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Evaluation et validation des équations de prédiction du risque de diabète dans la population lausannoise. Etude CoLaus

THESE

préparée sous la direction du Docteur Pedro Marques-Vidal
(avec la collaboration du Professeur Gérard Waeber)

et présentée à la Faculté de biologie et de médecine de
l'Université de Lausanne pour l'obtention du grade de

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par

Rémy SCHMID

Médecin diplômé de la Confédération Suisse
Originaire de Niedermuhlern (Berne)

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Evaluation et validation des équations de prédiction du risque de diabète dans la population lausannoise. Etude CoLaus

Rapport de synthèse

Le diabète de type 2 est une maladie fréquente et en augmentation dans le monde entier. Malheureusement, elle est souvent diagnostiquée à un stade ou des complications sont déjà apparues. Depuis quelques années, des scores ont été développés pour identifier les sujets à risque de développer cette maladie. L'utilisation d'un tel score par le praticien pourrait amener ces patients à des mesures préventives, telles que le changement d'hygiène de vie, ou la prescription d'un traitement médicamenteux. Le but de notre étude est de comparer et de valider différents scores de risques de diabète de type 2 et de déterminer leur capacité à prédire la survenue de cette maladie dans la population de la cohorte CoLaus.

Les premiers résultats, en étude transversale, ont tout d'abord montré de grandes différences quant à la population à risque d'un score à l'autre. En effet, le nombre de personnes à traiter varie considérablement selon la méthode utilisée. Ces différents scores ont donc nécessité une validation prospective. Ces résultats ont fait l'objet d'une publication (Schmid et col, Diabetes Care. 2011 Aug;34(8):1863-8).

Au moyen des données du suivi à 5 ans, il est sorti qu'un score de risque utilisant des variables biologiques et cliniques, ainsi qu'un score utilisant des variables uniquement cliniques, obtenaient de très bon résultats quant à la prédiction du diabète de type 2. En effet, un des scores testés donne une valeur prédictive positive d'environ 20% à 5 ans, ce qui signifie qu'un patient « détecté » sur 5 pourrait bénéficier d'une intervention précoce. Toutefois, ces résultats concernent la population lausannoise et ne sont donc pas forcément applicables à l'ensemble de la population suisse. De plus, de plus amples études sont nécessaires évaluer l'efficacité d'un tel score dans la prévention du diabète en Suisse. Ces résultats ont fait l'objet d'une seconde publication (Schmid et col, Arch Intern Med. 2012 Jan 23;172(2):188-9).

Dans un troisième volet de l'étude, l'impact de marqueurs génétiques a été évalué dans un sous-groupe de la population CoLaus. Les résultats n'ont toutefois montré qu'une très faible amélioration de la prédiction du risque en utilisant ces marqueurs. Ceci devrait nous encourager à intensifier les efforts de prévention sur le style de vie pour toute la population, plutôt qu'une approche ciblée sur les personnes génétiquement prédisposées. Ces résultats ont fait l'objet d'une troisième publication (Schmid et col, J Clin Endocrinol Metab. 2012 Apr 24. [Epub ahead of print]).

La même démarche méthodologique a été utilisée pour évaluer l'importance pronostique de plusieurs marqueurs inflammatoires (interleukines 1 et 6, TNF-, protéine C-réactive) hépatiques (GT) ou adipocytaires (leptine et adiponectine) dans la survenue du diabète. Ces résultats sont actuellement soumis au *Journal of Clinical Endocrinology and Metabolism*).

Le contenu de ce travail a été présenté lors des congrès suivants:

- Société Suisse de médecine interne, Lausanne, 11-13 Mai 2011 (1 poster)
- Société Européenne de Cardiologie, Paris, 28 Août 2011 (3 posters)
- Société Suisse d'Endocrinologie et Métabolisme, Berne, 2 Décembre 2011 (2 posters)

Estimating the Risk of Developing Type 2 Diabetes: A Comparison of Several Risk Scores

The Cohorte Lausannoise study

RÉMY SCHMID[1]
PETER VOLLENWEIDER, MD[2]
GÉRARD WAEBER, MD[2]
PEDRO MARQUES-VIDAL, MD, PHD[1]

OBJECTIVE—To compare in the Swiss population the results of several scores estimating the risk of developing type 2 diabetes.

RESEARCH DESIGN AND METHODS—This was a single-center, cross-sectional study conducted between 2003 and 2006 in Lausanne, Switzerland. Overall, 3,251 women and 2,937 men, aged 35–75 years, were assessed, of which 5,760 (93%) were free from diabetes and included in the current study. The risk of developing type 2 diabetes was assessed using seven different risk scores, including clinical data with or without biological data. Participants were considered to be eligible for primary prevention according to the thresholds provided for each score. The results were then extrapolated to the Swiss population of the same sex and age.

RESULTS—The risk of developing type 2 diabetes increased with age in all scores. The prevalence of participants at high risk ranged between 1.6 and 24.9% in men and between 1.1 and 15.7% in women. Extrapolated to the Swiss population of similar age, the overall number of participants at risk, and thus susceptible to intervention, ranged between 46,708 and 636,841. In addition, scores that included the same clinical variables led to a significantly different prevalence of participants at risk (4.2% [95% CI 3.4–5.0] vs. 12.8% [11.5–14.1] in men and 2.9% [2.4–3.6] vs. 6.0% [5.2–6.9] in women).

CONCLUSIONS—The prevalence of participants at risk for developing type 2 diabetes varies considerably according to the scoring system used. To adequately prevent type 2 diabetes, risk-scoring systems must be validated for each population considered.

Diabetes Care 34:1863–1868, 2011

Type 2 diabetes is a serious disease with increasing prevalence. This disease remains asymptomatic for years, being discovered only at a stage with preexisting complications (1). Recent studies (2) have shown that lifestyle or medication intervention could prevent the incidence of type 2 diabetes. Hence, screening tools are needed to identify participants with undiagnosed diabetes or those who are at risk for developing diabetes in the future. For this purpose, numerous risk scores recently have been proposed (3–6). Participants at high risk of developing type 2 diabetes, according to the risk score threshold, are thus amenable to preventive measures. A good diabetes risk score ideally should be easily completed by the physician and rely on easily and routinely accessible clinical and biological parameters, such as age, family history, hypertension, anthropometry, or lifestyle habits. Moreover, the risk score has to be accurate enough to provide targeted warnings for the patients. Some scores have been validated in selected populations (3–7), prompting their use in other countries (8,9). Nevertheless, recent studies (10) have shown that risk scores that are developed in the same country can lead to different results. Likewise, one equation validated in one country might not provide adequate estimates in another; for instance, the Framingham cardiovascular risk equations can over- or underestimate risk when directly applied to other populations (11). Finally, and to the best of our knowledge, no study has ever compared the results of differing scoring systems in Switzerland.

The current study aimed to compare the results of several scores that estimate the risk of developing type 2 diabetes using data from the Cohorte Lausannoise (CoLaus) study, a cross-sectional study conducted in Lausanne, Switzerland. The resulting number of subjects at risk for developing type 2 diabetes in Switzerland according to these different risk equations also was estimated.

RESEARCH DESIGN AND METHODS

Risk scores

We performed a PubMed search and selected risk scores for their relative novelty and their applicability to the Swiss population. The score from the Swiss Diabetes Association, available on the Internet (8), also was assessed. This score actually is an adaptation of the Finnish Diabetes Risk Score (FINDRISC) score (7). Overall, seven risk scores, including clinical (C) or clinical and biological variables (CB) were studied: 10-year risk scores from Kahn et al. (3) (C and CB); 8-year risk score from Wilson et al. (4) (CB); 9-year risk score from Balkau et al. (6) (C); the prevalent undiagnosed diabetes risk score from Griffin et al. (5) (C); the risk score from the Swiss Diabetes Association (8); and the FINDRISC (C), which is a 5- to 10-year risk score (7). The characteristics of the studies, where the scores were developed, and the variables included in each score are summarized in

From the [1]Institute of Social and Preventive Medicine, Centre Hospitalier Universitaire Vaudois and Faculty of Biology and Medicine, Lausanne, Switzerland; and the [2]Department of Medicine, Internal Medicine, Centre Hospitalier Universitaire Vaudois and Faculty of Biology and Medicine, Lausanne, Switzerland.
Corresponding author: Pedro Marques-Vidal, pedro-manuel.marques-vidal@chuv.ch.
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Supplementary Tables 1 and 2. From this point on, the scores will be referenced by the name of the first author, with a further differentiation by C or CB in the case of the Kahn and Balkau scores.

We used the thresholds recommended by the authors to define participants at high risk of developing type 2 diabetes (Supplementary Table 1). These thresholds were defined differently according to the study: Kahn (3), Wilson (4), and Balkau (6) used a probability, whereas the Swiss Diabetes Association and FINDRISC used a score above a given number of points. The initial publication from Griffin et al. (5) provided no threshold; hence, we used the 37% probability, which was used in another study (12). The scores from the Swiss Diabetes Association and FINDRISC included regular consumption of selected foods (fruits, vegetables, berries, and brown bread) and familial history of diabetes for second-degree parents (grandparents, cousins, and uncles). Because these data were not available in our study, the scoring system was adapted by reducing by one point the cutoff value for high-risk participants.

Recruitment

The CoLaus study is a cross-sectional study in the Caucasian population of Lausanne, Switzerland, a town of 117,161 inhabitants, of which 79,420 are of a Swiss nationality. This study was approved by the institutional ethics committee of the University of Lausanne. The study was designed to assess the prevalence and to identify the molecular determinants of cardiovascular risk factors. The population of Lausanne can be considered as representative of the whole country because a considerable proportion is non-Swiss or comes from other cantons (political regions of Switzerland). In 2006, of 128,231 Lausanne inhabitants, 38% were non-Swiss, 30% came from other cantons (including Italian and German-speaking cantons), and only 32% were actually from the Vaud canton (13).

The sampling procedure of the CoLaus study has been described previously (14). A complete list of Lausanne inhabitants, aged 35–75 years (n = 56,694), was provided by the population registry of the city. A simple, nonstratified random sample of 35% of the overall population was drawn. The following inclusion criteria were applied: *1*) provided written informed consent; 2) was aged 35–75 years; 3) was willing to take part in the examination and donate blood samples; and *4*) was of Caucasian origin, defined as having both parents and grandparents born in a restricted list of countries (available from the authors). Recruitment began in June 2003 and ended in May 2006. Participation rate was 41%, and 6,188 Caucasian participants (3,251 women and 2,937 men) took part in the study.

All participants attended the outpatient clinic of the University Hospital of Lausanne in the morning after an overnight fast (minimum fasting time 8 h). Data were collected by trained field interviewers in a single visit lasting ~60 min.

Clinical data

The participants first received a questionnaire to record information about their lifestyle factors, namely tobacco use, alcohol use, and physical activity. According to their smoking histories, participants were classified as never, current, or former smokers. Current smokers were defined as giving a positive answer to the statement "I currently smoke," former smokers were defined as giving a positive answer to the statement "I don't smoke anymore," and never smokers were defined as giving a positive answer to the statement "I have never smoked." Alcohol consumption included past and current drinking status as well as the number of alcoholic beverage units (wine, beer, and spirits) consumed over the week preceding the interview. A participant was considered to be physically active if he/she reported practicing at least 2 h of leisure-time physical activity per week.

During a second face-to-face meeting, the participants were asked if they or their first-degree family (i.e., parents, children) had presented with diabetes. The participants also were asked if they had been diagnosed with hypertension or if they currently were being treated for hypertension. Personal medicines, including prescription and self-prescribed drugs, were collected, together with their main indications. Only corticosteroids, being of systemic or topical use, were considered for testing the scores. Despite the fact that other medications, such as hydrochlorothiazide or ACE inhibitors, have been shown to influence diabetes status (15), they were not included in the risk scores.

Body weight and height were measured with participants standing without shoes in light indoor clothes. Body weight was measured in kilograms to the nearest 100 g, using a Seca scale, which was calibrated regularly. Height was measured to the nearest 5 mm using a Seca height gauge. Waist was measured with a nonstretchable tape over the unclothed abdomen at the narrowest point between the lowest rib and the iliac crest. Two measures were made, and the mean (expressed in centimeters) was used for analyses. Blood pressure and resting pulse were measured three times using an Omron HEM-907 automated oscillometric sphygmomanometer on the left arm, with an appropriately sized cuff, after at least 10 min rest in the seated position. The average of the last two measurements was used for analyses.

Biological analyses

Fasting plasma glucose, HDL cholesterol, LDL cholesterol, triglycerides, and uric acid levels were measured by the Centre Hospitalier Universitaire Vaudois Clinical Laboratory using fresh blood samples within 2 h of blood collection. All measurements were conducted in a Modular P apparatus (Roche Diagnostics, Basel, Switzerland). The following analytical procedures (with maximum interbatch and intrabatch coefficients of variation) were used: cholesterol by cholesterol oxidase-peroxide + 4-aminophenazone + phenol (PAP) (1.6–1.7%); HDL cholesterol by cholesterol oxidase-PAP plus polyethyleneglycol plus cyclodextrin (3.6–0.9%); glucose by glucose dehydrogenase (2.1–1.0%); triglycerides by glucose oxidase-PAP (2.9–1.5%); and uric acid by uricase-PAP (1.0–0.5%).

Diabetes

Diabetes was defined as fasting plasma glucose ≥7.0 mmol/L and/or the presence of oral hypoglycemic or insulin treatment. Type 2 diabetes was defined in cases of diabetes without self-reported type 1 diabetes. Impaired fasting glucose was defined as fasting plasma glucose between 6.1 and 6.9 mmol/L without antidiabetes treatment.

Statistical analysis

Of the initial 6,188 participants, 21 (0.3%) had missing data for the variables of interest, 407 (6.6%) had diabetes, and 655 had impaired fasting glucose (10.6%). Diabetic participants were excluded, and the remaining 5,760 (93.1%) participants were used in the analyses. Characteristics of the patients included in our study are available in Supplementary Table 1.

The prevalence of participants at risk for developing type 2 diabetes according to each score was determined and expressed

in percentages and 95% CIs. The number of participants at risk in Switzerland was then estimated for each score by applying the sex-specific and 10-year age-group–specific prevalence obtained to the corresponding diabetes-free population numbers, obtained by averaging the population estimates between 2003 and 2006, provided by the Swiss Federal Statistical Office (www.statistique.admin.ch). To assess the number of subjects without diabetes in the Swiss population, we assumed that the proportion of nondiabetic patients in our study was representative of the whole country. All statistical analyses were made using Stata version 11.1 (Stata, College Station, TX).

RESULTS

Prevalence of subjects at risk for type 2 diabetes

The prevalence of participants at risk for developing type 2 diabetes is shown in Fig. 1. In men, the prevalence of participants at high risk of developing type 2 diabetes was the following: 1.6% (1.2–2.2) (Wilson); 4.2% (3.4–5.0) (Balkau); 12.8% (11.5–14.1) (Kahn [C]); 13.5% (12.2–14.9) (Swiss Diabetes Association); 13.7% (12.4–15.0) (Kahn [CB]); 22.9% (21.3–24.5) (FINDRISC); and 24.9% (23.4–26.6) (Griffin). In women, the corresponding values were 1.1% (0.8–1.6) (Wilson); 2.9% (2.4–3.6) (Balkau); 6.0% (5.2–6.9) (Kahn [C]); 11.1% (10.0–12.3) (Swiss Diabetes Association); 6.1% (5.3–7.0) (Kahn [CB]); 15.7% (14.5–17.1) (FINDRISC); and 10.7% (9.6–11.8) (Griffin). Overall, men tended to present a higher risk of type 2 diabetes than women. Extrapolated to the Swiss population of the same age, the number of subjects at risk ranged from 46,708 to 636,841, more than a 13-fold variation (Table 1). Restricting the analysis to participants aged <65 years showed either slight increases (Wilson) or decreases (FINDRISC; Griffin) in the prevalence of subjects at risk for developing type 2 diabetes (Supplementary Table 4). Likewise, excluding from the analysis the 11 women with a possible pregnancy at examination did not change the results (data not shown).

Comparison between scores

We also checked whether the same participants were considered to be at risk according to the different scores. For this, we compared the participants at risk for type 2 diabetes according to the scores that led to the lowest prevalence (Wilson and Balkau) and also according to the scores that included the same clinical variables (Balkau and Kahn [C]). The results are presented in Fig. 2. The scores classified a total of 612 participants as being at risk: n = 78, Wilson; n = 201, Balkau; and n = 558, Kahn (C). Of 78 participants at risk according to Wilson et al. (4), only 21 (26.9%) also were considered at risk according to Balkau. Likewise, of 201 participants at risk according to Balkau, only 145 (72%) also were considered at risk according to Kahn (C). Only 19 patients were simultaneously classified as high-risk by all three scores.

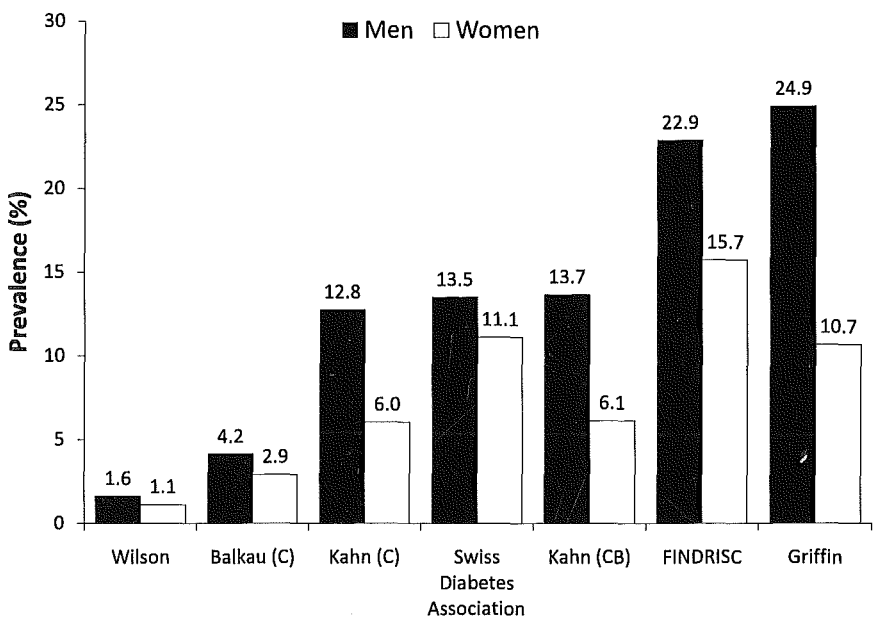

Figure 1—*Proportion of participants at high risk of developing type 2 diabetes according to each score, by sex. C and CB are only specified in the case of various equations provided by the authors.*

CONCLUSIONS—To our knowledge, this is one of the few studies that assessed the effect of differing type 2 diabetes risk–scoring systems in a given population. In agreement with previous studies (10,16), our results indicate that the prevalence of subjects at risk for developing type 2 diabetes varies considerably according to the scoring system used. This has a considerable impact in the number of subjects susceptible of benefiting from measures regarding the primary prevention of type 2 diabetes.

The risk-scoring systems compared in this study shared several types of variables (Supplementary Table 1). For instance, all of them included a genetic background (personal or family history), which can be explained by the association between certain genes and diabetes (17), and most of them also included age, which has been shown to be related to the risk of diabetes. Most scores also included obesity markers, such as BMI or waist circumference, as well as cardiovascular risk factors, such as hypertension and dyslipidemia, all of which are involved in the metabolic syndrome definition (18). Finally, some scores included lifestyle habits, whether protective, such as alcohol consumption and physical activity, or deleterious, such as smoking, also in agreement with previous findings (19). It should be noticed that in some studies nondrinkers and former drinkers were included in the same group (3) and that the nonlinear, U-shaped association between alcohol consumption and the risk of developing type 2 diabetes (20) was not considered. Overall, these findings suggest that any generic scoring system that included clinical variables known to be related to type 2 diabetes (age, obesity, cardiovascular risk factors, and lifestyle) could be used to derive diabetes risk scores but that the relative weight of each variable might be different according to the population considered. For instance, age, obesity, and the other factors mentioned vary by country, and this may result in a differential importance to predict diabetes. Finally, the inclusion of other variables, such as biological and genetic markers, also should be considered but is beyond the scope of our study (21).

Table 1—*Number of participants in the Swiss population at high risk of developing type 2 diabetes according to each score, by sex and age-group*

Sex and age-group	Total Swiss population	Wilson	Balkau (C)	Kahn (C)	Swiss Diabetes Association	Kahn (CB)	Griffin	FINDRISC
Men								
Age (years)								
35–44	620,900	4,964	12,046	36,924	18,462	34,745	35,471	29,116
45–54	529,600	11,275	15,066	44,500	55,775	60,165	80,869	86,506
55–64	441,700	9,281	24,394	84,151	77,181	85,325	145,119	146,256
65–75	304,300	1,360	18,430	47,762	75,055	47,762	157,613	94,240
Total	1,896,500	26,879	69,937	213,338	226,474	227,998	419,072	356,118
Women								
Age (years)								
35–44	615,900	4,262	8,523	15,647	11,385	10,654	7,854	21,309
45–54	522,500	5,133	11,434	20,022	37,148	23,427	25,714	55,443
55–64	449,100	7,670	19,132	48,363	77,083	46,914	71,330	104,865
65–75	361,700	2,765	13,166	20,802	72,050	25,641	88,014	99,106
Total	1,949,200	19,829	52,256	104,834	197,666	106,636	192,912	280,722
Total	3,845,700	46,708	122,192	318,172	424,140	334,634	611,984	636,841

C and CB are only specified in the case of various equations provided by the authors.

The two scoring systems that did not include age (i.e., Wilson and Balkau) gave the lowest prevalence rates of subjects at risk for type 2 diabetes, whereas the Griffin score, which includes a linear relationship with age (5), provided the greatest prevalence. It is interesting to note that the scoring systems using age-groups instead of age (3,8,9) provided intermediate prevalence rates. Considering how easy it is to collect age and the increasing prevalence of type 2 diabetes with age (18), we can postulate that this variable should be included in any risk-scoring system. Another possible explanation for the low prevalence rates of participants at risk using the Wilson score is the fact that it includes a low HDL cholesterol level, whose prevalence was 36.9% in the original study. However, in the CoLaus study (14), the prevalence of low HDL cholesterol was only 2.8%, which might lead to spurious results.

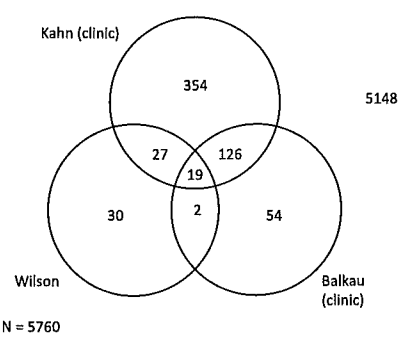

Figure 2—*Number of patients at high risk of developing type 2 diabetes according to three scores.*

Overall, these findings further stress the importance of not only including certain variables but also their relative weighting and even the way they are coded to compute the risk of developing type 2 diabetes.

Only two scoring systems (Wilson and Kahn [CB]) included fasting glucose. This was somewhat unexpected because fasting glucose has a strong predictive value for diabetes (22). Indeed, in the study from Balkau et al. (6), fasting glucose was considered to be the best predictor, but no scoring system that included fasting glucose was provided, possibly because of the fact that the objective was to derive a clinically based scoring system.

Most values for each variable included in the scoring systems were derived from logistic or Cox regression coefficients. Still, it should be noticed that some scoring systems (i.e., Swiss Diabetes Association) include variables (i.e., familial history) for which the scores were not based upon statistical analysis but on an "educated" proposal by the authors (7). As a subject might shift from a low-risk to a high-risk category by one single scoring unit, care should be taken when such non–evidence-based scores are applied. Furthermore, the FINDRISC score has been used (and in some cases modified) by others (8,9) without any complementary statistical analysis or validation; therefore, the results obtained by these modified, nonvalidated scores might be questionable. Finally, many scoring systems did not take into account the nonlinear association between some variables (i.e., alcohol consumption) and diabetes risk; the reason might be that introducing nonlinearity complicates the scoring system, but no precise rationale could be obtained from the literature.

The prevalence rates of participants at risk for developing type 2 diabetes varied almost 13-fold according to the scoring system used, leading to considerable differences in the number of subjects amenable to prevention measures in the corresponding Swiss population. This great variability can be partly explained by the differences between the scoring systems. First, the variables used and their corresponding coefficients varied considerably. Second, the thresholds used to define subjects at high risk also varied (30–46%), as shown in Table 1. Third, and as stated previously, the scoring systems were developed and validated in a given population, and applying them to a different population can lead to inconsistent results, as it has been underlined in a previous German study (16). Overall, our results suggest that the indiscriminate use of a nonvalidated scoring system might lead to considerable differences in the number of subjects to prevent, with a likely under- or overuse of the limited available preventive resources.

The agreement between the different scoring systems was disappointing. Indeed, we initially expected that two scoring systems detecting a low number of subjects at risk for diabetes would detect the same patients, but Fig. 2 shows that it is not the case. Likewise, even two scoring systems that included broadly the same

variables (i.e., Balkau and Kahn [C]) failed to detect the same participants. Hence, our results indicate that different scoring systems detect different subjects at risk for developing type 2 diabetes and thus are not interchangeable. Adequate validation of these scoring systems using prospective data is therefore necessary to select the best system applicable to the population under study. The ongoing follow-up of the CoLaus cohort will allow this validation.

Our study has several limitations. First, the predicting ability of the tested scores could not be achieved in the current study. Thus, it is unclear which of them will be the most accurate. The ongoing follow-up of the CoLaus cohort will enable such a comparison. Second, the prevalence rates according to Swiss Diabetes Association and FINDRISC may be over- or underestimated as a result of our lack of dietary data and second-degree familial history. Of interest, sensitivity analyses showed that decreasing the threshold of these scores by two and three points led to a 50% increase in the number of subjects at risk for developing type 2 diabetes (Supplementary Table 6). These findings suggest that minor changes in the scoring system can lead to considerable changes in the number of subjects at risk for developing type 2 diabetes and that any risk-scoring system should be adequately validated before being applied in a given population. Third, although the participation rate was similar to other epidemiological studies (23), it was rather low (41%), which might limit the generalization of findings. Indeed, the CoLaus study may not be representative of the Swiss population, but seeing the great variability in the number of high-risk patients, this mistake may not be of great relevance. In addition, there was no sex or ZIP code distribution difference between the source population, the random sample, and the CoLaus participants. On the other hand, the CoLaus sample had more women and was slightly younger than the corresponding Swiss population aged 35–75 years (Supplementary Table 7). Hence, it can be argued that although the CoLaus sample is not fully representative of the Swiss population, the differences in population structure are relatively small. Likewise, our population was at relatively low risk for diabetes, and it is unknown how this might influence the performance of some of the risk scores if applied in other populations or ethnic groups. Still, most equations we used have been developed in European countries and should thus be generalizable to the European population. On the other hand, it has been shown that risk scores developed in the same country lead to different results (10). Thus and again, a precise validation within a given of any risk score should be conducted before its application in clinical or public health practice. Fourth, diabetic subjects were excluded on the basis of fasting but not on 2-h plasma glucose; hence, diabetic subjects by 2-h glucose (but not by fasting glucose) were retained in the analysis. Nevertheless, because the number of subjects with type 2 diabetes (by 2-h glucose) is fixed, our results still indicate that the number of subjects at risk for developing type 2 diabetes varies considerably according to the risk score used. Finally, this article only included leisure-time physical activity, and occupational physical activity was not considered. Hence, it is possible that the risk of developing type 2 diabetes might be overestimated when using the equations that include physical activity.

In summary, our results indicate that the prevalence of participants at risk for developing type 2 diabetes varies considerably according to the scoring system used. To adequately prevent type 2 diabetes, risk-scoring systems should be validated for each population considered.

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R.S. researched data and wrote the manuscript. P.V., G.W., and P.M.-V. reviewed and edited the manuscript and contributed to discussion.

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Online-Only Material: The eAppendix, eTable, and eFigure are available at http://www.archinternmed.com.

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Validation of 7 Type 2 Diabetes Mellitus Risk Scores in a Population-Based Cohort: CoLaus Study

One of the challenges for public health in the coming years is the expected increase of type 2 diabetes mellitus (T2DM) prevalence and its resulting health burden and costs.[1,2] For the physician, although recommendations regarding who to screen for T2DM are available, the application of a validated risk score would enable a better targeting of high-risk subjects and thus an improvement of preventive measures. Indeed, numerous risk scores for T2DM have been developed, but few studies have compared them in populations different from those they have been derived from. It is also unclear whether all risk scores have the same prognostic validity.

The aim of this study was to assess the validity of various T2DM risk scores in predicting the incidence of T2DM in a Swiss population-based cohort.

Methods. Seven T2DM risk scores were selected in the present study. Four were based on clinical data: the 10-year risk score from Kahn et al[3] (Kahn clinical); the 9-year risk score from Balkau et al[4]; the prevalent undiagnosed diabetes risk score from Griffin et al[5]; the Finnish Type 2 Diabetes Risk Score (FINDRISC), which has been developed in 2 cohorts followed for 5 and 10 years[6]; and finally the risk score from the Swiss Diabetes Association, available online,[7] which is actually adapted from FINDRISC. The 2 remaining risk scores were based on the association of clinical and biological data: the 10-year risk score from Kahn et al[3] (Kahn clinical + biologic) and the 8-year risk score from Wilson et al.[8] We used the thresholds provided by the authors, and each score had its area under the receiver operating characteristic curve (AROC), sensitivity, specificity, and negative and positive predictive values assessed. We tested these scores in 3060 nondiabetic participants from Lausanne, Switzerland (44.6% men; mean [SD] age, 52.6 [10.6] years), followed up for 5 years (study period, 2003-2011).[9] Incident diabetes was defined as fasting plasma glucose level greater than or equal to 126.13 mg/dL (to convert to millimoles per liter, multiply by 0.0555) and/or presence of oral hypoglycemic or insulin treatment.

Results. A total of 169 patients (5.5%) developed T2DM during follow-up. Compared with participants who did not develop T2DM, they were more frequently male (69.8% vs 43.1%); were older (mean [SD] age, 57.1 [9.4] vs 52.3 [10.6] years); had a higher frequency of family history of T2DM (31.4% vs 19.3%) (all $P<.001$); and had a higher resting heart rate (69 [10] vs 67 [9] beats/min [$P<.05$]). They practiced less leisure-time physical activity (45.6% vs 60.3%); had higher body mass index (29.0 [3.9] vs 25.1 [4.0] [calculated as weight in kilograms divided by height in meters squared]), waist circumference (100.3 [10.9] vs 86.8 [12.2] cm), and fasting plasma glucose (110.45 [9.37] vs 95.32 [9.37] mg/dL), triglyceride (189.38 [184.07] vs 111.50 [79.65] mg/dL [to convert to millimoles per liter, multiply by 0.0113]), and uric acid (6.03 [1.32] vs 5.11 [1.35] mg/dL [to convert to micromoles per liter, multiply by 59.485]) levels; and had lower high-density lipoprotein cholesterol levels (53.28 [13.51] vs 64.09 [16.60]mg/dL [to convert to millimoles per liter, multiply by 0.0259]) (all $P<.001$). The performance of the 7 T2DM risk scores is given in the **Table**. Most risk scores had a high AROC, specificity, and negative predictive value, while their sensitivity and positive predictive values were low.

Comment. Most variables included in the risk scores were significantly different between participants who developed T2DM and those who did not, which confirms their prognostic role. The best results were obtained by the Kahn clinical + biologic risk score. However, a risk score based on simple clinical data (FINDRISC) also had a high AROC, which could be more convenient regarding health costs and acceptability by patients. Indeed, using data from our hospital, applying the Kahn clinical + biologic risk score would lead to an extra cost of US$ 12.02 per screened patient relative to the FINDRISC score.

Our study has several limitations. Follow-up time was limited to 5 years; still, our findings are in agreement with the performances reported in the original studies, suggesting that our results should also be reliable after a 10-year follow-up. Some factors such as fruit consumption and second-degree familial history could not be assessed in this study owing to lack of information; although we corrected for such missing data, it is possible that the performance of the corresponding risk scores might have been reduced. Still, one of these risk scores (FINDRISC) ranked second best in our study, suggest-

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Table. Performances of the Tested Scores

Risk Score	AROC (95% CI)	κ (95% CI)	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV (95% CI)	NPV (95% CI)
Balkau et al,[4] C	76.3 (73.1-79.5)	0.095 (0.038-0.152)	10.1 (6.0-15.6)	97.4 (96.8-98.0)	18.5 (11.1-27.9)	94.9 (94.0-95.6)
Kahn et al,[3] C	79.2 (76.0-82.3)	0.209 (0.152-0.266)	32.5 (25.5-40.2)	93.2 (92.2-94.1)	21.8 (16.9-27.4)	95.9 (95.1-96.6)
Griffin et al,[5] C	79.9 (76.9-82.9)	0.199 (0.154-0.243)	50.9 (43.1-58.6)	86.3 (85.0-87.5)	17.8 (14.5-21.6)	96.8 (96.0-97.4)
Wilson et al,[8] CB	83.0 (79.9-86.1)	0.123 (0.059-0.186)	8.9 (5.1-14.2)	99.1 (98.6-99.4)	35.7 (21.6-52.0)	94.9 (94.1-95.7)
Swiss Diabetes Association,[7] C	84.7 (82.2-87.2)	0.253 (0.201-0.305)	49.7 (41.9-57.5)	90.0 (88.9-91.1)	22.5 (18.4-27.1)	96.8 (96.1-97.5)
FINDRISC,[6] C	85.1 (82.7-87.6)	0.251 (0.207-0.294)	65.7 (58.0-72.8)	85.2 (83.8-86.5)	20.6 (17.3-24.3)	97.7 (97.0-98.2)
Kahn et al,[3] CB	89.9 (87.9-91.9)	0.339 (0.278-0.399)	49.1 (41.4-56.9)	93.7 (92.8-94.6)	31.4 (25.9-37.4)	96.9 (96.2-97.5)

Abbreviations: AROC, area under the receiver operating characteristic curve; C, clinical; CB, clinical + biologic; FINDRISC, Finnish Type 2 Diabetes Risk Score; NPV, negative predictive value; PPV, positive predictive value.

ing that the reduction in its predictive power may not be significant. In this study, physical activity was defined as at least 2 h/wk of leisure-time physical activity, but it was defined as 4 h/wk or 30-min/d in the original publications.[6,7] Finally, this study was limited to white participants and whether the results also apply to other ethnicities is unknown.

In conclusion, this is the first study, to our knowledge, to compare the prognostic validity of several risk scores for T2DM. The Kahn clinical + biologic risk score has the highest AROC, but the clinical FINDRISC score may be more practical and less expensive for screening. Further research is needed to assess the real impact of these scores in preventing T2DM.

Rémy Schmid
Peter Vollenweider, MD
François Bastardot, MD
Gérard Waeber, MD
Pedro Marques-Vidal, MD, PhD

Author Affiliations: Faculty of Biology and Medicine (Mr Schmid and Drs Vollenweider, Bastardot, Waeber, and Marques-Vidal), Institute of Social and Preventive Medicine (IUMSP) (Dr Marques-Vidal), and Division of Internal Medicine, Department of Medicine (Drs Vollenweider, Bastardot, and Waeber), Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland. Mr Schmid is a medical student at IUMSP, CHUV.
Correspondence: Dr Marques-Vidal, Institut Universitaire de Médecine Sociale et Préventive, 17, rue du Bugnon, 1005 Lausanne, Switzerland (Pedro-Manuel .Marques-Vidal@chuv.ch).
Author Contributions: *Study concept and design:* Schmid, Vollenweider, Waeber, and Marques-Vidal. *Acquisition of data:* Vollenweider, Bastardot, and Waeber. *Analysis and interpretation of data:* Schmid and Marques-Vidal. *Drafting of the manuscript:* Schmid. *Critical revision of the manuscript for important intellectual content:* Vollenweider, Bastardot, Waeber, and Marques-Vidal. *Statistical analysis:* Schmid. *Obtained funding:* Vollenweider and Waeber. *Administrative, technical, and material support:* Bastardot. *Study supervision:* Marques-Vidal.
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ONLINE FIRST

Frequent Fracture of TrapEase Inferior Vena Cava Filters: A Long-term Follow-up Assessment

Pulmonary thromboembolism (PTE) is one of the most significant complications of deep vein thrombosis (DVT) of the lower extremities. To prevent PTE, an inferior vena cava filter (IVCF) is often used.[1] The TrapEase IVCF (Cordis Endovascular, Johnson & Johnson) is one of the most popular permanent IVCFs

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Brief Report—Endocrine Research

Current Genetic Data Do Not Improve the Prediction of Type 2 Diabetes Mellitus: The CoLaus Study

Rémy Schmid, Peter Vollenweider, François Bastardot, Julien Vaucher, Gérard Waeber, and Pedro Marques-Vidal

Institute of Social and Preventive Medicine (R.S., P.M.-V.), University Hospital of Lausanne, CH-1010 Lausanne, Switzerland; Department of Medicine (P.V., F.B., J.V., G.W.), Internal Medicine, University Hospital of Lausanne Faculty of Biology and Medicine, CH-1011 Lausanne, Switzerland

Context: Several genetic risk scores to identify asymptomatic subjects at high risk of developing type 2 diabetes mellitus (T2DM) have been proposed, but it is unclear whether they add extra information to risk scores based on clinical and biological data.

Objective: The objective of the study was to assess the extra clinical value of genetic risk scores in predicting the occurrence of T2DM.

Design: This was a prospective study, with a mean follow-up time of 5 yr.

Setting and Subjects: The study included 2824 nondiabetic participants (1548 women, 52 ± 10 yr).

Main Outcome Measure: Six genetic risk scores for T2DM were tested. Four were derived from the literature and two were created combining all (n = 24) or shared (n = 9) single-nucleotide polymorphisms of the previous scores. A previously validated clinic + biological risk score for T2DM was used as reference.

Results: Two hundred seven participants (7.3%) developed T2DM during follow-up. On bivariate analysis, no differences were found for all but one genetic score between nondiabetic and diabetic participants. After adjusting for the validated clinic + biological risk score, none of the genetic scores improved discrimination, as assessed by changes in the area under the receiver-operating characteristic curve (range −0.4 to −0.1%), sensitivity (−2.9 to −1.0%), specificity (0.0–0.1%), and positive (−6.6 to +0.7%) and negative (−0.2 to 0.0%) predictive values. Similarly, no improvement in T2DM risk prediction was found: net reclassification index ranging from −5.3 to −1.6% and nonsignificant ($P \geq 0.49$) integrated discrimination improvement.

Conclusions: In this study, adding genetic information to a previously validated clinic + biological score does not seem to improve the prediction of T2DM. ***(J Clin Endocrinol Metab* 97: E0000–E0000, 2012)**

Prevalence of type 2 diabetes mellitus (T2DM) is increasing worldwide, and the identification of subjects at high risk of developing T2DM is needed (1). For this purpose, several T2DM risk scores have been developed; most include clinical and biological variables, but genetic scores have also been proposed (2–4). Whether these genetic scores improve the prediction of T2DM is still a matter of debate. Hence, we aimed to assess the improvement in predicting T2DM brought by genetic scores to a validated clinical and biological risk score.

Materials and Methods

A subsample of the Cohorte Lausannoise (CoLaus) study including 2824 participants (1548 women, aged 52 ± 10 yr) free from diabetes and with available 5-yr follow-up data (overall study period 2003–2010) was analyzed. The CoLaus Study is a cross-sectional study aimed at assessing the prevalence and identifying the molecular determinants of cardiovascular risk factors in the Caucasian population of Lausanne, Switzerland. Caucasian origin was defined as having both parents and grandparents born in a restricted list of countries (available from the authors). The methodology of the CoLaus Study has been described previously

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Abbreviations: CI, Confidence interval; CoLaus, Cohorte Lausannoise study; IDI, integrated discrimination improvement; NRI, net reclassification improvement; SNP, single-nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

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(5). The study was approved by the Ethics Committee of the Vaud Canton, and all subjects provided their written informed consent before be included in the study. Nuclear DNA was extracted from whole blood, and genotyping was performed using the Affymetrix 500 K single-nucleotide polymorphism (SNP) chip (Affymetrix, Santa Clara, CA). Genotypes were called using BRLMM (6), and a set of unmeasured SNP was imputed using IMPUTE version 0.2.0 (7) and CEU haplotypes from HapMap release 21. For imputation, only autosomal SNP present in HapMap release 21 were used; the data set used for imputation was 5,435 unrelated CoLaus individuals and 390,631 measured SNP. Four genetic risk scores for T2DM were computed as indicated (2–4). The score proposed by Meigs *et al.* (4) was computed without the *INS* gene because no valid imputed data were available. The scores by Lin *et al.* (2) were derived from the cross-sectional, baseline data of the CoLaus Study. The unweighted score was a linear combination of the SNP. Because the amplitude of the effect varies somewhat between diabetes susceptibility genes, in an attempt to penalize the SNP with a less reliable odds ratio estimate, a weighted score was also used by weighting each SNP using the log of the lower boundary of the reported 95% confidence interval (CI). Two other genetic scores were created: one combining all SNP of the previous scores and another combining the SNP shared by the scores. The list of SNP used is provided in the Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org. Incidental diabetes was defined as fasting plasma glucose level 7.0 mmol/liter or greater and/or the presence of oral hypoglycemic or insulin treatment.

Statistical analysis was conducted using Stata version 11.2 (Stata Corp LP, College Station, TX). The added predictive value for T2DM of each of these six genetic scores was assessed by logistic regression adjusting for a validated T2DM risk score (8). The score uses the following data to estimate the risk of developing T2DM: age, family history of T2DM, Black race (not used in this study), alcohol drinking, height, waist circumference, resting heart rate, hypertension (defined as a systolic blood pressure $\geq$ 140 mm Hg and/or a diastolic blood pressure $\geq$90 mm Hg or presence of antihypertensive drug treatment), fasting blood glucose, high-density lipoprotein cholesterol, triglycerides, and uric acid. A participant was considered as being at risk if his/her probability of presenting with T2DM was greater than 46% (9). Each genetic score was tested after adjusting for the continuous values of the risk of developing T2DM as assessed by the clinical and biological score (range 0–81%). The discrimination performances of each model including one genetic score were assessed using the area under the receiver-operating characteristic curve and corresponding 95% CI. The sensitivity, specificity, positive and negative predictive values, and corresponding 95% CI were also calculated using the exact binomial method. Calibration was visually checked by comparing the predicted probabilities with the observed incident cases of T2DM in each decile of prediction after including the genetic score (10). The improvement of T2DM prediction by including genetic scores was assessed by calculating the net reclassification improvement (NRI) and the integrated discrimination improvement (IDI). The 95% CI for the NRI was computed using normal approximation.

Results

Of the 2824 participants, 207 (7.3%) developed T2DM after 5 yr. Significant differences were found between participants who developed T2DM and those who did not for most parameters of the clinical risk score (Supplemental Table 2). On bivariate analysis, no differences were found for all but one genetic scores studied between nondiabetic and diabetic participants: Lin *et al.* (2) unweighted: 14.5 $\pm$ 2.4 *vs.* 15.0 $\pm$ 2.4 (mean $\pm$ SD), respectively, $P < 0.01$; Lin *et al.* weighted: 1.42 $\pm$ 0.27 *vs.* 1.45 $\pm$ 0.28, $P = 0.08$; Meigs *et al.* (24): 16.6 $\pm$ 2.5 *vs.* 16.9 $\pm$ 2.4, $P = 0.11$; Lyssenko *et al.* (3): 10.6 $\pm$ 2.1 *vs.* 10.8 $\pm$ 2.1, $P = 0.31$; shared SNP: 9.9 $\pm$ 1.7 *vs.* 10.1 $\pm$ 1.7, $P = 0.11$; and all SNP: 22.4 $\pm$ 3.4 *vs.* 22.9 $\pm$ 3.4, $P = 0.08$. Multivariate analysis by logistic regression adjusting for a validated clinical + biological T2DM risk score showed no significant improvement (and even in some cases a worsening) in all discrimination parameters and in risk prediction for all genetic scores studied (Tables 1 and 2).

Discussion

Our findings suggest that adding genetic information to a validated score based on clinical and biological variables

TABLE 1. Impact of adding different genetic scores in the predictive capacity of a clinical + biological risk score for T2DM, using a 46% probability threshold to define high-risk subjects

Risk score	AROC	Sensitivity	Specificity	Positive predictive value	Negative predictive value	NRI	IDI ($\times 10^3$)
Kahn *et al.* (clinical + biological) risk score (9)	86.3 (83.5; 88.3)	11.1 (7.2; 16.2)	98.7 (98.1; 99.1)	39.7 (27.0; 53.4)	93.3 (92.4; 94.2)		
+ Lin *et al.* (unweighted) (2)	86.2 (83.8; 88.5)	9.2 (5.6; 14.0)	98.7 (98.2; 99.1)	35.8 (23.1; 50.2)	93.2 (92.2; 94.1)	−3.52 (−8.48; 1.43)	1.57 (0.52)
+ Lin *et al.* (weighted) (2)	86.0 (83.6; 88.4)	8.2 (4.9; 12.8)	98.7 (98.2; 99.1)	33.3 (20.8; 47.9)	93.1 (92.1; 94.1)	−5.31 (−9.60; −1.02)	0.28 (0.51)
+ Meigs *et al.* (4)	86.1 (83.7; 88.5)	8.7 (5.2; 13.4)	98.8 (98.3; 99.2)	36.7 (23.4; 51.7)	93.2 (92.2; 94.1)	−4.26 (−8.90; 0.37)	0.09 (0.50)
+ Lyssenko *et al.* (3)	85.9 (83.5; 88.3)	9.7 (6.0; 14.5)	98.7 (98.2; 99.1)	37.7 (24.8; 52.1)	93.3 (92.3; 94.2)	−2.58 (−5.61; 0.46)	−0.14 (0.49)
+ Shared SNP by Lin *et al.*, Meigs *et al.*, and Lyssenko *et al.*	86.1 (83.7; 88.4)	10.1 (5.0; 15.1)	98.8 (98.3; 99.2)	40.4 (27.0; 54.9)	93.3 (92.3; 94.2)	−1.59 (−5.88; 2.71)	1.78 (0.52)
+ All SNP used by Lin *et al.*, Meigs *et al.*, and Lyssenko *et al.*	86.1 (83.7; 88.5)	8.2 (4.9; 12.8)	98.8 (98.3; 99.2)	34.7 (21.7; 49.6)	93.2 (92.1; 94.1)	−5.21 (−9.50; −0.91)	−0.10 (0.50)

Statistical analysis by logistic regression. Values are expressed as percentage and 95% CI or as value $\times 10^3$ and *P* value (for IDI). AROC, Area under the receiver operating curve.

TABLE 2. Impact of adding different genetic scores in the predictive capacity of a clinical + biological risk score for T2DM, using a 30% probability threshold to define high risk subjects

Risk score	AROC	Sensitivity	Specificity	Positive predictive value	Negative predictive value	NRI
Kahn *et al.* (clinical + biological) risk score (9)	85.9 (83.4; 88.3)	30.0 (23.8; 36.7)	96.1 (95.3; 96.8)	38.0 (30.6; 46.0)	94.6 (93.6; 95.4)	
+ Lin *et al.* (unweighted) (2)	86.2 (83.8; 98.5)	30.0 (23.8; 36.7)	96.1 (95.3; 96.8)	37.8 (30.4; 45.7)	94.5 (93.6; 95.4)	−0.05 (−5.61; 5.51)
+ Lin *et al.* (weighted) (2)	86.0 (83.6; 88.4)	30.4 (24.2; 37.2)	95.9 (95.0; 96.6)	36.8 (29.6; 44.5)	94.6 (93.6; 95.4)	0.54 (−2.51; 3.60)
+ Meigs *et al.* (4)	86.1 (83.7; 88.5)	29.5 (23.4; 36.2)	96.0 (95.2; 96.7)	37.0 (29.6; 44.8)	94.5 (93.6; 95.3)	−1.04 (−5.69; 3.61)
+ Lyssenko *et al.* (3)	85.9 (83.5; 88.3)	30.0 (23.8; 36.7)	96.1 (95.3; 96.8)	37.8 (30.4; 45.7)	94.5 (93.6; 95.4)	−0.05 (−5.61; 5.51)
+ Shared SNP by Lin *et al.*, Meigs *et al.*, and Lyssenko *et al.*	86.1 (83.7; 88.4)	29.0 (22.9; 35.7)	95.8 (95.0; 96.6)	35.5 (28.3; 43.2)	94.5 (93.5; 95.3)	−2.19 (−7.74; 3.37)
+ All SNP used by Lin *et al.*, Meigs *et al.*, and Lyssenko *et al.*	86.1 (83.7; 88.4)	30.0 (23.8; 36.7)	96.0 (95.2; 96.7)	37.1 (29.8; 44.9)	94.5 (93.6; 95.4)	−0.20 (−4.51; 4.11)

Statistical analysis by logistic regression. Values are expressed as percentage and 95% CI. AROC, Area under the receiver operating curve.

brings no extra benefit in predicting T2DM incidence over a 5-yr follow-up, a finding in agreement with other studies (2–4, 11, 12). These findings applied not only to all four genetic scores published, including one developed using the original baseline population (2), but also to other combinations of SNP related to diabetes. A possible explanation might rely on the fact that the clinical + biological score included family history of diabetes, which implicitly includes some genetic information. Finally, the fact that the genetic score developed using the original baseline data added no information to the prediction of T2DM emphasizes the importance of prospective studies in evaluating genetic markers for disease prediction (13). The fact that the unweighted score of Lin *et al.* (2) had a high degree of significance but added no information on the prediction of T2DM also shows that high statistical significance is not necessarily associated with clinical utility.

Our study has some limitations. It was not possible to impute the *INS* gene to compute the score of Meigs *et al.* (4). It is thus likely that the predictive capacity of the score is underestimated, but the magnitude of this possible bias could not be estimated. Because the predictive ability of the genetic scores increases with follow-up (3), it will be of interest to verify whether our findings hold true with a longer follow-up time. Indeed, the 46% threshold of the clinical + biological risk score was initially determined for a 10-yr follow-up period (9), which might be too high and explain the low sensitivity levels; nevertheless, reducing this threshold to 30% increased sensitivity but did not change the results for the genetic scores (Table 2). Still, given the little extra information provided by all genetic scores, their interest in general clinical practice appears to be rather modest. Furthermore, such genetic counseling requires specific equipment, which is expensive and could thus lead to a debatable commercial use (14). The genetic risk scores are based on additive effects only, and in future studies, the importance of nonlinear effects of genetic variants should be taken into account. The CoLaus Study recruited only subjects aged older than 35 yr, and it is likely that the genetic scores might be more interesting for predicting patients who will develop T2DM at a younger age and who also may not have clinical characteristics such as obesity. Finally, a beneficial effect of physical activity among genetically predisposed patients has been recently shown (15), which allows us to prefer a lifestyle modification approach for the whole population, regardless of genetic susceptibility (16) and a targeted intervention to the more at-risk individuals as assessed by clinical and biological data.

In summary, our study shows that adding genetic information does not seem to improve discrimination and risk prediction of T2DM compared with a score based on common, easily assessable clinical + biological variables.

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Address all correspondence and requests for reprints to: Pedro Marques-Vidal, Institut Universitaire de Médecine Sociale et Préventive, Route de la Corniche 10, 1010 Lausanne Switzerland. E-mail: pedro-manuel.marques-vidal@chuv.ch.

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