# Predicting diabetes - clinical, biological and genetic approaches: the D.E.S.I.R. Study.

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# Predicting diabetes – clinical, biological and genetic approaches: the D.E.S.I.R. Study

Running head: A score to predict incident diabetes in France

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**OBJECTIVES**—To provide a simple clinical diabetes risk score; to identify characteristics which predict later diabetes using variables available in clinic, then additionally biological variables and polymorphisms.

**RESEARCH DESIGN AND METHODS**—Incident diabetes was studied in 1863 men and 1954 women, 30-65 years at baseline, by treatment or by fasting plasma glucose ≥ 7.0 mmol/l at 3-yearly examinations over nine years. Sex-specific logistic regression equations were used to select variables for prediction.

**RESULTS**—140 men, 63 women developed diabetes. The predictive clinical variables were: waist circumference and hypertension in both sexes; for men: smoking, for women: diabetes in the family. Discrimination, as measured by the areas under the receiver operating curves (AROC), were 0.713 for men and 0.827 for women, a little higher than for the FINDRISC score, with fewer variables in the score. Combining clinical and biological variables, the predictive equation included for men: fasting glucose, waist circumference, smoking, γ-glutamyltransferase; for women fasting glucose, BMI, triglycerides, diabetes in family. The number of *TCF7L2* and *IL6* deleterious alleles was predictive in both sexes, but after including the above clinical and biological variables, this variable was only predictive in women ($p < 0.03$) and the AROC statistics increased only marginally.

**CONCLUSIONS**—The best clinical predictor of diabetes is adiposity, and baseline glucose is the best biological predictor. Clinical and biological predictors differed marginally between men and women. The genetic polymorphisms added little to the prediction of diabetes.

A number of diabetes risk scores have been developed to detect those who *should be screened* for diabetes (1). In the Data from an Epidemiological Study on the Insulin Resistance Syndrome (D.E.S.I.R.) cohort we have already studied the anthropometric variables *associated* with diabetic levels of fasting glucose and found that BMI, waist circumference and waist-hip ratio were equally useful in their identification of individuals with undiagnosed diabetes (2).

The first score to identify lifestyle and clinical parameters *predictive* of *later* diabetes was developed by Lindström and Tuomilehto (3), from a population-based sample of people who responded to questionnaires in 1987; 10-year incident diabetes was identified from a registry of diabetes treatment. A similar Finnish Diabetes Risk Score, FINDRISC, was used in a cross sectional study (4). In the American ARIC study, and in a Thai population, predictive risk factors were also identified, diabetes was defined by treatment or diabetic levels of fasting and 2 hr glucose from an oral glucose tolerance test (OGTT)(5,6). More recently Simmons published a score from the EPIC-Norfolk study, with incident diabetes defined by clinical identification of diabetes or an HbA1c > 7% (7), which included dietary factors and physical activity. Finally, dietary and other non-invasive factors associated with 5-year incident, self-reported cases of diabetes, were identified in the large EPIC-Potsdam study (8).

In the San Antonio Study, Stern published a score based on prospective clinical and biological data (9). In the Framingham cohort, four scores were proposed, a clinical score and three scores with both clinical and biological factors with incident diabetes identified at follow up by diabetic treatment and/or fasting glucose levels (10).

Other studies on diabetes risk factors include one in French men with impaired fasting glucose (6.1-6.9 mmol/l), which identified lifestyle, clinical and biological factors predictive of diabetes (11).

As risk scores cannot always be generalized from one country to another (12,13), the aim of this study was to describe sex-specific lifestyle and clinical diabetes risk factors in a French population followed over 9 years, which would aid in identifying those at risk for *incident* diabetes. The additional aims were to study the impact of biological factors and genetic polymorphisms in predicting diabetes.

## RESEARCH DESIGN AND METHODS

### Study population

The study population was men and women aged 30–64 years, who participated in the 9-year follow-up study, D.E.S.I.R. Participants were recruited from volunteers offered periodic health examinations free of charge by the French Social Security, in 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 treatment for diabetes or a fasting plasma glucose ≥ 7.0 mmol/l, at one of the three-yearly examinations, after exclusion of individuals with diabetes at baseline and those with unknown diabetic status at the 9-year examination; the 1863 men and 1954 women who had glucose, BMI and waist circumference available at baseline were studied.

**Measures**

Two measures of blood pressure, using a mercury sphygmomanometer, and of heart rate 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 and menopausal status in a clinical questionnaire; treatment for diabetes, hypertension and lipids were recorded. Hypertension was defined by systolic/diastolic blood pressures of at least 140/90 mmHg or being on antihypertensive medication. Smoking habits, alcohol consumption (glasses per day of wine, beer, cider, spirits) and degree of physical activity (at home, at work and sport) were assessed using a self-administered questionnaire.

All biochemical measurements were from one of four health-centre laboratories located in France at Blois, Chartres, La Riche or Orléans. Fasting plasma glucose, measured by the glucose-oxidase method, was applied to fluoro-oxalated plasma using a Technicon RA100 (Bayer Diagnostics, Puteaux, France) or a Specific or a Delta device (Konelab, Evry, France). Total cholesterol, HDL-cholesterol, triglycerides, alanine aminotransferase (ALT), $\gamma$-glutamyltransferase (GGT), and creatinine were assayed by DAX 24 (Bayer Diagnostics, Puteaux, France) or KONE (Evry, France). Insulin was quantified by micro particle enzyme immunoassay with an automated analyzer IMX (Abbott, Rungis, France). White cell counts were determined by a Technicon H* or a Technicon H3RTX (Bayer Diagnostics, Puteaux, France) or a JT2 (Beckman/Coulter, Roissy, France) or an Argos (ABX, Montpellier, France). The inter-laboratory variability was assessed monthly on normal and pathological values for each biologic variable.

Single nucleotide polymorphism (SNP) genotyping was performed with the SNPlex™ Technology (Applied Biosystems, Foster City, CA) based on the Oligonucleotide

Ligation Assay (OLA) combined with multiplex PCR target amplification (http://www.appliedbiosystems.com) (14).

**Statistical methods**

Statistical analysis used SAS Version 9.1 (SAS Institute Inc. Cary, NC USA). Alcohol intake, BMI, fasting glucose, insulin, ALT, GGT, triglycerides and white blood cell count were log-transformed because of their skewed distributions.

Characteristics of men and women with and without incident diabetes are shown by means (SDs) or numbers (percentages) and compared by t- or $\chi^2$-tests, or by linear regression for the polymorphisms with additive models. The logistic model was used to test for interactions with sex and *P-values* are reported; significant interactions ($P < 0.01$) provided the rational for sex-specific models.

The linearity of continuous parameters in logistic analyses was studied by adding a squared term and comparing nested models by likelihood ratio tests; all variables were *linearly* related with the logit of diabetes incidence excepting fasting glucose (log-transformed); in the models, glucose (log) was centred by subtracting its mean, and its square was systematically included.

Parsimonious logistic regression models were selected using forwards, backwards as well BEST model selection criteria using all parameters; the Hosmer-Lemeshow goodness-of-fit test was the principal criteria for selection of a model. Interactions with sex were tested. The area under the receiver operating characteristic sensitivity-specificity curve (AROC) quantified the discrimination between diabetic and non-diabetic participants. Bootstrap sampling was used to validate the choice of variables in the models, with 1000 samples of the same sizes as the study populations. The choice of variables was also validated in the Cox model.

To derive a simple *clinical* score from the clinical equations, we used the beta coefficients from the logistic regression analysis; for waist circumference four groups were defined, linearly, from the approximate sex-specific quartiles. The score was validated in two French cohorts, E3N and SU.VI.MAX (15,16) (On-line figure 1). The first study identified incident diabetes by self-questionnaire or treatment reimbursement, the second by fasting glucose or treatment.

Four polymorphisms were chosen for study (*Glucokinase: GCK-30 G/A rs1799884, Interleukine 6: IL6-174 G/C rs1800795, Kir6.2: KCNJ11 E23K rs5219 and TCF7L2 rs7903146*) following previous analyses in this population (14). Additive models discriminated best between diabetic and non-didabetic people. For the two polymorphisms found to be the most related with incident diabetes (IL6, TCF7L2), the number of deleterious alleles (as a continuous variable) was calculated, and added as a variable to the (clinical + biological) equations chosen above. As this analysis aimed to determine those who should be screened for diabetes, we have analysed all individuals, and have not excluded those born outside of mainland France. This analysis was on a smaller population (1655 men, 1740 women) where these two polymorphisms were available.

We compared our clinical risk score with the FINDRISC score (3) using the AROC-statistic; FINDRISC includes age, BMI, waist circumference, anti-hypertensive medication, physical activity, previously known high glucose and daily consumption of vegetables, fruits or berries; we were not able to include latter two items. Our (clinical + biological) equation was compared with the Stern equation, including age, sex, fasting glucose, systolic blood pressure, HDL-cholesterol, BMI, diabetes in the family; we did not include the factor for coding Mexican Americans (9).

## RESULTS

In the D.E.S.I.R. population, 140 men and 63 women had incident diabetes

### Clinical predictors of incident diabetes

All of the clinical variables showed similar relations with incident diabetes in both men and women with the exception of diabetes in the family: noted for 43% of women with incident diabetes, 19% in those without; for men 20% and 18% respectively ($P$ sex-interaction=0.003) (Table 1).

The first most predictive variable was waist circumference, closely followed by BMI, in both genders. The selected model in men included waist circumference, smoking and hypertension; for women, waist circumference, diabetes in the family, and hypertension (Table 2). These models showed a good fit (Hosmer-Lemeshow $P$-values: 0.7; 0.6, men; women respectively) and discriminated well the diabetic and non-diabetic populations (AROC 0.733; 0.839). In the bootstrap samples these were the most frequently chosen models. These variables were also chosen by the Cox modeling.

### Clinical risk score

From the above equations, clinical risk scores were derived (Table 3). These scores showed a good fit (Hosmer-Lemeshow $P$-values: 0.8; 0.9 men women respectively) and the discrimination was similar to the more exact equation with continuous values of waist circumference.

The ROC curves for the clinical equation and for the simplified clinical score are shown for men and women (Fig. 1A); the D.E.S.I.R. scores with three variables had AROC values slightly higher than for the five-variable FINDRISC score. The score predicted diabetes in the two French cohorts, with AROCS similar to those from D.E.S.I.R. (On-line Figure).

### Biologic predictors of incident diabetes

Fasting glucose was by far the factor the most predictive of incident diabetes with a no difference in its effect between men and women (*P* interaction = 0.1) (Table 1). Predictive factors differing between genders were triglycerides and HDL-cholesterol: both had a slightly stronger relation in women (*P* sex-interaction = 0.006, 0.008 respectively).

### Clinical+Biological predictors of incident diabetes

Fasting glucose (including its squared term) was the most predictive of all factors. After adjustment for fasting glucose, waist circumference was more predictive than BMI in men, but BMI was more predictive than waist in women (Table 2). In men, the predicting equation included fasting glucose, smoking status, waist circumference and GGT; for women, fasting glucose, BMI, diabetes in the family and triglycerides. The same variables were chosen by Cox modelling with five predictive variables.

Our (clinical + biological) equation was simpler than the Stern equation with only four variables, and discriminated similarly, incident diabetic individuals (Fig. 1B).

### Genetic polymorphisms as predictors of incident diabetes

None of the four polymorphisms was significantly related with incident diabetes in either men or women, using either the three genotypes or recessive, dominant or additive models of inheritance (On-line Table). There was no interaction with sex, and combining men and women, TCF7L2 and IL6 were significantly related with incident diabetes using additive models (*P* < 0.01, 0.03 respectively). In comparison to individuals with no deleterious alleles, those with four deleterious alleles had an odds ratio of incident diabetes of 3.60 (1.09-11.9) in men and 3.22 (0.62-16.5) in women. The number of

deleterious alleles was associated with incident diabetes, in both men and women (*P* < 0.008; 0.03 respectively) (Table 1).

Including the total number of deleterious alleles in the above determined (clinical + biological) equations, they showed an adequate fit but changed little the AROC (Table 2).

## DISCUSSION

Both the clinical and the (clinical+biological) equations are able to predict diabetes incidence over a 9-year follow-up, with different variables in the equations for men and women.  Age was not selected in any of the equations, but the effect of ageing would pass by other parameters such as adiposity, hypertension, glucose levels. Age was included in the equations of many (3,5,8-10) but not all of the other published studies of risk equations (7). Polymorphisms added little to these scores. As expected, the equations derived on our population performed slightly better than those derived in other populations. The clinical score performed well on two other French cohorts.

Our diabetes risk score based on clinical data, has the advantage that it is simple, and requires only three parameters. Given a larger population and a higher incidence of diabetes, other parameters might have been included in the equations, but the discrimination and model fit may not be greatly improved.

BMI and waist circumference had similarly predictive values in both men and women; once one was included, the other no longer entered the model. Similar comments can be made for GGT and ALT.

In contrast to other scores, we have studied men and women separately and found that the predictive equations differ. In both sexes, waist circumference was the clinical factor the most related with incident diabetes, then in men smoking, which was more common in men than women; diabetes in the family was a predictive factor only in the

women. Hypertension was predictive of diabetes in both sexes, a factor often present before diabetes (17). Smoking is recognised as a risk factor for diabetes, with a higher risk for the heavy smokers in comparison to the lighter and former smokers (18). Our observation that more diabetic women than men have diabetes in the family, is probably due to women being more aware of their family diabetes. In the multivariate equations physical activity was not predictive – this could be because of its negative correlation with waist circumference and hypertension and perhaps because our questions on self-reported physical activity were not sufficiently precise, in comparison to other data such as waist circumference and hypertension. Other studies have indeed included physical activity in their multivariate equations (3,7,8).

The overriding biological factor predictive of diabetes was the baseline glucose level. In the (clinical+biological) equation in men, the GGT also entered the equation, in women the triglycerides concentration. We have already shown that GGT is predictive of incident diabetes in this cohort, for both genders (19), and others have shown that triglycerides are predictive (5,10).

The polymorphisms studied provided little towards predicting diabetes: for the 1655 men and 1740 women with these data available, the Hosmer-Lemeshow tests showed a poorer fit for men when the genetic data was included, but identical AROCs. Of note, in women, the coefficient for the parameter: diabetes in the family, was only reduced from 0.80 to 0.75 when genetic parameters were included, indicating there are probably other genetic factors involved. A large panel of SNPs may be needed be to out-perform even simple clinical parameters.

One of the limitations is that we have not been able to include the 2-hour glucose concentration in our definition of diabetes: in France screening of diabetes with fasting glucose is common, so our score is appropriate in the local situation. A further limitation is that score is only for people between 30 and 65 years

The simplest clinical parameter for identifying those at risk of diabetes is adiposity – and taken alone, either waist circumference or BMI did equally well in predicting later diabetes during the nine year follow up. The addition of hypertension, and smoking in men, triglycerides in women provides a clinical score which discriminates well.

## ACKNOWLEDGMENTS

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**Figure Legends**

**Figure 1**—Receiver Operating Characteristic (ROC) curves and the AROC statistics in men and women for **A**. the D.E.S.I.R. French clinical equation, the French clinical risk score and the FINDRISC clinical score (3); **B**. the D.E.S.I.R (clinical+biological). French risk equation and the Stern risk equation (9).

**Table 1**—Clinical and biological characteristics [mean(SD) or number (%)] at baseline of men and women with and without incident diabetes during the 9 years of the D.E.S.I.R. study.

| | Men | | | Women | | | *P* for variable | *P* interaction with sex |
| | Diabetes n=140 | No diabetes n=1723 | *P** | Diabetes n=63 | No diabetes n=1891 | *P** | | |
|---|---|---|---|---|---|---|---|---|
| Age (years) | 50 (9) | 47 (10) | 0.0001 | 52 (8) | 47 (10) | 0.0005 | 0.0001† | 0.6 |
| Diabetes in the family | 28 (20%) | 312 (18%) | 0.6 | 27 (43%) | 368 (19%) | 0.0001 | ‡ | 0.003 |
| | | | | | | | | |
| Current smoker | 52 (37%) | 418 (24%) | 0.0009 | 10 (16%) | 249 (13%) | 0.5 | 0.001† | 0.3 |
| Alcohol intake (g/day) § | 34 (32) | 23 (22) | 0.005 | 8 (11) | 7 (11) | 0.5 | 0.006† | 0.2 |
| | | | | | | | | |
| Physical activity | | | | | | | | |
|   Little | 43 (31%) | 422 (24%) | | 22 (35%) | 465 (25%) | | | |
|   Moderate | 72 (51%) | 911 (53%) | 0.07 | 33 (52%) | 1036 (55%) | 0.04 | 0.03† | 0.7 |
|   Intensive | 25 (18%) | 388 (23%) | | 8 (13%) | 386 (20%) | | | |
| | | | | | | | | |
| Waist circumference (cm) | 96 (10) | 89 (9) | 0.0001 | 90 (12) | 76 (10) | 0.0001 | 0.0001† | 0.3 |
| BMI (kg/m²) § | 27.5 (4.0) | 25.1 (3.0) | 0.0001 | 29.2 (5.1) | 23.7 (3.8) | 0.0001 | 0.0001† | 0.3 |
| | | | | | | | | |
| Menopause | | | | 30 (48%) | 718 (38%) | 0.1 | | |
| Large baby, birth weight ≥ 4 kg | | | | 16 (27%) | 284 (15%) | 0.02 | | |
| | | | | | | | | |
| Hypertension‖ | 87 (62%) | 678 (39%) | 0.0001 | 39 (62%) | 527 (28%) | 0.0001 | 0.0001 | 0.1 |
| Heart rate (min) | 68 (10) | 66 (10) | 0.007 | 71 (11) | 68 (9) | 0.02 | 0.0005† | 0.7 |
| Treatment for lipids | 20 (14%) | 126 (7%) | 0.004 | 9 (14%) | 129 (7%) | 0.03 | 0.0003† | 0.9 |
| Fasting glucose (mmol/l) § | 6.05 (0.55) | 5.39 (0.49) | 0.0001 | 5.96 (0.58) | 5.11 (0.46) | 0.0001 | 0.0001† | 0.1 |
| GGT (IU/l) § | 64.3 (67.2) | 39.5 (38.3) | 0.0001 | 36.4 (33.6) | 21.7 (21.2) | 0.0001 | 0.0001† | 0.4 |
| ALT (UI/l) § | 41.7 (28.3) | 30.3 (18.1) | 0.0001 | 28.9 (22.2) | 20.1 (13.8) | 0.0001 | 0.0001† | 0.4 |
| Triglycerides (mmol/l) § | 1.79 (1.45) | 1.26 (0.80) | 0.0001 | 1.50 (0.78) | 0.93 (0.50) | 0.0001 | ‡ | 0.006 |
| HDL-cholesterol (mmol/l) | 1.41 (0.37) | 1.50 (0.38) | 0.01 | 1.53 (0.34) | 1.80 (0.42) | 0.0001 | ‡ | 0.008 |
| Total-cholesterol (mmol/l) | 6.06 (1.05) | 5.82 (0.97) | 0.009 | 5.94 (1.04) | 5.61 (0.96) | 0.02 | 0.0001† | 0.6 |
| Creatinine (µmol/l) | 91.0 (13.9) | 89.1 (11.1) | 0.06 | 77.1 (10.7) | 74.1 (10.0) | 0.02 | 0.006† | 0.4 |
| White Blood Cell count ($10^9$/l) § | 6.9 (2.1) | 6.4 (1.7) | 0.002 | 7.3 (4.0) | 6.2 (1.6) | 0.0002 | 0.0001† | 0.2 |
| | n=135 | n=1617 | | n=61 | n=1782 | | | |
| Number of TCF7L2, IL6 deleterious alleles | 2.0 | 1.8 | 0.008 | 2.2 | 1.8 | 0.03 | 0.0007 | 0.7 |

\* *P*-value comparing means and percentages, by t- and χ² tests
† *P*-value for variable in logistic model with only variable and sex, as interaction not significant
‡ *P*-value for variable not given, as the interaction is significant
§ log-transformation because of a non-symmetric distributions
‖ hypertension: systolic / diastolic blood pressures ≥ 140 / 90 mmHg or medication for hypertension

**Table 2**—Beta coefficients for the clinical, (clinical+biological), (clinical+biological+genetic) equations. The D.E.S.I.R. Study

**Men**

| Variable | Clinical Equation 140 diabetic men, n=1860 | | Clinical + Biological Equation 140 diabetic men, n=1860 | | Clinical + Biological + Genetic Equation 128 diabetic men, n=1655 | |
|---|---|---|---|---|---|---|
| | beta | P | beta | P | beta | P |
| Intercept | -10.45 | | -10.53 | | 10.91 | |
| Current smoker | 0.72 | 0.0002 | 0.88 | 0.0001 | 0.94 | 0.0001 |
| Waist circumference (cm) | 0.081 | 0.0001 | 0.060 | 0.0001 | 0.060 | 0.0001 |
| Hypertension * | 0.50 | 0.01 | | | | |
| Fasting glucose (mmol/l) † | | | 10.15 | 0.0001 | 10.17 | 0.0001 |
| Fasting glucose² † | | | 24.16 | 0.002 | 22.42 | 0.007 |
| GGT (IU/l) † | | | 0.39 | 0.01 | 0.42 | 0.007 |
| Number of TCF7L2, IL6 deleterious alleles | | | | | 0.14 | 0.2 |
| AROC-statistic | 0.733 | | 0.850 | | 0.851 | |
| Hosmer-Lemeshow fit test | P = 0.7 | | P = 0.8 | | P = 0.1 | |

* glucose and GGT were log-transformed

**Women**

| | Clinical Equation 63 diabetic women n=1954 | | Clinical + Biological Equation 63 diabetic women n=1954 | | Clinical + Biological + Genetic Equation 58 diabetic women, n=1740 | |
|---|---|---|---|---|---|---|
| | beta | P | beta | P | beta | P |
| Intercept | -11.81 | | -18.91 | | -20.43 | |
| Diabetes in the family | 1.09 | 0.0001 | 0.80 | 0.01 | 0.75 | 0.02 |
| Waist circumference (cm) | 0.095 | 0.0001 | | | | |
| BMI (kg/m²) † | | | 4.38 | 0.0001 | 4.69 | 0.0001 |
| Hypertension * | 0.64 | 0.03 | | | | |
| Fasting glucose (mmol/l) † | | | 9.66 | 0.001 | 9.35 | 0.001 |
| Fasting glucose² † | | | 23.89 | 0.06 | 22.39 | 0.08 |
| Triglycerides (mmol/l) † | | | 0.95 | 0.003 | 0.86 | 0.01 |
| Number of TCF7L2, IL6 deleterious alleles | | | | | 0.36 | 0.04 |
| AROC-statistic | 0.839 | | 0.917 | | 0.912 | |
| Hosmer-Lemeshow fit test | P = 0.6 | | P = 0.9 | | P =0.8 | |

* hypertension: systolic / diastolic blood pressures $\geq$ 140 / 90 mmHg or medication for hypertension

† fasting glucose, GGT, BMI and triglycerides were log-transformed

**Table 3**— A clinical diabetes risk score of 5 confers a more than 30% chance of diabetes in the following 9 years,The D.E.S.I.R. Study

| Men | | Scores to sum | Women | | Scores to sum |
|---|---|---|---|---|---|
| Waist circumference | < 80 cm | 0 | Waist circumference (cm) | < 70 cm | 0 |
| | 80-89 cm | 1 | | 70-79 cm | 1 |
| | 90-99 cm | 2 | | 80-89 cm | 2 |
| | ≥ 100 cm | 3 | | ≥ 90 cm | 3 |
| Current Smoker - yes | | 1 | Diabetes in the family - yes | | 1 |
| Hypertension* - yes | | 1 | Hypertension - yes | | 1 |
| AROC-statistic | 0.713 | | AROC-statistic | 0.827 | |
| Hosmer-Lemeshow fit test | $P = 0.8$ | | Hosmer-Lemeshow fit test | $P = 0.9$ | |

*  hypertension: systolic / diastolic blood pressures ≥ 140 / 90 mmHg or medication for hypertension