# **BMJ Open** Change in fasting plasma glucose and incident type 2 diabetes mellitus: results from a prospective cohort study

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#### ABSTRACT

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**Objective:** To investigate the association between changes in fasting plasma glucose (FPG) values and incident type 2 diabetes (T2D) in a cohort of the Iranian population.

Design: Prospective cohort study.

Setting: This study was conducted within the framework of the Tehran Lipid and Glucose Study (TLGS) to investigate the association between change in FPG between baseline examination (1999-2001) and the second visit (2002–2005) with incident T2D. Participants: A total of 3981 non-diabetic participants aged  $\geq 20$  years.

Outcome measure: T2D was defined if the participant was using antidiabetic drugs or if FPG was  $\geq$ 7 mmol/L or if the 2 h post-challenge plasma glucose (2-hPCG) was  $\geq$ 11.1 mmol/L.

**Results:** During a median follow-up of 6.17 years. after the second examination, 288 new cases of T2D were identified. In a multivariate Cox proportional hazard analysis using age as timescale, we presented a simple model including FPG change (HR 1.19, 95% CI 1.07 to 1.33) and baseline waist circumference (WC) (HR 1.004, 95% CI 1.001 to 1.008) with a discriminative power (C-index) of 72%. Furthermore, we showed that the highest quartile of FPG change enhanced the T2D risk to 1.65 (95% CI 1.2 to 2.27) compared with the lowest quartile (p for trend=0.004). The independent risk of FPG change resisted further adjustment with 2-hPCG change. Adding the 2-hPCG change only slightly increased the discriminative power of the model including FPG change and baseline value of WC (0.73% vs 0.72%). After the study population had been limited to those with normal fasting glucose/ normal glucose tolerance, FPG change remained an independent predictor (HR 1.57, 95% CI 1.31 to 1.88). Conclusions: Two measurements of FPG obtained about 3 years apart can help to identify populations at risk of incident T2D independently of important traditional risk factors and their changes, including 2-hPCG change.

#### INTRODUCTION

Each year over 3.8 million people die from type 2 diabetes (T2D) and its complications

## Strengths and limitations of this study

- The reasonable size of the population.
- Use of direct measurements of the glucose indices and anthropometric data rather than selfreported information for both predictors and outcomes.
- Its design as a long-term community-based prospective study conducted on a large sample of Middle Eastern men and women, a region with high incidence rates of T2D.

worldwide.<sup>1</sup> The occurrence of T2D has risen rapidly over the past few decades. It has been estimated that between 2010 and 2030, there will be a 69% increase in numbers of adults with T2D in developing countries and a 20% increase in developed countries.<sup>2</sup>

data mining, Even though most of the investigations have been conducted in Western populations,<sup>3–5</sup> it seems that the Middle East will have the greatest increase in the prevalence of T2D by 2030.<sup>6</sup> <sup>7</sup> Despite the fact that Middle Eastern populations bear the highest incidence of T2D, data on the dynamics of T2D in this region continue to be lacking.

The rapidly rising prevalence of T2D mandates a more systematic understanding of the natural history of the disease and its potential risk factors. The role of recognised risk factors such as aging, family history of dia-betes, obesity, impaired fasting glucose, hyper-tension, sedentary lifestyle consequent to increasing rates of urbanisation, and some factors such as aging, family history of diawell-known genetic factors have been shown in the occurrence of the disease.<sup>7-9</sup> However, a complex process exists between these and other risk factors, which varies between populations with different ethnicities and demographic characteristics.<sup>10</sup> <sup>11</sup> Investigators have tried to implement risk assessment models that can reflect this complexity and at the same time can be simply used in clinical practice.  $9^{12}$  13

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Of the different components of T2D risk assessment models,<sup>13</sup> the level of fasting plasma glucose (FPG) as the core component in most of these models, and its association with increased risk of T2D incidence, has been well investigated. Analysis from the Whitehall II study showed a linear trend of FPG from 13 to 3 years before diagnosis of T2D, which was followed by a quadratic increase starting 3 years before diagnosis of T2D.<sup>14</sup> Furthermore, the independent association between changes in values of T2D risk factors such as anthropometric measurements<sup>15</sup> and triglyceride (TG) levels<sup>16</sup> has been studied. The present study aimed to examine the impact of change in FPG level on T2D prediction during 6 years of follow-up of urban Iranians in a population-based study called the Tehran Lipid and Glucose Study (TLGS).

# **METHODS**

#### Study population

The TLGS is a large-scale, longitudinal, communitybased prospective study performed on a representative sample of an urban population of Tehran (the capital of Iran). The study was started in 1999-2001 to estimate the prevalence of non-communicable disease risk factors. Data collection is ongoing and designed to continue for at least 20 years on a triennial basis. The rationale and study design of the TLGS has been discussed elsewhere.<sup>17</sup>

Members of the TLGS who attended both first (1999-2001) and second (2002-2005) examinations of the cohort were eligible for the present study. Of a total of 10 368 individuals aged  $\geq$ 20 years, after exclusion of participants with prevalent diabetes (having newly diagnosed T2D or using glucose-lowering drugs) (n=1192), missing data on FPG and 2 h post-challenge plasma glucose (2-hPCG) (n=4527), missing data on other covariates including systolic and diastolic blood pressure (SBP, DBP, respectively), body mass index (BMI), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), TG, waist circumference (WC), smoking status and education level (n=363) and no follow-up data (n=305), 3981 subjects were left, who were followed-up until 20 March 2010 (median 6.17 years, IQR 5.4-6.87 years after their second measurement). In the second analysis, we repeated all analyses for participants with normal glucose tolerance (NGT) and normal fasting glucose (NFG) by excluding individuals with FPG  $\geq$ 5.5 mmol/L and 2-hPCG  $\geq$ 7.7 mmol/L.

The ethics committee of the Research Institute for Endocrine Sciences, Shahid Beheshti University of Medical Sciences approved the design of the TLGS, and all participants provided written informed consent.

#### Medical history, clinical examination and laboratory measurements

Participants were interviewed in private by trained interviewers. A standard questionnaire was used to obtain

demographic information. Subjects were questioned about their current smoking status and taking of any antidiabetic or hypertension drugs. SBP and DBP were measured twice, with subjects in a seated position, in the right arm using a standard mercury sphygmomanometer; the mean value was considered to evaluate their SBP and DBP. Weight was measured, with subjects minimally clothed without shoes, using digital scales (Seca 707; range 0.1-

150 kg) and recorded to the nearest 100 g. Height was u measured using a tape measure, with subjects standing without shoes with shoulders in normal alignment. WC was measured at the umbilical level and that of the hip ŝ at the maximum level over light clothing, using a tape measure, without any pressure to the body surface; mea-8 surements were recorded to the nearest 0.1 cm. BMI was calculated as weight in kilograms divided by height in metres squared.

All measurements of lipid variables and glucose were made in venous samples drawn between 07:00 and 09:00 after 12-14 h overnight fasting into Vacutainer tubes, which were centrifuged within 30-45 min of collection. FPG and 2-hPCG was measured by an enzymatic coloriuses related metric method using oxidase on the day of blood collection; inter- and intra-assay coefficients of variation (CVs) at baseline and follow-up phases were both <2.3%.

Total cholesterol (TC) was assayed using the enzymatic colorimetric method with cholesterol esterase and cholç esterol oxidase. HDL-C was measured after precipitation text of the apolipoprotein B-containing lipoproteins with phosphotungstic acid. TG was assaved using glycerol phosphate oxidase. Both inter- and intra-assay CVs were <1.9%, 3% and 2.1% for TC, HDL-C and TG, respectively, in all baseline and follow-up assays. We used a modified Friedewald formula to calculate LDL-C.18 Analyses were performed using Pars Azmon kits (Pars Azmon, Tehran, Iran) and a Selectra 2 auto-analyzer training, and similar (Vital Scientific, Spankeren, Netherlands). All samples were analysed when internal quality control met acceptable criteria.

#### **Definition of terms**

T2D was considered present if the participant was using or if the technolog of 7.8– 0f 2h-PCG g antidiabetic drugs or if FPG was  $\geq 7 \text{ mmol/L}$  or if the 2-hPCG was  $\geq$ 11.1 mmol/L.<sup>19</sup> Prediabetes was defined as FPG of 5.6-6.9 mmol/L and or 2 h-PCG of 7.8-FPG 11.0 mmol/L. <5.6 mmol/L and <7.8 mmol/L was defined as NFG/NGT.<sup>19</sup> A current **B** smoker was defined as a person who smokes cigarettes daily or occasionally. A positive family history of T2D was defined as having at least one parent or sibling with T2D. We defined individuals participating in a vigorous physical activity programme of at least 3 days/week as physically active.<sup>7</sup> We classified amount of education into three groups: <6 years, 6-12 years and  $\geq 12$  years. Hypertension was defined as SBP ≥140 mm Hg or DBP  $\geq$ 90 mm Hg or using any hypertension drugs.

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#### Statistical analysis

Mean±SD values for continuous variables, and frequencies (%) for categorical variables, of the baseline characteristics were reported for diabetic and non-diabetic participants. Comparisons of baseline characteristics between respondents (those with FPG and 2-hPCG data in both phases I and II, who had follow-up until the end of the study) and non-respondents (those with missing data on FPG and 2-hPCG and covariates in either phase I or II or loss to follow-up) as well as diabetic versus non-diabetic participants were performed by Student's t test for continuous variables, the  $\chi^2$  test for categorical variables, and the Mann–Whitney U statistic for skewed variables.

A univariate analysis was conducted for each potential covariate to be integrated into the multivariate analysis, including gender (female vs male), family history of diabetes, education, current smoking, age, BMI, WC, TG/ HDL-C, TC/HDL-C, LDL-C, physical activity and lipid-lowering drugs as well as change in BMI, WC, TC/ HDL-C, TG/HDL-C, LDL-C, FPG and 2-hPCG and the hypertension change category. Regarding the effect of changes in smoking habits, we created four groups based on the first (1999-2001) and second (2002-2005) examination (yes/yes, yes/no, no/yes and no/no). We also defined the hypertension change category based on the first (1999-2001) and second (2002-2005) examination (yes/yes, yes/no, no/yes and no/no). Variables that had a p value <0.2 in univariate analysis were selected to be included in the multivariate Cox model, with age as the timescale<sup>20</sup> (see online supplementary table S1).

We checked the interaction between all of the baseline covariates and FPG change in multivariate analysis, and no significant interaction was found. Variance inflation factor was used to check multi-collinearity among anthropometric measurements and their changes (FPG change and 2-hPCG change; lipid measurements and their changes), and there was no multi-collinearity. In the multivariate analysis, three models were designed (the details of covariate adjustment in each model is abbreviated in the tables and defined in footnotes). All adjusted HRs with their 95% CIs were reported for 1SD increase in each variable and their changing values. In addition, analyses were repeated for quartiles of FPG change.

The proportionality of the multivariate Cox model was evaluated using Schoenfeld's global test of residuals, and all proportionality hypotheses were appropriate. In addition, to better clarify the linear association between FPG change and incident T2D during follow-up, we applied the scaled Schoenfeld proportional hazard assumption graphically. As shown in online supplementary figure S1, no violation of the Schoenfeld proportional hazard assumption was found for FPG changes and incident diabetes during the follow-up.

To measure the relative quality of the predictive models, the Akaike information criterion (AIC) was used. Better fit can be checked with a lower value of AIC.<sup>21</sup> Harrell's C-index was used to check the discriminative ability of the models. A value of 1 indicates perfect discrimination, and a value of 0.5 is no better than probability.<sup>22</sup> All analyses were performed using Stata V.12 SE, with a two-tailed p value <0.05 being considered significant.

## RESULTS

Baseline characteristics of subjects with and without incidence diabetes as well as whole population are summarised in table 1. In comparison with individuals without incident T2D, those with T2D were older and less educated. There was no significant difference regarding gender, current smoking status, HDL-C, LDL-C and physical activity levels in subjects with and without incident T2D. The comparison between nonrespondents and respondents is shown in online supplementary table S2. The respondents were older and had higher BMI and DBP, but they had lower rates of smoking and mean level of FPG.

Baseline characteristics of the total study population (3981 cases) in accordance with quartiles of FPG change are shown in online supplementary table S3. As demonstrated, subjects within the highest quartile of FPG change ( $\geq 0.4 \text{ mmol/L}$ ) had higher BMI, TC and TG.

Among the non-diabetic study population, we found 288 (115 men and 173 women) new T2D cases (overall incidence rate 7.84 per 1000 person-years) during a median of 6.17 years of follow-up after second examination measurement.

and Results of multivariate Cox proportional hazard analysis for 1SD increase in FPG change and other significant covariates for incidence of T2D among the study З populations are given in table 2. Model I showed a positive association between FPG change and T2D inci-≥ dence. In model II (in the presence of other T2D risk factors as well as their changes), we also found that the FPG change (HR 1.19, 95% CI 1.07 to 1.33) and base-Bu line WC (HR 1.004, 95% CI 1.001 to 1.008) showed positive association with T2D incidence. According to model III, FPG change (HR 1.13, 95% CI 1.01 to 1.26) and <u>0</u> 2-hPCG change (HR 1.28, 95% CI 1.14 to 1.42) remained as independent predictors. We also observed that WC remained in the final model (HR 1.004, 95% technolog CI 1.001 to 1.008). We did not see any association between other baseline anthropometric and lipid measurements and their changes with T2D incidence (see online supplementary table S4).

With respect to the discriminative power, most differences among the models' C-index were seen between model I and II (model II vs model I: 72% to 55%). As reported by AIC, FPG change had the best fit in model III (AIC 3619) followed by model II and model I.

We also checked the association between the incidence of T2D and quartiles of FPG change. A total of 96 incident cases of T2D were identified in the highest quartile (incident rate 11.63 per 1000 person-year) in

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and Glucose Study (TLGS) (2001-2010)

Table 1

Characteristic	Total study population (N=3981)	Without incident diabetes (N=3693)	With incident diabetes (N=288)	p Value
Female	2297 (57.7)	2124 (57.5)	173 (60.1)	0.4
Age (years)	42.68±13.32	42.24±13.32	48.26±12.0	<0.001
Education				<0.001
<6 years	1370 (34.4)	1231 (33.3)	139 (48.3)	
6–12 years	2118 (53.2)	1994 (54.0)	124 (43.1)	
≥12 years	439 (12.4)	468 (12.7)	25 (8.7)	
Family history of diabetes	1027 (25.8)	929 (25.2)	98 (34.0)	0.003
Current smokers	483 (12.1)	457 (12.4)	26 (9.0)	0.09
Body mass index (kg/m <sup>2</sup> )	26.90±4.45	26.72±4.38	29.3±4.66	<0.001
Systolic blood pressure (mm Hg)	118.24±17.38	117.67±17.21	125.64±17.85	<0.001
Diastolic blood pressure (mm Hg)	77.58±10.23	77.25±10.14	81.81±10.45	<0.001
Total cholesterol (mmol/L)	5.43±1.15	5.4±1.13	5.81±1.24	<0.001
High-density lipoprotein cholesterol (mmol/L)	1.1±0.28	1.1±0.28	1.07±0.27	0.15
Low-density lipoprotein cholesterol (mmol/L)	3.03±1.14	3.04±1.13	2.93±1.27	0.14
Triglyceride* (mmol/L)	1.61 (1.22)	1.60 (1.19)	2.07 (6.53)	<0.001
Fasting plasma glucose (mmol/L)	5.0±0.51	4.93±0.50	5.46±0.58	<0.001
2 h post-challenge plasma glucose (mmol/L)	5.86±1.55	5.75±1.48	7.26±1.75	<0.001
Physical activity				
More than 3 times a week	999 (25.1)	923 (25.0)	76 (26.4)	0.6
Medication use	· ·	· · /	· · /	
Hypertension drug	243 (6.1)	210 (5.7)	33 (11.5)	<0.001
Lipid drug	92 (2.3)	78 (2.1)	14 (4.9)	0.003

Baseline characteristics of participants with and without incident diabetes and total study population: Tehran Lipid

values are meanable (continuous variables) with p value calculated with student sit test, or n (%) (categorical variables) calculated according to  $\chi^2$ .

\*Triglyceride is shown as median (inter-quartile range) and the p value was calculated according to the Mann–Whitney U test. Low-density lipoprotein cholesterol was calculated using the modified Friedewald formula test.

comparison with the lowest quartile (incident rate 6.85 per 1000 person-year) (table 3). Crude HRs for prediction of T2D across quartiles of FPG change reached 1.71 (95% CI 1.24 to 2.33) for the highest quartile compared

with the lowest (p for trend =0.001). With further adjustment in model II, the HR of FPG change decreased to 1.65 (95% CI 1.20 to 2.27) for the highest quartile compared with the lowest quartile (p for trend=0.004). After

 Table 2
 HRs for predicting type 2 diabetes in different models of FPG changes; Tehran Lipid and Glucose Study (TLGS)

 (2001–2010)\*

	Significant covariates†	HR (95% CI)	p Value	Harrell's C	AIC
				0.55	3701
Model I	FPG change	1.22 (1.09 to 1.36)	0.001		
				0.72	3637
Model II	FPG change	1.19 (1.07 to 1.33)	0.002		
	WC	1.004 (1.001 to 1.008)	0.009		
				0.73	3619
Model III	FPG change	1.13 (1.01 to 1.26)	0.03		
	2-hPCG change	1.28 (1.14 to 1.42)	<0.001		
	WC	1.004 (1.001 to 1.008)	0.012		

Model I: FPG change (crude model). Model II: model I+baseline measurements of current smoking, family history of diabetes, education, BMI, WC, TG/HDL-C ratio and its change, TC/HDL-C ratio and its change, lipid drug and hypertension change categories. Model III: model II +2-hPCG change.

We defined the hypertension change category based on the first (1999–2001) and second (2002–2005) examination (yes/yes, yes/no, no/yes and no/no).

\*Multivariate Cox analyses were conducted using age as timescale; 1SD change in FPG: 0.5 mmol/L; 1SD change in 2-hPCG: 1.57 mmol/L; 1SD change in baseline value of WC: 11.5 cm.

†Covariates with p value <0.05 are shown.

2-hPCG, 2 h post-challenge plasma glucose, mmol/L; AIC, Akaike information criterion; BMI, body mass index; FPG, fasting plasma glucose, mmol/L; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

Table 3	HRs (95% CI) for prediction of type 2 diabetes with respect to F	PG change quartiles; Tehran Lipid and Glucose
Study (TI	_GS) (2001–2010)	

Quartile of interest	1 (lowest)	2	3	4 (highest)	p <sub>trend</sub>	Harrell's C	AIC
FPG change, mmol/L*	<-0.29	-0.29-0.06	0.07–0.39	≥0.40	_	-	_
Diabetes cases	64	71	57	96	-	_	-
Person-years	9335	9981	9162	8253	-	_	-
Incidence (per 1000	6.85	7.11	6.22	11.63	-	_	-
person-year)							
Model I	1.00	1.08 (0.77 to 1.52)	0.96 (0.67 to 1.37)	1.71 (1.24 to 2.33)	0.001	0.65	3700.65
Model II	1.00	1.11 (0.79 to 1.56)	0.98 (0.68 to 1.40)	1.65 (1.2 to 2.27)	0.004	0.72	3636.42
Model III	1.00	1.06 (0.76 to 1.5)	0.9 (0.63 to 1.29)	1.43 (1.03 to 1.98)	0.06	0.73	3619.2

Significant values (p<0.05) are shown in bold typeface.

Model I: FPG change categories (crude model). Model II: model I+baseline measurements of current smoking, family history of diabetes, education, BMI, WC, TG/HDL-C ratio and its change, TC/HDL-C ratio and its change, lipid drug and hypertension change categories. Model III: model II+2-hPCG change.

We defined the hypertension change category based on the first (1999–2001) and second (2002–2005) examination (yes/yes, yes/no, no/yes and no/no). AIC, Akaike information criterion.

\*1st quartile (<-0.29 mmol/L); 2nd quartile (-0.29-0.06 mmol/L); 3rd quartile (0.07-0.39 mmol/L); 4th quartile (≥0.4 mmol/L); multivariate Cox analyses were conducted using age as timescale.

2-hPCG, 2 h post-challenge plasma glucose, mmol/L; BMI, body mass index; FPG, fasting plasma glucose, mmol/L; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; WC, waist circumference.

further adjustment in model III, we found that this risk decreased to 1.43 (95% CI 1.03 to 1.98) (table 3).

Finally, we removed all prediabetes cases at baseline and limited the study population to NGT/NFG participants. All analyses were repeated for these subgroups and results were similar to the main study population. Accordingly, FPG change remained an independent predictor (HR 1.57, 95% CI 1.31 to 1.88) (see online supplementary tables S5 and S6).

#### DISCUSSION

To the best of our knowledge, this study is among the few prospective population-based ones to examine the association of changes in FPG and 2-hPCG with incident T2D. Our results reveal that, after adjustment for traditional risk factors and their changes, baseline WC and change in FPG and 2-hPCG remained significant predictors. Furthermore, we showed that data on FPG change in combination with a baseline value of WC had a discriminative power of 72% in the prediction of T2D. However, adding the 2-hPCG change only slightly increased the discriminative power of model II (0.73% vs 0.72%). We also showed that the change in FPG, even in subjects with NFG and NGT at baseline, was a significant predictor of T2D.

Numerous epidemiological studies have demonstrated that baseline FPG and 2-hPCG are highly predictive of T2D.<sup>9</sup> <sup>14</sup> <sup>23</sup> <sup>24</sup> Nevertheless, the association between changing the values of different T2D risk factors and incident T2D has been investigated. Tirosh *et al*<sup>16</sup> in a cohort of young men showed the relation between changes in TG levels and increased risk of T2D. In addition, the association between changes in anthropometric measurements and incident dysglycaemia has been investigated in the TLGS.<sup>15</sup>

Protected by copyright, including Many different risk scores and models have been ð developed that estimate the risk of T2D, but most are hardly ever used because they involve tests not routinely used or they were developed without a specific user.<sup>25 26</sup> In a population sample including 3140 men and women related in the Framingham Offspring Study, Wilson et  $al^{27}$ showed that, instead of using complex risk models, utilising a combined simple clinical and personal model can efficiently identify subjects at elevated risk of T2D. Applying a simple risk score, we showed that a cluster of data, including SBP, family history of T2D, TG/HDL-C and FPG level, revealed an area under receiver operating characteristic (AROC) of 85%.9

There is now growing evidence that central adiposity correlates better with T2D than general adiposity, which has made WC a more suitable T2D risk predictor than BMI.<sup>28 29</sup> The finding of this obvious advantage of WC over BMI observed in many studies can probably be explained by the physiological functions of visceral fat tissue, which is known to have endocrine functions and to be an independent risk factor for T2D.<sup>28 30</sup> In this regard, Mamtani *et al*,<sup>31</sup> in a study conducted on 808 members of Mexican American families, has shown that WC is the strongest anthropometric index that is assotechnolog ciated with insulin resistance and T2D. Moreover, our results reveal that, after adjustment for traditional risk factors and their changes, WC remained a significant predictor of T2D.

Subjects with impaired glucose tolerance (IGT) are at increased risk of developing T2D and it has become the standard method for recognising people at risk of T2D.<sup>32</sup> However, detection of IGT requires a costly and time-consuming oral glucose tolerance test (OGTT). Furthermore, it has been shown that only 50% of IGT subjects converted to T2D within 10 years of follow-up.<sup>32</sup> Thus, investigators have developed risk assessment models based on fasting state values, which perform

equally well in predicting future T2D in comparison with the 2 h plasma glucose concentration during the OGTT.<sup>33–38</sup> In addition, Stern *et al*<sup>33</sup> showed that adding the 2-hPCG value to the prediction model results in only a slight improvement, at a greater cost and inconvenience. In our previous study, we showed that adding 2-hPCG to the simple model, despite achieving statistical significance, failed to reach clinical importance.<sup>9</sup> In the present study, we showed that model III, which included 2-hPCG change, outperformed model II with respect to Harrell's C-index and highlighted better fit considering the AIC. However, this gain was clinically negligible. In accordance with Stern *et al*,<sup>33</sup> our results show that adding 2-hPCG change to the prediction model did not appreciably increase the predictive power.

In our data analyses we also showed that even those with NFG/NGT at baseline highlighted significant risk of changing values of FPG regarding incident T2D. Recently, a J-shaped FPG-diabetes relationship was shown in the Tehranian adult population. In other words, the risk of T2D increased linearly in individuals with FPG  $\geq 5.05 \text{ mmol/L}$ .<sup>39</sup> In fact, applying a simple T2D risk score, we found that 5 mmol/L  $\leq$ FPG level  $\leq 5.5 \text{ mmol/L}$  had a score of 12 in the prediction of T2D.<sup>9</sup> Hence, it might be predictable that a significant association between change in FPG value and incident T2D in subjects with NFG/NGT had occurred in those with FPG  $\geq 5 \text{ mmol/L}$ .

The strengths of the present prospective study are the reasonable size of the population and the use of direct measurements of glucose indices and anthropometric data rather than self-reported information for both predictors and outcomes. A further strength is its design as a long-term community-based prospective study conducted on a large sample of Middle Eastern men and women, a region with high incidence rates of T2D.<sup>7</sup> Some limitations of the study, which are inherent to any prospective study, need to be addressed. About 57% of the study participants with missing data or lost to follow-up were not examined at follow-up. However, respondents were older and had a higher BMI, but a lower rate of current smoking and lower level of FPG compared with non-respondents; hence, this might not significantly affect the incidence of T2D in this population. Moreover, our subjects were selected from a sample of the Iranian population, and further studies should be conducted to determine whether our findings are applicable to other populations and ethnicities. Unfortunately, we did not have any data on the changes in physical activity or nutritional habits of the study population during the study; however, true assessments of these measures can be very difficult to achieve with adequate precision.<sup>40</sup>

In summary, we have shown that, after adjustment for traditional risk factors for T2D and their changes, there is a positive association between FPG change and the incidence of T2D. Furthermore, we have also shown that, even in subjects with NFG and NGT, the same positive association exists. We present a simple model, including WC and FPG change with high discriminative power in the prediction of T2D. Our findings also suggest that adding 2-hPCG change to the enhanced prediction model slightly improves the predictive power but at greater cost and inconvenience. Finally, it should be considered that attenuating the change in FPG value through alteration of nutritional habits, physical activity level or pharmacological therapy may potentially weaken the risk of T2D in the Iranian population.

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