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Impaired fasting glucose, type 2 diabetes mellitus, and lifetime risk of cardiovascular disease among women and men: the Rotterdam Study

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ABSTRACT

Introduction Data on sex-specific lifetime risk of cardiovascular disease (CVD) across the glycemic spectrum, in particular in impaired fasting glucose (IFG) state, are scarce. Whether overweight/obesity modifies the CVD burden also remains unclear.

Research design and methods Using a prospective population-based Rotterdam Study, normoglycemia, IFG, and type 2 diabetes mellitus (T2D) were defined. First incident cases of coronary heart disease, heart failure, and stroke during a follow-up time until January 1, 2015 were identified and formed the composite CVD end point. The remaining lifetime risks of CVD were estimated in each glucose category at 55, 65, 75, and 85 years of age, using a modified version of survival analysis adjusted for the competing risk of death.

Results Among 5698 women and 3803 men free of CVD at baseline, the mean age was 64.5 years (SD 9.6) and 60.0% of participants were women. At age 55 years, the remaining lifetime risk of any CVD event among women was 55.1% (95% CI 48.3 to 61.9) for IFG, compared with 52.7% (95% CI 49.5 to 55.9) for normoglycemia and 61.5% (95% CI 54.7 to 68.3) for T2D. For men, the remaining lifetime risk of any CVD event was 62.1% (95% CI 55.2 to 69.1) for IFG, compared with 59.1% (95% CI 55.5 to 62.7) for normoglycemia and 60.3% (95% CI 53.1 to 67.5) for T2D. At age 55 years, the lifetime risk for incident CVD was higher, although not statistically significant, among women and men with IFG who were overweight or had obesity compared with normal-weight women and men.

Conclusion IFG carried a large lifetime risk for incident CVD among both women and men compared with normoglycemia. In particular among men, the risk was comparable to that of T2D. Overweight/Obesity modifies the risk and conferred a larger burden of lifetime CVD risk among women and men with IFG.

Significance of this study

What is already known about this subject?

- Type 2 diabetes (T2D) is a strong cardiovascular disease (CVD) risk factor. However, the impact of impaired fasting glucose (IFG) on lifetime CVD risk and the possible sex differences in this regard remains unclear. Moreover, whether overweight/obesity modifies the CVD burden across the glycemic spectrum remains unclear.

What are the new findings?

- In a well-designed population-based study with long-term follow-up:
  - The lifetime risk estimate for CVD was high in both women and men with IFG.
  - Notably, the lifetime CVD risk in men with IFG was substantially high and as large as in men with T2D.
  - Overweight/Obesity modified the CVD burden across the glycemic spectrum, particularly in middle-aged women and men with IFG.

How might these results change the focus of research or clinical practice?

- Our results highlight the importance of efficient cardiovascular prevention strategies among middle-aged individuals, particularly men with high-normal glucose levels. We also underscore the poor metabolic profile associated with overweight/obesity, particularly in middle-aged women and men with IFG.

INTRODUCTION

As diabetes develops and progresses toward microvascular and macrovascular complications, treatment becomes more challenging, and the costs dramatically rise.[1] Impaired fasting glucose (IFG), known as prediabetes, is a state of elevated blood glucose level, yet below the threshold of type 2 diabetes mellitus (T2D).[2] IFG is a high-risk state of T2D with a conversion rate of 5%–10% annually.[3] The prevalence rate of IFG is increasing and the worldwide prevalence is estimated to reach 548.4 million in 2045.[1]

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality among individuals with hyperglycemia.[4] Independently from other conventional risk factors, diabetes alone confers about the twofold excess risk for CVD.[5] However, metabolic and physiological

features are dysregulated in individuals with IFG, and traditional CVD risk factors such as obesity, and dyslipidemia become more prevalent among this population.[6] Therefore, the IFG state also carries a considerable risk for CVD.[7] However, large-scale population-based studies addressing the long-term CVD burden across the entire glycemic spectrum are limited.[8 9]

While men are at a larger risk for clinical vascular damages earlier in life, women are more susceptible to age-related vascular changes at midlife.[10] Sex differences are a major contributor to CVD heterogeneity at older ages. However, sex differences in the long-term CVD burden across the entire glycemic spectrum, in particular IFG state, remain unclear. Several studies have shown hyperglycemia associated with long-term CVD risk among men only,[8] while others indicated that the risk for CVD is higher in women.[9] Besides, whether obesity modifies the CVD burden across the glycemic spectrum in women and men remains unclear.

Using data from the large population-based Rotterdam study, we evaluated the 10-year and lifetime risk for incident CVD across the glycemic spectrum among women and men. In particular, we focused on the CVD risk among women and men with IFG. We have previously shown that among the general population and at age 55 years, although men and women have similar lifetime risks of CVD, there are considerable differences in the first manifestation. Men were more likely to develop coronary heart disease (CHD) as a first event, while women were more likely to have a heart failure (HF) or stroke as their first event.[11] Therefore, we evaluated the differences in first manifestations of CVD across different glycemic spectrums. We further studied whether the lifetime CVD burden differed by overweight/obesity status.

METHODS

Study setting

This study is embedded within the framework of the Rotterdam Study, a prospective population-based cohort among participants of European ancestry aged ≥40 years living in the well-defined Ommoord district of Rotterdam, the Netherlands. Initially, in 1990 all inhabitants (n=10 215) aged 55 years or over were invited to participate; 7983 of invitees agreed to participate. In 2000, 3011 participants who had reached the age of 55 years (out of 4472 invitees) were invited to participate in the second cohort. In 2006, a third cohort included inhabitants aged 45 years and older (n=3932), bringing the total study population to 14 926 individuals by the end of 2008. There were no eligibility criteria to enter the Rotterdam Study apart from the minimum age and residential area based on postal codes. The Rotterdam Study has been entered into the Netherlands National Trial Register (NTR; www.trialregister.nl) and into the WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/ictrp/network/primary/en/) under shared catalog number NTR6831. Ninety-eight per cent of participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. The complete design and rationale behind the Rotterdam Study have been described in a separate publication.[12]

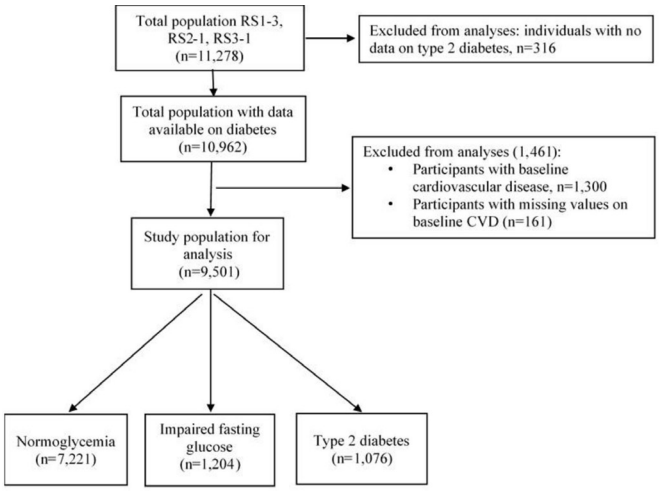

Figure 1 Flow chart for the study population. CVD, cardiovascular disease.

Population for analysis

This study included participants from the third examination of the first cohort (1997–1999), the first examinations of the second (2000–2001) and the third (2006–2008) cohorts. We included participants if they had information on prevalent diabetes status with at least one baseline interview or clinical examination (n=10 962). We excluded prevalent CVD cases at baseline (n=1300), and participants with missing values on prevalent CVD (n=161), eventually including 9501 eligible people for the present analyses. Figure 1 shows the flow chart of the study population.

Baseline measurements

At baseline, information was obtained on individuals' characteristics, health status, medical and medication history, and lifestyle factors. Normoglycemia, IFG, and T2D were defined based on WHO guideline[13]: normoglycemia defined as a fasting blood glucose concentration of 6.0 mmol/L or lower; IFG defined as a fasting blood glucose concentration between 6.1 and 6.9 mmol/L; T2D defined as a fasting blood glucose concentration of 7.0 mmol/L or higher or the use of blood glucose-lowering medications. The American Diabetes Association (ADA) and WHO use different thresholds for defining normoglycemia and IFG. Therefore, due to considerable debate regarding the definition of IFG, as a sensitivity analysis, we also repeated our analyses according to the ADA guideline:[14] normoglycemia defined as a fasting blood glucose concentration below 5.6 mmol/L, IFG defined as a fasting blood glucose concentration between 5.6 and 6.9 mmol/L, and T2D as a fasting blood glucose concentration of 7.0 mmol/L or

higher or the use of blood glucose-lowering medications. Body mass index (BMI) was calculated as body weight (in kg) divided by the square of length (in meters). Overweight/Obesity were defined as BMI ≥25 kg/m^2 versus normal BMI (18.5<BMI<25 kg/m^2). All biochemical variables were assessed in serum samples taken after overnight fasting. Serum glucose (mmol/L concentration was measured using the glucose hexokinase method and insulin concentration by metric assay (Biosource Diagnostics, Camarillo, California, USA). Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or a prescription for an antihypertensive agent. Serum total cholesterol (TC) (mmol/L) and high-density lipoprotein-cholesterol (HDL-c) (mmol/L) were both measured on the COBAS 8000 Modular Analyzer (Roche Diagnostics, Germany).

Follow-up measurements

Follow-up data on vital status and CVD events for all individuals included in the study were available. Outpatient clinic reports, hospital discharge letters, electrocardiograms, and imaging data were collected from general practitioner records and hospital records. Information on vital status was obtained from the central registry of the municipality of the city of Rotterdam. Follow-up started at baseline and individuals were followed until the occurrence of the first incident CVD event; including incident CHD, HF, and stroke, or death or the end of follow-up, January 1, 2015.

Assessment of cardiovascular diseases

Incident CVD was a composite end point that comprised first incident CHD, HF, or stroke. Definitions and procedures on the adjudication of cardiovascular outcomes have been described in detail previously.[15 16] *Incident CHD* was defined as fatal or non-fatal myocardial infarction, surgical or percutaneous coronary revascularisation procedure, or death from CHD. *Incident HF* was defined following the guidelines of the European Society of Cardiology as the combination of typical symptoms and signs, confirmed by objective evidence of cardiac dysfunction or a positive response to initiated treatment. *Incident stroke* was defined according to WHO criteria as a syndrome of rapidly developing clinical signs of focal (or global) disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent origin other than vascular.

Statistical analysis

Data were first assessed visually for normality. We performed descriptive statistics by reporting mean (SD) or median (IQR) for continuous variables and numbers (percentage) for categorical variables. Baseline characteristics in individuals with different levels of baseline serum glucose were compared using the analysis of variance test.

All analyses were performed across different levels of baseline serum glucose including normoglycemia, IFG, and T2D, separately for women and men. Among women and men with normoglycemia, IFG, and T2D, we calculated the remaining lifetime risks for any CVD (first incident of CHD, HF, or stroke) at age 55, 65, 75, and 85 years taking into account competing risks in all calculations of observed risks. The lifetime risk estimates reflect the remaining risk at the indexed age to the age of last observation; in our study maximum age was 105.8 years.

To compare the lifetime risks with the absolute risks in a shorter period, we further calculated a 10-year risk for all outcomes of interest at all index ages. We used a modified version of survival analysis for the calculation of the absolute short and lifetime risks. In this type of analysis, at each age category, the incidence of each CVD outcome is calculated during follow-up.[17] When there is a competing event, the cumulative incidence function (CIF) uses the overall survival function S(t) that counts failures from competing events in addition to the event of interest. By using the overall survival function, CIF bypasses the need to make unverifiable assumptions of independence of censoring on competing events.

To assess the impact of overweight/obesity, the analyses were additionally stratified by BMI (BMI ≥25 kg/m^2 compared with 18.5<BMI<25 kg/m^2).

As a sensitivity analysis, we repeated the analyses based on ADA-defined thresholds to test whether the different thresholds for normoglycemia and IFG according to the ADA guideline influence the results. In another set of sensitivity analyses, individuals on lipid-lowering medications were excluded from the analyses. We also calculated the lifetime risk of any CVD event only among individuals with diabetes on glucose-lowering medication at baseline, as they are a group of patients with a more severe diabetes profile.

We also compared the overall difference of lifetime risk estimates in women and men across glycemic categories and subgroup analyses by the Fine-Gray method based on subhazard distributions.[18] Fine-Gray proposes a proportional hazards model by treating the CIF curve as a subdistribution function.

Missing values on CVD risk factors were imputed using 10-fold multiple imputations. Covariates included in our imputation models were baseline age, sex, prevalent IFG, T2D/glycemic status, first incident outcomes, vital status, hypertension, total cholesterol, HDL-cholesterol, and lipid-lowering medications. We used $p<0.05$ as the significance level. All measures of association are presented with 95% CIs. All analyses were conducted in SPSS software V.26 (IBM SPSS Statistics for Windows, IBM, Armonk, New York, USA) and R statistical software, V.3.6.3.

RESULTS

We used data from 9501 participants of the Rotterdam Study. In total, the mean age of the population was 64.1 years (SD 9.7) and 5698 (60.0%) participants were women. On average, women were older than men. At baseline, the majority had normoglycemia (76.0%), whereas 12.7%

Table 1 Baseline characteristics of women and men in the study population across the glycemic spectrum

	Women (n=5698)			Men (n=3803)		
	Normoglycemia (n=4468)	Impaired fasting glucose (n=634)	Type 2 diabetes mellitus (n=596)	Normoglycemia (n=2753)	Impaired fasting glucose (n=570)	Type 2 diabetes mellitus (n=480)
Age, mean (SD)	63.8 (9.8)	67.0 (9.6)	68.3 (10.3)	62.7 (9.2)	64.1 (8.3)	65.5 (9.0)
BMI, kg/m^2, mean (SD)	26.8 (4.3)	29.0 (5.0)	30.2 (5.2)	26.5 (3.3)	28.0 (3.6)	28.7 (4.4)
Prevalent overweight/obese (BMI ≥25 kg/m^2), n (%)	2777 (62.2)	509 (80.3)	508 (85.2)	1830 (66.5)	468 (82.1)	382 (79.6)
Hypertension,* n (%)	2392 (53.5)	472 (74.4)	479 (80.4)	1499 (54.4)	410 (71.9)	387 (80.1)
Hypertension medication, n (%)	1184 (26.5)	260 (41.0)	315 (52.9)	607 (22.0)	184 (32.3)	215 (44.8)
Total cholesterol, mmol/L, mean (SD)	5.9 (1.0)	5.9 (0.9)	5.7 (1.0)	5.6 (0.9)	5.7 (1.0)	5.3 (1.1)
HDL-cholesterol, mmol/L, mean (SD)	1.6 (0.4)	1.5 (0.4)	1.3 (0.4)	1.3 (0.3)	1.2 (0.3)	1.1 (0.3)
Lipid-lowering medication, n (%)	628 (14.1)	124 (19.6)	139 (23.3)	366 (13.3)	82 (14.4)	128 (26.7)

P values for all cardiovascular risk factors for both women and men were significant at <0.001.
*Hypertension was defined as systolic blood pressure of ≥140 mm Hg and/or diastolic blood pressure of ≥90 mm Hg and/or a current prescription for antihypertensive medication.
BMI, body mass index; HDL, high-density lipoprotein.

had IFG and 11.3% had T2D. Prevalence rates of IFG and T2D were significantly higher among men (15.0% and 12.6%, respectively) compared with women (11.1% and 10.5%, respectively) (table 1). In both women and men, compared with normoglycemia, individuals with IFG or T2D had a more unfavorable CVD risk profile including higher BMI, and a larger proportion of individuals used blood pressure-lowering or lipid-lowering medications.

During a median follow-up of 8.4 years, 1,071 CVD events (18.9 per 1000 person-years (PY)) occurred among women and 910 CVD events (26.0 per 1000 PY) among men. The corresponding numbers of events were 352 for CHD (6.1 per 1000 PY), 489 for HF (8.2 per 1000 PY), and 474 for stroke (8.0 per 1000 PY) among women and 463 for CHD (13.0 per 1000 PY), 323 for HF (8.5 per 1000 PY), and 330 for stroke (8.7 per 1000 PY) among men. CVD mortality rates were almost 8% in both women and men.

As shown in table 2 and figure 2, at age 55 years, the remaining lifetime risk of incident CVD event was 55.1% (95% CI 48.3 to 61.9) for IFG, compared with 52.7% (95% CI 49.5 to 55.9) for normoglycemia, and 61.5% (95% CI 54.7 to 68.3) for T2D in women. Among women, the lifetime risk for CVD was larger among individuals with T2D compared with individuals without diabetes and the difference was statistically significant.

In men, the remaining lifetime risk for incident CVD event was 62.1% (95% CI 55.2 to 69.1) for IFG, compared with 59.1% (95% CI 55.5 to 62.7) for normoglycemia, and 60.3% (95% CI 53.1 to 67.5) for T2D. Among men at 65 years of age, corresponding estimates were 59.4% (95% CI 52.1 to 66.7) for IFG, compared with 55.5% (95% CI 51.7 to 59.4) for normoglycemia, and 56.4% (95% CI 48.9 to 63.9) for T2D. In men, the magnitude of differences in lifetime CVD risk between the three glucose categories was smaller and the risk in men with IFG was as high as men with T2D.

The gradient in cumulative incidence risk of any CVD across the glycemic spectrum event differed by sex. Compared with women, the overall remaining lifetime risk for incident CVD events was higher in men with baseline glucose levels below the threshold of T2D (both normoglycemia and IFG). In both women and men, the cumulative incidence of CVD increased steadily with age (table 2 and figure 2).

Compared with the lifetime risks, the 10-year risk of any CVD events was lower at all glucose spectrums and all the index ages (table 2).

At age 55 years, the lifetime risks of CHD were 18.0% (95% CI 12.8 to 23.1) for IFG, compared with 18.8% (95% CI 16.4 to 21.2) for normoglycemia, and 24.0% (95% CI 18.0 to 30.2) for T2D among women and 30.2% (95% CI 23.7 to 36.6) for IFG, 33.3% (95% CI 29.9 to 36.6) for normoglycemia, and 30.9% (95% CI 24.2 to 37.6) for T2D among men. Compared with women, men were more likely to develop CHD as the first manifestation of CVD across all glucose spectrum (p<0.001).

At age 55 years, the lifetime risks of HF were 32.6% (95% CI 26.4 to 38.9) for IFG, 26.9% (95% CI 24.0 to 29.9) for normoglycemia, and 35.1% (95% CI 28.6 to 41.6) for T2D among women and 31.8% (95% CI 25.2 to 38.5) for IFG, 30.3% (95% CI 26.7 to 33.9) for normoglycemia, and 31.2% (95% CI 25.2 to 37.2) for T2D among men. Among women, there was a clear trend for increasing the remaining lifetime risk of HF from normoglycemia to T2D (p=0.02). This trend did not exist among men.

At age 55 years, the lifetime risks of stroke were 27.5% (95% CI 21.5 to 33.5) for IFG, 25.5% (95% CI 22.8 to 28.2) for normoglycemia, and 33.1% (95% CI 26.4 to 39.8) for T2D among women and 28.2% (95% CI 21.6

Table 2 Remaining lifetime risks vs 10-year risks of first incident cardiovascular disease by glycemic status among women and men

		Normoglycemia		Impaired fasting glucose		Type 2 diabetes	
		Cumulative incidence, % (95% CI)		Cumulative incidence, % (95% CI)		Cumulative incidence, % (95% CI)	
		Women (n=4468)	Men (n=2753)	Women (n=634)	Men (n=570)	Women (n=596)	Men (n=480)
CVD							
N events		740	608	149	147	182	155
Age 55	10 years	47.7 (44.3 to 51.1)	53.9 (50.1 to 57.7)	47.2 (39.9 to 54.4)	56.5 (49.0 to 64.0)	65.3 (58.6 to 72.1)	63.8 (56.9 to 70.7)
	Lifetime	52.7 (49.5 to 55.9)	59.1 (55.5 to 62.7)	55.1 (48.3 to 61.9)	62.1 (55.2 to 69.1)	61.5 (54.7 to 68.3)	60.3 (53.1 to 67.5)
Age 65	10 years	46.6 (43.1 to 50.1)	47.5 (43.3 to 51.8)	45.9 (38.5 to 53.3)	52.5 (44.6 to 60.4)	63.7 (57.3 to 70.1)	57.5 (50.1 to 64.9)
	Lifetime	52.4 (49.2 to 55.7)	55.5 (51.7 to 59.4)	49.9 (48.1 to 61.8)	59.4 (52.1 to 66.7)	61.4 (54.8 to 67.9)	56.4 (48.9 to 63.9)
Age 75	10 years	43.2 (39.2 to 47.2)	39.7 (34.4 to 45.0)	43.0 (34.3 to 51.7)	46.9 (37.0 to 56.7)	58.8 (51.7 to 66.0)	50.2 (41.0 to 59.3)
	Lifetime	50.8 (47.1 to 54.5)	51.3 (46.5 to 56.0)	53.6 (45.5 to 61.7)	56.0 (47.0 to 65.1)	58.1 (50.9 to 65.4)	51.1 (42.0 to 60.3)
Age 85	10 years	37.4 (32.1 to 42.7)	32.8 (23.7 to 41.8)	34.2 (22.9 to 45.4)	36.6 (20.0 to 53.2)	45.9 (35.3 to 56.5)	44.9 (29.0 to 60.8)
	Lifetime	43.9 (38.8 to 49.0)	48.1 (39.9 to 56.3)	49.7 (39.3 to 60.2)	46.0 (29.7 to 62.4)	47.9 (37.5 to 58.4)	45.6 (29.0 to 62.2)
CHD							
N events		238	328	50	65	64	70
Age 55	10 years	16.8 (14.4 to 19.2)	29.3 (26.2 to 32.5)	15.1 (10.4 to 19.7)	25.9 (19.4 to 32.3)	28.7 (22.2 to 35.1)	34.7 (27.8 to 41.6)
	Lifetime	18.8 (16.4 to 21.2)	33.3 (29.9 to 36.6)	18.0 (12.8 to 23.1)	30.2 (23.7 to 36.6)	24.0 (18.0 to 30.2)	30.9 (24.2 to 37.6)
Age 65	10 years	15.5 (13.1 to 17.9)	21.1 (18.2 to 24.1)	13.4 (9.1 to 17.8)	18.9 (13.3 to 24.6)	25.0 (19.3 to 30.8)	27.9 (21.6 to 34.3)
	Lifetime	18.0 (15.6 to 20.4)	27.5 (24.2 to 30.8)	17.6 (12.5 to 22.7)	24.6 (18.7 to 30.6)	21.0 (15.6 to 26.4)	27.1 (20.7 to 33.4)
Age 75	10 years	12.5 (10.0 to 15.0)	13.1 (10.1 to 16.0)	10.4 (6.2 to 14.7)	11.3 (5.8 to 16.9)	19.2 (13.8 to 24.6)	20.8 (14.3 to 27.4)
	Lifetime	15.7 (13.2 to 18.3)	21.2 (17.5 to 24.8)	14.3 (9.0 to 19.6)	18.9 (12.6 to 25.1)	18.0 (12.7 to 23.3)	22.2 (15.5 to 29.0)
Age 85	10 years	9.9 (7.0 to 12.9)	8.0 (4.1 to 12.0)	3.2 (0.1 to 6.3)	6.9 (0.3 to 13.5)	12.6 (6.6 to 18.6)	10.4 (2.4 to 18.3)
	Lifetime	11.8 (8.9 to 14.8)	16.1 (10.8 to 21.5)	11.1 (5.1 to 17.0)	7.5 (1.1 to 13.9)	12.7 (6.6 to 18.8)	14.8 (5.2 to 24.4)
HF							
N events		329	212	76	51	84	60
Age 55	10 years	23.2 (20.3 to 26.1)	24.2 (20.9 to 27.5)	23.8 (18.0 to 29.6)	29.5 (22.9 to 36.1)	35.0 (28.4 to 41.6)	32.9 (26.8 to 39.0)
	Lifetime	26.9 (24.0 to 29.9)	30.3 (26.7 to 33.9)	32.6 (26.4 to 38.9)	31.8 (25.2 to 38.5)	35.1 (28.6 to 41.6)	31.2 (25.2 to 37.2)
Age 65	10 years	22.9 (20.0 to 25.9)	23.2 (19.8 to 26.6)	23.1 (17.3 to 28.9)	28.5 (21.9 to 35.2)	32.9 (26.8 to 39.0)	31.3 (25.4 to 37.3)
	Lifetime	27.2 (24.2 to 30.2)	29.8 (26.1 to 33.6)	32.3 (26.0 to 38.7)	31.0 (24.3 to 37.7)	33.5 (27.4 to 39.6)	30.3 (24.4 to 36.2)
Age 75	10 years	22.0 (18.8 to 25.2)	20.6 (16.8 to 24.4)	22.0 (15.6 to 28.4)	26.8 (19.3 to 34.2)	27.3 (21.2 to 33.4)	30.0 (23.3 to 36.8)
	Lifetime	27.3 (24.0 to 30.6)	28.3 (24.1 to 32.6)	32.5 (25.3 to 39.7)	31.1 (23.6 to 38.7)	29.5 (23.4 to 35.6)	30.5 (23.8 to 37.2)
Age 85	10 years	18.8 (14.8 to 22.8)	18.8 (12.9 to 24.7)	14.8 (7.5 to 22.1)	22.5 (11.1 to 33.8)	18.3 (11.0 to 25.6)	19.9 (10.4 to 29.5)
	Lifetime	23.4 (19.3 to 27.6)	28.9 (22.1 to 35.8)	29.0 (20.1 to 37.8)	28.2 (16.6 to 39.8)	24.2 (16.5 to 31.9)	21.7 (12.0 to 31.4)

Continued

Table 2 Continued

		Normoglycemia		Impaired fasting glucose		Type 2 diabetes	
		Cumulative incidence, % (95% CI)		Cumulative incidence, % (95% CI)		Cumulative incidence, % (95% CI)	
		Women (n=4468)	Men (n=2753)	Women (n=634)	Men (n=570)	Women (n=596)	Men (n=480)
Stroke							
N events		322	213	64	52	88	65
Age 55	10 years	22.7 (20.0 to 25.5)	22.2 (18.8 to 25.5)	23.9 (18.2 to 29.7)	24.8 (18.3 to 31.2)	37.6 (30.1 to 45.2)	30.7 (24.4 to 37.1)
	Lifetime	25.5 (22.8 to 28.2)	24.9 (21.5 to 28.3)	27.5 (21.5 to 33.5)	28.2 (21.6 to 34.8)	33.1 (26.4 to 39.8)	28.7 (22.5 to 34.9)
Age 65	10 years	22.1 (19.4 to 24.5)	20.6 (17.1 to 24.1)	24.5 (18.6 to 30.4)	22.4 (16.5 to 28.3)	33.2 (27.1 to 39.4)	24.0 (18.6 to 29.5)
	Lifetime	25.3 (22.6 to 28.1)	24.2 (20.7 to 27.6)	28.1 (22.0 to 34.2)	26.1 (20.0 to 32.3)	31.7 (25.6 to 37.8)	23.0 (17.6 to 28.4)
Age 75	10 years	20.7 (17.7 to 23.6)	16.7 (12.7 to 20.6)	20.7 (14.4 to 27.0)	19.7 (13.2 to 26.2)	30.8 (24.6 to 37.1)	20.9 (14.9 to 26.8)
	Lifetime	24.0 (21.1 to 27.0)	21.1 (17.1 to 25.0)	24.8 (18.1 to 31.5)	22.4 (15.6 to 29.3)	29.0 (22.8 to 35.2)	21.6 (15.6 to 27.7)
Age 85	10 years	17.3 (13.7 to 20.8)	14.7 (8.5 to 20.9)	17.2 (9. to 24.5)	12.3 (3.6 to 21.1)	24.8 (16.9 to 32.7)	20.2 (10.6 to 29.8)
	Lifetime	18.5 (15.0 to 22.0)	19.9 (13.8 to 26.1)	22.9 (14.9 to 30.9)	16.7 (7.1 to 26.4)	22.8 (15.1 to 30.6)	21.2 (11.2 to 31.1)

CHD, coronary heart disease; CVD, cardiovascular disease; HF, heart failure.

Figure 2 Cumulative incidence of cardiovascular disease defined as the composite end point of coronary heart disease, heart failure, and stroke in individuals aged 55 years, adjusted for the competing risk of death. LTR, the lifetime risk.

to 34.8) for IFG, 24.9% (95% CI 21.5 to 28.3) for normoglycemia, and 28.7% (95% CI 22.5 to 34.9) for T2D among men. Compared with men with T2D, women with diabetes were more likely to develop stroke as the first manifestation of CVD (p<0.001).

Stratification by BMI showed that individuals who were overweight or had obesity had an increased risk of CVD throughout the glucose spectrum. At age 55 years, among IFG category, compared with women (48.5% (95% CI 34.6 to 62.5)) and men (56.9% (95% CI 40.6 to 73.1)) with normal BMI, the lifetime risk of CVD was higher among both women (56.4% (95% CI 48.6 to 64.2) and men (66.1% (95% CI 58.3 to 74.0)) who were overweight or had obesity. The lifetime risk of CVD was statistically significantly the highest among women with T2D who were overweight or had obesity (64.7% (95% CI 57.5 to 71.6)), compared with women with diabetes with normal BMI (42.8% (95% CI 25.5 to 60.1)). In men, the patterns were different in which men with diabetes with normal BMI (75.1% (95% CI 61.5 to 88.8)) compared with men with diabetes who were overweight or had obesity (55.8% (95% CI 47.2 to 64.4)) were more likely to develop CVD events (online supplemental table S1, figures 3 and 4).

When we defined IFG according to the ADA guideline, men with IFG at age 55 years had greater attenuation in remaining lifetime risk for incident CVD event (59.6%

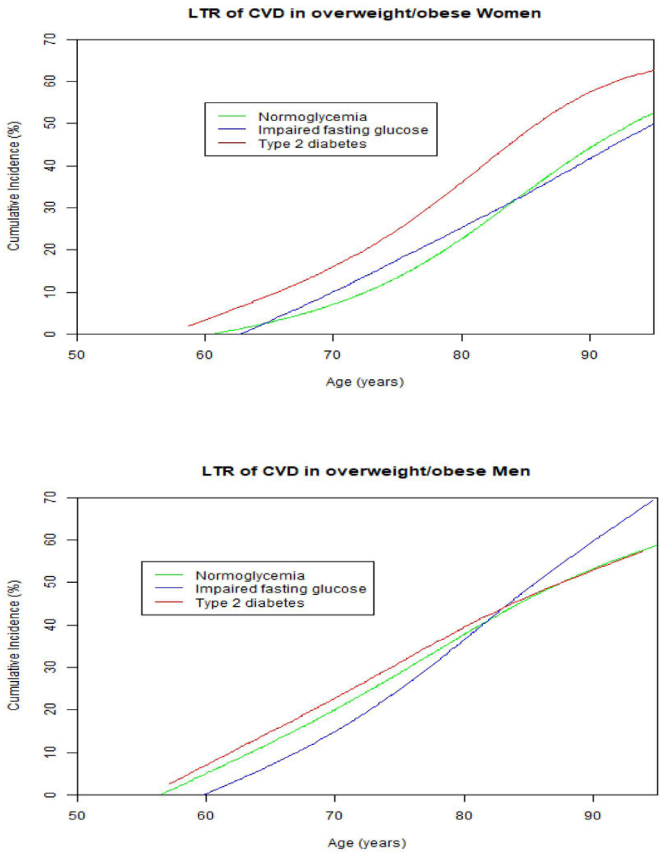

Figure 3 Cumulative incidence of cardiovascular disease defined as the composite end point of coronary heart disease, heart failure, and stroke in individuals aged 55 years, adjusted for the competing risk of death, for women and men who were overweight or had obesity. CVD, cardiovascular disease; LTR, the lifetime risk.

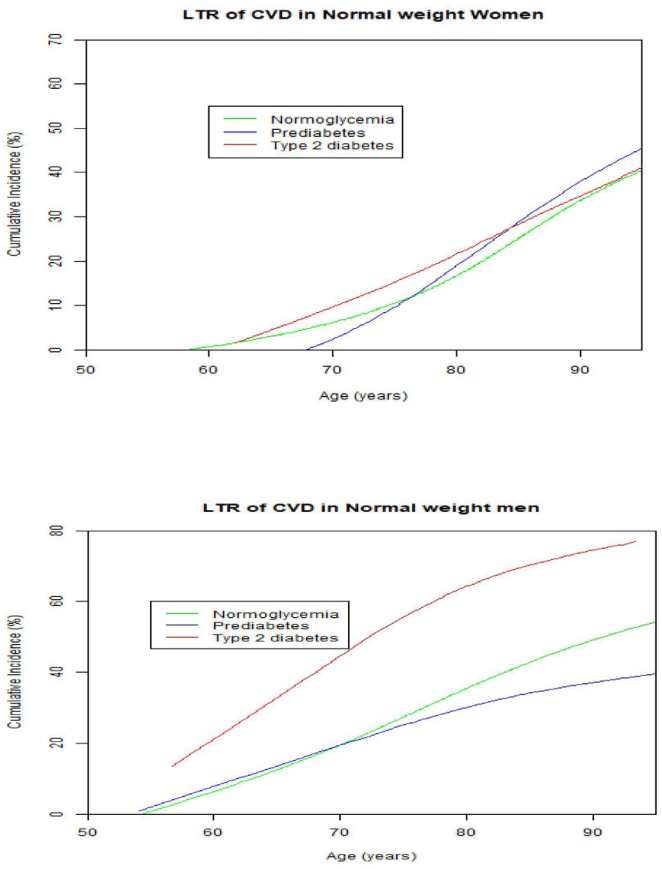

Figure 4 Cumulative incidence of cardiovascular disease defined as the composite end point of coronary heart disease, heart failure, and stroke in individuals aged 55 years, adjusted for the competing risk of death, for women and men with normal weight. CVD, cardiovascular disease; LTR; the lifetime risk.

(95% CI 55.1 to 64.0)) compared with women with IFG (54.5% (95% CI 50.3–58.8)) (online supplemental figure S1). Excluding individuals on lipid-lowering medications did not change the overall picture (data not shown). When the analyses were limited to only individuals with T2D who took glucose-lowering medications at baseline, the remaining lifetime risk of any CVD event at age 55 remained the same (data not shown).

DISCUSSION

In a large well-designed prospective population-based study, IFG at age 55 years carried a large lifetime risk for CVD among both women and men. In particular among men, the remaining lifetime risk of CVD in those with IFG was comparable to that of T2D. At age 55 years, the lifetime risk of any CVD event was higher among individuals with IFG who were overweight or had obesity compared with normal-weight individuals, although not statistically significant.

IFG is a prevalent condition in the general population. In our study, the prevalence rate of IFG was 11% in women and 15% in men. Although several studies have suggested that individuals with IFG are not necessarily at increased risk of CVD,[9 19] it is well established that the initiation and progression of vascular dysfunction occur during the prediabetes stage.[20] Similar to diabetes, IFG coincides with the presence of other common cardiovascular risk factors such as obesity, hypertension, and dyslipidemia. Therefore, individuals with IFG are at high risk of developing CVD outcomes. Several common pathophysiological features underlie the effect of long-term hyperglycemia on vascular damage. Among them, the excess glucose level in the bloodstream may contribute to endothelial dysfunction through an imbalance between endothelium-derived relaxing and contracting factors. NADPH oxidases (NOX) are membrane-bound proteins that catalyze the conversion of oxygen to superoxide particularly under conditions of hyperglycemia. It has been well established that endothelial dysfunction contributes to the onset of CVD.[21]

In our study, at age 55 years, IFG carried a large lifetime risk for CVD particularly among men that were comparable to that of T2D. In line with our findings, in the Koran Heart Study including 408 022 individuals, a greater CVD risk has been associated with IFG only in men.[22] While a previous meta-analysis of 29 prospective studies (n=1 94 658) in 2004 and the Framingham Heart Study (n=4058) in 2008 have reported a greater CVD risk

only in women.[23 24] Similar CVD risks for women and men (n=237 468) have been reported in the Asia Pacific region.[25] Levels of cardiovascular risk factors have been shown to differ between normoglycemic women and men before the conversion to prediabetes and, eventually, diabetes.[26 27] Sex differences might, at least partly, be explained by sex-specific patterns in the management of hypertension and dyslipidemia. In our study, men compared with women with IFG, had lower proportions of antihypertensive (34% vs 44%) and lipid-lowering (14% vs 20%) medication use. Controlling blood pressure and lipid levels is widely recommended to prevent vascular risk in individuals with hyperglycaemia. Our findings, together with previous results, raise a question of whether sex differences in CVD burden associated with IFG are due to biological differences (eg, sex hormones), or are driven by a coincidence of several metabolic and behavioral risk factors (eg, BMI and physical activity) than sex-differences per se.

The lifetime risk at age 55 years for developing CVD among individuals with T2D was 62% for women and 60% for men through 106 years of age (in our study maximum age was almost 106 years). In line with our study, the Framingham Heart Study showed a greater risk of developing CVD among individuals with diabetes: 57% for women and 67% for men through 95 years of age.[28] However, in a recent study performed in seven observational cohorts of US black and white men and women, the reported risk was almost 20% lower compared with our results.[8] Different CVD risk estimates might be due to several factors including demographic differences in participants included in these studies. In particular different cardiovascular risk profiles at baseline, different practices to treat cardiovascular risk factors or more effective prevention of CVD outcomes, varying definitions of CVD events, and CVD burden in different populations, as well as the different durations of follow-up. Additionally, different methods of assessing glucose levels such as fasting glucose or glycosylated hemoglobin A_{1c} level (HbA_{1c}) may have contributed to the heterogeneous results so far.[29] Of note, most of the studies, including the previous study by Bancks *et al*,[8] have not included HF as an outcome. Several previous studies have reported that the risk of HF in patients with T2D is more than twice compared with individuals free of diabetes. In our study, the lifetime risk of HF was significantly higher among individuals with IFG and T2D compared with normoglycemic individuals. The increased risk for HF in patients with hyperglycemia could partly be explained by shared risk factors such as age, obesity, dyslipidemia, and hypertension.[30]

The 10-year risk of any CVD events was lower at all glucose spectrums and all the index ages when compared with the lifetime risks. The 10-year risk corresponds to the risk for an individual to develop CVD in the coming 10 years while lifetime risk for an individual is the risk to develop CVD for the remaining of his/her lifespan and thus over a longer course than 10 years.

Overweight/obesity modifies the CVD risk in which women and men with IFG who were overweight or had obesity had a greater lifetime risk of CVD compared with their counterparts with normal BMI. Our study also revealed that women with T2D who were overweight or had obesity had a higher lifetime risk of CVD compared with women with diabetes with normal BMI. This implies that the risk of cardiovascular complications associated with hyperglycemia could partly be driven by overweight/obesity. Moreover, despite that the lifetime risk of CVD among men with IFG who were overweight or had obesity was higher than women with IFG (66% vs 56%), this risk was higher in women with T2D than their men counterparts (65% vs 56%). Different risk profiles in women and men could be due to physiological differences between women and men including the levels of subcutaneous fat storage, hormonal, or genetic differences.[27] A higher risk of CVD that we observed in women with T2D compared with men with T2D may be the result of greater deterioration in cardiovascular risk profile in women with diabetes.[31] Women need to attain a larger average BMI to be diagnosed with T2D.[27] Therefore, compared with men, women with diabetes might require a greater metabolic deterioration to develop CVD. Better management of hyperglycemia through sex-tailored or gender-tailored lifestyle or pharmacological interventions helps to modify BMI, which can eventually be used as an effective tool to prevent both IFG and T2D and their complications. Previous studies suggest that lifestyle interventions result in significant improvements in reducing CVD risk,[32] particularly in women.[33]

Strengths and limitations

This study has some strengths and limitations. The population-based nature, the large sample size, long-term follow-up, and the availability of detailed data on various forms of cardiovascular events, as well as cardiovascular risk factors, are among the strengths of our study. However, the limitations of our study also merit attention. To categorize the status of IFG and T2D, HbA_{1c} measurement was not available, and we used fasting serum glucose measurements which may have led to some misclassification of T2D. However, our findings indicated that fasting glucose level, even in the non-diabetic range, could be a marker of CVD risk. Moreover, the measurements of fasting blood glucose were at baseline, which could have led to participants' misclassification during follow-up. Our results regarding the magnitude of the differences between women and men in several categories did not reach statistical significance. This might be due to the relatively small sample size of individuals with IFG and T2D and therefore limited statistical power to detect the potential sex differences. Furthermore, to estimate the impact of BMI on the lifetime risk of CVD, we used anthropometric data at baseline. This may lead to some misclassifications as BMI tends to change with age. Finally, as nearly all the Rotterdam Study participants are

from European ancestry, our results may not be generalizable to other ethnicities.

Conclusion

Our results underscore the importance of cardiovascular risk assessment across the glycemic spectrum particularly among individuals with IFG. Our study suggests that guideline recommendations to prevent CVD need to go beyond the diabetes status and also consider the high risk of CVD in the prediabetes stage, in particular among middle-aged men. Future studies are warranted to investigate the sex-specific impact of modifiable cardiovascular risk factors over time and their preventive implications for women and men.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The Rotterdam Study has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare, and Sport (Population Screening Act WBO, license number 1071272-159521-PG).

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