.40	<0.001
	IMD 4	1.33	1.23	1.44	<0.001
	IMD 5 (least deprived)	1.46	1.34	1.59	<0.001
BMI at Initial Assessment	Underweight/healthy				
	Overweight	1.16	1.08	1.24	<0.001
	Obese	1.27	1.18	1.36	<0.001
HbA1c measurement at Initial Assessment	NDH (≥ 42 to < 48 mmol/mol)				
	Normoglycaemic (<42mmol/mol)	0.71	0.67	0.75	<0.001
	Diabetes >(47mmol/mol)*	0.32	0.28	0.35	<0.001

Random-effects Parameters	Estimate	Std. Err.	[95% Conf.	Interval]
Local referral area: Identity var(_cons)	1.16	0.27	0.74	1.84

LR test vs logisitic model: chibar = 1851.98 Prob>=chibar2= <0.001

*Participants with a HbA1c > 51 mmol/mol are taken off the Programme and put on to Type 2 diabetes treatment pathways **For Ingeus, the Intial Assessment is spread across the first intervention session and not comparable to other providers, therfore was not included in the regression analysis

Conclusion

Summary of key findings

Data from 73,703 participants in the NHS DPP show significant reductions between referral laboratory measured HbA1c and HbA1c re-measured using a POC device on first attendance of the programme. Acknowledging the effects of regression to the mean, the magnitude of the reduction in HbA1c observed was associated with the POC device used, the POC testing pathway, individual participant factors including age, ethnicity and social deprivation, and time between measurements. Furthermore, reductions in HbA1c were greater than concurrent weight change would suggest is attributable to behaviour change, although it is possible that other behavioural modification, independent of weight change, and not captured in this study, were also associated with the mean HbA1c difference. POC HbA1c in the normoglycemic range were associated with lower subsequent intervention attendance. However, it is important to note that this study does not attempt to assess the accuracy of POC testing, but rather examines the implications of using POC in the NHS DPP.

Use of POC HbA1c devices

There is increasing interest in the use of POC diagnostics internationally, where the provision of results in real-time might positively impact patient care.[8] Despite reasonable POC HbA1c testing performance in laboratory method evaluations, performance has been variable in some research studies,[9-11] although newer generation analysers have shown improved analytical performance. [12-13] While the use of POC HbA1c in community settings has generated interest,[14-18] performance of POC HbA1c away from highly regulated, specialist supported laboratories within the narrow NDH range, remains unclear.

The NHS DPP does not generate contemporaneously measured POC and laboratory-measured HbA1c and cannot robustly validate POC device performance against a reference. However, significant differences in the mean HbA1c between referral and IA were demonstrated for all pathways and devices. POC pathway and device had significant associations with the observed HbA1c difference, independent of other variables, including the time between measurements. The association of higher referral HbA1c values with larger differences suggests regression to the mean. However, the mean HbA1c differences were significantly larger for all devices and pathways than the mean HbA1c differences between two laboratory HbA1c measurements as part of a previously published regional study, the Norfolk Diabetes Prevention Study.[19, 20] While regression to the mean is likely contributory, there is no obvious reason why the contribution should be so much greater for NHS DPP compared to the previous regional study, although the regional population was smaller, less ethnically diverse with less variation by age and over a shorter time period. One potential explanation for the observed differences in our study is the introduction of a significant negative bias (attributable to both pathway and device) when POC HbA1c testing was applied in the community setting.

The significant differences in the SDs of IA POC HbA1c between pathways may reflect differences in the level of training of the user, location and transportation of devices, or other factors such as device

maintenance and calibration, although the POC HbA1c device used was a significant independent factor with significant differences between all three devices, suggesting the underlying assay methodology was an important contributor.

Use of POC HbA1c assays in the NDH range

The IFCC taskforce (TF) published performance criteria for HbA1c methods using total allowable error, a concept applied to the measurement of any analyte that encompasses both assay bias and imprecision.[21] Total allowable error that falls within the biological variability of an analyte or below the threshold for a clinically meaningful change is considered acceptable. For HbA1c, a total allowable error of 5mmol/mol is an internationally derived performance standard for HbA1c assays.[21,22] Laboratory environments are highly controlled with specialists available to identify errors and troubleshoot them quickly. In contrast, POC application in community settings may struggle with recognition of quality issues without adequate support.[18,21,22,23] Indeed, in one study, many non-laboratory practitioners did not appreciate the impact of biological variability and analytical imprecision on small changes in HbA1c.[24] However, while this allowable error is acceptable when applied to the values of HbA1c commonly encountered in diabetes care, it nearly completely traverses the NDH range, challenging meaningful interpretation despite appropriate quality frameworks.

The EurA1c study assessed both laboratory and POC devices in different countries and settings, using the 5mmol/mol total allowable error criteria set by the IFCC TF.[25] Data from the most recent round of this study showed a mean bias of +0.5mmol/mol and coefficient of variation (CV) of 4.1% in the UK. The Afinion device reported a bias of -1.7mmol/mol and CV of 3.3% and the DCA Vantage device a bias of -0.6mmol/mol and CV of 3.7%. The A1CNow device was not studied. These data reflect observations in the NHS DPP and suggest that bias of devices within the NHS DPP lie within the allowable error.

Clinical implications of using POC HbA1c devices

The use of HbA1c to track responses to interventions in those with NDH has not previously been evaluated in terms of reliability of results or effects on behaviour. It has been suggested that the immediacy of POC HbA1c results may have beneficial effects on motivation and behaviour.[26, 27] However, in this context, POC HbA1c testing in the NHS DPP moved a large proportion of people into the normoglycaemic range, which in turn was associated with reduced subsequent attendance, although regression to the mean may have accounted for some of this effect, irrespective of the methodology used for re-testing HbA1c. However, it is possible that other behavioural changes not captured in this study, may have influenced participants decisions not to continue to attend the programme.[28]

HbA1c measurements within the NHS DPP were only used to assess response to the intervention, and not for diagnosis. A POC HbA1c value in the diabetes range did lead to a repeat laboratory-measured HbA1c value, but POC HbA1c values in the normoglycaemic range were not repeated. The risk of a delayed diagnosis of Type 2 diabetes resulting from lower POC HbA1c values within the NHS DPP

should be mitigated by the routine application of NICE guideline PH38 [2], which recommends annual reassessment of glycaemic status for people with NDH. Annual rechecks of HbA1c in those with NDH in England will also be incentivised in future via general practice pay-for-performance.[29]

The same POC HbA1c device and pathway was used for each individual to track response to the intervention, so at cohort level mean changes in HbA1c pre-/post-intervention provided a useful marker of overall programme effectiveness, irrespective of any potential negative bias and higher variability.[30]

EQA is a reliable mechanism for identifying assay drift, and for identifying poor performance beyond total allowable error, although this relies on the ability to identify and resolve quality issues, which maybe challenging for non-specialists.[24] Some national schemes where POC HbA1c has been implemented in standardised community locations have had some success, though performance is variable despite intensive education and not all devices can undergo EQA.[23,31]

Other factors associated with HbA1c change

Other significant associations in the change in HbA1c include age (with those under 40 years with the greatest decrease), ethnicity (Asian, black and mixed participants have a significantly smaller decrease compared to white participants), and socioeconomic status (with the least deprived having the greatest decrease). The change in HbA1c varied by the number of days between tests, with the HbA1c difference between referral and IA becoming larger from the <28 days category up to the 84-111 days category and then some decrease. This could be consistent with people modifying their behaviour initially after diagnosis of non-diabetic hyperglycaemia (assuming at referral) and then lapsing. It is possible that the association between measurement change and some of the above-mentioned parameters relates to differences in the extent of behaviour change following referral/diagnosis of non-diabetic hyperglycaemia and prior to attendance at IA. However, using weight change between referral and IA as a surrogate for behaviour change, which shows more weight gain than weight loss, suggests against this.

Limitations

A limitation to the current analysis is that it is not possible to fully determine the extent of regression to the mean. The HbA1c reductions seen in these analyses were certainly much larger than those seen in a study applied to a very similar but smaller homogeneous population, where repeat values were also assessed after an interval,[19, 20] suggesting an impact of additional contributors in the current analyses.

We assumed all referral HbA1c values were laboratory-measured, but a small proportion, although not routine practice in the UK, may have been POC-measured. Differences in mean HbA1c reduction may also reflect variability in the referral HbA1c values from different laboratory methods, which were not harmonised across the programme but are all assumed to be IFCC-calibrated.

There was a large variation in time between referral and IA. However, associations between HbA1c change and pathway and device were independent of time elapsed in the regression analyses. We

were not able to formally assess bias of POC methods but used regression models to demonstrate that devices and pathways had associations with observed HbA1c differences.

Device selection was left to the Providers who were supplied with guidance around expected minimum performance criteria.

Conclusion

In summary, we show that a variety of modifiable and non-modifiable factors are associated with differences between laboratory measured HbA1c in the NDH range and subsequent POC measurements in the NHS DPP, including POC device but also, how it is used and implemented (POC pathway). Critically, we show that the difference in measured HbA1c may indicate values in the normoglycaemic range at IA and that this is associated with a reduction in subsequent attendance at diabetes prevention intervention sessions. We propose that particular attention be paid to the modifiable factors identified in this analysis, such as the POC device selected and pathway of implementation, as the observed changes in some cases have the potential to alter subsequent participant engagement with the programme.

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Competing of interests

JV is the National Clinical Director for Diabetes and Obesity at NHS England and is the Clinical Lead for the Healthier You: NHS Diabetes Prevention Programme. EB is the Head of Health Intelligence (diabetes) for Public Health England and leads analysis of the Diabetes Prevention Programme. CB is the Primary Care Advisor to the NHS Diabetes Programme. BY is Clinical Lead of the National Diabetes Audit for England and Wales and a Trustee of Diabetes UK. KK was Chair of the Programme Development Group for the National Institute for Health and Care Excellence (NICE) public health guidance on Type 2 diabetes: prevention in people at high risk (NICE PH38). KK is also Co-Director of the Leicester Diabetes Centre (LDC), and one of the Programme Providers, Ingeus UK Ltd, provide interventions based on the type 2 diabetes prevention programme developed by LDC. NW was Chair of the Programme Development Group for NICE public health guidance on Type 2 diabetes prevention: population and community-level interventions (NICE PH35). JS represents Public Health England on the NHS England Diabetes Programme Board. SON is the Clinical Director

at Diabetes UK. MS is Primary Investigator for the NDPS programme. WGJ was chair of the IFCC-WG on Haemoglobin A1c Standardisation and of the IFCC-TF.

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Contributors

JV, SM and EB conceived the study. EB managed the data and did the statistical analysis. All authors collaborated in interpretation of the results and drafting and revision of the report.

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Figure 1

A. Mean HbA1c change between laboratory measured HbA1c at referral and Point-of-Care re-measurement at Initial Assessment by the number of days between measurements and device
B. Standard deviation of Initial Assessment Point-of-care re-measurement HbA1c by the number of days between HbA1c measurements and device