Impact of Pre-diabetes alone or in combination with Hypertension, Dyslipidemia, or both on Major Adverse Cardiovascular Events

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Research article

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Abstract

Background Whether pre-diabetes in the absence of hypertension (HTN) or dyslipidemia (DLP) is a risk factor for occurrence of major adverse cardiovascular events (MACE) is not fully established. We investigated the effect of impaired fasting glucose (IFG) alone and in combination with HTN, DLP or both on subsequent occurrence of MACE as well as individual MACE components. Methods This longitudinal population-based study included 9,831 inhabitants of Northeastern Iran. The participants were free of any cardiovascular disease at baseline and were followed yearly from 2010 to 2017. Cox proportional hazard models were fitted to measure the hazard of IFG alone or in combination with HTN and DLP on occurrence of MACE as the primary endpoint. Results 297 MACE were recorded during 6.2±0.1 years follow up. IFG alone compared to normal fasting glucose (NFG) was not associated with increased in occurrence of MACE (HR, 1.05; 95% CI, 0.59-1.86; p, 0.8). However, combination of IFG and HTN (HR, 2.75; 95% CI, 1.93-3.90; p, 0.001) or HTN + DLP (HR, 2.85; 95% CI, 1.79-4.54; p, 0.001) significantly increased the hazard of MACE. In contrast, IFG with DLP at baseline did not increase the hazard of MACE compared to normoglycemic- normolipemic individuals (p,0.2). The results also indicated IFG with HTN, DLP, or HTN+DLP were associated with significant higher HRs for some individual components of MACE. Conclusion IFG, per se, does not appear to increase hazard of MACE. However, IFG with HTN or HTN + DLP conferred a significant hazard for MACE in an incremental manner.

Background

Pre-diabetes (pre-DM) is often taken as a warning sign. Individuals with pre-DM have a glycemic state that is higher than normal but not high enough to be classified as type 2 diabetes (T2DM). The pre-diabetes state is characterized by impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or HbA1c of 39 mmol/mol (5.7%) to 46 mmol/mol (6.4%). The significance of pre-DM is the associated risk for progression to T2DM which is disproportionately greater at the higher end of the pre-DM range and with the combined presence of IFG and IGT[1]. Pre-DM and T2DM are parts of a continuous spectrum that share in their pathophysiology, and are associated with a common phenotype that includes obesity, hypertension (HTN), and dyslipidemia (DLP) [2]. It is well established that aggregation of the traditional cardiovascular (CV) risk factors such as HTN and DLP in patients with T2DM is associated with the increased risk of cardiovascular disease (CVD) and events [3, 4]. Furthermore, insulin resistance per se that is present in the vast majority of individuals with T2DM is associated with the increased risk of CVD independent of other CV risk factors [5, 6].

In addition to T2DM, pre-DM is also associated with an increased risk of CVD [7, 8]. Considering that traditional CV risk factors are frequently present in individuals with pre-diabetes, the question arises that to what extent is the effect of pre-DM on CVD risk mediated by having pre-DM alone or by the associated risk factors [9, 10]. Since some studies did not fully adjust for concomitant CV risk factors, their findings should be interpreted with caution. Hence, whether pre-DM or IFG alone in the absence of HTN or DLP or their combination carries increased risk for CVD has remained an unanswered issue.

We conducted a prospective cohort study among a population of Iranian people to investigate the impact of IFG alone or in combination with HTN or DLP or both on the primary composite endpoint of major adverse cardiovascular events (MACE) as well as its individual components.
Methods

Study design and population

We extracted data from the longitudinal Golestan Cohort Study (GCS) that was launched in Northeastern Iran [11]. The primary aim of GCS is to investigate risk factors of esophageal cancer in this region. Participants in this cohort were also followed for CVD outcomes. In this analysis we examined data from a total number of 11,374 participants that were enrolled from rural and urban areas between April 2010 and March 2012. Participants were followed annually till March 2017. The exclusion criteria of the Golestan cohort were: unwillingness to participate at any stage of the study for any reason, and having a current or previous history of any known CVD events. The study protocol was approved by the ethical review committees of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the US National Cancer Institute, and the International Agency for Research on Cancer. Before interview, the written informed consent was obtained from each participant. They were interviewed by a trained general physician who has recorded demographic and medical information through a questionnaire.

Height, weight, waist and hip circumference were measured at baseline, and body mass index (BMI) was calculated. Blood pressure (BP) was measured twice, with a 10-min interval, from both arms in the sitting position using Richter auscultator sphygmomanometers. Blood samples (10 ml) were collected by a trained technician. Fasting blood glucose (FBS), triglyceride (TG), cholesterol, and high density lipoprotein (HDL) were measured in all individuals at the time of enrollment.

Follow up

Participants were followed up by annual phone calls from their date of recruitment (2010–2012) until the first occurrence of any of MACE components, death from any cause, or end of the study (March 2017). Each cohort member was also instructed at the time of enrollment to contact the team in case of certain conditions such as hospitalization or development of a new major disease. These contacts were registered and subsequently followed by a staff member. Follow-up assessed at the end of the Golestan study was successful for over 99% of the study participants. If a death was identified, a general practitioner visited the home of the deceased. Causes of death were ascertained through verbal interview and investigation of medical documents [12]. Using the collected documents, two internists independently determined the cause of death with ICD-10 codes. If the two were concordant, a diagnosis was made. Otherwise, the cause of death was determined by a third senior internist.

Definition of IFG, HTN, and DLP

IFG was diagnosed when a participant did not have DM, but had an FBS of 5.6 to <7.0 mmol/L, according to the American Diabetes Association criteria (ADA) [1]. Patients with diagnosed T2DM, defined as a self-reported diagnosis, or being treated with glucose lowering drugs, or those with FBS ≥ 7 mmol/L were excluded from the current analysis. Normal fasting glucose (NFG) was defined as FBS< 5.6 mmol/L. Hypertension was defined as self-reported hypertension and currently taking antihypertensive drugs, or systolic blood pressure (SBP) ≥140 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg based on the JNC-7 criteria [13]. DLP was defined
as fasting TG $\geq$ 1.69 mmol/L, or total cholesterol $\geq$ 6.20 mmol/L, or HDL<1.29 mmol/L in women and <1.03 mmol/L in men, or receiving lipid lowering medications.

**Statistical Analysis:**

Data are presented as means (SE) and numbers (percentage). In all cases, final analysis was based on presence or absence of a risk factor (or factors) in both the IFG and NGT groups using fully adjusted models. Student t-test and Pearson $\chi^2$ (or Fisher Exact) tests were used to compare continuous and categorical variables, respectively. Risk analysis was conducted in patients with IFG, and Poisson regression model was used to identify predictors of MACE (fatal MI, fatal stroke, non-fatal MI, and non-fatal stroke). Regarding the time to event for MACE and its components, Kaplan-Meyer method was used to estimate the survival probabilities, and Cox proportional hazard models were fitted to measure the hazard ratios. Statistical analyses were performed with Stata software for Windows version 13.0. Values of $p < 0.05$ was considered statistically significant.

**Results**

**Baseline characteristics**

The entire prospective cohort included 11,374 participants from the Northern provinces of Iran. Among the cohort 1,543 had DM at baseline and were excluded from this analysis. Among the remaining 9,831 participants, 2,410 (24.5%) had IFG, and 7,421 (75.5%) had normal fasting glucose (NFG), and they were included in this analysis.

Baseline characteristics of the study population are demonstrated in Table 1. The prevalence of HTN (44.2 vs. 34.7%; $p < 0.000$) and DLP (49.9 vs. 39.7%; $p < 0.000$) were significantly higher in IFG population compared to the normoglycemic group. Moreover, compared to NFG group, the IFG group were older and had a significantly higher level of BMI, waist circumference (WC), SBP, DBP, TG, cholesterol, and low density lipoprotein (LDL) ($p=0.000$, all). Participants with IFG were more likely to use a statin medication than did the NFG group (3.7 vs. 2.7%; $p < 0.007$). However, sex difference (47.3 vs. 48.4%; $p < 0.3$), smoking status (8.1 vs. 9.2%; $p < 0.08$), and HDL level (61.4 vs. 61.2; $p < 0.7$) were not significantly different between the two groups.

**IFG and CVD outcomes**

Over a mean follow up of 6.2 ($\pm$ 0.1) years, 297 MACE (199 CVD deaths, 43 non-fatal MI, and 55 non-fatal strokes) were reported. CVD death comprised of 108 fatal MI, 74 fatal strokes, and 17 deaths due to heart failure.

Table 2 shows HRs and 95% CI of MACE according to glycemic status, HTN, and DLP. The occurrence of MACE was not significantly different between those with IFG but without HTN or DLP compared to NFG participants who also did not have HTN or DLP (fully adjusted HR, 1.05; 95% CI, 0.59-1.86; $p < 0.8$). However, presence of both HTN and DLP with IFG was associated with significantly higher hazard of MACE compared to the reference group (fully adjusted HR, 2.85; 95% CI, 1.79-4.54; $p < 0.000$). The presence of HTN+DLP in normoglycemic participants confers a considerable hazard for MACE (fully adjusted HR, 2.58; 95% CI, 1.72-
3.87; P, 0.000), however, it is somewhat less than hazard of MACE imposed by HTN+ DLP in individuals with IFG. When participants were categorized based on glycemic status with the presence or absence of HTN alone, individuals with IFG plus HTN showed significantly higher hazard of MACE compared to those with NFG and without HTN (fully adjusted HR, 2.75; 95% CI, 1.93-3.90; p, 0.000). However, IFG without HTN did not increase the hazard of MACE compared to NFG without HTN (fully adjusted HR, 1.19; 95% CI, 0.77-1.84; p, 0.4). The presence of HTN in normoglycemic participants was associated with significantly higher HR of MACE compared to the reference group (fully adjusted HR, 2.57; 95% CI, 1.92-3.43; P, 0.000). HRs for MACE was also evaluated according to glycemic status in the presence or absence of DLP. Compared to the reference group, IFG with DLP did not increase the hazard of MACE (fully adjusted HR, 1.24; 95% CI, 0.88-1.77; p, 0.2).

Kaplan-Meier analysis with log-rank test shows that addition of IFG to HTN, DLP, or both did not decrease MACE free survival (Figure 1; p > 0.05 for all comparisons).

We next examined the effect of IFG with HTN, DLP, or both HTN + DLP on the occurrence of individual components of MACE in greater detail. Table 3 shows the effect of IFG in the presence of HTN+DLP on the occurrence of the individual components of MACE. IFG plus both HTN and DLP was associated with a significant increase in the hazard of fatal MI (fully adjusted HR, 2.74; 95% CI, 1.20-6.21; p, 0.01). However, IFG in the absence of neither HTN nor DLP did not increase the hazard of fatal MI (fully adjusted HR, 1.20; 95% CI, 0.47-3.01; P, 0.6). The combination of IFG with both HTN and DLP did not increase the risk of non-fatal MI (fully adjusted HR, 1.12; 95% CI, 0.23-5.46; p, 0.9) compared with NFG in the absence of HTN+DLP. Considerably, IFG in the presence of both HTN and DLP conferred a significantly higher hazard (fully adjusted) of both fatal stroke (HR, 5.13; 95% CI, 2.08-12.63; p, 0.000) and non-fatal stroke (HR, 2.52; 95% CI, 1.06-6.02; p, 0.04), compared to NFG in the absence of HTN+DLP. However, IFG in the absence of either HTN or DLP was not associated with increased hazard of fatal (fully adjusted HR, 1.37; 95% CI, 0.43-4.40; p, 0.6) or non-fatal stroke (fully adjusted HR, 0.52; 95% CI, 0.12-2.30; p, 0.4).

The results indicated that IFG in the presence of HTN is associated with a significantly higher hazard of fatal MI (fully adjusted HR, 2.66; 95% CI, 1.48-24.78; p, 0.001) but not non-fatal MI (fully adjusted HR, 1.57; 95% CI, 0.56-4.46; p, 0.4) compared to NFG in the absence of HTN (Table 4). IFG plus HTN was associated with the higher hazard of both fatal (fully adjusted HR, 3.72; 95% CI, 1.84-7.55; p, 0.000) and non-fatal (fully adjusted HR, 2.34; 95% CI, 1.18-4.62; p, 0.01) stroke. However, IFG in the absence of HTN did not increase the hazard of any of the above cardiovascular events (Table 4).

IFG in the presence of DLP, compared to NFG in the absence of DLP, was associated with an increased risk of fatal stroke both in unadjusted model (HR, 2.17; 95% CI, 1.22-3.88; p, 0.009) and in adjusted models number 1 (HR, 2.40; 95% CI, 1.33-4.31; p, 0.003) and number 2 (HR, 2.47; 95% CI, 1.34-4.53; p, 0.004). However, IFG in the presence of DLP did not increase the risk of fatal MI (fully adjusted HR, 1.50; 95% CI, 0.84-2.70; p, 0.2), non-fatal MI (fully adjusted HR, 0.72; 95% CI, 0.21-2.52; p, 0.6), and non-fatal stroke (fully adjusted HR, 1.31; 95% CI, 0.66-2.58; p, 0.4). Likewise, IFG in the absence of DLP did not increase the hazard of any of the above cardiovascular events (Table 5).

Discussion
The major findings of the present study on composite CVD outcomes (MACE) in a group of individuals with IFG are that IFG, per se, in the absence of HTN and DLP was not associated with an increase in the hazard for MACE. In contrast, IFG in the presence of HTN or HTN+DLP was associated with an incremental and significant increase in the hazard of MACE. Further analyses regarding the impact of IFG in the presence of HTN, DLP, or HTN+DLP on the individual components of MACE demonstrated that IFG in the presence of HTN or HTN+DLP incrementally increased the hazard of fatal MI as well as fatal and non-fatal stroke. Additionally, the combination of IFG and DLP was associated with an increase in the risk of fatal stroke.

Whether pre-DM, per se, is an independent risk factor for CVD has been a matter of debate. In the current study, IFG in the absence of other CV risk factors did not increase the risk of adverse cardiovascular events. Likewise, other longitudinal population-based studies, also did not find an association between pre-DM alone and CVD risk [14,15]. However, other studies have indicated that dysglycemia within pre-diabetic glucose range was associated with an increase in the risk of CVD [6, 16, 17]. Most studies have suggested that impaired glucose tolerance (IGT) is a stronger predictor than IFG for CVD events [18, 19]. However, Barr et al. showed IFG but not IGT is an independent predictor for CVD mortality [20]. Results from a recent review suggested that IGT and HbA1C correlate more with CVD risk than IFG [21]. These inconsistencies might be due to differences in analytical methods, different definitions for pre-diabetes, and ethnic origins of the participants included in the studies.

It is generally agreed that individuals with pre-diabetes or T2DM have higher than normal CV risk factors. This is probably due to the fact that T2DM and pre-DM share common underlying pathophysiologic disturbances such as insulin resistance [2]. In our study, as expected, participants with IFG had significantly higher BMI, WC, SBP, DBP, TG, total cholesterol, and LDL compared to normoglycemic subjects. Moreover, they were more likely to have HTN and DLP than those with NFG. Similar results are frequently reported in previous studies investigating the presence of CV risk factors in individuals with pre-DM [9, 10, 22].

Aggregation of CV risk factors in individuals with pre-DM is known to place them at higher risk for CV events [10]. In the current study we found that IFG when associated with HTN significantly increased the risk of composite end-point of MACE. This result is in line with the results of some previous studies in which the coexistence of pre-DM and HTN, but not pre-DM without HTN, significantly increased the risk of CVD events [14, 15]. Another study showed that pre-DM defined as IFG or IGT even in the presence of prehypertension, defined as SBP between 120 to 139 or DBP between 80 to 89 mm Hg, significantly increases the risk for CVD events [23]. HTN is a well-known and powerful risk factor for almost all different types of CVD events [24]. Similarly, the current analysis indicated HTN alone in normoglycemic participants is associated with higher HRs for both MACE and all individual components of MACE. The reason why coexistence of pre-DM and HTN, but not pre-DM without HTN, leads to higher CVD events might reflect the fact that both of them induce endothelial dysfunction and inflammation through elevation of inflammatory factors such as tumor necrosis factor α (TNF α) and intercellular adhesion molecule-1 (ICMA-1) [25]. Hence, co-occurrence of HTN, or even pre-HTN, with pre-DM results in higher levels of inflammatory factors and more severe endothelial damage conferring additive risk for subsequent occurrence of composite end-point of MACE.

DLP, characterized by elevated TG, low concentration of HDL, and an increased number of small dense LDL, plays a critical role in acceleration of atherosclerosis and is reported as an important independent risk factor
Several studies have demonstrated that individuals with pre-diabetes have deranged lipid profiles compared to normoglycemic subjects.\textsuperscript{9,22} The frequent association of DLP with pre-DM, which may reflect the underlying insulin resistance, has led to frequent treatment of DLP in the pre-diabetes\textsuperscript{27,28}. Despite the importance of screening and treatment of DLP in individuals with pre-diabetes, we have not found studies that combined pre-DM and DLP together in the analysis for predicting CVD risk. Nevertheless, when we compared the impact of IFG plus DLP with that of NFG without DLP, we found that coexistence of DLP and IFG did not confer any additional risk for development of the composite end-point of MACE. One possible explanation for this finding is that individuals with IFG were more likely to use statin compared to normoglycemic individuals. Nowadays, statin therapy is widely recommended for both primary and secondary prevention of CV disease in a wide range of individuals, even in those without hyperlipidemia\textsuperscript{29,30}. Statins exert their beneficial effects not only through lowering of LDL, but also by improving endothelial function\textsuperscript{31}, reducing vascular inflammation\textsuperscript{30,32}, and exerting antithrombotic actions\textsuperscript{33}.

With regard to the addition of both HTN+DLP to IFG, the present analyses showed an incremental increase in the occurrence of composite end-point of MACE. Although addition of DLP to IFG did not increase the hazard of MACE, co-existence of DLP+HTN increased the hazard for MACE even more than addition of HTN alone to IFG. Our findings support the results of previous studies showing that the risk of CV events associated with co-existence of HTN and DLP, labelled as “lipitation”, is greater than the sum of the CV risks for HTN and DLP alone\textsuperscript{34}. The interaction between these two risk factors occurs at the vascular endothelial level and results in increased oxidative stress and endothelial dysfunction, disproportionate vascular contractility, elevation of BP in dyslipidemic patients, further elevation of BP in hypertensive patients and accelerates the development and progression of atherosclerotic lesions\textsuperscript{35}. A similar finding has been reported in a large recent study conducted among patients with 5-6 year duration of T2DM. The results of this study showed that patients with T2DM who had no CV risk factors had little or no excess risk of CVD events or death compared with general population with no diabetes\textsuperscript{36}. The findings highlight the significance of control of CV risk factors both in patients with pre-DM and T2DM.

Considering the effect of IFG combined with CV risk factors on the individual components of MACE, we found that IFG did not increase the hazard of any of the individual outcomes in the absence of other CV risk factors. Addition of DLP, HTN, or HTN+DLP to IFG was associated with an incremental increase in the hazard of fatal stroke. In addition, IFG combined with HTN alone or HTN+DLP significantly increased the hazard of non-fatal stroke. However, IFG combined with DLP was not associated with an increase in the hazard of non-fatal stroke. The reason why the risk of non-fatal stroke did not increase in such an incremental manner might be due to the beneficial effect of antihypertensive therapy that is shown to prevent the occurrence of non-fatal stroke but not death\textsuperscript{37}. Moreover, the results showed IFG in the presence of HTN or HTN + DLP is associated with an increase in the hazard of fatal MI but not non-fatal MI. However, IFG combined with DLP did not increase the hazard of fatal and non-fatal MI. These inconclusive findings could be due to the small number of events in each group. In addition, further use of statin might protect participants with IFG + DLP from some individual CV events.

This study has several strengths. It is the first study that investigated the impact of IFG combined with HTN, DLP, or HTN + DLP, on the occurrence of MACE. We included an adequately large number of participants without any known CVD at baseline and the study had 99% follow-up of participants. In addition, we adjusted...
for multiple confounding factors including most of the traditional CVD risk factors. Finally, the occurrence of individual CV outcomes, including fatal MI, fatal stroke, non-fatal MI, and non-fatal stroke, was assessed. Weaknesses include the fact that, due to non-availability of 2 h post-prandial blood glucose, the effect of only IFG as a component of pre-diabetes could be examined. Although evidence shows that IFG is useful for screening of pre-diabetes in the general population, use of IGT and HbA1C might be stronger predictors of cardiovascular events [19, 38]. Finally, being a prospective observational study, our findings are subject to confounding factors, and the level of risk factors measured at baseline might have changed during the follow up.

Conclusions

In summary, although IFG, per se, did not increase the hazard of MACE, the association of IFG with HTN or HTN+ DLP conferred a significant hazard of MACE in an incremental manner. These findings support the idea that emphasis should be placed on identification and treatment of multiple CV risk factors in people with pre-diabetes.

Abbreviations

Pre-DM: pre-diabetes; T2DM: type 2 diabetes; IFG: impaired fasting glucose; IGT: impaired glucose tolerance; HTN: hypertension; DLP: dyslipidemia; CV: cardiovascular; CVD: cardiovascular disease; MACE: major adverse cardiovascular events; GCS: Golestan Cohort Study; BMI: body mass index; BP: blood pressure; FBS: fasting blood glucose; TG: triglyceride; HDL: high density lipoprotein; ADA: American Diabetes Association criteria; DBP: diastolic blood pressure; SBP: systolic blood pressure; NFG: normal fasting glucose; WC: waist circumference; LDL: low density lipoprotein.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethical review committees of the Digestive Disease Research Institute of Tehran University of Medical Sciences, the US National Cancer Institute, and the International Agency for Research on Cancer. Before interview, the written informed consent was obtained from each participant.

Consent for publication

Not applicable.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.
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Authors' contributions

M.E.Kh and M.M contributed to study concept and design. N.H.M and M.A.A drafted the manuscript. H.P and M.N, acquired data. R.M and S.G.S contributed to the analysis and interpretation of data. F.I.B critically revised the manuscript. A.Kh contributed to statistical analysis. M.E.Kh is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Tables

Table1 Baseline characteristics of the participants according to the glycemic status.
| Variables          | Total (N=9831) | NFG (N=7421) | IFG (N=2410) | p-value* |
|-------------------|---------------|--------------|--------------|----------|
| Age (yr.)         | 56.0 (0.1)    | 55.8 (0.1)   | 56.7 (0.2)   | 0.000    |
| Sex (%M)          |               |              |              | 0.3      |
| Smoking (%)       |               |              |              | 0.08     |
| Past              | 8.1 %         | 7.8 %        | 8.8 %        |          |
| Current           | 8.9 %         | 9.2 %        | 8.1 %        |          |
| Never             | 83.0 %        | 83.0 %       | 83.1 %       |          |
| Alcohol (%)       | 2.7 %         | 2.7 %        | 2.6 %        | 0.6      |
| Statin (%)        | 2.9 %         | 2.7 %        | 3.7 %        | 0.007    |
| BMI (kg/m²)       | 26.8 (0.1)    | 26.5 (0.1)   | 27.6 (0.1)   | 0.000    |
| WC (cm)           | 93.4 (0.1)    | 92.6 (0.2)   | 96.5 (0.4)   | 0.000    |
| W/H               | 0.43 (0.001)  | 0.43 (0.001) | 0.44 (0.001) | 0.000    |
| SBP (mmHg)        | 124.9 (0.2)   | 123.9 (0.2)  | 128.0 (0.4)  | 0.000    |
| DBP (mmHg)        | 77.2 (0.1)    | 76.8 (0.1)   | 78.4 (0.3)   | 0.000    |
| FBS (mmol/L)      | 5.15 (0.1)    | 4.87 (0.1)   | 6.00 (0.1)   | 0.000    |
| TG (mmol/L)       | 1.49 (0.9)    | 1.43 (1.0)   | 1.64 (1.9)   | 0.000    |
| Chol (mmol/L)     | 5.22 (0.5)    | 5.18 (0.6)   | 5.35 (0.9)   | 0.000    |
| LDL (mmol/L)      | 3.04 (0.6)    | 3.01 (0.7)   | 3.13 (1.0)   | 0.000    |
| HDL (mmol/L)      | 1.59 (0.3)    | 1.58 (0.3)   | 1.59 (0.8)   | 0.7      |
| DLP %             | 4147 (42.2 %) | 2945 (39.7 %)| 1202 (49.9 %)| 0.000    |
| HTN %             | 3642 (37.1 %) | 2578 (34.7 %)| 1064 (44.2 %)| 0.000    |

Data are presented as mean (SE), number (percentage).

* Comparing NFG and IFG groups

BMI; body mass index, WC; waist circumference, W/H; waist to hip ratio, SBP; systolic blood pressure, DBP; diastolic blood pressure, FBS; fasting blood glucose, TG; triglyceride, Chol; cholesterol, LDL; low density lipoprotein, HDL; high density lipoprotein, DLP; dyslipidemia, HTN; hypertension.

**Table 2** Cox regression models predicting MACE according to glycemic status, HTN, and DLP.
| Category       | Unadjusted model | Adjusted model 1 | Adjusted model 2* |
|---------------|-----------------|-----------------|-----------------|
| NFG/-HTN/-DLP | 1.0             | 1.0             | 1.0             |
| NFG/+HTN/+DLP | 2.81 (1.92-4.11) | 2.51 (1.70-3.69) | 2.58 (1.72-3.87) |
|               | P=0.000         | P=0.000         | P=0.000         |
| IFG/-HTN/-DLP | 1.13 (0.64-2.02) | 1.06 (0.59-1.88) | 1.05 (0.59-1.86) |
|               | P=0.6           | P=0.8           | P=0.8           |
| IFG/+HTN/+DLP | 3.24 (2.10-5.01) | 2.77 (1.78-4.32) | 2.85 (1.79-4.54) |
|               | P=0.000         | P=0.000         | P=0.000         |

| Category       | Unadjusted model | Adjusted model 1 | Adjusted model 2** |
|---------------|-----------------|-----------------|-------------------|
| NFG/-HTN      | 1.0             | 1.0             | 1.0               |
| NFG/+HTN      | 3.09 (2.34-4.09) | 2.47 (1.86-3.28) | 2.57 (1.92-3.43) |
|               | P=0.000         | P=0.000         | P=0.000           |
| IFG/-HTN      | 1.22 (0.80-1.89) | 1.18 (0.77-1.82) | 1.19 (0.77-1.84) |
|               | P=0.3           | P=0.4           | P=0.4             |
| IFG/+HTN      | 3.40 (2.43-4.76) | 2.67 (1.90-3.76) | 2.75 (1.93-3.90) |
|               | P=0.000         | P=0.000         | P=0.000           |

| Category       | Unadjusted model | Adjusted model 1 | Adjusted model 2*** |
|---------------|-----------------|-----------------|-------------------|
| NFG/-DLP      | 1.0             | 1.0             | 1.0               |
| NFG/+ DLP     | 0.99 (0.75-1.30) | 1.12 (0.84-1.48) | 1.06 (0.79-1.41) |
|               | P=0.9           | P=0.4           | P=0.6             |
| IFG/-DLP      | 1.18 (0.83-1.67) | 1.09 (0.77-1.55) | 1.05 (0.74-1.50) |
|               | P=0.35          | P=0.6           | P=0.7             |
| IFG/+DLP      | 1.34 (0.96-1.88) | 1.43 (1.01-2.01) | 1.24 (0.88-1.77) |
|               | P=0.08          | P=0.03          | P=0.2             |

**Model 1**: adjusted for age + sex. **Model 2***: adjusted for age + sex + BMI + smoking (Never as reference). **Model 2**: adjusted for age + sex + BMI + DLP + smoking (Never as reference). **Model 2**: adjusted for age + sex + BMI + HTN + smoking (Never as reference). NFG; normal fasting glucose, IFG; impaired fasting glucose, HTN; hypertension, DLP; dyslipidemia.

Table 3 Cox regression models predicting individual components of MACE according to glycemic status, HTN, DLP.
### HR (95% CI) for incident fatal MI

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2* |
|--------------|------------------|------------------|------------------|
| NFG/-HTN/-DLP | 1.0              | 1.0              | 1.0              |
| NFG/+HTN/+DLP | 2.83 (1.50-5.36) | 2.44 (1.28-4.67) | 2.87 (1.44-5.69) |
| P= 0.00      | P= 0.007         | P=0.003          |
| IFG/-HTN/-DLP| 1.25 (0.50-3.15) | 1.17 (0.47-2.93) | 1.20 (0.47-3.01) |
| P= 0.6       | P=0.7            | P=0.6            |
| IFG/+HTN/+DLP| 2.78 (1.29-5.98) | 2.31 (1.06-5.04) | 2.74 (1.20-6.21) |
| P=0.009      | P=0.04           | P=0.01           |

### HR (95% CI) for incident non-fatal MI

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2** |
|--------------|------------------|------------------|-------------------|
| NFG/-HTN/-DLP | 1.0              | 1.0              | 1.0               |
| NFG/+HTN/+DLP | 3.94 (1.68-9.22) | 4.17 (1.75-9.91) | 3.80 (1.51-9.60)  |
| P=0.002      | P=0.001          | P=0.005          |
| IFG/-HTN/-DLP| 0.91 (0.20-4.20) | 0.87 (0.19-4.04) | 0.85 (0.18-3.97)  |
| P=0.9        | P=0.8            | P=0.8            |
| IFG/+HTN/+DLP| 1.18 (0.26-5.48) | 1.25 (0.27-5.88) | 1.12 (0.23-5.46)  |
| P=0.8        | P=0.7            | P=0.9            |

### HR (95% CI) for incident fatal stroke

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2*** |
|--------------|------------------|------------------|---------------------|
| NFG/-HTN/-DLP | 1.0              | 1.0              | 1.0                 |
| NFG/+HTN/+DLP | 2.84 (1.18-6.86) | 2.45 (1.01-5.97) | 2.42 (0.96-6.12)    |
| P= 0.01      | P= 0.05          | P=0.06           |
| IFG/-HTN/-DLP| 1.60 (0.50-5.11) | 1.41 (0.44-4.52) | 1.37 (0.43-4.40)    |
| P=0.4        | P=0.6            | P=0.6            |
| IFG/+HTN/+DLP| 6.43 (2.78-14.88)| 5.20 (2.21-12.24)| 5.13 (2.08-12.63)   |
| P=0.000      | P=0.000          | P=0.000          |

### HR (95% CI) for incident non-fatal stroke

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2*** |
|--------------|------------------|------------------|---------------------|
| NFG/-HTN/-DLP | 1.0              | 1.0              | 1.0                 |
| NFG/+HTN/+DLP | 1.54 (0.65-3.68) | 1.24 (0.51-3.00) | 1.10 (0.44-2.74)    |
| P= 0.3       | P= 0.6           | P=0.8            |
**Model 1**: adjusted for age + sex, **Model 2***: adjusted for age + sex + BMI + smoking (Never as reference). **Model 2**: adjusted for age + sex + BMI + DLP + smoking (Never as reference). **Model 2***: adjusted for age + sex + BMI + HTN + smoking (Never as reference). NFG; normal fasting glucose, IFG; impaired fasting glucose, HTN; hypertension, DLP; dyslipidemia.

**Table 4** Cox regression models predicting individual components of MACE according to glycemic status and HTN.
### HR (95% CI) for incident fatal MI

| Category   | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|------------|------------------|------------------|------------------|
| NFG/-HTN   | 1.0              | 1.0              | 1.0              |
| NFG/+HTN   | 3.02 (1.91-4.80) | 2.37 (1.48-3.79) | 2.56 (1.59-4.13) |
|            | P= 0.000         | P=0.00           | P= 0.000         |
| IFG/-HTN   | 1.41 (0.73-2.77) | 1.37 (0.70-2.67) | 1.41 (0.72-2.76) |
|            | P=0.3            | P=0.4            | P=0.3            |
| IFG/+HTN   | 3.16 (1.79-5.57) | 2.46 (1.39-4.38) | 2.66 (1.48-4.78) |
|            | P=0.000          | P=0.002          | P=0.001          |

### HR (95% CI) for incident non-fatal MI

| Category   | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|------------|------------------|------------------|------------------|
| NFG/-HTN   | 1.0              | 1.0              | 1.0              |
| NFG/+HTN   | 2.65 (1.36-5.19) | 2.66 (1.34-5.28) | 2.59 (1.29-5.22) |
|            | P= 0.004         | P=0.005          | P= 0.008         |
| IFG/-HTN   | 0.72 (0.20-2.47) | 0.71 (0.20-2.46) | 0.70 (0.20-2.44) |
|            | P=0.6            | P=0.6            | P=0.6            |
| IFG/+HTN   | 1.60 (0.58-4.38) | 1.63 (0.58-4.56) | 1.57 (0.56-4.46) |
|            | P=0.4            | P=0.3            | P=0.4            |

### HR (95% CI) for incident fatal stroke

| Category   | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|------------|------------------|------------------|------------------|
| NFG/-HTN   | 1.0              | 1.0              | 1.0              |
| NFG/+HTN   | 3.74 (2.04-6.87) | 2.73 (1.48-5.05) | 2.83 (1.52-5.27) |
|            | P= 0.000         | P=0.001          | P= 0.001         |
| IFG/-HTN   | 2.22 (1.01-4.90) | 2.12 (0.96-4.68) | 2.10 (0.95-4.64) |
|            | P=0.047          | P=0.06           | P=0.07           |
| IFG/+HTN   | 5.06 (2.55-10.01)| 3.63 (1.81-7.26) | 3.72 (1.84-7.55) |
|            | P=0.000          | P=0.000          | P=0.000          |

### HR (95% CI) for incident non-fatal stroke

| Category   | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|------------|------------------|------------------|------------------|
| NFG/-HTN   | 1.0              | 1.0              | 1.0              |
| NFG/+HTN   | 2.49 (1.43-4.36) | 1.83 (1.04-3.22) | 1.87 (1.05-3.33) |
|            | P= 0.001         | P=0.04           | P= 0.03          |
| IFG/-HTN   | 0.65 (0.23-1.90) | 0.64 (0.22-1.84) | 0.63 (0.22-1.83) |
|            | P=0.4            | P=0.4            | P=0.4            |
| IFG/+HTN   | 3.22 (1.67-6.21) | 2.29 (1.18-4.46) | 2.34 (1.18-4.62) |
|            | P=0.000          | P=0.02           | P=0.01           |

Model 1: adjusted for age + sex, Model 2: adjusted for age + sex + BMI + DLP + smoking (Never as reference). MACE major adverse cardiovascular events, NFG; normal fasting glucose, IFG; impaired fasting glucose, HTN; hypertensi DLP; dyslipidemia.

Table 5 Cox regression models predicting individual components of MACE according to glycemic status and DLP.
### HR (95% CI) for incident fatal MI

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|--------------|------------------|------------------|------------------|
| NFG/- DLP    | 1.0              | 1.0              | 1.0              |
| NFG/+DLP     | 1.03 (0.65-1.63) | 1.19 (0.75-1.90) | 1.22 (0.76-1.96) |
|              | P=0.9            | P=0.5            | P=0.4            |
| IFG/- DLP    | 1.29 (0.73-2.29) | 1.20 (0.68-2.12) | 1.20 (0.68-2.13) |
|              | P=0.4            | P=0.5            | P=0.5            |
| IFG/+ DLP    | 1.32 (0.75-2.34) | 1.45 (0.82-2.57) | 1.50 (0.84-2.70) |
|              | P=0.3            | P=0.2            | P=0.2            |

### HR (95% CI) for incident non-fatal MI

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|--------------|------------------|------------------|------------------|
| NFG/- DLP    | 1.0              | 1.0              | 1.0              |
| NFG/+DLP     | 1.81 (0.93-3.53) | 2.01 (1.03-3.92) | 1.91 (0.97-3.78) |
|              | P=0.08           | P=0.04           | P=0.06           |
| IFG/- DLP    | 1.15 (0.42-3.14) | 1.12 (0.41-3.08) | 1.11 (0.41-3.04) |
|              | P=0.8            | P=0.8            | P=0.8            |
| IFG/+ DLP    | 0.70 (0.21-2.42) | 0.77 (0.22-2.66) | 0.72 (0.21-2.52) |
|              | P=0.6            | P=0.7            | P=0.6            |

### HR (95% CI) for incident fatal stroke

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|--------------|------------------|------------------|------------------|
| NFG/- DLP    | 1.0              | 1.0              | 1.0              |
| NFG/+DLP     | 0.79 (0.43-1.45) | 0.95 (0.52-1.75) | 0.99 (0.53-1.84) |
|              | P=0.5            | P=0.9            | P=0.1            |
| IFG/- DLP    | 1.07 (0.51-2.24) | 0.97 (0.46-2.04) | 0.98 (0.46-2.06) |
|              | P=0.9            | P=0.9            | P=0.1            |
| IFG/+ DLP    | 2.17 (1.22-3.88) | 2.40 (1.33-4.31) | 2.47 (1.34-4.53) |
|              | P=0.009          | P=0.003          | P=0.004          |

### HR (95% CI) for incident non-fatal stroke

| Category     | Unadjusted model | Adjusted model 1 | Adjusted model 2 |
|--------------|------------------|------------------|------------------|
| NFG/- DLP    | 1.0              | 1.0              | 1.0              |
| NFG/+DLP     | 0.72 (0.40-1.30) | 0.78 (0.43-1.42) | 0.77 (0.42-1.42) |
|              | P=0.2            | P=0.4            | P=0.4            |
| IFG/- DLP    | 0.76 (0.34-1.72) | 0.71 (0.31-1.59) | 0.69 (0.31-1.56) |
|              | P=0.5            | P=0.4            | P=0.4            |
| IFG/+ DLP    | 1.33 (0.69-2.56) | 1.34 (0.69-2.60) | 1.31 (0.66-2.58) |
|              | P=0.4            | P=0.4            | P=0.4            |

**Model 1**: adjusted for age + sex, **Model 2**: adjusted for age + sex + BMI + HTN + smoking (Never as reference). MACI major adverse cardiovascular events, NFG; normal fasting glucose, IFG; impaired fasting glucose; HTN; hypertension, D dyslipidemia.

**Figures**
Figure 1

The cumulative event-free survival analysis for occurrence of MACE according to (a) glycemic status, HTN, and DLP; (b) glycemic status and HTN; (c) glycemic status and DLP; (d) IFG, HTN, and DLP alone. MACE; major adverse cardiovascular events, NFG; normal fasting glucose, IFG; impaired fasting glucose, HTN; hypertension, DLP; dyslipidemia.