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J-shaped association between plasma glucose concentration and cardiovascular disease mortality over a follow-up of 32 years

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Abstract: **OBJECTIVE:** We aimed at examining the association between plasma glucose (PG) concentration and cardiovascular mortality in a population sample from Switzerland over a follow-up time of 32 years. **METHODS:** We analyzed 7984 men and women enrolled in the first National Research Program (NRP1A, 1977-1979) and followed up for survival until 2008. Mortality hazard ratios (HR) were calculated using adjusted Cox regression models. PG was measured in fasting state or randomly with known fasting time. Models were adjusted for age, sex, socio-demographic, lifestyle and cardiovascular risk factors. **RESULTS:** PG concentrations ≥ 6.1 mmol/L were associated with increased risk of cardiovascular disease (CVD) and all-cause mortality. Compared to normal PG (3.8-4.9 mmol/L) the adjusted HR (95% CI) for CVD mortality was 1.26 (1.01-1.58) for PG ≥ 6.1 -6.9 mmol/L, 1.56 (1.18-2.06) for PG ≥ 7 mmol/L, 1.67 (1.22-2.30) for known diabetes. All-cause mortality essentially showed the same patterns. All-cause mortality was increased [HR (95% CI): 1.35 (1.01-1.80)] also for PG < 3.8 mmol/L. **CONCLUSION:** Plasma glucose remained significantly and independently associated with CVD mortality even after full follow-up. The relationship was J-shaped. In order to prevent premature death, persons with abnormal PG concentrations on both extremes should be screened and counseled for other CVD risk factors.

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J-shaped association between plasma glucose concentration and cardiovascular disease mortality over a follow-up of 32 years

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Abstract

Objective: We aimed at examining the association between plasma glucose (PG) concentration and cardiovascular mortality in a population sample from Switzerland over a follow-up time of 32 years.

Methods: We analyzed 7,984 men and women enrolled in the first National Research Program (NRP1A, 1977–1979) and followed up for survival until 2008. Mortality hazard ratios (HR) were calculated using adjusted Cox regression models. PG was measured in fasting state or randomly with known fasting time. Models were adjusted for age, sex, socio-demographic, lifestyle and cardiovascular risk factors.

Results: PG concentrations ≥ 6.1 mmol/L were associated with increased risk of cardiovascular disease (CVD) and all-cause mortality. Compared to normal PG (3.8–4.9 mmol/L) the adjusted HR (95% CI) for CVD mortality was 1.26 (1.01–1.58) for PG ≥ 6.1 –6.9 mmol/L, 1.56 (1.18–2.06) for PG ≥ 7 mmol/L, 1.67 (1.22–2.30) for known diabetes. All-cause mortality essentially showed the same patterns. All-cause mortality was increased [HR (95% CI): 1.35 (1.01–1.80)] also for PG < 3.8 mmol/L.

Conclusion: Plasma glucose remained significantly and independently associated with CVD mortality even after full follow-up. The relationship was J-shaped. In order to prevent premature death, persons with abnormal PG concentrations on both extremes should be screened and counselled for other CVD risk factors.

Introduction

The worldwide prevalence of diabetes mellitus is increasing rapidly (Danaei et al., 2011; Whiting et al., 2011; Wild et al., 2004). Diabetes is associated with increased risk of cardiovascular disease (CVD) and all-cause mortality (Sarwar et al., 2010; Seshasai et al., 2011) but there may be an increased risk below the glycemic threshold for the diagnosis of diabetes (fasting plasma glucose ≥ 7 mmol/L) (Balkau et al., 2004; Barr et al., 2007; Danaei et al., 2006; Sarwar et al., 2010). The association between plasma glucose (PG) and mortality has been examined previously, however, most studies had a relatively short follow-up (Balkau et al., 2004; Barr et al., 2007; Sarwar et al., 2010). The few studies with longer follow-up time were nearly all restricted, e.g. regarding age, sex or specific population groups (Balkau et al., 1998; Batty et al., 2008; Brunner et al., 2006).

Information from a general population about the long-term consequences of a specific PG concentration would be valuable. It would enable practitioners and public health authorities to define risk groups in order to prevent premature disease and death. Our aim was to examine the association between a single PG measurement and all-cause and cause-specific mortality over a follow-up time of 32 years in a general population sample from Switzerland while considering factors potentially modifying / confounding this relationship. In Switzerland, mortality (in particular CVD mortality) has substantially decreased over the past three decades, resulting in relatively low rates compared to other countries (OECD, 2011; Berrut et al., 2008; Wang et al., 2013). In contrast, the prevalence of major CVD risk factors remained relatively stable or only slightly declined, but is still lower than in most other countries (OECD, 2011; Finucane et al., 2011). The prevalence of diabetes is comparably low, but still increasing in Switzerland (OECD, 2011), particularly among men (Bopp et al., 2011).

Methods

Study population

The National Research Program 1A (NRP 1A) was a community health promotion initiative focused on CVD prevention conducted between 1977 and 1979 in Switzerland. A drawn sample of 4,386 participants was recruited and 4,245 additional persons participated spontaneously. Age at baseline ranged 16-92 years. Participants attended a health examination, including fasting or non-fasting plasma sampling and completed a detailed self-administered questionnaire [for details see (Gutzwiller et al., 1985)]. We obtained mortality follow-up by anonymously linking the NRP 1A data with the Swiss National Cohort (SNC) (Bopp et al., 2012). The SNC encompasses all residents of Switzerland enumerated in the

national 1990 or 2000 censuses as well as data from death and emigration registries (Bopp et al., 2009). Overall 8,008 out of 8,631 original participants (92.8%) could be linked, loss to follow-up between 1980 and 2000 was 5.8%. Median follow-up was 30.8 years (IQR: 22.4 – 31.1 years, 95th centile: 31.2 years). In total 1,234 men and 1,193 women died, of whom 471 and 466, respectively, from CVD (Bopp et al., 2012). Since there was no census at the end of the observation period, loss to follow-up after the 2000 census could not be determined, i.e. all 5,019 individuals linked to the 2000 census but not to a succeeding death or emigration record were assumed to have survived (Bopp et al., 2012). After exclusion of 17 persons with missing glucose measurement and 7 persons younger than 16 years the study population comprised 7,984 individuals.

Exposure and outcome

Blood sampling and measurements were described in detail (Gutzwiller et al., 1985). Briefly, 5ml of blood were sampled and centrifuged immediately thereafter for 10 min at 3000 rpm. Plasma samples were kept at 4° C and sent within 24 h to a laboratory in Bern where they were analyzed with a Greiner Electronic Selective Analyzer (GSA) II. The results of the internal and external quality control were excellent (day-to-day variability based on the lowest age-specific variance was 1.78% and 2.7%) (Gutzwiller et al., 1985). Some samples were not taken in fasting state. However, exact times of sampling and of last meal were reported (see below). PG concentrations were categorized according to the American Diabetes Association (American Diabetes Association, 2010): impaired fasting glucose (IFG)1: 5.6-6.0 mmol/L; IFG2: 6.1-6.9 mmol/L; Diabetes (DM, first diagnosed): ≥ 7 mmol/L. Known diabetes (KDM, self-report, n=203) was categorized separately. In order to determine the shape of the association between PG and mortality, we plotted multinodal spline models. Based on this we further categorized into: low fasting glucose (LFG): < 3.8 mmol/L; normal fasting glucose (NFG)1: 3.8-4.9 mmol/L; NFG2: 5.0-5.5 mmol/L. Fasting time was the time between blood sampling and the previous meal. In sensitivity analyses, inclusion of this variable showed no significant impact on the association between PG and mortality. We nevertheless included fasting time in all our models. Out of a wide range of available variables we selected (criteria see below) the following covariates: 1) socio-demographic parameters: town of residence (Aarau, Solothurn, Nyon, Vevey and Lugano), marital status (single, married, widowed and separated or divorced); 2) proxies for a healthy lifestyle: eating pattern “three main meals per day”, a score for physical activity (for details see (Faeh et al., 2011)); 3) CVD risk factors: systolic blood pressure (mmHg, mean of four measurements), total serum cholesterol (mmol/L), body mass index (BMI = measured weight [kg] divided by square of measured height [m^2]), smoking (number of cigarettes per

day). CVD risk factors were included as continuous variables in the models. For stratification (Figure 3) we defined hypertension as blood pressure ≥ 90 mmHg (diastolic) and/or ≥ 140 mmHg (systolic); high cholesterol as total cholesterol ≥ 6.2 mmol/L; overweight as BMI ≥ 25 kg/m²; current smokers as smoking ≥ 1 cigarette / day. Mortality was defined according to the International Classification of Diseases revisions 8 and 10 [ICD-8, ICD-10, (World Health Organization, 2012)]: CVD deaths were defined as ICD-8: 390-458 (until 1994) and ICD-10: I00-I99 (thereafter), cancer death was defined as ICD-8: 140-239 and ICD-10: C00-D48 (Swiss Federal Statistical Office, 2012).

Statistical analyses

For descriptive analyses, we calculated counts, means, and proportions of the variables of interest (Table 1). Mortality rates by sex were age-standardized with the direct method to the World Health Organization's European standard age structure. Trends (p- and z-value) for continuous variables were calculated using the STATA "nptrend" command and for categorical variables using Chi² tests. Kaplan Meier survival curves for different glucose categories were computed (Figure 1). In order to estimate the influence of the glucose concentration on survival time, hazard ratios (HR) and 95% CI were calculated using different Cox regression models, including an increasing number of covariates (Table 2). In order to render all models comparable, individuals with missing values in any of the covariates were excluded from these analyses. We used three models with additive adjustment with the covariates described above [1)-3)]. The reference category was NFG1. All models were performed separately by sex and for all-cause and CVD deaths. Selection of covariates was based on sensitivity analyses using Akaike's information criterion (AIC) and the Bayesian information criterion (BIC). Thereby other potential confounders like mode of participation (sampled versus spontaneous participation), nationality and educational classes could be omitted. To obtain more statistical power for the investigation of an association between the lower ranges of PG and mortality, we pooled sexes. In sensitivity analyses, deaths occurred within the first 5 years were omitted in order to reduce the probability of reversed causality (i.e. the reason of death being an underlying disease also leading to high or low glucose concentrations). We also performed sensitivity analyses by age group (16-39, 40-64, ≥ 65 years) and follow-up time (5, 10, 15, 20, 25, 30 years) (see Appendices). Analyses were performed with Stata 10.1 (Stata Corp, Texas, USA; 2009).

Results

The descriptive Table 1 shows the participants' characteristics. In men, mean PG was higher than in women. About two third of participants were in the normal glucose categories.

Compared to women, proportionally fewer men were in the low glucose category and more in the high glucose categories. The prevalence of diabetes was higher in men. Besides total cholesterol, the prevalence of CVD risk factors was generally higher in men than in women: the prevalence of high blood pressure, overweight and current smoking was substantially higher.

For comparability reasons 184 participants had to be excluded from the analyses due to missing values in the respective covariates, resulting in 7,800 participants (3,607 men and 4,193 women). Over all categories the means for age, systolic blood pressure, total cholesterol and BMI and the proportions for deaths, high blood pressure and overweight increased gradually with increasing glucose categories (Details see Appendices Table A1). Trend tests showed a significant association between PG concentration and most covariates (see Appendices Table A2). Kaplan-Meier survival curves by glucose category were continuously diverging. In women the span between normal glucose and diabetic categories appeared to become broader than in men (Figure 1). The results of three Cox regression models including PG as continuous variable are listed in Table 2. After adjustment for socio-demographic, lifestyle and CVD risk factors, the HR of PG remained practically the same and statistically significant for all-cause and CVD mortality in men and in women. Age, cholesterol, systolic blood pressure and smoking also had a significant influence on CVD mortality. Over 32 years of follow-up, J-shaped risk curves were found for the relationship between glucose categories and mortality (Figure 2). In men, the risk was elevated only for those with known diabetes, whereas in women elevated HRs were already found for concentrations above 5.6 mmol/L (for details see Appendices Table A3). Also, PG <3.8 mmol/L was associated with higher mortality risk for all causes [HR (95% CI) 1.35 (1.01-1.80)] (Details see Appendices Table A4 and Figure A5). In separate sensitivity analyses with additional adjustment for alcohol consumption (in grams per day) and for chronic CVD (self reported) the HR for LFG remained virtually unchanged. The association between PG and mortality did not differ significantly between age groups (see Appendices Table A6).

Differences between persons with versus without single selected CVD risk factors are shown in Figure 3. Current smokers tended to have constantly higher HRs over all glucose categories than non-smokers. However, HR curves tended to deviate in the extreme categories. Persons with hypertension tended to be more at risk than those with normal blood pressure over all glucose categories except the lowest. No differences were found for high versus normal cholesterol and overweight versus normal weight.

Discussion

In this population from Switzerland, PG was independently associated with mortality over a follow-up period of 32 years. The general pattern was the same in men and women and in different age groups. The glucose-mortality relationship was J-shaped with optimum glucose concentrations ranging 3.8-4.9 mmol/L. Premature CVD mortality mainly determined this pattern. Persons with low glucose concentrations (LFG, <3.8 mmol/L) also tended to have an increased risk, which was predominantly not due to pre-existing conditions.

A dose-response relationship between PG and all-cause and/or CVD mortality was reported previously mostly as J-shape curve or linear slope (Balkau et al., 1999, 2004, 1998; Barr et al., 2007; Batty et al., 2008; Brunner et al., 2006; Wei et al., 2000). Our J-shaped curves correspond best to results of studies including low glucose concentrations as a separate category (Wandell and Theobald, 2005, 2007). A meta-analysis of 38 studies (Levitan et al., 2004) showed similar results regardless of type of PG assessment. DM (≥ 7 mmol/L) as a known CVD risk factor (Expert committee, 2003; World Health Organization, 2006) and PG concentrations below the threshold showed elevated risks in most studies (Balkau et al., 1999, 2004, 1998; Barr et al., 2007; Batty et al., 2008; Brunner et al., 2006; Wei et al., 2000). There were, however, inconsistencies regarding the cutoff for IFG: 6.1 mmol/L (Balkau et al., 2004; Brunner et al., 2006; Sorkin et al., 2005) or 5.6 mmol/L (Levitzky et al., 2008; Seshasai et al., 2011). Our results support previous findings suggesting lower thresholds for risk increase in women (IFG) than in men (DM) (Balkau et al., 2004; Levitzky et al., 2008). In line with our study, in the WOSCOPS study (Preiss et al., 2010) (15 year-follow-up), the association between non-diabetic glucose concentrations and long-term mortality was not significant in men. In contrast, the Whitehall study (Brunner et al., 2006) (33 year-follow-up) reported an elevated CVD mortality among 40-64 year old male civil servants. The different results may, however, only be due to differences in power. In fact, in our study there was a tendency for higher mortality differentials in women. In line with ours, most studies reported higher mortality risks (up to two-fold) associated with increased PG in women than in men (Levitan et al., 2004). Our findings also support the concept of using a lower cutoff for IFG for women (Levitzky et al., 2008).

Adjustment for all 4 other CVD risk factors may result in over-adjustment and in underestimation of the risk. Although full adjustment attenuated the estimates, it didn't outweigh the relationship in our, as well as in most studies adjusting for two or more CVD risk factors (Balkau et al., 2004; Brunner et al., 2006; Seshasai et al., 2011; Wandell and Theobald, 2005; DECODE study group, 2003). Similarly to others, adjustment for smoking had the strongest impact, followed by hypertension. In our analyses, total cholesterol

appeared to have a somewhat opposite effect: as a risk factor in men and as a protective factor in women (Table 2). Compared to the other risk factors, smoking appeared to be more independent from the effect of blood glucose on CVD mortality (Figure 3). In contrast, blood pressure and particularly cholesterol and BMI added only little to the explanation of CVD risk associated with PG, which partially corroborates the concept of the metabolic syndrome (Huang, 2009).

Similarly to our results, other studies considering low glucose concentrations also reported a J-shaped glucose-mortality-relationship (Expert Committee, 2003; Wandell and Theobald, 2007; Wei et al., 2000). Interestingly, increased mortality risk among persons with LFG was mainly due to current smokers and overweight / obese persons (Figure 3). In line with others (Wandell and Theobald, 2005, 2007), we found no indication that persons with LFG died because of pre-existing disease (reversed causality) or because of hazardous alcohol consumption. The LFG mortality relationship remained significant over almost the entire follow-up period and only minimally changed after exclusion of the first five years. This was also the case for persons with higher than normal PG, although, as shown by another study (Preis et al., 2009), the strengths of the relationship weakened over time.

Our study had several limitations. PG and the other CVD risk factors were assessed only once at baseline. Thus, we have no follow-up information on exposure. PG was measured partially as a random, non-fasting sample. Even if fasting time is known and adjusted for, the validity of the results is lower than in studies using a standardized PG measurement.

However, studies using a non-fasting sample show similar associations between PG and mortality (Levitan et al., 2004). In fact, sensitivity analyses showed no remarkable impact from the exclusions of persons having reported a meal within 2 hours before blood sampling. Although this had virtually no effect, we adjusted all our models by fasting time. However, HbA1c may be a better predictor of CVD and all-cause mortality than PG, also because it can be measured and interpreted independently of fasting state (Faeh et al., 2013).

Unfortunately, HbA1c was not available at the time the study was conducted. Furthermore, chronic kidney disease as another known CVD risk factor could not be included in the models as no renal marker was measured. Renal markers should be considered as predictive factors when planning interventions (Athiros et al., 2011; Malyszko and Banach, 2013). Participants of the NRP 1A study were presumably healthier compared to the general population (Bopp et al., 2010). Some of the original study participants could not be linked (7.2%), emigrated (2.7%) or were lost to follow-up (3.8%) (Bopp et al., 2012). However, even on the long run, this proportion remains rather modest. Our end-point was limited in the sense that we were restricted to fatal CVD besides all-cause death. CVD mortality data from

death certificates is reliable for young and middle aged persons but may be prone to misclassification in the elderly (Lloyd-Jones et al., 1998).

Conclusion

A single PG measurement remained significantly associated with CVD mortality over a follow-up time of 32 years and after adjustment for other CVD risk factors. While risk mechanisms among persons with increased glucose concentrations are quite well known, those of individuals with particularly low glucose concentrations remain to be elucidated. Our results suggest that persons at both extremes should be screened and counselled for other risk factors such as smoking or high blood pressure in order to prevent premature death.

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Tables

Table 1. Characteristics of 7,984 participants of NRP 1A, for all and by sex, Switzerland 1977-1979, 16-92 years at baseline

	Men	Women	All
Participants (n)	3683	4301	7984
Participants (% of all)	46.1	53.9	100
Age (mean, years)	42.1	43.5	42.8
Follow-up (mean, years)	25.0	26.5	25.8
median (5%-95%, years)	30.8 (5.4-31.2)	30.8 (9.1-31.2)	30.8 (7.1-31.2)
Mortality			
All-cause (counts)	1230	1192	2422
All-cause (% of total n, by sex)	33.4	27.7	30.3
CVD (counts)	469	465	934
CVD (% of total n, by sex)	12.7	10.8	11.7
Cancer (counts)	379	358	737
Cancer (% of total n, by sex)	10.3	8.3	9.2
Plasma glucose (mean, mmol/L)	5.46	5.24	5.34
LFG (<3.8 mmol/L, %)	1.9	2.9	2.4
NFG1 (3.8-4.9 mmol/L, %)	27.0	35.7	31.7
NFG2 (5.0-5.5 mmol/L, %)	33.8	31.6	32.6
IFG1 (5.6-6.0 mmol/L, %)	19.1	16.0	17.4
IFG2 (6.1-6.9 mmol/L, %)	10.6	8.4	9.4
Diabetes (≥7.0 mmol/L, %)	4.8	3.1	3.9
Known diabetes (%)	3.0	2.4	2.7
Fasting time (h, mean, 125 missings)	4.4	4.1	4.2
Fasting <2h (% of total n, by sex)	24.9	22.7	23.7
Smoking			
Current smokers (≥1 cig/d, %)	36.5	25.8	30.8
Number of cigarettes (per day, mean, smokers only)	18.0	12.7	15.6
Blood pressure (mmHg)			
Mean systolic blood pressure	130	125	127
≥140/≥90 (systolic/diastolic, %)	27.8	20.9	24.1
Total cholesterol			
Mean serum cholesterol (mmol/L)	5.9	6.0	5.9
>6.2mmol/l (%)	26.5	28.3	27.5
Body mass index (2 missings)			
Mean BMI (kg/m ²)	24.8	23.4	24.1
Overweight & obesity (≥25, %)	44.8	27.9	35.7
Lifestyle			
Physical activity score (0-8, mean, 41 missings)	3.8	3.4	3.6
Three main meals per day (% , 23 missings)	65.8	73.7	70.1
Marital status (1 missing)			
Single (%)	21.1	21.3	21.2
Married (%)	73.9	65.7	69.5
Widowed (%)	1.4	8.1	5.0
Divorced or separated (%)	3.6	4.9	4.3

Table 2. Adjusted hazard ratios for all-cause and CVD mortality by plasma glucose and sex

	All-cause mortality					CVD mortality				
	Model 1		Model 2	Model 3		Model 1		Model 2	Model 3	
	HR	(95% CI)	HR	HR	(95% CI)	HR	(95% CI)	HR	HR	(95% CI)
Men (n=3607)										
Glucose per mmol/L)	1.06	(1.03-1.10)	1.05	1.05	(1.01-1.09)	1.08	(1.03-1.14)	1.07	1.06	(1.00-1.12)
Age (per year)	1.09	(1.09-1.10)	1.10	1.10	(1.09-1.10)	1.13	(1.12-1.14)	1.14	1.13	(1.12-1.15)
Fasting time (per h)	1.00	(0.98-1.02)	0.99	0.99	(0.97-1.01)	1.01	(0.98-1.03)	1.00	1.00	(0.97-1.02)
Married			1	1				1	1	
Widowed			1.41	1.32	(0.97-1.79)			1.48	1.47	(0.97-2.22)
Divorced or separated			1.17	1.06	(0.79-1.42)			1.21	1.14	(0.70-1.83)
Single			1.45	1.44	(1.19-1.74)			1.30	1.29	(0.91-1.82)
Physical activity score (per point)			0.93	0.95	(0.92-0.98)			0.93	0.95	(0.90-1.01)
Three main meals per day			0.80	0.87	(0.76-1.00)			0.77	0.98	(0.70-1.14)
BMI (per kg/m ²)				1.01	(0.99-1.03)				1.02	(0.99-1.05)
Cholesterol (per mmol/L)				0.98	(0.90-1.07)				1.18	(1.03-1.35)
Systolic blood pressure (per mmHg)				1.01	(1.01-1.01)				1.01	(1.01-1.02)
Smoking (per cig/day)				1.03	(1.02-1.03)				1.03	(1.02-1.04)
Women (n=4193)										
Glucose per mmol/L)	1.10	(1.06-1.15)	1.09	1.08	(1.04-1.13)	1.13	(1.06-1.20)	1.11	1.10	(1.04-1.17)
Age (per year)	1.11	(1.11-1.12)	1.11	1.11	(1.11-1.12)	1.17	(1.16-1.18)	1.17	1.17	(1.15-1.18)
Fasting time (per h)	1.01	(0.99-1.03)	1.01	1.01	(0.99-1.02)	1.01	(0.98-1.04)	1.01	1.00	(0.97-1.03)
Married			1	1				1	1	
Widowed			1.10	1.05	(0.89-1.23)			0.98	0.91	(0.71-1.16)
Divorced or separated			0.86	0.81	(0.61-1.07)			1.13	1.09	(0.73-1.63)
Single			1.31	1.31	(1.11-1.54)			1.31	1.30	(0.99-1.70)
Physical activity score (per point)			0.95	0.96	(0.92-1.00)			0.94	0.95	(0.89-1.01)
Three main meals per day			0.83	0.85	(0.73-1.00)			0.74	0.76	(0.59-0.98)
BMI (per kg/m ²)				1.00	(0.99-1.02)				1.00	(0.97-1.02)
Cholesterol (per mmol/L)				0.90	(0.83-0.98)				1.01	(0.89-1.14)
Systolic blood pressure (per mmHg)				1.01	(1.00-1.01)				1.01	(1.01-1.02)
Smoking (per cig/day)				1.03	(1.02-1.04)				1.03	(1.02-1.05)

Model 1: adjusted for age, town of residence and fasting time

Model 2: additionally adjusted for marital status, three main meals per day and physical activity score

Model 3: additionally adjusted for CVD risk factors: smoking, BMI, total cholesterol and blood pressure

Population sample: 7,800 participants of NRP 1A, 3,607 male and 4,193 female, Switzerland 1977-1979, 16-92 years at baseline

Figure legends

Figure 1.

Kaplan-Meier survival curves for all-cause mortality, by glucose category and sex, 7,984 participants of NRP 1A in Switzerland 1977-1979, 16-92 years at baseline

Figure 2.

Adjusted hazard ratios (HR and 95% CI) for CVD and all-cause mortality by glucose category and sex, adjusted for age, fasting time, town of residence and additionally for sex if calculated for all participants. Glucose categories: LFG: <3.8 mmol/L, NFG1: 3.5-4.9 mmol/L, NFG2: 5.0-5.5 mmol/L, IFG1: 5.6-6.0 mmol/L, IFG2: 6.1-6.9 mmol/L, DM: Diabetes ≥ 7 mmol/L, KDM: Known diabetes. Reference: NFG1: 3.8-4.9 mmol/L. Population sample: 7,800 participants, 3,607 male and 4,193 female participants of NRP1A, Switzerland 1977-1979, 16-92 years at baseline

Figure 3.

Stratification for cardiovascular risk factors: Adjusted hazard ratios (HR and 95% CI) for CVD mortality, by glucose category and CVD risk factors at risk versus not at risk: current smoking, high cholesterol (>6.2 mmol/L), hypertension (systolic ≥ 140 mmHg and/or diastolic ≥ 90 mmHg) and overweight (BMI>25). Adjusted for age, sex, fasting time and town of residence. Glucose categories: LFG: <3.8 mmol/L, NFG1: 3.5-4.9 mmol/L, NFG2: 5.0-5.5 mmol/L, IFG1: 5.6-6.0 mmol/L, IFG2: 6.1-6.9 mmol/L, DM: Diabetes ≥ 7 mmol/L, KDM: Known diabetes. Reference: NFG1: 3.8-4.9 mmol/L. Population sample: 7,800 participants, 3,607 male and 4,193 female participants of NRP1A, Switzerland 1977-1979, 16-92 years at baseline.