Are the Same Clinical Risk Factors Relevant for Incident Diabetes Defined by Treatment, Fasting Plasma Glucose, and HbA_{1c}?

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OBJECTIVE—To compare incidences and risk factors for diabetes using seven definitions, with combinations of pharmacological treatment, fasting plasma glucose (FPG) ≥7.0 mmol/L, and HbA_{1c} ≥6.5%.

RESEARCH DESIGN AND METHODS—Participants aged 30–65 years from the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) cohort were followed for 9 years.

RESULTS—More men had incident diabetes as defined by FPG ≥7.0 mmol/L and/or treatment than by HbA_{1c} ≥6.5% and/or treatment: 7.5% (140/1,867) and 5.3% (99/1,874), respectively ($P < 0.009$); for women incidences were similar: 3.2% (63/1,958) and 3.4% (66/1,954). Known risk factors predicted diabetes for almost all definitions. Among those with incident diabetes by FPG alone versus HbA_{1c} alone, there were more men (78 vs. 35%), case patients were 8 years younger, and fewer were alcohol abstainers (12 vs. 35%) (all $P < 0.005$). A diabetes risk score discriminated well between those with and without incident diabetes for all definitions.

CONCLUSIONS—In men, FPG definitions yielded more incident cases of diabetes than HbA_{1c} definitions, in contrast with women. An FPG-derived risk score remained relevant for HbA_{1c}-defined diabetes.

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HbA_{1c} is proposed as the first of four diagnostic criteria for diabetes (1). Risk factors for diabetes as defined by self-reported diabetes, by treatment, by fasting plasma glucose (FPG), or by both fasting and 2-h glucose following an oral glucose tolerance test have been well studied, including in our own cohort (2–6). Risk factors for different definitions have not been compared; it is tacitly assumed they are the same.

We compare seven definitions of diabetes, using combinations of pharmacologic treatment, FPG ≥7.0 mmol/L, and HbA_{1c} ≥6.5% to evaluate the incidences of diabetes and compare baseline risk factors for men and women separately. Furthermore, we evaluate the odds ratios of risk factors and the ability of the Data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) clinical risk factor score (2) to discriminate those with and without incident diabetes.

RESEARCH DESIGN AND METHODS

—Men and women aged 30–65 years, from the 9-year follow-up study DESIR (2), were included. Incidences of diabetes by FPG and HbA_{1c} definitions were compared with the McNemar test.

Odds ratios for potential risk factors are given for incident diabetes according to the seven definitions of diabetes (Table 1). Sex-risk factor interactions were tested, and in consequence, sex-specific odds ratios are given for smoking and familial diabetes.

The DESIR diabetes risk score (2) includes waist circumference, hypertension, and for men, current smoking, or for women, familial diabetes; the score was derived with diabetes defined by treatment and/or FPG ≥7.0 mmol/L (Supplementary Table 1). The discrimination of this score was evaluated, for each of the seven definitions, by the area under the receiver operating characteristic curve (AROC).

RESULTS

—At inclusion, men and women were on average aged 47 years, and 19% had familial diabetes, 25% were sedentary, and mean BMI was 24.6 kg/m^2 (Supplementary Table 2). Mean FPG was higher in men than women, with a constant difference of 0.35 mmol/L over the age range ($P_{interaction}$= 0.6) (Supplementary Fig. 1). Mean HbA_{1c} was also higher in men, but this difference decreased with age ($P_{interaction}$= 0.0001): mean HbA_{1c} was 0.25% higher in men 30–34 years and identical in men and women 60–65 years.

For diabetes defined by FPG and/or treatment, in comparison with HbA_{1c} and/or treatment, incidences were higher in men: 7.5% (95% CI 6.3–8.9) and 5.3% (4.2–6.5) ($P < 0.0003$); in women the incidences were similar: 3.2% (2.4–4.2) and 3.4% (2.6–4.3) (Supplementary Table 3).

Characteristics of case patients with incident diabetes varied according to the definition of diabetes (Supplementary Tables 2 and 3). For diabetes defined by treatment alone, risk factors were age, waist circumference, BMI, hypertension, and lipid treatment (all $P < 0.006$). For men only, additional factors were smoking,

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Table 1—*Odds ratios (95% CI), univariable analysis, for incident diabetes according to seven definitions of diabetes: the DESIR study*

	Treatment	FPG ≥7.0 mmol/L	HbA_{1c} ≥6.5%	FPG ≥7.0 mmo/L and/or HbA_{1c} ≥6.5%	FPG ≥7.0 mmol/L and/or treatment	HbA_{1c} ≥6.5% and/or treatment	FPG ≥7.0 mmol/L and/or HbA_{1c} ≥6.5% and/or treatment
Women	0.51 (0.34–0.77)	0.38 (0.26–0.53)	0.66 (0.46–0.95)	0.48 (0.36–0.63)	0.41 (0.30–0.56)	0.62 (0.45–0.86)	0.50 (0.38–0.65)
	0.0010	<0.0001	0.0242	<0.0001	<0.0001	0.0038	<0.0001
Age (1 year)	1.08 (1.05–1.10)	1.03 (1.01–1.05)	1.07 (1.05–1.10)	1.05 (1.04–1.07)	1.04 (1.02–1.06)	1.07 (1.05–1.10)	1.06 (1.04–1.07)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Diabetes in family							
Men	1.55 (0.89–2.68)	1.02 (0.63–1.65)	1.35 (0.77–2.36)	1.19 (0.78–1.80)	1.12 (0.73–1.74)	1.54 (0.96–2.46)	1.30 (0.89–1.91)
	0.1197	0.9330	0.2875	0.4168	0.5929	0.0712	0.1745
Women	3.30 (1.72–6.32)	3.38 (1.90–6.01)	1.49 (0.80–2.79)	2.06 (1.27–3.34)	3.11 (1.86–5.20)	1.76 (1.02–3.01)	2.06 (1.31–3.21)
	0.0003	<0.0001	0.2087	0.0036	<0.0001	0.0395	0.0016
Current smoker							
Men	2.27 (1.39–3.70)	1.89 (1.28–2.79)	1.46 (0.89–2.42)	1.70 (1.20–2.42)	1.83 (1.28–2.64)	1.59 (1.03–2.44)	1.68 (1.21–2.35)
	0.0009	0.0012	0.1331	0.0031	0.0009	0.0344	0.0022
Women	0.36 (0.08–1.53)	1.49 (0.71–3.11)	1.20 (0.55–2.58)	1.45 (0.80–2.62)	1.25 (0.62–2.49)	1.04 (0.50–2.13)	1.27 (0.72–2.25)
	0.1674	0.2899	0.6452	0.2211	0.5292	0.9175	0.4041
Alcohol (g/day)							
0	1	1	1	1	1	1	1
0–19	1.01 (0.56–1.80)	1.48 (0.89–2.43)	0.75 (0.44–1.26)	1.04 (0.69–1.57)	1.32 (0.84–2.06)	0.82 (0.52–1.31)	0.95 (0.65–1.39)
20–39	1.28 (0.74–2.19)	1.73 (1.08–2.78)	0.86 (0.53–1.39)	1.38 (0.95–2.00)	1.63 (1.07–2.47)	1.00 (0.65–1.52)	1.31 (0.93–1.84)
≥40	3.16 (1.70–5.87)	4.75 (2.79–8.08)	2.69 (1.57–4.61)	3.38 (2.17–5.28)	4.01 (2.47–6.51)	2.62 (1.60–4.30)	3.00 (1.98–4.55)
	0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Sedentary	1.65 (1.10–2.47)	1.30 (0.92–1.83)	2.12 (1.47–3.05)	1.56 (1.17–2.07)	1.45 (1.06–1.97)	2.07 (1.50–2.86)	1.67 (1.28–2.17)
	0.0144	0.1265	<0.0001	0.0024	0.0171	<0.0001	0.0002
Waist (1 cm)	1.13 (1.10–1.16)	1.09 (1.07–1.11)	1.09 (1.07–1.12)	1.09 (1.08–1.11)	1.10 (1.08–1.12)	1.10 (1.08–1.12)	1.10 (1.08–1.11)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
BMI (1 kg/m^2)	1.32 (1.26–1.38)	1.23 (1.18–1.28)	1.25 (1.20–1.31)	1.23 (1.19–1.27)	1.25 (1.20–1.30)	1.28 (1.22–1.33)	1.25 (1.21–1.29)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Hypertension	6.80 (4.29–10.76)	2.94 (2.14–4.03)	3.48 (2.40–5.03)	2.99 (2.28–3.94)	3.27 (2.44–4.38)	4.48 (3.19–6.28)	3.37 (2.60–4.37)
	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Lipid treatment	3.14 (1.91–5.14)	1.98 (1.24–3.16)	3.18 (2.00–5.06)	2.19 (1.47–3.25)	2.19 (1.45–3.31)	3.01 (1.98–4.57)	2.2 (1.56–3.25)
	<0.0001	0.0040	<0.0001	0.0001	0.0002	<0.0001	<0.0001
AROC curve (95% CIs) for the DESIR diabetes risk score							
DESIR score*	0.86 (0.83–0.89)	0.74 (0.70–0.78)	0.77 (0.72–0.82)	0.75 (0.71–0.78)	0.76 (0.72–0.80)	0.80 (0.76–0.83)	0.76 (0.73–0.80)

Data are expressed as OR (95% CI) *P*. *N*, case patients with incident diabetes: treatment, 108/3,872; FPG ≥7.0 mmol/L, 168/3,790; HbA_{1c} ≥6.5%, 126/3,789; FPG ≥7.0 mmol/L and/or HbA_{1c} ≥6.5%, 228/3,800; FPG ≥7.0 mmol/L and/or treatment, 203/3,825; HbA_{1c} ≥6.5% and/or treatment, 165/3,828; and FPG ≥7.0 mmol/L and/or HbA_{1c} ≥6.5% and/or treatment, 264/3,836. *Reference 2.

alcohol intake, and sedentarity (all $P < 0.05$), and for women only, an additional factor was familial diabetes ($P < 0.0001$). When comparing case patients with incident diabetes screened only by FPG and case patients screened only by HbA_{1c}, more were men (78 vs. 35%), case patients were 8 years younger (after sex adjustment), and fewer were alcohol abstainers (12 vs. 36% after adjusting for age and sex) (all $P < 0.01$) (Supplementary Table 4).

Although the classical risk factors sex, age, alcohol intake, waist, BMI, hypertension, and lipid treatment were associated with incident diabetes, no matter what the definition (Table 1), the univariable odds ratios for the various definitions differed. The most marked difference was for hypertension, where the odds ratios ranged from a low of 2.94 (2.14–4.03) when diabetes was defined by FPG alone to 6.80 (4.29–10.76) when defined by treatment alone.

The DESIR diabetes risk score (2) performed well for all definitions of diabetes, particularly so when diabetes was defined by treatment alone, with an AROC (95% CI) of 0.86 (0.83–0.89), in comparison with 0.76 (0.72–0.80) when diabetes was defined by FPG and/or treatment, the definition on which the score was derived.

CONCLUSIONS—The age profile of HbA_{1c} and FPG differed for men and women, with FPG always higher in men, whereas HbA_{1c} was higher in younger men but identical in the oldest age range, 60–65 years. For men only, the incidence of diabetes was lower for diabetes defined by HbA_{1c} rather than by FPG. There has been little discussion in the literature on the differences between men and women for either FPG or HbA_{1c}.

For the incident diabetic case patients diagnosed by treatment, the classic risk factors for diabetes were mainly higher than for other definitions—age, diabetes in the family, adiposity, hypertension, with smoking and alcohol drinking in men. This is probably because of the general practitioner recognizing these as risk factors and screening for diabetes, subsequently diagnosing and treating the patient. Hypertension and lipid treatment were risk factors with high odds ratios in those who had incident diabetes by treatment, probably for the same reason.

For the definitions of diabetes with FPG there were more men, case patients were younger, and fewer were alcohol abstainers than for definitions with HbA_{1c}. Despite this, the diabetes risk score discriminated well for all definitions of diabetes, best for diabetes defined by treatment and worst for diabetes defined by FPG alone, but all AROCs were over 0.74.

In Inter99, the cross-sectional profiles were similar for those screened diabetic only by HbA_{1c} and only by FPG and 2-h plasma glucose (7); however, diabetes prevalence was higher when screened by HbA_{1c}, in contrast with our incidence study. Mean HbA_{1c} in Inter99 appears higher than in other cohorts, and this is probably the reason for the observed difference (8). Differences in men and women were not studied in Inter99.

Because blood was only sampled at one time point to evaluate FPG and HbA_{1c}, this study is limited to diabetes screening—not diagnosis. Furthermore, although our HbA_{1c} assay conformed to the Diabetes Control and Complications Trial (DCCT)/National Glycohemoglobin Standardization Program (NGSP) standards, it was not linked to the International Federation of Clinical Chemistry reference method (1).

In summary, the main differences between those who become diabetic according to the FPG and HbA_{1c} definitions of diabetes were the higher frequency of men and the younger mean age by the FPG definitions. FPG screened more incident diabetes in men than HbA_{1c}; for women, the percentages were similar.

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