

# The roles of first phase, second phase insulin secretion, insulin resistance, and glucose effectiveness of having prediabetes in nonobese old Chinese women

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## Abstract

It has been established that prediabetes can cause significant comorbidities, particularly in the elderly. The deterioration of glucose metabolism are generally considered to be results of the impairment of the 4 factors: first, second insulin secretion (FPIS, SPIS, respectively), glucose effectiveness (GE), and insulin resistance. In this study, we enrolled older women to investigate their relationships with prediabetes.

Five thousand four hundred eighty-two nonobese, nondiabetic women were included. They were divided into normal glucose tolerance and prediabetes groups. Receiver operating characteristic curve was performed to investigate the effects on whether to have prediabetes for each factor. Two models were built: Model 1: FPIS+SPIS, and Model 2: model 1+GE. The area under the receiver operating characteristic (aROC) curve was used to determine the predictive power of these models.

The aROC curve of GE was significantly higher than the diagonal line followed by SPIS and FPIS accordingly. The aROC curve of Model 1 (0.611) was not different from GE. However, Model 2 improved significantly up to 0.663. Based on this model, an equation was built ( $-0.003 \times GE - 212.6 \times SPIS - 17.9 \times \text{insulin resistance} + 4.8$ ). If the calculated value is equal or higher than 0 ( $\geq 0$ ), then the subject has higher chance to have prediabetes (sensitivity=0.607, specificity=0.635).

Among the 4 factors, GE is the most important contributor for prediabetes in older women. By building a model composed of FPIS, SPIS, and GE, the aROC curve increased significantly. The equation built from this model could predict prediabetes precisely.

**Abbreviations:** aROC = area under the receiver operating characteristic, BMI = body mass index, FPG = fasting plasma glucose, FPIS = first phase insulin secretion, GE = glucose effectiveness, IR = insulin resistance, NGT = normal glucose tolerance, ROC = receiver operating characteristic, SPIS = second phase insulin secretion, T2DM = type 2 diabetes.

**Keywords:** first phase insulin secretion, glucose effectiveness, insulin resistance, prediabetes, second phase insulin secretion

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## 1. Introduction

Type 2 diabetes (T2DM) and its comorbidities have always been the top fifth cause of death in Taiwan.<sup>[1,2]</sup> The phenomenon is not found only in Taiwan, but as well as many other countries.<sup>[3]</sup> At the same time, the prevalence of T2DM has increased dramatically in recent 2 decades. This might be due to the simultaneous increased incidence of overweight and obesity.<sup>[4,5]</sup> However, aging of the society might also play a role.<sup>[5-7]</sup> According to the statistics of the Ministry of Health and Welfare, Taiwan officially becomes an aging society at year of 2014 with 11.7% of the population.<sup>[8]</sup> Thus, how to early detect and prevent diabetes become major society interests. Since prediabetes is predecessor of T2DM, its role is critical in the aged people. Anjana et al have shown that about 58.9% of the prediabetes will eventually become frank T2DM within 10 years.<sup>[9]</sup> Evidence have shown that patients with prediabetes are also increased risk of cardiovascular disease.<sup>[10,11]</sup> Early intervention for these individuals could reduce the development of T2DM and the risk of cardiovascular disease in the future.

It is well-known both insulin resistance (IR) and impaired insulin secretion are the most important 2 pathophysiologies for prediabetes.<sup>[12]</sup> Many literatures have focused on the roles of these 2 factors on the initiation of prediabetes.<sup>[13-16]</sup> However, very few studies were focusing on role of glucose effectiveness (GE) which is the ability of glucose to eliminate itself through glucose utilization and decrease production.<sup>[17]</sup> At the same time, whenever discussed insulin secretion, it should be noted that there are 2 phases, that is, the first phase (first phase insulin secretion [FPIS]) and second phase (second phase insulin secretion [SPIS]).<sup>[18,19]</sup> The lack of thorough studies on effects of these 4 factors on the prediabetes might be due to the difficulties of the quantifying methods. For example, frequently sampled intravenous glucose tolerance test could quantify FPIS, GE and insulin sensitivity (the reciprocal of the IR).<sup>[20]</sup> Another gold standard test, the hyperglycemic clamp, could measure both FPIS, SPIS and insulin sensitivity. But both tests are time- and labor-consuming.<sup>[21]</sup> These tests are not practical to be used in the large cohort study.

The life expectancy of men and women are different.<sup>[22]</sup> It is interesting to know that, for diabetes, the age of onset, disease behavior, complications, and so on also have gender differences.<sup>[23]</sup> Therefore, to explore glucose metabolism, different genders should be discussed separately.

By using the components of metabolic syndrome and other demographic data, our group published 4 equations to quantify the aforementioned 4 factors.<sup>[24-27]</sup> In the present study, we enrolled 3825 older women and measured IR, GE, FPIS, and SPIS. In this cross-sectional study, there were 2 purposes. The first one is to compare which one of these factors has the most significant effect on the appearance of prediabetes. Second, we hope to build a model to predict future prediabetes.

## 2. Material and methods

### 2.1. Data sources

We randomly enrolled 5482 females whose age was over 65 years old (included) who underwent routine medical check-ups at the Tri-service General Hospital (TSGH), Cardinal Tien

Hospital (CTH), and MJ Health Screening center (MJHSC). TSGH is a north Taiwan medical center, CTH is a north Taiwan district hospital and MJHSC is a large health screening center in Taiwan and has provided health screening services for over 1 million persons. Institutional Review Board of the Cardinal Tien Hospital. The protocol No./IRB No.: CTH-106-2-5-041. MJHSC Health Screening Centers are a privately owned chain of clinics located throughout Taiwan that provide regular health examinations to their members. The definition of age was based on the world health organization.<sup>[28]</sup> The combination of these 3 different levels of health provider would lower the selection bias in the present study. The study protocol was approved by the institutional review board of the institution. Participants who were obese (body mass index [BMI]  $\geq 25$  kg/m<sup>2</sup>), diabetic (fasting plasma  $\geq 7.0$  mmol/L) and on medications known to affect blood pressure, glucose, and lipids levels were all excluded. In the end, 3825 qualified subjects were analyzed. They were further divided into normal and prediabetic groups.<sup>[29]</sup>

### 2.2. Study design and sampled participants

On the day of the study, senior nursing staff obtained subjects' medical history, including information on any current medications, thorough questionnaire, and complete physical examinations were performed. Waist circumference was measured horizontally at the level of the natural waist, which was identified as the level at the hollow molding of the trunk when the trunk was laterally concave. BMI was calculated as the subject's body weight (kg) divided by the square of the subject's height (m). Both systolic blood pressure and diastolic blood pressure were measured by nursing staff using standard mercury sphygmomanometers on the right arm of each subject when seated. After the subject had fasted for 10 hours, blood samples were drawn from the antecubital vein for biochemical analysis. Plasma was separated from blood within 1 hour and stored at 30°C until analysis for fasting plasma glucose (FPG) and lipid profiles. FPG was measured using a glucose oxidase method (YSI 203 glucose analyzer, Yellow Springs Instruments, Yellow Springs). Total cholesterol and triglycerides were measured using a dry, multilayer analytical slide method with the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film, Tokyo, Japan). Serum high-density lipoprotein cholesterol and low-density lipoprotein cholesterol concentration were analyzed using an enzymatic cholesterol assay following dextran sulfate precipitation.

The equations used to calculate IR, FPIS, SPIS, and GE are as following. It should be noted that all the units are in international unit. The journals they were published are coded after each equation.

$$\text{IR} = \log_{10}(1.439 + 0.018 * \text{sex} - 0.003 * \text{age} + 0.029 * \text{BMI} - 0.001 * \text{SBP} + 0.006 * \text{DBP} + 0.049 * \text{TG} - 0.046 * \text{HDL} - 0.0116 * \text{FPG}) * 10^{3.333} [26]$$

$$\text{FPIS} = 10^{(1.477 - 0.119 * \text{FPG} + 0.079 * \text{BMI} - 0.523 * \text{HDL})} [24]$$

$$\text{GE} = (29.196 - 0.103 * \text{age} - 2.722 * \text{TG} - 0.592 * \text{FPG}) * 10^{-3} [27]$$

$$\text{SPIS} = 10^{(-2.4 - 0.088 * \text{FPG} + 0.072 * \text{BMI})} [25]$$

### 2.3. Statistical analysis

All statistical analyses were performed using SPSS 19.0 (IBM Inc, Armonk, NY). Data are presented as mean  $\pm$  standard deviation. All data were tested for normal distribution with Kolmogorov–Smirnov test and for homogeneity of variances with Levene test. Data were log transformed before analysis if data were not normally distributed. The *t* test was used to evaluate the differences between the normal and prediabetic groups. The receiver operating characteristic (ROC) curve was used to calculate the area under the ROC curve (aROC curve). At the same time, binary logistic regression was used to calculate the predictive performance of the individual parameters for the prediabetes which would further be used to build the models and draw their ROC curve. During this procedures, we only selected the aROC curve with significance (higher than the diagonal line). Starting from the one with the smallest, and gradually add larger aROC curve onto the model. There were 2 models as following:

Model 1: FPIS and SPIS

Model 2: Model 1 + GE

The comparisons of whether the aROC curve of different factors and models were significantly different, MedCalc Software was used (1, 2015 Downloaded from 8 Broekstraat, Mariakerke, Belgium).

We did not put confounding factors such as age, blood pressure, or BMI into the aROC curve since the equations to calculate the 4 diabetes factors contain these parameters. Therefore, the equations are already ‘adjusted’.

### 3. Results

Table 1 shows the demographic data of our study groups. It could be noted that other than the age and IR, the prediabetes group had higher BMI, blood pressure, FPG, low-density lipoprotein cholesterol, triglycerides, FPIS, SPIS, and GE. In the meanwhile, high-density lipoprotein cholesterol was lower which is not surprising.

Figure 1 represents the ROC curves of the 4 factors. Higher aROC curve stands for more precise prediction of the occurrence of 1 event than lower one. In our present study, the aROC curves of the 4 factors, from the highest to the lowest are GE, SPIS, FPIS, and IR (0.613, 0.611, 0.566, and 0.485, respectively), which is

shown in Table 2. Other than the IR, all other 3 aROC curves of the factors are higher than the diagonal line. This means that the predictability for prediabetes is statistically significant.

To further improve the prediction accuracy, models were built. The aROC curves of Model 1 was only 0.611 which is not significantly higher than that of GE (Table 3). After adding the effect of GE on to model 1, the aROC curves of model increases (0.663) which is better than model 1 (Table 3). Based on this model, an equation was built ( $-0.003 \times GE - 212.6 \times SPIS - 17.9 \times IR + 4.8$ ). If the calculated value is equal or higher than 0 ( $\geq 0$ ), then the subject has higher chance to have prediabetes (shown in Fig. 2; sensitivity = 0.607, specificity = 0.635).

### 4. Discussion

In the present study, we have shown that among the 4 diabetogenesis factors, GE is the most important one and, in the same time, IR has the smallest area under ROC curve. The model by adding FPIS, GE, and SPIS together, the area increases up to 0.663. The sensitivity and specificity of this model is 0.607 and 0.635, respectively.

It is generally considered that aging per se could increase IR.<sup>[30–32]</sup> This view point comes from the direct observation that the higher prevalence of T2DM is found in the older adults.<sup>[33–35]</sup> At the same time, evidences from many basic animal or cellular studies also support this hypothesis.<sup>[36–38]</sup> However, results from Amati et al have shown that the deterioration of the IR actually comes from obesity and sedentary life style but not from aging.<sup>[39]</sup> In the present study, we have shown that the IR of older subjects did not contribute to the occurrence of T2DM. The area under the ROC curve was only 0.49. Compared to other 3 factors, its effect is the least important one. This finding supports the hypothesis that, at least in the elderly, the IR does not deteriorate further. This does not exclude the possibility that IR might increase in one’s early adulthood and eventually reach its plateau at middle-age.

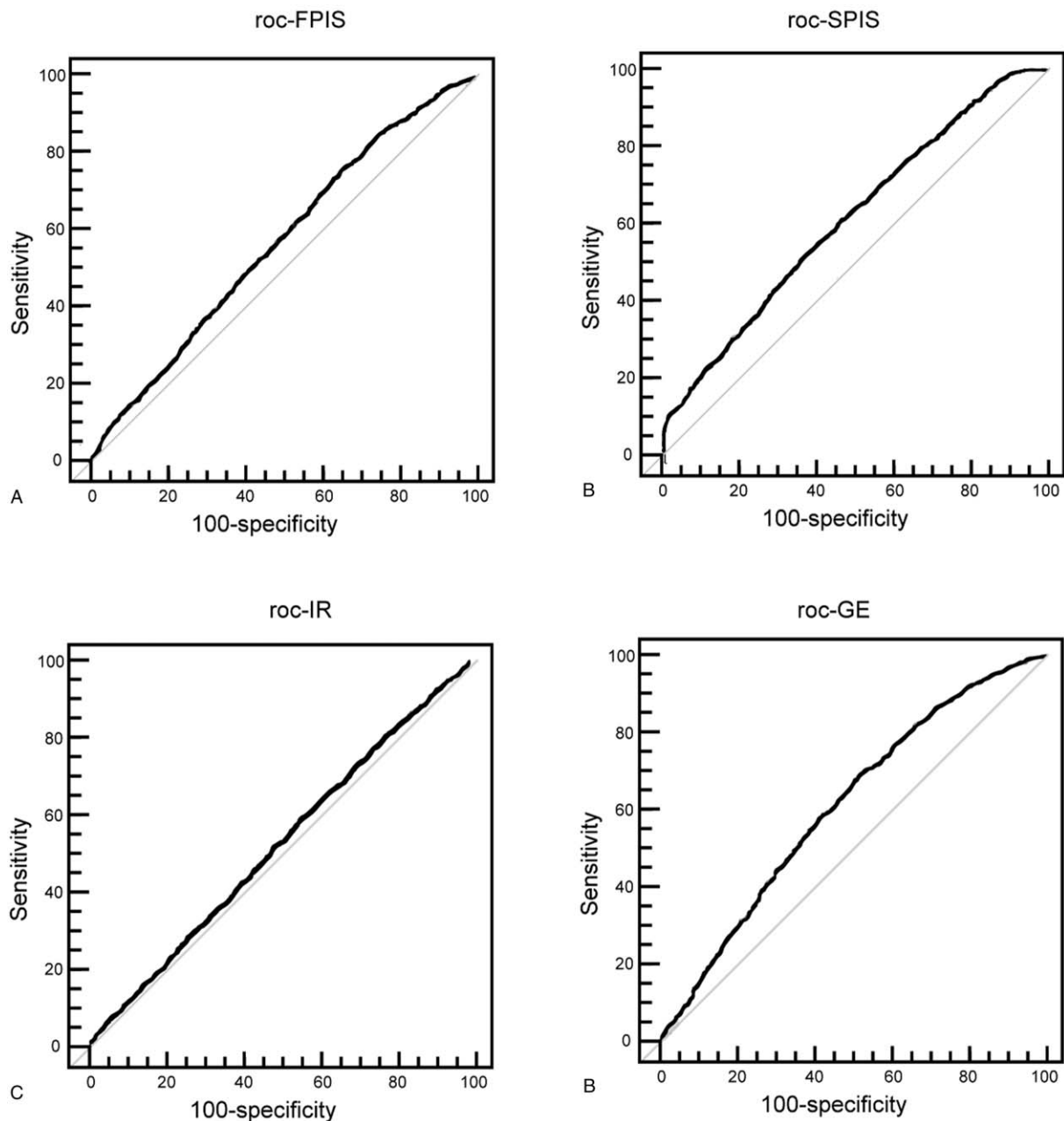
Whether IR or impaired beta-cell function centered the evolution of diabetes is still under debating.<sup>[31,40,41]</sup> However, it is well documented that in the presence of IR, beta-cells try hard to maintain a balanced glucose metabolism. Eventually, years after the IR, beta-cells are unable to compensate which causes hyperglycemia. It would further worsen insulin secretion. This downward spiral ultimately leads to frank diabetes.<sup>[42]</sup> Many

**Table 1**

**The demographic data and the 4 parameters of glucose metabolism in normal glucose tolerance and prediabetes groups.**

N	NGT	Prediabetes	P-value
	2318	1507	
Age, yr	61.8 $\pm$ 5.7	66.3 $\pm$ 5.4	.057
Body mass index, kg/m <sup>2</sup>	23.5 $\pm$ 1.8	23.7 $\pm$ 1.8	<.001
SBP, mm Hg	132.0 $\pm$ 19.7	136.4 $\pm$ 18.9	<.001
DBP, mm Hg	76.9 $\pm$ 11.0	78.2 $\pm$ 10.6	<.001
FPG, mmol/L	5.1 $\pm$ 0.3	5.9 $\pm$ 0.4	<.001
Triglyceride, mmol/L	1.4 $\pm$ 0.7	1.5 $\pm$ 0.7	.001
HDL-C, mmol/L	1.34 $\pm$ 0.37	1.31 $\pm$ 0.36	.002
FPIS, $\mu$ U/min	123.0 $\pm$ 69.3	106.2 $\pm$ 58.5	<.001
SPIS, pmol/mmol	0.073 $\pm$ 0.022	0.064 $\pm$ 0.019	<.001
IR, 10 <sup>-4</sup> ·min <sup>-1</sup> ·pmol <sup>-1</sup> ·L <sup>-1</sup>	3.68 $\pm$ 0.02	3.68 $\pm$ 0.02	.139
GE, 10 <sup>-2</sup> ·dL·min <sup>-1</sup> ·kg <sup>-1</sup>	0.016 $\pm$ 0.002	0.015 $\pm$ 0.002	<.001

DBP = diastolic blood pressure, FPG = fasting plasma glucose, FPIS = first phase insulin secretion, GE = glucose effectiveness, HDL-C = high-density lipoprotein cholesterol, IR = insulin resistance, NGT = normal glucose tolerance, SBP = systolic blood pressure, SPIS = second phase insulin secretion.



**Figure 1.** Receiver operating characteristic curve of the 4 index in predicting subjects with prediabetes. (A) First phase insulin secretion; (B) second phase insulin secretion; (C) insulin resistance; (D) glucose effectiveness.

possible hypotheses were proposed to explain this failure of beta-cell, such as the decrease of beta-cell replication and regeneration capacity.<sup>[43–46]</sup> However, there are some other researchers showed completely opposite findings.<sup>[47–52]</sup> This controversy might come from the different methods used to quantify insulin secretion. At the same time, whether other factors, such as IR, were adjusted might also contribute. It would not be surprising that the role of aging on beta-cell function remains to be controversial since the interaction between insulin secretion and IR is complicated and dynamic. In the present study, we observed that FPIS has less powerful effect on the appearance of prediabetes compared to the SPIS. This is expected because of the following 2 reasons. First, it has been established that FPIS reduces before prediabetes occurs

and completely disappears after T2DM occurs.<sup>[53–55]</sup> Second, from the clinical observation, the blood glucose could be controlled well by oral medications years after the diagnosis of diabetes. It is obvious that this phenomenon could only be explained by the existence of SPIS. The present study provides important information about the difference between these 2 phases of insulin secretion in older Chinese. In the future, unique treatment could be designed based on this finding.

GE has long been overlooked. Part of the reason might be because of the difficulties in its measurement. Only limited numbers of studies were published.<sup>[56–58]</sup> GE could be divided into 2 components, that is, the basal insulin effect and glucose effect at zero insulin. Till now, study done by Lorenzo et al is the



**Table 2**

**Area under the receiver operating characteristic curves of clinical metabolic variables and models predicting prediabetes.**

Models	Area under the ROC curve $\pm$ SE (95% CI)	P-value
FPIS	0.566 $\pm$ 0.009 (0.593–0.629)	<.001
SPIS	0.611 $\pm$ 0.009 (0.593–0.629)	<.001
IR	0.515 $\pm$ 0.010 (0.497–0.534)	.107
GE	0.613 $\pm$ 0.009 (0.595–0.530)	<.001
Model 1	0.611 $\pm$ 0.009 (0.593–0.629)	<.001
Model 2	0.663 $\pm$ 0.009 (0.645–0.680)	<.001

FPIS=first phase insulin secretion, GE=glucose effectiveness, IR=insulin resistance, Model 1=FPIS and SPIS, Model 2=Model 1+GE, ROC curve=receiver operating characteristic curve, SPIS=second phase insulin secretion.

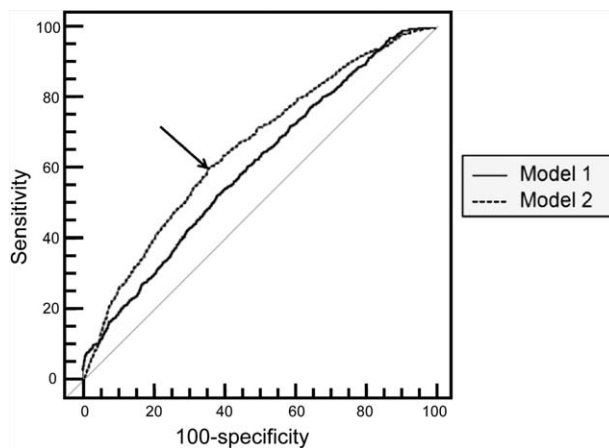
**Table 3**

**Comparison of the area under the receiver operating characteristic curves of models predicting prediabetes.**

Pairwise comparison test between aROC curves of each models	P-value*
FPIS versus IR	<.001
SPIS versus IR	<.001
GE versus IR	<.001
Model 1 versus GE	.911
Model 2 versus Model 1	<.001

aROC=area under receiver operating characteristic curves, FPIS=first phase insulin secretion, GE=glucose effectiveness, IR=insulin resistance, Model 1=FPIS and SPIS, Model 2=Model 1+GE, ROC curve=receiver operating characteristic curve, SPIS=second phase insulin secretion.

most important article discussing the effect of age on GE. In their study, 827 subjects were followed for 5 years. Unfortunately, although there were 3 ethnic groups, no Asians were enrolled. In the longitudinal follow-up, they have shown that only basal insulin effect, but not glucose effect at zero insulin or GE, was significantly lower. The result of our study suggests that among the 4 factors GE is the most decisive one among these 4 factors. It



**Figure 2.** Area under the receiver operating characteristic curve of the models. The arrow indicates the arbitrarily selected risk cut-off point (0.398) of Model 2, which has a sensitivity and specificity of 62.2% and 62.1%, respectively.

is not surprising since GE has been shown to be one of the important components of glucose intolerance or diabetes in other studies.<sup>[17,59]</sup> Their results suggest that GE makes a major contribution to glucose disposal under fasting condition (basal insulin concentrations) estimated at ~70%, while during exposure to postabsorptive insulin concentration imposed during a hyperinsulinemic-euglycemic clamp the relative contribution of GE drops to ~30%.

Although there are other major studies investigate IR, FPIS, SPIS, and GE. However, the present study has important contributions. We focused on the older Chinese which has never been reported in the past. And then, we studied these 4 components simultaneously which provides an interesting comparison between them in the same subjects. However, there are limitations. First, this is a cross-sectional study. Although the number is big, a longitudinal-design study might provide more convincing result. Second, the methods we used to quantified these 4 components are less accurate than other complicated methods such as frequently sampled intravenous glucose tolerance test or clamp. However, this would not be possible to perform such labor-intensive and expensive tests on a large cohort. At the same time, we believe that the large cohort might reduce this drawback. Finally, again, it should be remembered that these 4 components interact with each other. Thus, our results could only demonstrate one's "present condition." Cautious must be taken when interpreting our findings.

## 5. Conclusion

In conclusion, among the 4 factors, GE is the most and IR is the least important contributor for prediabetes in older women. By building a model composed of FPIS, SPIS, and GE, the aROC increased significantly. The equation built from this model could predict prediabetes more precisely.

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## Author contributions

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**Writing – review and editing:** Chung-Ze Wu, Jin-Biou Chang, Yen-Lin Chen, Dee Pei.

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