

# 学位論文の要旨

Development and validation of prediction models for the 5-year  
risk of type 2 diabetes in a Japanese population: Japan Public  
Health Center-based Prospective (JPHC) Diabetes Study

(5年間の2型糖尿病罹患リスクの予測モデルの開発および  
検証: 多目的コホート糖尿病研究)

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## Introduction

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (American Diabetes Association, 2014). According to the International Diabetes Federation, the global prevalence of diabetes in 2021 was estimated to be 10.5% (537 million people) and was expected to rise to 12.2% (783 million) by 2045 (Sun et al., 2022). Diabetes is thought to be one of the top 10 causes of adult death (Vos et al., 2020). In Japan, because of its aging population, the absolute number of people with diabetes is expected to substantially increase in the coming decades (Goto et al., 2016). Since several intervention studies in different ethnic populations have demonstrated that type 2 diabetes mellitus (T2DM) can be effectively prevented through diet and lifestyle modifications in high-risk individuals (American Diabetes Association, 2002; Tuomilehto et al., 2001; Knowler et al., 2002; Pan et al., 1997a), identifying high-risk

individuals and having them make diet and lifestyle changes is important for preventing diabetes onset.

A disease risk score is a calculated number or score that estimates the probability or rate of disease occurrence, derived from the risk factors of the disease. At present, there are several diabetes risk scores (Lindström and Tuomilehto, 2003; Glümer et al., 2004; Aekplakorn et al., 2006; Hippisley-Cox et al., 2009; Sun et al., 2009). However, the substantial differences in diabetes incidence among ethnic groups (McBean et al., 2004; Oldroyd et al., 2005) impact the performance of each model (He et al., 2012). Although there are at least six diabetes risk prediction models for the Japanese population (Sasai et al., 2008; Doi et al., 2012; Heianza et al., 2012; Nanri et al., 2015; Hu et al., 2018; Miyakoshi et al., 2016), none are based on a general population across multiple areas in Japan. Although invasive risk scores are likely to have better predictive performance, non-invasive risk scores may be useful because they are less expensive and more convenient than invasive risk scores in large-scale screening.

Therefore, we aimed to develop regression models that used non-invasive and invasive predictors to predict the 5-year incidence of diabetes in a Japanese population and validate them externally in an independent Japanese population.

## **Methods/Design**

Based on previous literature, we selected 16 potential diabetes predictors which were non-invasive predictors (age, sex, body mass index [BMI], physical activity, family history of DM, systolic blood pressure, and diastolic blood pressure [DBP]) and invasive predictors (alanine aminotransferase, aspartate aminotransferase,  $\gamma$ -glutamyl transferase, high-density lipoprotein, total cholesterol, triglyceride, estimated glomerular filtration rate, fasting plasma glucose [FPG], and glycated hemoglobin [HbA1c]).

Data from 10,986 participants (aged 46–75 years) in the development cohort of the Japan Public Health Center-based Prospective Diabetes Study (JPHC Diabetes Study) and 11,345

participants (aged 46–75 years) in the validation cohort of the Japan Epidemiology Collaboration on Occupational Health Study (J-ECOH Study) were used to develop and validate the risk scores.

After using multiple imputations, logistic regression models were used to develop prediction models for diabetes incidence and to estimate  $\beta$  coefficients, odds ratios, and 95% confidence intervals. The models were presented as formulas based on the logistic regression coefficients. Thereafter, the risk score was calculated using an Excel spreadsheet (Microsoft; Redmond, WA, USA) created according to the formula.

The JPHC Study was approved by the ethics committees of Yokohama City University (A151126009) and the National Cancer Center, Japan, and was also approved by the ethics committee of the National Center for Global Health and Medicine, Japan. The J-ECOH study was approved by the Ethics Committee of the National Center for Global Health and Medicine, Japan.

## **Results**

We considered non-invasive (sex, body mass index, family history of diabetes mellitus, and diastolic blood pressure) and invasive (HbA1c and FPG) predictors to predict the 5-year probability of incident diabetes. Sex, BMI, family history of DM, and DBP were selected for model 1, family history of DM and HbA1c for model 2, and family history of DM, HbA1c, and FPG for model 3.

The area under the receiver operating characteristic curve (AUC) was 0.643 for the non-invasive risk model (model 1), 0.786 for the invasive risk model with HbA1c but not FPG (model 2), and 0.845 for the invasive risk model with HbA1c and FPG (model 3). The optimism for the performance of all models was small by internal validation with AUCs slightly decreased to 0.639, 0.785, and 0.844, respectively. In the internal-external cross-validation, these models tended to show similar discriminative ability across different areas

(the AUCs of model 1 ranged from 0.532 to 0.723, the AUCs of model 2 ranged from 0.742 to 0.851, and the AUCs of model 3 ranged from 0.807 to 0.895). The discriminative ability of each model was confirmed in the J-ECOH Study; the AUCs were 0.692, 0.831, and 0.874 in models 1, 2, and 3, respectively.

The calibration curves indicated that the prediction models fitted the data well in the development cohort. Among these models, the invasive risk model with only HbA1c was well-calibrated in the validation cohort.

## **Discussion**

In this study, we developed three 5-year models for predicting the incidence of T2DM, with high discrimination and calibration, which were developed and validated in the population-based study among a Japanese population.

All models showed good discrimination and calibration in internal validations. The internal-external cross-validation indicated that these models showed similar discriminative ability across eight areas. Although the AUC values decreased after optimism correction, all remained reliable, as also observed in the internal-external cross-validation and external validation cohort. The AUC values were higher in the J-ECOH Study than in the JPHC Diabetes Study, indicating that the developed models were generally good at discrimination. For the calibration performance, however, calibration plots of models 1 and 3 were poor in the validation cohort. This indicates that the predicted probabilities overestimated the observed probabilities in the validation cohort. In comparison, model 2 was well-calibrated in the J-ECOH Study. Since model 2 tended to underestimate the observed probability in the highest decile of the predicted probability in the J-ECOH Study, the model should be used with caution, especially for those with a high predicted probability.

In conclusion, our invasive risk models are expected to discriminate between high- and low-risk individuals with T2DM in a Japanese population.

## **Keywords**

Diabetes, risk score, prediction model, Japanese population, Japan Public Health Center-based Prospective (JPHC) Study

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# Publication List

## I. 主論文 (本人を筆頭とする原著論文)

Development and validation of prediction models for the 5-year risk of type 2 diabetes in a Japanese population: Japan Public Health Center-based Prospective (JPHC) Diabetes Study

**Xu, J.**, Goto, A., Konishi, M., Kato, M., Mizoue, T., Terauchi, Y., Tsugane, S., Sawada, N., Noda, M., for the JPHC Study Group<sup>†</sup>

(<sup>†</sup>Japan Members listed in <http://epi.ncc.go.jp/en/jphc/781/3838.html>.)

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## II. 参考論文 (主論文の内容以外の論文)

1. Prediction models for neutralization activity against emerging SARS-CoV-2 variants: A cross-sectional study

Goto, A., Miyakawa, K., Nakayama, I., Yagome, S., **Xu, J.**, Kaneko, M., Ohtake, N., Kato, H., and Ryo A.:

Frontiers in Microbiology. Vol 14, pp. 1~10, 2023

2. Usual source and better quality of primary care are associated with lower loneliness scores: a cross-sectional study

Kaneko, M., Shinoda, S., Nakayama, I., **Xu, J.**, Yagome, S., Goto, A.:

Family Practice. cmad049, pp. 1~9, 2023