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Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study

F. de Vegt, J. M. Dekker, H. G. Ruhé, C. D. A. Stehouwer, G. Nijpels, L. M. Bouter, R. J. Heine

Institute for Research in Extramural Medicine, Vrije Universiteit, Amsterdam, The Netherlands

Abstract

Aims/hypothesis. The degree of glycaemia has been shown to be associated with all-cause and cardiovascular mortality in diabetic subjects. Whether this association also exists in the general population is still controversial. We studied the predictive value of fasting plasma glucose, 2-hour post-load glucose and HbA_{1c} in a population-based cohort of 2363 older (50–75 years) subjects, without known diabetes.
Methods. Relative risks (RR) of all-cause and cardiovascular mortality were estimated by Cox proportional hazards model, adjusting for age and sex, and additionally for known cardiovascular risk factors.
Results. During 8 years of follow-up, 185 subjects died; 98 of cardiovascular causes. Fasting plasma glucose was only predictive in the diabetic range, although the risks started to increase at about 6.1 mmol/l. Post-load glucose and HbA_{1c} values were, even within the non-diabetic range, associated with an increased risk (p for linear trend < 0.05). These increased risks were mostly, but not completely, attributable to known cardiovascular risk factors. After exclusion of subjects with newly diagnosed diabetes or with pre-existent cardiovascular disease ($n = 551$), a 5.8 mmol/l increase of post-load glucose (corresponding to two standard deviations of the population distribution) was associated with a higher age-adjusted and sex-adjusted risk of all-cause (RR 2.24) and cardiovascular mortality (RR 3.40) ($p < 0.05$). After additional adjustment for known cardiovascular risk factors, these relative risks were still statistically significant, with values of 2.20 and 3.00 respectively ($p < 0.05$).
Conclusion/interpretation. High glycaemic variables, especially 2-h post-load glucose concentrations and to a lesser extent HbA_{1c} values, indicate a risk of all-cause and cardiovascular mortality in a general population without known diabetes. [Diabetologia (1999) 42: 926–931]

Keywords Glucose, HbA_{1c}, hyperglycaemia, cardiovascular mortality, Hoorn population.

Longitudinal epidemiological studies have shown that the risk of cardiovascular disease (CVD) mortality in diabetic subjects is more than double that of subjects without diabetes [1, 2]. In diabetic patients, the risk of CVD mortality increases with increasing plasma glucose concentrations and HbA_{1c} values [3, 4].

Whether the associations between glycaemic variables and CVD mortality are also present in non-diabetic subjects is still controversial; the results of prospective studies on hyperglycaemia and CVD mortality are inconsistent. Some observed no effect [5, 6], some observed linear associations [7, 8] and some a threshold effect [5, 7, 9, 10]. Comparison between the different studies is very difficult because different indicators of glycaemia are presented and because of the differences in follow-up time and sex and age of the subjects. For a good comparison, the relation of glycaemic variables with all-cause and CVD mortali-

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Corresponding author: F. de Vegt MSc, Institute for Research in Extramural Medicine, Vrije Universiteit, Van der Boechorststraat 7, 1081 BT Amsterdam, The Netherlands
Abbreviations: FPG, Fasting plasma glucose; 2h-PG, 2-h post-load glucose; CVD, cardiovascular disease; RR, relative risk.

ty should be investigated and compared in the same study group. Therefore, we compared the associations between fasting plasma glucose (FPG), 2-h post-load glucose (2h-PG) and HbA_{1c} with all-cause and CVD mortality in a population-based study of 2363 men and women, aged 50–75 years, without known diabetes. Furthermore, we investigated whether the associations observed were independent of known cardiovascular risk factors.

Subjects and methods

Subjects. The Hoorn Study is a cohort study on glucose intolerance in a Dutch population of older subjects, which started in 1989. The study cohort and baseline measurements have been described in detail previously [11]. Briefly, 3553 men and women aged 50–75 years were randomly selected from the population register of the middle-sized Dutch town of Hoorn. Of the 2540 subjects (71.5 %) who agreed to participate, 56 non-Caucasians were excluded. Thus, the study cohort of the Hoorn Study consisted of 2484 men and women. Subjects who were already using insulin, blood glucose lowering agents or a diet for diabetes were classified as 'known diabetic patients' ($n = 90$). This group was excluded from the present analyses. We also excluded 17 subjects with missing information on HbA_{1c} or plasma glucose values. The subjects for whom the causes of death could not be retrieved ($n = 14$) were excluded in all analyses so that the study cohort was the same in all analyses. Consequently, the analyses were done in the remaining 2363 subjects. All subjects had given their written informed consent. The study was approved by the ethics committee of the Vrije Universiteit Hospital.

Follow-up. In 1995, the follow-up of the Hoorn Study cohort was started in cooperation with the population register of the city of Hoorn, the local hospital and general practitioners. Vital status was obtained from the register for the time since the start of the Hoorn Study. Since 1995, a prospective registration of vital status has been implemented. Causes of death were extracted from the medical records of the general practitioners and the local hospital and were coded according to the International Classification of Diseases, Injuries, and Causes of Death, ninth revision (ICD-9) [12] by two of the authors. Cardiovascular mortality was defined as ICD-9 codes 390–459 ('Diseases of the circulatory system') or 798 ('Sudden death, cause unknown'), because sudden death in general is of CVD origin [13]. Coding was checked in a sample ($n = 23$) by a certified nosologist from the local hospital; agreement within selected categories was nearly perfect. Of those who had moved out of Hoorn ($n = 160$; 6.8 %), only the vital status was checked in the population registers of the cities to which the subjects had moved. Eight subjects (0.3 % of the study cohort) were lost to follow-up.

Glycaemic variables and examinations. A fasting blood sample was taken from all subjects and subsequently, an oral 75-g glucose load was given. Fasting (FPG) and 2-h post-load plasma glucose concentrations (2h-PG) were determined with a glucose dehydrogenase method (Merck, Darmstadt, Germany). Glycated haemoglobin (HbA_{1c}) was determined by ion-exchange high performance liquid chromatography, using a Modular Diabetes Monitoring System (Bio-Rad, Veenendaal, the Netherlands). Fasting specific insulin concentration was quantified with an insulin-specific double-antibody radioimmunoassay (antibody SP21; Linco, St. Louis, Mo., USA).

Blood pressure (BP) was measured twice on the right arm with subjects sitting in a chair, using a random-zero sphygmomanometer (Hawksley-Gelman Ltd, Lancing, UK). The average of two measurements was used for analyses. Subjects were considered hypertensive when systolic BP was 160 mmHg or more, diastolic BP 95 mmHG or more and/or when using anti-hypertensive medication [14]. Weight and height were measured with subjects wearing underwear only and body mass index (BMI) was calculated as body weight divided by height (m^2). Waist and hip circumferences were measured according to a standardised procedure [15]. Waist-hip ratio (WH ratio) was defined as waist circumference divided by hip circumference. Total and HDL-cholesterol were determined from fasting blood samples by enzymatic techniques (Boehringer-Mannheim, Mannheim, Germany). The Friedewald formula was used to calculate the concentration of LDL-cholesterol [16]. This formula was not applied in subjects with serum triglyceride concentrations more than 8.0 mmol/l ($n = 6$).

Information on current cigarette smoking habits (yes/no) was obtained by questionnaire. Information on pre-existent cardiovascular diseases (myocardial infarction, angina pectoris, stroke and peripheral atherosclerotic disease) was obtained from the subjects using a translated version of the Rose questionnaire from the London School of Hygiene [17].

Statistical methods. Subjects were categorised according to approximate tertiles of HbA_{1c}, FPG and 2h-PG. Subsequently, the highest tertiles of FPG and 2h-PG were divided into subgroups with cut-off points used for the clinical diagnosis of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes: for FPG 6.1–7.0 mmol/l (IFG) and 7.0 mmol/l or more diabetes, and for 2h-PG 7.8–11.1 mmol/l (IGT) and 11.1 mmol/l or more diabetes [18, 19]. The highest tertile of HbA_{1c} was divided into two subgroups by the cut-off of 6.5 %, corresponding to the optimal target for the treatment of diabetes [20]. Baseline characteristics were calculated for categories of HbA_{1c}, FPG and 2h-PG. Age-adjusted and sex-adjusted differences relative to the lowest categories of HbA_{1c}, FPG and 2h-PG were tested with analysis of covariance (ANCOVA). Regression analysis with ordered categories was used to test linear trends in baseline characteristics over the categories of HbA_{1c}, FPG and 2h-PG, adjusting for age and sex. Hazard ratios for all-cause and cardiovascular mortality, which can be interpreted as relative risks (RRs), and 95 % confidence intervals (CI) were estimated by Cox proportional hazards model, adjusting for age and sex. Linear trends were tested using ordered categories in the Cox regression models. The known CVD risk factors hypertension, WH ratio, triglycerides, LDL-cholesterol and cigarette smoking were, in addition, considered as confounders because these variables had the strongest influences on the estimated RRs in bivariate analyses. Because of differences in the units of the glycaemic variables, we also compared RRs expressed per two standard deviations (SD) of the population distribution. Pearson's correlation coefficients were calculated for the correlations between FPG, 2h-PG and HbA_{1c}. To assess whether effect modification was present, we included product terms between sex and glycaemic variables. Analyses were done using the Statistical Package for the Social Sciences (SPSS for Windows 6.1) [21]. *P*-values were based on two-sided tests and the cut-off point for statistical significance was 0.05.

Table 1. Baseline characteristics in categories of HbA_{1c}

HbA_{1c} (%)[b] *n*	< 5.2 (752)	5.2–5.5 (798)	5.6–6.4 (730)	≥ 6.5 (83)	*p* for linear trend[d]
Age (years)	59.9 ± 7.1	61.3 ± 7.3[a]	62.9 ± 7.2[a]	65.3 ± 7.0[a]	< 0.01
Sex (% men)	45.1	45.5	47.5	50.6	0.10
Fasting specific insulin (pmol/l)[c]	74.8 (56.3–98.1)	75.0 (55.8–104.6)	78.9[a] (57.8–112.5)	110.6[a] (73.6–165.3)	< 0.01
Hypertension (%)	24.2	29.4	35.4[a]	54.2[a]	< 0.01
BMI (kg/m^2)	26.1 ± 3.2	26.4 ± 3.3	26.7 ± 3.8[a]	28.7 ± 4.2[a]	< 0.01
WH ratio	0.88 ± 0.09	0.89 ± 0.09[a]	0.90 ± 0.08[a]	0.97 ± 0.07[a]	< 0.01
Chol (mmol/l)	6.46 ± 1.15	6.64 ± 1.10[a]	6.88 ± 1.23[a]	6.91 ± 1.55[a]	< 0.01
HDL-chol (mmol/l)	1.39 ± 0.37	1.35 ± 0.37[a]	1.27 ± 0.34[a]	1.13 ± 0.31[a]	< 0.01
LDL-chol (mmol/l)	4.44 ± 1.07	4.62 ± 1.03[a]	4.83 ± 1.18[a]	4.66 ± 1.40	< 0.01
Trigl (mmol/l)[c]	1.20 (0.90, 1.80)	1.30[a] (0.90, 1.90)	1.50[a] (1.10, 2.28)	2.00[a] (1.38, 3.12)	< 0.01
Cigarette smoking (%)	23.7	30.6[a]	40.5[a]	38.3[a]	< 0.01

chol: cholesterol, HDL-chol: high density lipoprotein cholesterol, LDL-chol: low density lipoprotein cholesterol, trigl.: triglycerides
Results are means ± SD, percentage or median (20,80 percentile)

[a] Significantly different from HbA_{1c} < 5.2, adjusted for age and sex
[b] Tertiles of HbA_{1c} were made and the highest tertile was divided into 2 subgroups by the cut-off point 6.5 %
[c] Tested after log-transformation
[d] Adjusted for age and sex

Table 2. Relative risk (95 % CI) of all-cause and cardiovascular mortality by categories of HbA_{1c}

HbA_{1c} (%)[a] *n*	< 5.2 (752)	5.2–5.5 (798)	5.6–6.4 (730)	≥ 6.5 (83)	*p* for linear trend
all-cause mortality (*n*)	41	55	72	17	
model 1	1	1.03 (0.68–1.55)	1.24 (0.84–1.84)	2.23 (1.24–4.01)	0.03
model 2	1	0.94 (0.62–1.40)	0.97 (0.65–1.45)	1.38 (0.74–2.55)	0.59
CVD mortality (*n*)	16	32	39	11	
model 1	1	1.56 (0.85–2.84)	1.69 (0.93–3.06)	3.58 (1.60–8.00)	< 0.01
model 2	1	1.30 (0.71–2.38)	1.09 (0.59–2.00)	1.79 (0.77–4.16)	0.49

model 1: adjusted for age and sex
model 2: additionally adjusted for hypertension, waist : hip ratio, triglycerides, LDL-cholesterol and cigarette smoking

[a] Tertiles of HbA_{1c} were made and the highest tertile was divided into 2 subgroups by the cut-off point 6.5 %

Results

Follow-up was complete by October 1997. During this follow-up period of 8 years, 185 subjects died. For 98 subjects (53 %), the cause of death was cardiovascular. Mean HbA_{1c} in the study cohort of 2363 subjects was 5.4 ± 0.7 %, mean FPG 5.6 ± 1.1 mmol/l and mean 2h-PG 6.1 ± 2.9 mmol/l. The Pearson's correlation coefficient was 0.66 between HbA_{1c} and FPG, 0.57 between HbA_{1c} and 2h-PG and 0.75 between FPG and 2h-PG (all $p < 0.01$).

Table 1 shows baseline characteristics in categories of HbA_{1c}. Compared with subjects with HbA_{1c} values less than 5.2, subjects with HbA_{1c} 6.5 % or more were statistically significantly older, had a higher BMI, and were more often hypertensive and cigarette smokers. They also had a higher fasting specific insulin concentration, a higher WH ratio and a more unfavourable lipid profile ($p < 0.05$). For all these variables a linear trend was observed with increasing HbA_{1c} ($p < 0.01$). For the categories of FPG and 2h-PG the same linear patterns were seen, although no statistically significant linear trends were observed for LDL-cholesterol and cigarette smoking (data not shown).

Table 2 shows RRs for all-cause and cardiovascular mortality in categories of HbA_{1c}.

As expected, the highest age-adjusted and sex-adjusted RRs were found for subjects with HbA_{1c} 6.5 % or more: 2.23 (95 % CI 1.24–4.01) for all-cause mortality and 3.58 (95 % CI 1.60–8.00) for CVD mortality. The risks of all-cause and CVD mortality started to increase in the lower range of HbA_{1c} (p for linear trend < 0.05). After additional adjustment for known CVD risk factors, the RRs were, however, smaller and no longer statistically significant.

The RRs for categories of FPG are presented in Table 3. Age and sex-adjusted RRs start to increase, although not statisitically significantly, at FPG 6.1 mmol/l or more. After additional adjustment for known cardiovascular risk factors, the associations between FPG and all-cause and CVD mortality disappeared. Subjects with FPG 5.2–6.0 mmol/l had

Table 3. Relative risk (95 % CI) of all-cause and cardiovascular mortality by categories of fasting plasma glucose

FPG (mmol/l)[a] *n*	< 5.2 (712)	5.2–5.5 (682)	5.6–6.0 (567)	6.1–6.9 (282)	≥ 7.0 (120)	*p* for linear trend
all-cause mortality (*n*)	47	49	37	33	19	
model 1	1	1.03 (0.69–1.55)	0.84 (0.54–1.30)	1.45 (0.92–2.26)	1.75 (1.01–3.03)	0.06
model 2	1	0.96 (0.64–1.45)	0.73 (0.47–1.14)	1.17 (0.74–1.87)	1.24 (0.69–2.21)	0.56
CVD mortality (*n*)	26	25	17	19	11	
model 1	1	0.90 (0.52–1.57)	0.63 (0.34–1.19)	1.43 (0.79–2.60)	1.67 (0.80–3.48)	0.19
model 2	1	0.82 (0.47–1.44)	0.52 (0.28–0.99)	1.07 (0.57–1.98)	1.06 (0.49–2.33)	0.98

model 1: adjusted for age and sex
model 2: additionally adjusted for hypertension, waist : hip ratio, triglycerides, LDL-cholesterol and cigarette smoking

[a] Tertiles of FPG were made and the highest tertile was divided into subgroups by the cut-off points 6.1 and 7.0 mmol/l

Table 4. Relative risk (95 % CI) of all-cause and cardiovascular mortality by categories of 2-h plasma glucose

2 h-PG (mmol/l)[a] *n*	< 4.9 (811)	4.9–6.2 (749)	6.3–7.7 (438)	7.8–11.0 (255)	≥ 11.1 (110)	*p* or linear trend
all-cause mortality (*n*)	39	62	34	30	20	
model 1	1	1.57 (1.04–2.35)	1.30 (0.82–2.08)	1.73 (1.06–2.84)	2.74 (1.57–4.79)	< 0.01
model 2	1	1.45 (0.96–2.19)	1.15 (0.71–1.86)	1.48 (0.88–2.49)	2.03 (1.10–3.75)	0.07
CVD mortality (*n*)	18	36	18	15	11	
model 1	1	2.11 (1.18–3.77)	1.58 (0.81–3.09)	1.92 (0.93–3.94)	3.31 (1.50–7.31)	0.02
model 2	1	1.77 (0.99–3.19)	1.25 (0.63–2.48)	1.48 (0.70–3.16)	2.22 (0.94–5.23)	0.24

model 1: adjusted for age and sex
model 2: additionally adjusted for hypertension, waist : hip ratio, triglycerides, LDL-cholesterol and cigarette smoking

[a] Tertiles of 2 h-PG were made and the highest tertile was divided into subgroups by the cut-off points of 7.8 and 11.1 mmol/l

lower RRs than those with FPG less than 5.2 mmol/l, although these RRs were not statistically significant.

Table 4 shows RRs for categories of 2h-PG. Statistically significant age-adjusted and sex-adjusted associations for all-cause and CVD mortality were found for subjects with 2h-PG 11.1 mmol/l or more (RR 2.74; 95 % CI 1.57–4.79 and 3.31; 95 % CI 1.50–7.31). These associations were still (borderline) significant after additional adjustment for known CVD risk factors. The risks were increased for 2h-PG 4.9 mmol/l or more (p for linear trend < 0.03; age-adjusted and sex-adjusted).

Because of the linear trends observed for HbA_{1c} and 2h-PG, we used continuous glycaemic variables in subsequent analyses. Table 5 shows the results of these analyses, with RRs expressed per two standard deviations (SD) of the population distribution. The strongest age-adjusted and sex-adjusted RRs were found for 2h-PG: 1.54 for all-cause mortality and 1.64 for CVD mortality ($p < 0.05$) per 5.8 mmol/l increase, corresponding to two SD of the population distribution. After additional adjustment for hypertension, WH ratio, triglycerides, LDL-cholesterol and cigarette smoking, the RRs remained statistically significant ($p < 0.05$). After exclusion of newly diagnosed diabetic subjects, with FPG or 2h-PG values in the diabetic range ($n = 164$) [18,19], the age-adjusted and sex-adjusted RRs were even higher for 2h-PG as well as for HbA_{1c}, but only statistically significant for 2h-PG (all-cause mortality RR 1.78; 95 % CI 1.06–2.98). When subjects with pre-existent cardiovascular diseases ($n = 433$) were excluded [17], the RRs for HbA_{1c} and for 2h-PG were also higher than the RRs of the total study cohort and were all statistically significant ($p < 0.05$). When both groups (subjects with glucose values in the diabetic range [18,19] and subjects with pre-existent CVD) [17] were excluded, the RRs were higher than the RRs of the total study cohort, and statistically significant for 2h-PG ($p < 0.05$).

Discussion

In this follow-up study of 2363 older men and women, 2h-PG and HbA_{1c} were, even in the non-diabetic range, associated with increased risk of all-cause and CVD mortality. This increased risk was mostly, but not completely, attributable to known CVD risk factors.

The Hoorn Study is a prospective study of subjects who were randomly selected from the population register of Hoorn; thus selection bias can be excluded. Glucose concentrations and HbA_{1c} values were assessed only once. In a sub-group of 1109 subjects, in whom a second OGTT was done after 2 to 6 weeks, the intra-individual coefficient of variation was 6.5 % for FPG and 16.7 % for 2h-PG, indicating larger variability for 2h-PG than for FPG [22]. This is in line with observations in other studies [23,24]. This variability may have caused some random misclassification in the categories of 2h-PG and to a lesser extent in the categories of FPG. Unfortunately, no duplicate measurements of HbA_{1c} were done. In the Is-

Table 5. Relative risk for all-cause and cardiovascular mortality (95 % CI) for HbA_{1c} and 2 h-PG as continuous variables expressed per 2 standard deviations[a]

	HbA_{1c}	2 h-PG
Total cohort (n = 2363)		
all-cause mortality		
model 1	1.39 (1.15–1.67)	1.54 (1.28–1.85)
model 2	1.22 (0.97–1.53)	1.43 (1.15–1.79)
CVD mortality		
model 1	1.51 (1.20–1.88)	1.64 (1.29–2.08)
model 2	1.34 (0.99–1.82)	1.56 (1.16–2.11)
Subjects with newly diagnosed diabetes excluded (n = 2199)[b]		
all-cause mortality		
model 1	1.46 (0.93–2.29)	1.78 (1.06–2.98)
model 2	1.06 (0.66–1.68)	1.54 (0.89–2.68)
CVD mortality		
model 1	1.71 (0.91–3.20)	1.76 (0.86–3.60)
model 2	0.96 (0.50–1.83)	1.32 (0.61–2.87)
pre-existent CVD excluded (n = 1930)[c]		
all-cause mortality		
model 1	1.49 (1.16–1.91)	1.75 (1.40–2.19)
model 2	1.32 (1.00–1.75)	1.71 (1.32–2.20)
CVD mortality		
model 1	1.92 (1.47–2.51)	2.24 (1.70–2.94)
model 2	1.62 (1.18–2.23)	2.12 (1.54–2.91)
Subjects with newly diagnosed diabetes and/or with pre-existent CVD excluded[b, c] (n = 1812)		
all-cause mortality		
model 1	1.61 (0.93–2.79)	2.24 (1.20–4.18)
model2	1.25 (0.71–2.20)	2.20 (1.11–4.33)
CVD mortality		
model 1	2.12 (0.94–4.77)	3.40 (1.35–8.53)
model 2	1.16 (0.51–2.63)	3.00 (1.08–8.30)

model 1: adjusted for age and sex
model 2: additionally adjusted for hypertension, waist : hip ratio, triglycerides, LDL-cholesterol and cigarette smoking
[a] 2 SD: for HbA_{1c} 1.4 % and for 2 h-PG 5.8 mmol/l
[b] FPG $\geq$ 7.0 mmol/l and/or 2 h-PG $\geq$ 11.1 mmol/l
[c] Obtained from the subjects using a translated version of the Rose questionnaire from the London School of Hygiene

lington Diabetes Survey, however, the coefficient of variation for HbA_{1c} among subjects without known diabetes was 13.7 % [25].

In our study, the predictive values of FPG, 2h-PG and HbA_{1c} were compared in the same general population without known diabetes. Results of previous studies on the associations of glycaemic variables with (cardiovascular) mortality have been inconclusive. In a cross-sectional study, the association between three glycaemic variables and prevalent coronary heart disease (CHD) were compared. A linear increase of CHD over quartiles of both 2h-PG and HbA_{1c}, with 2h-PG being the best predictor, was observed [26]. The results of a combined analysis of the Whitehall study, Paris Prospective study and Helsinki Policemen study have recently been reported. It was found that men in the upper 2.5 % of the FPG and 2h-PG distribution were at higher risk of CVD mortality during 20 years of follow-up than men in the lower 80 % of these distributions [9]. The RRs for subjects in these lower categories were, however, not presented and because of differences in the OGTTs in the three studies mentioned, the distributions of the 2h-PG concentrations were not fully comparable. In the Rancho Bernardo Study, a linear relation was found between FPG and ischaemic heart disease mortality for men but a threshold effect was observed for women [7]. In a Finnish study of 3267 men there was no clear association between post-load glucose concentration and CVD mortality [5] whereas the Honolulu Heart Program showed a linear increase [8]. Less is known about the predictive value of HbA_{1c} in a general population. In one prospective study, HbA_{1c} but not FPG or 2h-PG, was related to CVD mortality in women but not in men [10].

In a few studies, which studied the associations of glycaemic variables with CVD mortality separately for men and women, the associations were stronger in women than in men [2, 7, 10, 27]. In our study, no clear consistent differences between men and women were observed (all p-values for product terms were 0.20 or more; data not shown).

Our study shows no clear independent association between FPG and mortality, although the risk started to increase, though not statistically significantly, at 6.1 mmol/l or more. In contrast, 2h-PG and HbA_{1c} were associated with mortality even within the non-diabetic range. Significant linear trends were seen for both variables ($p < 0.05$). The increased risk was to a considerable extent attributable to known CVD risk factors, such as WH ratio, hypertension, LDL-cholesterol, triglycerides and cigarette smoking, as in other studies [5, 8, 9]. After exclusion of subjects with newly diagnosed diabetes or with pre-existent CVD, a 5.8 mmol/l increase of 2h-PG (corresponding to 2 SD of the population distribution) was, however, associated with a higher risk of all-cause (RR 2.24) and CVD mortality (RR 3.40) ($p < 0.05$). So it appears that 2h-PG, especially, is a good predictor of mortality in subjects without diabetes or CVD. It can be speculated that the lower mortality risk of previously undiagnosed subjects, who were diagnosed with diabetes by the Hoorn Study, was due to the subsequent treatment of CVD risk factors by their general practitioners, who were informed about their diabetic status. After adjustment for known CVD risk factors, the RRs for 2h-PG were still statistically significant, with RRs of 2.20 and 3.00 for all-cause and CVD mortality, respectively ($p < 0.05$).

A possible explanation for these findings could be insulin resistance and the insulin resistance syndrome, a clustering of metabolic disorders, including glucose intolerance, obesity, hypertension and lipid abnormalities [28–30]. Because insulin sensitiviy declines slowly and monotonically with increasing

2h-PG concentrations, the increased risk associated with 2h-PG could partly be due to this multifaceted syndrome [31]. Additional adjustment of fasting specific insulin did not, however, change the results (data not shown). In addition, the impact of postprandial, or post-load, glucose spikes could also explain our results. A short-term increase in blood glucose concentrations may induce oxidative stress, which might be an important factor in the aetiology of vascular complications in diabetic subjects [32, 33].

The increased risk associated with a fasting plasma glucose concentration higher than 6.1 mmol/l, supports the cut-off point which is used for the category 'impaired fasting glucose' in the new ADA-criteria [18]. In addition, the results of this study suggest that an OGTT is also warranted to distinguish subjects with a higher risk for mortality.

In conclusion, high glycaemic variables, especially 2h-PG concentrations and to a lesser extent HbA_{1c} values, may be indicators of increased risk of CVD mortality in a general older population without known diabetes. This may be of value for risk stratification in clinical practice.

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