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ARTICLE

HbA_{1c} and cardiovascular risk score identify people who may benefit from preventive interventions: a 7 year follow-up of a high-risk screening programme for diabetes in primary care (ADDITION), Denmark

T. Lauritzen · A. Sandbaek · M. V. Skriver · K. Borch-Johnsen

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Abstract
Aims/hypothesis The measurement of HbA_{1c} is suggested as a diagnostic test for diabetes. Screening for diabetes also identifies individuals with elevated cardiovascular risk but who are free of diabetes. This study aims to assess whether screening by HbA_{1c} or glucose measures alone, or in combination with a cardiovascular risk assessment, identifies people who may benefit from preventive interventions, i.e. people with screen detected diabetes and people belonging to groups with excess mortality, during a median follow-up of 7 years.
Methods A population-based, stepwise high-risk screening programme was performed in 193 family practices from 2001 to 2006. Individuals aged between 40 and 69 years (N=163,185) were sent a diabetes risk questionnaire. Of these, 20,916 people at risk of diabetes were stratified by glucose measures (normal glucose tolerance [NGT], impaired fasting glucose [IFG], impaired glucose tolerance [IGT] and diabetes), HbA_{1c} (<6%; 6.0–6.4%; or ≥6.5%) and cardiovascular risk (heart SCORE <5 or ≥5). People were followed for a median of 7 years or until death. Excess mortality was calculated using the Cox hazard ratio (HR).
Results SCORE≥5 identified 91.7% (95% CI 91.1–92.3%) of those who might benefit from preventive interventions. SCORE≥5 in combination with HbA_{1c}≥6.0% identified 96.7% (95% CI 96.3–97.0%), compared with 97.6% (95% CI 97.2–97.9%) in combination with glucose measures. Glucose measures or HbA_{1c} alone identified 26.1% (95% CI 25.2–27.0%) and 19.8% (95% CI 19.0–20.6%), respectively.
Conclusion/interpretation In a population-based high risk screening programme in primary care, HbA_{1c}≥6.0% combined with an elevated cardiovascular risk assessment (SCORE≥5) can feasibly be used to identify those who may benefit from preventive lifestyle intervention and/or polypharmacy.

Trial registration ClinicalTrials.gov NCT 00237549.
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Keywords All-cause mortality · Cardiovascular risk · HbA_{1c} · SCORE · Screening · Type 2 diabetes mellitus

Abbreviations

ADDITION	The Anglo–Danish–Dutch Study of Intensive Treatment of People with Screen Detected Type 2 Diabetes in Primary Care
FBG	Fasting blood glucose
IFG	Impaired fasting blood glucose

T. Lauritzen (✉) · A. Sandbaek · M. V. Skriver · K. Borch-Johnsen
Department of General Practice, School of Publich Health, Aarhus University,
Bartholins Allé 2,
DK 8000 Aarhus C, Denmark
e-mail: tl@alm.au.dk

K. Borch-Johnsen
Steno Diabetes Centre,
Gentofte, Denmark

K. Borch-Johnsen
Institute of Public Health,
Research Centre for Quality in Health Care,
University of Southern Denmark,
Odense, Denmark

IGT	Impaired glucose tolerance
NGT	Normal glucose tolerance
SCORE	Systematic Coronary Risk Evaluation

Introduction

Type 2 diabetes and cardiovascular disease are common lifestyle diseases [1] sharing many risk factors and often leading to reduced lifespan and disabling complications [2–4]. Both diseases are burdensome and costly for the individual as well as for society. For every individual with diagnosed type 2 diabetes there is another one with undiagnosed diabetes and an additional two with a high risk of developing diabetes based on the presence of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) [5–8]. The number of individuals without diabetes, but with an undetected high risk of developing cardiovascular disease, is even higher [9].

Patients with diabetes suffer a general increase in mortality compared with non-diabetic controls and this excess mortality is predominantly due to cardiovascular disease (heart disease and stroke in particular) [2–4].

Current screening strategies for diabetes are generally based on the use of fasting blood glucose (FBG) and the OGTT, tests that are cumbersome and inconvenient. Recently, the use of HbA_{1c} as a diagnostic test was suggested by an international expert committee [10]. They argue that HbA_{1c}, when properly measured and standardised, shows less biological intra-individual variability than fasting and post-load glucose measures, and less pre-analytic instability, and that it is more convenient as it can be measured at any time of the day.

Consequently, the aim of this study is to assess whether screening by HbA_{1c} or glucose measures alone, or in combination with a cardiovascular risk assessment, identifies people who may benefit from preventive interventions, i.e. people with screen detected diabetes defined by glucose measures and people belonging to groups with excess mortality, during a median follow-up of 7 years.

The paper is based on the Danish arm of the Anglo–Danish–Dutch Study of Intensive Treatment of People with Screen Detected Type 2 Diabetes in Primary Care (ADDITION) Study [11].

Methods

Study design Participants in the ADDITION study were identified through a population-based, stepwise high risk screening programme. The screening period was from April 2001 until the end of December 2006. All persons (N=163,185) aged from 40 to 69 years, registered with the 193 participating practices in five counties in Denmark, received as the first step of the high risk screening procedure an invitation with a risk score questionnaire [12], and persons with a risk score of at least 5 were recommended to visit their family physician (second step). Altogether, 25,640 people visited their family physician, and of these, 20,916 had a cardiovascular risk assessment using the heart SCORE model (Systematic Coronary Risk Evaluation) [13], together with measurement of a random blood glucose sample and HbA_{1c}. All people with random blood glucose ≥5.5 mmol/l or HbA_{1c} ≥5.8% were considered to be at high risk of having diabetes and were invited for diagnostic testing (overnight FBG and an OGTT if needed [third step]). The OGTT was carried out in individuals with a non-diabetic FBG if they had IFG or if HbA_{1c} was ≥5.8%. Individuals were classified by glucose measures as having normal glucose tolerance (NGT), isolated IFG, isolated IGT, combined IFG/IGT or diabetes, in accordance with the WHO's recommendation, including a confirmatory diagnostic test for those with a diabetic value [14]. Based on the HbA_{1c} taken as part of the screening, all participants were classified in accordance with the suggested new diagnostic criteria, i.e. <6%; 6.0–6.4% or ≥6.5%. Furthermore, participants were classified as having high or low risk of cardiovascular disease, i.e. SCORE≥5 or below. Screening was done in general practice and the general practitioners thus knew to which category each patient belonged.

Biochemical assessment Whole blood glucose was analysed by near-patient testing using the HemoCue Glucose Analyzer (HemoCue, Angelholm, Sweden). Calibration stability was checked on a daily basis using control cuvettes. All machines were registered with the HemoCue quality assurance scheme and were externally calibrated at the start of screening and regularly calibrated subsequently. The mean of two glucose values was used for diagnostic purposes, a procedure well validated against plasma glucose measures carried out in a laboratory setting [15]. HbA_{1c} was analysed in venous samples sent to five local laboratories. In all laboratories, HbA_{1c} analysis was standardised according to standards of the Diabetes Control and Complications Trial and the UK Prospective Diabetes Study. Fasting serum samples were analysed for total cholesterol using standard enzymatic methods.

Clinical measures Anthropometric measurements were undertaken at baseline following standard operating procedures, with height being measured to the nearest 0.1 cm and weight in light indoor clothing measured to the nearest 0.1 kg. Blood pressure was measured in the

right arm after 5 min of rest with the participant in a sitting position. Smoking status was obtained from a self-reported questionnaire.

Register data Based on the unique civil registration number, death or date of emigration data was obtained from the nationwide Danish Civil Registration System, and details of ischaemic heart disease (ICD-10 I20.0–25.9), stroke (ICD-10: 60.0–69.8) and cancer (ICD-10: C00.0–97.9; www.who.int/classifications/icd/en/) prior to screening were obtained from the Danish National Hospital Discharge Register. Prescription data was obtained from the Danish Prescription Database.

Statistical analysis All-cause mortality was estimated by Cox proportional hazard models. HRs were adjusted for the presence of ischaemic heart disease, stroke and cancer occurring before screening. Each person was followed from the date of screening until the date of death, emigration (censoring), or 31 October 2009, whichever came first. All analyses were performed using Stata version 10.1 and 95% CI are given. Prescription rates were calculated as the percentage of people who redeemed one or more prescription for lipid-, blood pressure- and glucose-lowering drugs within the following three periods: (1) 1 year before screening; (2) the 1st year following screening; and (3) a mean of 4 years following screening.

All-cause mortality was not calculated for those classified with diabetes as they are actively treated and intervened against [11] in contrast to all other groups in this observational study.

Ethics The study was approved by the local scientific ethics committee and was conducted in accordance with the principles of the 1996 Helsinki Declaration. All participants provided informed consent.

Results

Baseline characteristics are shown in Table 1. Median follow-up time was approximately 7 years.

Adjusted hazard ratios for total mortality are shown in Table 2. Participants were stratified by HbA_{1c} (top row). Within each HbA_{1c}-strata participants were further stratified by cardiovascular risk SCORE into high (≥5) or low (<5) cardiovascular risk. Finally, all participants were stratified by glucose measures as defined by the WHO. For each combination of glycated haemoglobin, SCORE and the class-defined glucose measures, the percentage of people compared with the total (n=20,916, lower right) and the HR for total mortality, adjusted for ischaemic heart disease, stroke and cancer before screening, are given. People with NGT, HbA_{1c}<6.0% and low cardiovascular risk were chosen as the reference group for mortality (HR=1).

Of the total population, it was found that 45.2% (95% CI 45.5–45.8%; n=9,447) might benefit from preventive interventions, either because of screen detected diabetes or

Table 1 Baseline characteristics for people participating in the stepwise diabetes screening programme

Variable	NGT	IFG	IGT	Combined IFG/IGT	Diabetes
n	17,322	1,020	676	729	1,169
Age; median (interquartile range)	59 (54–63)	58 (54–63)	61 (55–65)	60 (55–65)	59 (54–64)
Female; number (%)	8,350 (48.2)	452 (44.3)	379 (56.1)	365 (50.1)	507 (43.4)
Smoking: yes; number (%)	4,974 (29.7)	335 (32.8)	192 (28.4)	219 (30.0)	401 (34.3)
BMI					
Median (interquartile range)	27.1 (24.7–29.9)	28.6 (25.9–31.8)	28.8 (25.5–32.1)	29.9 (27.1–33.6)	31.0 (27.5–34.2)
Missing	16 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	6 (0.5)
Systolic blood pressure (mmHg); median (interquartile range)	138 (125–150)	140 (127–150)	140 (130–150)	140 (130–150)	140 (125–150)
Ischaemic heart disease before screening; number (%)	811 (4.7)	46 (4.5)	50 (7.4)	64 (8.8)	98 (8.4)
Stroke before screening, *n* (%)	399 (2.0)	20 (2.0)	20 (3.0)	28 (3.8)	27 (2.3)
Cancer before screening, *n* (%)	730 (4.2)	53 (5.2)	39 (5.8)	36 (4.9)	47 (4.0)
HbA_{1c} (%)					
<6.0	16,355 (94.4)	707 (69.3)	338 (50.0)	367 (50.3)	234 (20.0)
6.0 to <6.5	906 (5.2)	277 (27.2)	299 (44.2)	299 (41.0)	381 (32.6)
≥6.5	61 (0.4)	36 (3.5)	39 (5.8)	63 (8.6)	554 (47.4)
Follow-up; days, median (min–max)	2,427 (35–3141)	2,256 (109–3139)	2,282 (192–3128)	2,272 (39–3134)	2,287 (133–3132)
Total follow-up days	41,717,282	2,219,431	1,493,957	1,568,391	2,541,376
Number of deaths (%)	842 (4.9)	50 (4.9)	45 (6.7)	62 (8.5)	99 (8.5)

excess mortality, during a median follow-up of 7 years (HRs with lower 95% CI≥1.0, Table 2). SCORE≥5 identified 91.7% (95% CI 91.1–92.3%) of those who could benefit from preventive interventions. HbA_{1c}≥6.0% in combination with SCORE≥5 identified 96.7% (95% CI 96.3–97.0%) of those who might benefit from preventive interventions, compared with 97.6% (95% CI 97.2–97.9%) using the classification recommended by the WHO in combination with SCORE≥5. Using the criteria recommended by the WHO alone, or HbA_{1c} alone, identified 26.1% (95% CI 25.2–27.0%) and 19.8% (95% CI 19.0–20.6%), respectively. Analysis without adjustment for ischaemic heart disease, stroke and cancer before screening showed similar results (data not shown).

People with normoglycaemia and HbA_{1c}≥6.5 were among those with highest HRs for mortality (Table 2), 3.2 (95% CI 1.0–10.0) for those with SCORE<5 and 7.9 (95% CI 3.3–19.2) for those with SCORE≥5.

Table 3 shows the percentages and 95% CI intervals for participants who have redeemed a prescription for one or more lipid-, blood pressure- or glucose-lowering drugs within 1 year prior to screening and the first year following screening. In short, the table illustrates that 4.6% to 22.1% of participants redeemed lipid-lowering drugs before screening, rising to 7.8–33.3% during the first year following screening. For blood pressure-lowering drugs the corresponding figures are 21.0–48.4% before screening and 25.1–56.3% during the first year following screening. No one redeemed glucose-lowering drugs before screening, 0–9.4% redeemed glucose-lowering drugs during the first year following screening.

Table 4 shows percentages and 95% CI intervals for participants who have redeemed a prescription for one or more lipid-, blood pressure- and glucose-lowering drugs within a mean period of 4 years following screening. More people redeemed prescriptions during the 4 year period following screening than during the first year following screening (Table 3). Further, there was a tendency towards more frequent prescription with higher levels of HbA_{1c} and cardiovascular risk (Fisher's exact test for comparison of SCORE≥5 to SCORE<5 was significant in seven cells in Table 4).

Overall, the tendency was that, following screening, people with higher HbA_{1c} levels redeemed prescriptions for more medicines than those with low HbA_{1c} values, and people with high SCORE values redeemed prescriptions for more medicines than those with low SCORE values.

Discussion

In summary, the analysis of this stepwise high risk diabetes screening programme in primary care using HbA_{1c} or the glucose based criteria recommended by the WHO, in combination with a cardiovascular risk assessment, identified approximately 97% of all individuals belonging to groups who might benefit from preventive lifestyle interventions and polypharmacy, compared with 92% when using cardiovascular risk assessment alone. The corresponding figures when using the classification recommended by the WHO alone or HbA_{1c} alone were 26.1% and 19.8% respectively. People with normoglycaemia and HbA_{1c}≥6.5 were among those with highest HRs of mortality.

The International Expert Committee [10] that suggested HbA_{1c} as a diagnostic criteria stated: 'The ultimate goal is to identify individuals at risk for diabetes complications so that they can be treated' and 'The A1C diagnostic level of 6.5% accomplishes this goal'. From a screening perspective, this goal can be taken a step further: the ultimate goal being to identify individuals who may benefit from preventive lifestyle interventions and polypharmacy in order to prevent premature death. The results of this study indicate that HbA_{1c}, in combination with a cardiovascular risk score, can identify a large majority of these people (96.7%) in a high risk screening programme in primary care practices, whereas the criteria recommended by the WHO, combined with cardiovascular risk assessment, identified 97.6%. The latter performed 0.9% better. Although this difference is statistically significant, it is so small that we do not find the difference to be clinically relevant.

Using HbA_{1c} and cardiovascular assessment missed out 3.3% of people who might benefit from preventive interventions, i.e. people with HbA_{1c}<6.0% and either IGT or diabetes at baseline (Table 2). As screening is an ongoing process, repeated screening rounds are most likely to identify these people. Thus the use of cardiovascular risk assessment combined with HbA_{1c} seems to be highly effective in identifying people who may benefit from preventive lifestyle interventions and polypharmacological treatment. This method may also be more cost effective as HbA_{1c} is more convenient for patients and physicians, because people do not need to meet fasting requirements and fewer consultations are needed for screening and diagnosis compared with the use of glucose measurements alone or in combination with a cardiovascular risk assessment.

High risk screening by HbA_{1c} alone or glucose measures alone is ineffective, as these measures identified only 20–25% of those who may benefit from preventive interventions. Although the cardiovascular risk assessment identified 92% of these people, it misses out 5% of those at highest risk, i.e. people with diabetes. This group should not be left out as screening for diabetes has been found to be cost effective [16].

Table 2 HRs for total mortality, adjusted for ischaemic heart disease, stroke and cancer before screening, for participants stratified by HbA_{1c}, cardiovascular risk (SCORE [13]) and by glucose measures, according to the criteria recommended by the WHO

Variable	HbA_{1c} <6.0%				HbA_{1c} 6.0 to <6.5%				HbA_{1c}≥6.5%				All (%)
	Heart SCORE				Heart SCORE				Heart SCORE				
	<5		≥5		<5		≥5		<5		≥5		
	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)	%	HR (95% CI)	
NGT	47.2	1	31.1	2.6 (2.3–3.0)	2.3	1.3 (0.8–2.1)	2.0	3.5 (2.5–4.9)	0.2	3.2 (1.0–10.0)	0.1	7.9 (3.3–19.2)	82.8
Isolated IFG	2.0	1.2 (0.7–2.1)	1.4	2.9 (1.9–4.5)	0.6	1.1 (0.3–3.0)	0.7	2.8 (1.5–5.1)	0.1	1.9 (0.3–13.2)	0.1	2.2 (0.3–15.6)	4.9
Isolated IGT	0.9	1.4 (0.6–3.2)	0.8	3.0 (1.7–5.4)	0.7	0.8 (0.3–2.4)	0.7	3.8 (2.3–6.2)	0.1	3 (0.7–11.9)	0.1	10.9 (4.5–26.5)	3.2
Combined IFG/IGT	0.9	2.1 (1.1–4.0)	0.8	5.1 (3.4–7.9)	0.8	0.8 (0.2–2.4)	0.7	5.3 (3.3–8.4)	0.1	2.5 (0.5–8.7)	0.2	6.7 (2.8–16.3)	3.5
Diabetes	0.6	The ADDITION Study	0.6	The ADDITION Study	0.9	The ADDITION Study	0.9	The ADDITION Study	1.3	The ADDITION Study	1.4	The ADDITION Study	5.6
All (%)	51.5		34.6		5.3		5.0		1.8		1.8		100.0

n=20,916 for this study

HRs were not calculated for those classified with diabetes as they are actively treated and intervened against as part of the ADDITION Study [11]. This is in contrast with all other groups in this observatory study, which were treated according to routine care

Of the total population, 45.2% (95% CI 45.5–45.8%; n=9,447) might benefit from preventive interventions because of either screen detected diabetes or excess mortality, during a median follow-up of 7 years (HRs with lower 95% CI≥1.0)

Table 3 Percentages and 95% CIs for participants who have redeemed a prescription for one or more lipid-, blood pressure- or glucose-lowering drugs within the period 1 year prior to and in the 1st year following screening

Variable	HbA_{1c} (%)											
	<6.0				6.0 to <6.0				≥6.5			
Cardiovascular risk, SCORE	<5		≥5		<5		≥5		<5		≥5	
Period before or after screening	1 year before	1 year after	1 year before	1 year after	1 year before	1 year after	1 year before	1 year after	1 year before	1 year after	1 year before	1 year after
Number of participants												
NGT	9,859	9,859	6,496	6,496	484	484	422	422	32	32	29	29
IFG												
IGT	180	180	158	158	149	149	150	150	24	24	15	15
IFG+IGT	194	194	173	173	159	159	140	140	31	31	32	32
Participants who have redeemed one or more prescriptions for lipid-lowering drugs, % (95% CI)												
NGT	4.6 (4.2–5.1)	7.8 (7.3–8.4)	7.6 (7.0–8.3)	12.8 (12.0–13.6)	8.3 (6.0–11.1)	13.6 (10.7–17.0)	10.7 (7.9–14.0)	15.9 (12.5–19.7)	12.5 (3.5–29.0)	15.6 (5.3–32.8)	6.9 (0.8–22.8)	27.6 (12.7–47.2)
IFG	7.5 (5.1–10.4)	11.6 (8.7–15.0)	8.6 (5.6–12.4)	12.7 (9.1–17.0)	12.1 (7.1–18.9)	18.2 (12.0–25.8)	7.6 (3.8–13.2)	20 (13.8–27.4)	5.3 (0.1–26.0)	15.8 (3.4–39.6)	5.9 (1.5–28.7)	29.4 (10.3–56.0)
IGT	10.6 (6.5–16.0)	15.6 (10.6–21.7)	12.7 (7.9–18.9)	16.5 (11.0–23.2)	12.1 (7.3–18.4)	21.5 (15.2–28.9)	17.3 (11.6–24.4)	28 (20.7–35.9)	8.3 (1.0–27.0)	16.7 (4.7–37.4)	20 (4.3–48.1)	33.3 (11.8–61.6)
IFG+IGT	11.9 (7.7–17.3)	19.1 (13.8–25.3)	11.6 (7.2–17.3)	21.4 (15.5–28.3)	14.5 (9.4–20.9)	25.2 (18.6–32.6)	22.1 (15.6–29.9)	30.7 (23.2–39.1)	16.1 (5.4–33.7)	25.8 (11.9–44.6)	9.4 (2.0–25.0)	21.9 (9.3–40.0)
Participants who have redeemed one or more prescriptions for blood pressure-lowering drugs, % (95% CI)												
NGT	22.5 (21.7–23.3)	25.1 (24.2–26.0)	27 (25.9–28.1)	33.9 (32.8–35.1)	25 (21.2–29.1)	27.1 (23.2–31.3)	29.1 (24.9–33.7)	35.1 (30.5–39.8)	43.8 (26.4–62.3)	43.8 (26.4–62.3)	34.5 (17.9–54.3)	31 (15.3–50.8)
IFG	24.1 (20.1–28.5)	26.7 (22.5–31.3)	27.1 (22.0–32.5)	34.2 (28.8–40.0)	31.8 (24.0–40.5)	34.8 (26.8–43.6)	27.6 (20.5–35.6)	35.9 (28.1–44.2)	21 (6.1–45.6)	36.8 (16.3–61.6)	47.1 (23.0–72.2)	58.8 (32.9–81.6)
IGT	37.2 (30.1–44.7)	38.9 (31.7–46.4)	32.3 (25.1–40.2)	39.2 (31.6–47.3)	42.3 (34.2–50.6)	50.3 (42.0–58.6)	40 (32.1–48.3)	50 (41.7–58.3)	37.5 (18.8–59.4)	45.8 (25.6–67.2)	40 (16.3–67.7)	53.3 (26.6–78.7)
IFG+IGT	34 (27.4–41.2)	40.7 (33.7–48.0)	42.2 (34.7–49.9)	50.3 (42.6–58.0)	47.8 (39.8–55.9)	48.4 (40.4–56.5)	45 (36.6–53.6)	48.6 (40.0–57.2)	48.4 (30.2–66.9)	48.4 (30.2–66.9)	46.9 (29.1–65.3)	56.3 (37.7–73.6)
Participants who have redeemed one or more prescriptions for glucose-lowering drugs, % (95% CI)												
NGT	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0.8)	0.2 (0–1.1)	0 (0–0.9)	0 (0–0.9)	0 (0–10.9)	0 (0–10.9)	0 (0–11.9)	0 (0–11.9)
IFG	0 (0–0.9)	0 (0–0.9)	0 (0–1.3)	0 (0–1.3)	0 (0–2.8)	1.5 (1.8–5.4)	0 (0–2.5)	0 (0–2.5)	0 (0–17.6)	5.3 (1.3–26.0)	0 (0–19.5)	0 (0–19.5)
IGT	0 (0–2.0)	0.6 (0–3.1)	0 (0–2.3)	0 (0–2.3)	0 (0–2.4)	0.7 (0–3.7)	0 (0–2.4)	0 (0–2.4)	0 (0–14.2)	0 (0–14.20)	0 (0–21.8)	6.7 (0.2–31.9)
IFG+IGT	0 (0–1.9)	0.5 (0–2.8)	0 (0–2.1)	0 (0–2.1)	0 (0–2.3)	3.8 (1.4–8.0)	0 (0–2.6)	2.9 (0.8–7.2)	0 (0–11.2)	3.2 (0.1–16.7)	0 (0–10.9)	9.4 (2.0–25.0)

Table 4 Percentages and 95% CIs for participants who have redeemed a prescription for one or more lipid-, blood pressure- and glucose-lowering drugs within a mean period of 4 years following screening

Variable	HbA_{1c} (%)					
	<6.0		6.0 to <6.0		≥6.5	
Cardiovascular risk, SCORE	<5	≥5	<5	≥5	<5	≥5
Number of participants (*n*)						
NGT	9,859	6,496	484	422	32	29
IFG	415	292	132	145	19	17
IGT	180	158	149	150	24	15
IFG+IGT	194	173	159	140	31	32
Participants who have redeemed one or more prescriptions for lipid-lowering drugs, % (95% CI)						
NGT (%)	16.2 (15.5–17.0)	25.2** (24.2–26.3)	24 (20.2–28.0)	30.6* (26.2–35.2)	28.1 (13.7–46.7)	48.3 (29.4–67.5)
IFG (%)	20.2 (16.5–24.4)	26.4 (21.4–31.8)	31.1 (23.3–39.7)	54.5** (46.0–62.8)	42.1 (20.3–66.5)	58.8 (32.9–81.6)
IGT (%)	26.7 (20.4–33.8)	34.8 (27.4–42.8)	40.3 (32.3–48.6)	46.7 (38.5–55.0)	54.2 (32.8–74.4)	53.3 (26.6–78.7)
IFG+IGT	34 (27.4–41.2)	41 (33.6–48.8)	46.5 (38.6–54.6)	50 (41.4–58.6)	64.5 (45.4–80.8)	43.8 (26.4–62.3)
Participants who have redeemed one or more prescriptions for blood pressure-lowering drugs, % (95% CI)						
NGT	34.7 (33.8–35.7)	47.8** (46.6–49.1)	35.1 (30.1–39.6)	47.9** (43.0–52.8)	46.9 (29.1–65.3)	44.8 (26.4–64.3)
IFG	32.4 (30.8–40.2)	46.6** (40.7–52.5)	60.6 (51.7–69.0)	57.9 (49.5–66.1)	57.9 (33.5–79.7)	64.7 (38.3–85.8)
IGT	46.7 (39.2–54.2)	48.7 (40.7–56.8)	59.1 (50.7–67.0)	60 (51.7–67.9)	58.3 (36.6–77.9)	60 (32.3–83.7)
IFG+IGT	51.5 (44.3–58.8)	71.1** (63.7–77.7)	59.1 (51.1–66.8)	65.7 (57.2–73.5)	67.7 (48.6–83.3)	65.6 (46.8–81.4)
Participants who have redeemed one or more prescriptions for glucose-lowering drugs, % (95% CI)						
NGT	0.3 (0.2–0.4)	0.4 (0.3–0.6)	1 (0.3–2.4)	0.7 (0.1–2.0)	0 (0–10.9)	6.9 (0.8–22.8)
IFG	1.7 (0.7–3.4)	1 (0.2–3.0)	5.3 (2.2–10.6)	8.3 (4.3–14.0)	15.8 (3.4–39.6)	11.8 (1.5–36.4)
IGT	1.7 (0.3–4.8)	2.5 (0.7–6.4)	6.7 (3.3–12.0)	6 (2.8–11.1)	16.7 (4.7–37.4)	6.7 (0.2–31.9)
IFG+IGT	7.7 (4.4–12.4)	6.4 (3.2–11.1)	16.4 (11.0–23.0)	12.9 (7.8–19.6)	35.5 (19.2–54.6)	18.8 (7.2–36.4)

*$p<0.05$, **$p<0.01$ (Fisher's exact test comparing SCORE ≥5 with SCORE <5)

The International Expert Committee [10] suggests that HbA_{1c} measurement should be repeated when used as a diagnostic criterion. In this study we only measured HbA_{1c} once, at the time of screening. Despite this, we achieved a good separation into high and low risk categories for excess mortality, and the potential misclassification introduced by this procedure seems not to be a major problem; this is in agreement with the high precision of measures of glycated haemoglobin compared with FBG and 2 h pre-load glucose test. If, however, we had used the mean of two HbA_{1c} measurements, misclassification would be further reduced, and this would have led to even more precise classification into high and low risk categories for excess mortality. The fact that, for logistical reasons, HbA_{1c} was measured in five different laboratories might have increased the risk of misclassification and therefore underestimated the true excess risk in the 'high risk groups'.

The long follow-up time, with a median of approximately 7 years for mortality and 4 years for prescriptions redeemed by participants, and the 100% follow-up of all participants, represent major strengths of this study. Complete follow-up is possible due to the unique Danish civil registration number and the possibility of using this to link to the national registers for death or date of emigration. Data on prescriptions were obtained for up to a mean of 4 years following screening, i.e. 3 years before the end of collection of mortality data. Data for the last 3 years are not yet available. The lack of data for the last 3 years should be viewed in the light of the legacy effect, that is, there is a period between initiation of pharmacological treatment and changes in outcome data [17, 18]. The population-based approach ensures the generalisability of our results. The study was performed in normally operating family practices using strictly validated near-patient glucose measures [15], that is, the study was performed in the setting in which it was implemented.

Changes in lifestyle and prescription rates of drugs lowering cardiovascular risk are confounders in this study. As this is a register study, we cannot account for changes in lifestyle. Overall prescription rates of lipid-, blood pressure- and glucose-lowering drugs increased following screening, and more so in people with higher HbA_{1c} and SCORE values. Thus the separation in HRs between the different strata in Table 2 would probably be greater had general practitioners not reacted to the clinical data and laboratory

results indicating risk of diabetes and cardiovascular disease. The increased prescription rates of glucose-lowering drugs following screening indicate that some people have developed diabetes.

The apparent inconsistency in Table 2 showing non-significant increased HRs for people with $HbA_{1c} \geq 6.5\%$ and isolated IFG, and for people in the same HbA_{1c} category with isolated IGT and SCORE<5, as well as for people with combined IFG/IGT, are probably due to the small numbers (approximately 20) in each of these categories.

People with screen detected diabetes during routine clinical care are known to have excess mortality [2–4] and may benefit from preventive interventions. In this follow-up study, HRs have not been calculated for people with screen detected diabetes as they were actively treated and intervened against as part of the ADDITION Study [11]. In contrast, other risk groups in this study were treated during usual clinical care. People who were identified at screening as being free of diabetes, but with increased cardiovascular risk, seem to be under-treated with a considerable delay in the first prescription of lipid-lowering drugs [19].

A low attendance rate of approximately 50% is a weakness, which is common in all screening programmes for diabetes, including the ADDITION study [20–23]. In addition to the inconvenience of glucose measures, the low attendance may be caused by the perception that diabetes is not a serious disease. The attendance rate was, however, no higher in another study in which people in Denmark were invited to screening for cardiovascular risk and diabetes by a research organization [6]. However, when people in Denmark were invited for a broad health test and health conversation by their family physician, the attendance rate was 75% in the first screening round, and rose to 85% following the second screening round 5 years later [24]. Thus, an invitation from the family physician to a general health test not related to a specific disease seems advantageous compared with a disease-specific screening programme with an invitation from an anonymous health agent.

In conclusion, a high risk screening programme based on the newly suggested criteria, HbA_{1c} combined with cardiovascular risk assessment, is feasible and effective in a real life setting in primary care, as the majority of people who may benefit from preventive lifestyle interventions and polypharmacy are identified. Screening for diabetes and cardiovascular risk should be seen as integrated issues.

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Duality of interest K. Borch-Johnsen was a member of the International Expert Committee on the Role of the A1C Assay in the Diagnosis of Diabetes, and was until late 2010 director of the Steno Diabetes Centre, which is owned by Novo Nordisk and holds shares in Novo Nordisk. T. Lauritzen has been lecturing for Novo Nordisk, holds shares in Novo Nordisk and has received unrestricted funding as described above. A. Sandbaek has been lecturing for Novo Nordisk. Apart from this, and the funding described in the abstract, the authors declare no conflict of interest associated with this manuscript.

Appendix

This publication describes a cohort follow-up of all people attending screening, independently of whether they were found to have screen detected diabetes. The main ADDITION study is a randomised controlled trial evaluating intensive treatment vs 'as usual treatment' in those with screen detected diabetes. The study is an international cooperation between primary care in the UK, the Netherlands and Denmark. The main results were presented at the annual meeting of the European Association for the Study of Diabetes in September 2010.

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