

Are the same clinical risk factors relevant for incident diabetes defined by treatment, fasting plasma glucose and by HbA1c ?

Data from an Epidemiological Study on the Insulin Resistance Syndrome (D.E.S.I.R.)

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Need to add another definition !!!

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OBJECTIVES—To compare risk factors for incident diabetes using six definitions with combinations of treatment, fasting plasma glucose (FPG) ≥ 7.0 mmol/l, HbA1c $\geq 6.5\%$.

RESEARCH DESIGN AND METHODS—Participants, 30-65 years from the D.E.S.I.R. cohort, followed nine-years.

RESULTS—For diabetes defined by treatment or FPG ≥ 7.0 mmol/l, 140/1867 (7.5%) men, 63/1958 (3.2%) women had incident diabetes; for diabetes defined by treatment or HbA1c $\geq 6.5\%$, 5.3% and 3.4% respectively. Male gender, age, adiposity, familial diabetes in women, smoking in men, alcohol intake, sedentarity, and treatment for hypertension or lipids were risk factors for incident diabetes for almost all definitions. Incident diabetes by HbA1c compared to FPG, yielded fewer men, older individuals, more treated for hypertension or lipids, fewer women but more men with familial diabetes, and similar BMI and waist circumferences. A diabetes risk score discriminated those with and without incident diabetes, for all definitions.

CONCLUSIONS—Risk factors for incident diabetes were similar for differing diabetes definitions.

150 words

Key words: epidemiology, fasting plasma glucose, HbA1c, incidence, risk factors, type 2 diabetes

HbA1c is proposed as the first of four diagnostic criteria for diabetes (1). Risk factors for diabetes when diabetes was defined by self reported diabetes, by treatment, by fasting plasma glucose (FPG) or by both fasting and 2 hour glucose following an OGTT have been well studied, including in our own cohort (2-6). To our knowledge, risk factors have not been compared - it is tacitly assumed that they are the same for all definitions.

We compare six definitions of diabetes, using combinations of treatment, $\text{FPG} \geq 7.0 \text{ mmol/l}$, $\text{HbA1c} \geq 6.5 \%$. For each definition we evaluate the incidence of diabetes, risk factors, and the ability of the D.E.S.I.R. clinical risk factor score (2) to discriminate those with and without incident diabetes.

RESEARCH DESIGN AND METHODS—The study population included men and women, 30-65 years, from the 9-year follow-up study D.E.S.I.R. (2), and more fully in the on-line appendix (xxx). Participants were examined at inclusion, and every three years, over nine years.

Odds ratios for potential risk factors are given for incident diabetes. Sex-risk factor interactions were tested, and sex-specific odds ratios are given for smoking and familial diabetes.

The D.E.S.I.R. diabetes risk score (2) includes waist circumference, hypertension and for men, current smoking, for women, familial diabetes; diabetes was defined by treatment and/or $\text{FPG} \geq 7.0 \text{ mmol/l}$. Score discrimination was compared using the area under the receiver operating characteristic curve (AROC).

RESULTS—At inclusion, the men and women in our study were on average 47 years, 19% had familial diabetes, 25% were sedentary with mean BMI 24.6 kg/m^2 (Supplementary Table 1). At baseline, FPG was higher in men than women, with a constant difference over the age-range ($P_{\text{interaction}} = 0.6$) (Fig). HbA1c was also higher in men than women, but this difference decreased with age ($P_{\text{interaction}} = 0.0001$); the HbA1c levels were very similar in the older age range, where diabetes is more frequently screened.

For the definitions of diabetes with FPG there were more incident cases of men than for the HbA1c definitions, whereas the incidences were similar for women. For the classical definition of diabetes: FPG and/or treatment, incidences were 7.5% in men, 3.2%

in women, whereas for diabetes defined by HbA1c and/or treatment, they were 5.3% and 3.4% (Supplementary Table 2).

The characteristics of incident diabetes cases varied according to the definition of diabetes: FPG definitions included more men, and cases were younger than for HbA1c definitions (Supplementary Table 2). The definition HbA1c and/or treatment compared with FPG and/or treatment, for men included more sedentary men and more treated for hypertension for. In comparison to incident diabetes by other definitions, those with incident diabetes by treatment alone differed most from the others. They had more frequently: diabetes in the family, greater adiposity (BMI and waist circumference), hypertension, and for the men, they smoked and drank more alcohol.

The classical risk factors: gender, age, alcohol intake, waist, BMI, hypertension, lipid treatment were associated with incident diabetes, no matter what the definition (Table). However, the odds ratios associated with the various definitions differed – for example for hypertension the odds ratios ranged from 2.94 when defined by FPG to 6.80 when defined by treatment. Sex specific characteristics were diabetes in the family, only significant in women, and smoking, only significant in men with exceptions for the case where diabetes was defined only by HbA1c. A sedentary behaviour was not associated with diabetes defined by FPG, but was associated with other definitions, and when diabetes was defined with HbA1c, sedentarity had odds ratios over two.

The D.E.S.I.R. diabetes risk score (2) derived from diabetes defined by FPG and/or treatment, performed well for all definitions of diabetes, particularly so when diabetes was defined by treatment, with an AROC of 0.859, in comparison to 0.760 for original definition.

CONCLUSIONS—The diabetes phenotype differs according to these six definitions – with the main differences being adiposity, hypertension, and smoking and alcohol intake in men, in those diagnosed by treatment. This is probably due to the general practitioner recognising these as risk factors and proposing a screening test for diabetes, and subsequently diagnosing and treating his 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 definition with FPG in comparison with HbA1c, those screened diabetic were younger, more had diabetes in the family, more smoked, and fewer were sedentary, hypertensive or treated for dyslipidaemia.

Of note is that when HbA1c is used to define diabetes, the incidences for men and women were more similar than when FPG was used, with lower incidences in men when HbA1c was used. HbA1c levels are more similar between men and women than FPG levels in the older age groups.

Cross-sectional risk profiles in Inter99 of those *screened* diabetic by the OGTT and by HbA1c (7), showed a higher frequency of diabetes by HbA1c, in contrast to our incidence study, however mean HbA1c in Inter99 appears higher than in other cohorts (8).

The genetic determinants of glucose and HbA1c differ. A genome-wide scan of SNPs related with HbA1c found some SNPs in common with hyperglycaemia: GCK, SLC30A8, G6CP2 but the SNP HK1 (rs7072268) was only associated with HbA1c (9); the T allele may be associated with a pro-anemic effect (10).

As there was only one blood draw to evaluate FPG and HbA1c, this study is limited for diabetes diagnosis. Further, while our HbA1c assay conformed to the DCCT/NGSP standards, it was not linked to the International Federation of Clinical Chemistry reference method (1).

In summary, one of the main differences between the phenotypes according to the FPG and the HbA1c definitions of diabetes, is a sex difference. FPG screens more incident diabetes in men than does HbA1c, whereas for women, the percentages are very similar.

Author contributions: BB is principal investigator of the D.E.S.I.R. study, analysed the data and wrote the article; CL analysed the data, reviewed and edited the manuscript; SS, AG, JT, SV reviewed and edited the manuscript and contributed to the discussion.

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FIGURE LEGEND

Figure 1—Mean values at baseline of fasting plasma glucose and HbA1c by age class, in men and women from the D.E.S.I.R. study, who were not treated for diabetes. The difference was constant over age classes of fasting plasma glucose ($P_{\text{interaction}} = 0.6$), but not for HbA1c ($P_{\text{interaction}} = 0.0001$)

Table —Odds ratios (95% CI), univariable analysis, for incident diabetes according to six definitions of diabetes: the D.E.S.I.R. Study

	Definitions of incident diabetes						
	treatment	FPG ≥ 7.0 mmol/l	HbA1c ≥ 6.5%	FPG ≥7.0mmo/l or HbA1c ≥6.5%	FPG ≥ 7.0 mmol/l or treatment	HbA1c ≥ 6.5% or treatment	FPG≥7.0mmol/l or HbA1c≥6.5% or treatment
Numbers of cases of incident diabetes /N	108/3872	168/3790	126/3789	228/3800	203/3825	165/3828	264/3836
	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>	<i>P</i>
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)		0.0004	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
	zero	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)
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/m²)		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)	2.25 (1.56-3.25)
		<0.0001	0.0040	<0.0001	0.0001	0.0002	<0.0001	<0.0001
Areas under the receiver operating characteristic curve for the D.E.S.I.R. diabetes risk score								
D.E.S.I.R. 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)

* Reference 2: Balkau B, Lange C, Fezeu L, Tichet J, de Lauzon-Guillain B, Czernichow S, Fumeron F, Froguel P, Vaxillaire M, Cauchi S, Ducimetière P, Eschwège E. Predicting diabetes: clinical, biological, and genetic approaches: data from the Epidemiological Study on the Insulin Resistance Syndrome (DESIR). Diabetes Care 2008;31:2056-2061

SUPPLEMENTARY INFORMATION AND RESULTS

RESEARCH DESIGN AND METHODS

Study population

The study population was men and women aged 30 to 65 years, who participated in the 9-year follow-up study, Data from an Epidemiological Study on the Insulin Resistance syndrome (D.E.S.I.R.) (3). Participants were recruited from volunteers attending free-of-charge health examinations, provided by the French Social Security, and recruited from 10 health examinations centres in western France. All subjects signed an informed consent and the protocol was approved by an ethics committee.

Incident cases of diabetes were identified by

- A. treatment for diabetes at one of the three-yearly examinations in 1896 men and 1976 women not treated for diabetes at baseline;
- B. FPG ≥ 7.0 mmol/l, at one of the three-yearly examinations in the 1846 men and 1944 women not treated for diabetes at baseline and with baseline FPG < 7.0 mmol/l;
- C. HbA1c ≥ 6.5 %, at one of the three-yearly examinations in the 1849 men and 1940 women not treated for diabetes at baseline and with baseline HbA1c < 6.5 %;
- D. treatment for diabetes or a FPG ≥ 7.0 mmol/l at one of the three-yearly examinations in the 1867 men and 1958 women, not treated for diabetes at baseline and with baseline FPG < 7.0 mmol/l;
- E. treatment for diabetes or HbA1c ≥ 6.5 % at one of the three-yearly examinations in the 1867 men and 1952 women not treated for diabetes at baseline and with baseline HbA1c < 6.5 %;
- F. treatment for diabetes or FPG ≥ 7.0 mmol/l and/or HbA1c ≥ 6.5 % at one of the three-yearly examinations in the 1840 men and 1940 women not treated for diabetes at baseline and with baseline FPG < 7.0 and HbA1c < 6.5 %.

All individuals studied had data available for glucose, HbA1c, BMI and waist circumference. Missing data for other variables were replaced by the mean value; values were imputed for at most nine individuals.

There were

Measures

Two measures of blood pressure were taken in a supine position after 5 minutes rest; mean values were used. Weight and height were measured in lightly clad participants, and BMI calculated. The waist circumference, the smallest circumference between the lower ribs and the iliac crests, was also measured.

The examining physician noted the family history of diabetes, as well as treatment for diabetes, hypertension and lipids. Hypertension was defined by systolic/diastolic blood pressures of at least 140/90 mmHg or being on antihypertensive medication. Smoking habits, alcohol intake (consumption per day of wine, beer, cider and spirits) and degree of physical activity (at home, at work and sport) were assessed using a self-administered questionnaire. Alcohol consumption was classed according to pure alcohol intake as: zero, under 20 g/day, 20 to under 40 g/day, 40 g/day or above, and physical activity in two classes, sedentary versus some activity.

All biochemical measurements were from one of four health-centre biological laboratories located in France at Blois, Chartres, La Riche or Orléans. Fasting plasma glucose, was measured by the glucose-oxidase method in fluoro-oxalated plasma using a Technicon RA100 (Bayer Diagnostics, Puteaux, France) or a Specific or a Delta device (Konelab, Evry, France). HbA1c was quantified by High Performance Liquid Chromatography using a L9100 automated ion-exchange analyser (Hitachi/ Merck-VWR, Fontenay-sous-Bois) or a Radiant 1 (Bio-rad, Marne la Coquette, France), or by Immunoassay using a DCA2000 (Bayer Diagnostics, Puteaux, France). FPG and HbA1c have been standardized over laboratories and time periods, according to gender and age.

Statistical methods

Statistical analysis used SAS Version 9.1 (SAS Institute Inc. Cary, NC USA).

Men and women not treated for diabetes at baseline, were characterised by means (SDs) or percentages, and compared by t and χ^2 tests according to whether they were treated or not after 9 years of follow-up. Mean FPG and HbA1c were determined by age group, and the gender-age interaction was tested in a linear regression model. The frequencies of diabetes defined by FPG alone, HbA1c alone or by both FPG and HbA1c were determined.

For each definition of diabetes, the logistic model was used to determine odds ratios for incident diabetes for potential risk factors. Interactions between risk factors and sex were tested, and in consequence, sex specific odds ratios are given for smoking and diabetes in the family, for

all definitions of diabetes. The linearity of continuous risk factors was checked by the inclusion of a squared term.

We compared the discriminative ability of the D.E.S.I.R. diabetes risk score (3), developed for incident diabetes defined by treatment and/or FPG ≥ 7.0 mmol/l. This score includes waist circumference, hypertension and current smoking for men, and for women, waist circumference, hypertension and family history of diabetes, using the area under the receiver operating characteristic curve (AROC).

Supplementary Table 1—Characteristics of men and women (mean (SD) or %), not treated for diabetes at baseline, according to whether or not they were treated for incident diabetes over the 9 years of follow-up: the D.E.S.I.R. study.

	Men			Women		
	treatment for diabetes over the 9 year follow-up			treatment for diabetes over the 9 year follow-up		
	yes n=70	no n=1826	<i>P</i>	yes n=38	no n=1938	<i>P</i>
Age (years)	53 (9)	47 (10)	<0.0001	55 (8)	47 (10)	0.0001
Diabetes in family	26%	18%	0.1170	45%	20%	0.0001
Current smoker	43%	25%	0.0007	5%	13%	0.1499
Alcohol (g/day)						
zero	8%	12%	0.0033	39%	37%	0.4860
0-19	13%	24%		45%	37%	
20-39	49%	49%		16%	25%	
≥ 40	30%	15%		0%	1%	
Sedentary	36%	25%	0.0381	34%	25%	0.1801
Waist (cm)	101 (9)	89 (9)	<0.0001	93 (11)	76 (10)	0.0001
BMI (kg/m ²)	29.2 (3.6)	25.1 (3.0)	<0.0001	30.1 (5.3)	23.8 (3.8)	0.0001
Hypertension (%)	84%	40%	<0.0001	66%	28%	<0.0001
Lipid treatment	20%	7%	0.0001	18%	7%	0.006

Supplementary Table 2—Characteristics (mean (SD) or %) of those with incident diabetes, according to the six definitions of diabetes: the D.E.S.I.R. Study

MEN	Definitions of incident diabetes						
	treatment	FPG ≥7.0mmol/l	HbA1c ≥6.5%	FPG ≥7.0mmol/l or HbA1c ≥6.5%	FPG ≥7.0mmol/l or treatment	HbA1c ≥6.5% or treatment	FPG ≥7.0mmol/l HbA1c≥6.5 % or treatment
Numbers of incident diabetes cases/N (%)	70/1896 (3.7%)	119/1846 (6.4%)	74/1849 (4.0%)	150/1857 (8.1%)	140/1867 (7.5%)	99/1874 (5.3%)	171/1878 (9.1%)
Age (years)	53 (9)	50 (9)	52 (10)	51 (9)	50 (9)	53 (9)	51 (9)
Diabetes in family	26%	18%	23%	21%	20%	25%	22%
Current smoker	43%	38%	32%	35%	37%	34%	35%
Alcohol (g/day)							
zero	8%	11%	11%	11%	11%	10%	11%
0-19	13%	19%	15%	16%	18%	15%	16%
20-39	49%	41%	39%	45%	43%	44%	46%
≥ 40	30%	29%	35%	28%	28%	31%	27%
Sedentary	36%	30%	45%	35%	31%	42%	36%
Waist (cm)	101 (9)	95 (10)	97 (10)	96 (10)	96 (10)	98 (10)	96 (10)
BMI (kg/m ²)	29.2 (3.6)	27.4 (4.0)	28.1 (4.3)	27.4 (3.9)	27.5 (4.0)	28.3 (4.1)	27.6 (3.9)
Hypertension	84%	59%	66%	59%	62%	72%	63%
Lipid treatment	20%	14%	20%	14%	14%	17%	13%

WOMEN	Definitions of incident diabetes						
	treatment	FPG ≥7.0mmol/l	HbA1c ≥6.5%	FPG ≥7.0mmol/l or HbA1c ≥6.5%	FPG ≥7.0mmol/l or treatment	HbA1c ≥6.5% or treatment	FPG ≥7.0mmol/l, HbA1c≥6.5% or treatment
Numbers of incident diabetes cases/N (%)	38/1976 (1.9%)	49/1944 (2.5%)	52/1940 (2.7%)	78/1943 (4.0%)	63/1958 (3.2%)	66/1954 (3.4%)	93/1958 (4.7%)
Age (years)	55 (8)	50 (8)	56 (7)	53(9)	51 (8)	55 (8)	53 (8)
Diabetes in family	45%	45%	27%	33%	43%	30%	33%
Current smoker	5%	18%	15%	18%	16%	14%	16%
Alcohol (g/day)							
zero	39%	24%	44%	34%	29%	43%	38%
0-19	45%	47%	35%	40%	44%	36%	38%
20-39	16%	29%	21%	26%	27%	21%	24%
≥ 40	0%	0%	0%	0%	0%	0%	0%
Sedentary	34%	29%	35%	29%	35%	36%	33%
Waist (cm)	93 (11)	89 (12)	89 (11)	88 (11)	90(12)	90 (11)	89 (11)
BMI (kg/m ²)	30.1 (5.3)	28.9 (5.5)	28.5 (5.7)	28.1 (5.2)	29.2 (5.1)	28.9 (5.4)	28.4 (5.0)
Hypertension	66%	61%	60%	60%	62%	65%	62%
Lipid treatment	18%	10%	19%	14%	14%	20%	16%