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Casual blood glucose and subsequent cardiovascular disease and all-cause mortality among 159 731 participants in Cohort of Norway (CONOR)

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ABSTRACT

Introduction Our aim was to assess the association between casual blood glucose level and subsequent cardiovascular disease (CVD) and mortality among community-dwelling adults without a diagnosis of diabetes.

Research design and methods In this community-based cohort study, 159 731 individuals with a measurement of casual blood glucose were followed from their participation date in Cohort of Norway (CONOR) (1994–2003) until a CVD episode, death or 31 December 2009. All analyses were done using Cox proportional hazard regression, and the results are reported as multivariable-adjusted HRs with 95% CI.

Results Compared with those with normal glucose levels (<7.8 mmol/L), participants categorized as having borderline (7.8–11.0 mmol/L) levels showed an increased risk of a stroke (HR 1.29; 95% CI 1.12 to 2.49) and cardiovascular (HR 1.29; 95% CI 1.12 to 2.48), and all-cause (HR 1.27; 95% CI 1.16 to 1.38) mortality, while participants with high glucose levels (>11.0 mmol/L) had an even more increased risk. One mmol/L increase in glucose level was associated with an increased risk of all four endpoints among participants with borderline as well as within normal glucose levels. In analyses stratified by sex and age group, the CVD risk estimates tended to be higher in women than in men and in those <65 years of age but no significant interactions were found.

Conclusion An increase in casual blood glucose levels, even within the range of normal and borderline levels, was positively associated with increased risk of CVD and mortality among community-dwelling adults without a known diagnosis of diabetes.

Significance of this study

What is already known about this subject?

- Suboptimal fasting blood glucose levels are associated with increased risk of coronary heart disease and strokes.

What are the new findings?

- Increase in casual blood glucose levels, even within the range of normal and borderline levels, is positively associated with increased risk of cardiovascular disease and mortality.

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

- The current study emphasizes that the risk of cardiovascular disease starts before the diagnostic cut-off point for diabetes and that screening for casual blood glucose levels, also among those who are not suspected of having diabetes, is important.

INTRODUCTION

Diabetes is an increasing public health problem, and when uncontrolled, it has serious consequences for individuals' health and well-being.[1] Diabetes is well known to be a key risk factor for cardiovascular disease (CVD) and premature death.[1–6] Furthermore, suboptimal blood glucose levels are associated with increased risk of coronary heart disease and strokes.[2] It is not clear, however, whether glucose levels may predict CVD risk among individuals without known diabetes and, furthermore, whether casual blood glucose levels may predict CVD in the same way as fasting glucose levels. Such knowledge is of relevance for general practitioners since the majority of individuals at risk of diabetes and CVD are treated in the primary care service. From an individual's perspective, better glycemic control may prevent, or at least delay, CVD complications, which will have a great impact on the individual's health and well-being.

In the UK, more than one-third of the adult population have pre-diabetes, which puts people at high risk of developing diabetes and CVD.[7] Pre-diabetes may be defined as increased blood glucose levels that are not yet high enough to be diagnosed as diabetes.[8] The metabolic process that leads to elevated blood glucose in individuals at risk of developing diabetes typically starts years before the diagnosis,[9] and several trials have

demonstrated that early identification and intervention in relation to high-risk individuals can prevent or delay the development of diabetes and its complications.[10–12] Finally, when assessing hyperglycemia and CVD risk among men and women without diabetes, studies often require participants to be fasting for blood sampling purposes. In some settings, however, it is unrealistic to require all participants to be fasting, for instance, in community-based studies. Moreover, people are seldom fasting when they visit their general practitioner with various health problems or for routine annual consultations for adults. It is therefore important to investigate whether casual blood glucose level (ie, no instructions to participants as regards fasting) is associated with future CVD risk.

To our knowledge, studies examining the association between casual blood glucose and future risk of CVD in both women and men, especially in older adults, are missing. In Norway, health data from several regional community-based health surveys of more than 170 000 individuals are combined in the Cohort of Norway (CONOR) database.[13] In the current study, CONOR was linked to the Cardiovascular Disease in Norway Project (CVDNOR), which includes information on all hospital stays with a cardiovascular or diabetes-related diagnosis from 1994 to 2009. Using these data, we aimed to assess the association between casual blood glucose level and subsequent CVD and mortality among community-dwelling adults without a known diagnosis of diabetes. We also aimed to outline the impact of age and sex on this association.

METHODS

Data sources

By using the national identification number that is unique to every Norwegian resident, we linked information in the CONOR database to the CVDNOR project in order to study the association between casual blood glucose level and future CVD and/or mortality. CONOR contains health data and blood sample data from various regional health surveys conducted from 1994 to 2003.[13] The CONOR database includes information obtained from self-administered questionnaires, physical examinations, and results of analyses of biological samples.

CVDNOR (https://cvdnor.w.uib.no/) was established as a collaborative research project between the University of Bergen and the Norwegian Knowledge Centre for the Health Services (now part of the Norwegian Institute of Public Health). Information on all hospital stays with a cardiovascular or diabetes-related diagnosis was retrieved from the electronic Patient Administrative Systems from 1994 to 2009.[14 15] Data include patients' age at hospitalization, the time and date of hospitalization and discharge, main and secondary diagnoses (up to 20), and medical procedures (up to 30) performed during the hospital stay.

Study population

A total of 174 322 men and women participated in a CONOR survey from 1994 to 2003. We excluded participants with a previous diagnosis of acute myocardial infarction (AMI) or stroke (n=9371), allowing us to examine incident (first) events. Participants with known diabetes mellitus (n=4205) or who used antidiabetic medication (n=10) were also excluded, as were participants with blood glucose, cholesterol, weight, height or systolic blood pressure values under/above the 0.1/99.9% percentile (n=1005). The numbers of participants with missing data for each variable of interest after exclusions were as follows: serum glucose: 25 544 (16.0%), marital status: 573 (0.4%), educational level: 28 698 (18.0%), cholesterol: 259 (0.2%), systolic blood pressure: 427 (0.3%), body mass index (BMI): 4774 (0.5%), smoking: 1697 (1.1%), and time since last meal: 7967 (5.0%). Using multiple imputation (see statistical analyses below), the final sample consisted of 159 731 participants: 69 148 women and 61 853 men.

Exposure and endpoints

The exposure for the current study was casual blood glucose measured at participation date in CONOR, examined both as a continuous and a categorical variable (normal <7.8 mmol/L, borderline 7.8–11.0 mmol/L, and high >11.0 mmol/L).

The endpoints include cardiovascular and all-cause mortality, as well as incident AMI and strokes. AMI was defined as a hospitalization with an AMI as the discharge diagnosis (International Classification of Diseases (ICD)-9 codes 410; ICD-10 codes I21–I22) or out-of-hospital death from coronary heart disease (ICD-9 codes 410–414; ICD-10 I20–25). Stroke was defined as a hospitalization with, or death from, a stroke (ICD: ICD-9 codes 430–434 and 436; ICD-10 codes I60–I61 and I63–I64, except I63.6). CVD mortality was defined as ICD-9 codes 390–459 and ICD-10 codes I00–I99.

Statistical analyses

The relationship between blood glucose and study outcomes was modelled using Cox proportional hazard regression, and the results are reported as HRs with 95% CIs. Follow-up time was calculated as the time from the participation date in CONOR until the study endpoint or 31 December 2009 (whichever occurred first). Blood glucose was introduced in the models as: (1) a three-level categorical variable (using the category <7.8 mmol/L as the reference) and (2) a continuous variable.

Glucose was introduced as a continuous variable using two different approaches: (1) we estimated the HR associated with a 1 mmol/l increment in glucose by including glucose as a continuous variable in the Cox model, assuming one common slope for the entire range of glucose values; and (2) we allowed for different slopes within each glucose category by modelling continuous glucose levels as linear splines with knots at 7.8 mmol/L and 11 mmol/L. Within each of the three glucose

categories, we estimated the HR associated with a 1 mmol/L increase in glucose levels.

In addition to analyses for the total study sample, we tested for potential interaction between glucose levels and sex and age group (≤65 and >65 years). The proportional hazard assumption was checked by inspecting log-(log) survival plots for categorical data and by using the estat phtest for continuous variables.

The following potential confounding variables were included in the models: age (years), sex, educational level (basic, upper secondary or tertiary education), marital status (married/cohabitant or other), daily smoking (yes or no), BMI (kg/m^2), time since last meal (hours), total cholesterol (mmol/L), and systolic blood pressure (mm Hg). Age, cholesterol, blood pressure, and BMI were adjusted as linear variables in the models.

Multiple imputation by chained equations was used to address missing data for relevant variables.[16] Serum blood glucose was not measured in one of the health surveys included in CONOR, and missing data for glucose are therefore considered to be missing completely at random. For the current study, we imputed missing values for the exposure variable blood glucose (15.4%), as well as for marital status (0.4%), educational level (18%), cholesterol (0.2%), systolic blood pressure (0.3%), smoking (1.1%), BMI (0.3%), and time since last meal (5.0%). Imputation was done separately for each endpoint and each representation of glucose (categorical or continuous), with stratification by sex and age group. We created 20 imputed datasets for each combination of endpoint and glucose representation. Imputation models included endpoint variables (binary endpoint-variable and time-variable) and all potential confounders. Continuous variables (glucose, cholesterol, systolic blood pressure, BMI, and time since last meal) were imputed using linear regression, ordinal categorical variables (glucose category and level of education) were imputed using ordinal logistic regression, and binary variables (smoking, marital status) were imputed using binary logistic regression. The average relative variance reports the average relative increase in variance of the estimates due to the missing values. It varied from 0.0572 to 0.1357 in the present study. The closer this number is to zero, the less effect missing data have on the variance.[17]

The level of significance was defined as <0.05 and STATA V.16 was used in all analyses.

Ethical considerations

All CONOR survey participants signed a written informed consent to research and linkage of their data to health registries.

RESULTS

Sociodemographic and health characteristics of the CONOR survey participants (n=159 731) are presented in table 1. A total of 69 148 (82.3%) women had normal glucose levels, while 1152 (1.4%) had borderline levels and 126 (0.2%) had high levels. The corresponding numbers for men were 61 853 (81.7%), 1692 (2.2%) and 216 (0.3%), respectively.

Both women and men with high glucose levels were older at the time of enrollment in CONOR (64.9 years vs 48.3 years among women and 57.7 years vs 49.6 years among men) and had less education compared with those with normal glucose levels (table 1). Compared with women with normal glucose levels, women with high levels had higher serum total cholesterol (6.3 mmol/L vs 5.7 mmol/L) and higher systolic blood pressure (152.8 mm Hg vs 129.8 mm Hg), and a higher proportion had obesity (52.3% vs 15.5%). Women with the highest levels of glucose smoked less (17.5%) than women with normal (29.7%) or borderline (26.1%) glucose levels. Similar results were found for men. Compared with men with normal glucose levels, those with high levels had higher serum total cholesterol (6.1 mmol/L vs 5.8 mmol/L) and higher systolic blood pressure (149.0 mm Hg vs 136.3 mm Hg), and a higher proportion had obesity (41.2% vs 13.4%). In men, however, the highest proportion of smokers was found among those with borderline levels of glucose.

Multivariable Cox regression models comparing glucose categories are presented in figure 1. Participants categorized as having a high glucose level showed an increased risk of a stroke (HR 1.79; 95% CI 1.31 to 2.43), cardiovascular mortality (HR 1.90; 95% CI 1.42 to 2.55), and all-cause mortality (HR 1.69; 95% CI 1.38 to 2.05) when compared with those with a normal glucose level (figure 1). Individuals with borderline glucose levels also showed an increased risk compared with those with normal glucose levels, but HRs were somewhat weaker compared with high glucose levels. Cox models only adjusted for age, sex, and time since last meal instead of full adjustment are presented in online supplemental table S1. HRs were generally stronger in these models than in the fully adjusted models in figure 1. Sensitivity analyses on data without imputations are presented in online supplemental table S2 and are comparable with the results from analyses done on imputed data.

When analyzing glucose as a continuous variable, a 1 mmol/L increase was associated with an increase in the risk of all endpoints, ranging from 3.0% to 16.0% (table 2). When using linear splines with knots at 7.8 and 11.0 (allowing for different linear slopes within each category), we observed that a 1 mmol/L increase in glucose levels was associated with a statistically significant increased risk of AMI, stroke and CVD, and all-cause mortality in participants with glucose levels <7.8 mmol/L, and in the risk of a stroke, CVD, and all-cause mortality in participants with glucose levels between 7.8 mmol/L and 11.0 mmol/L (table 2). The association between glucose levels and study endpoints was not significant in participants with glucose levels >11.0 mmol/L.

In analyses stratified by sex, we observed higher risk estimates for high and borderline glucose versus normal glucose for all four endpoints in women compared

Table 1 Sociodemographic and health characteristics of 159 731 participants in Cohort of Norway from 1993 to 2004

	Casual blood glucose level at baseline				
	Normal (<7.8 mmol/L)	Borderline (7.8–11.0 mmol/L)	High (>11.0 mmol/L)	P value*	Missing†
Women (n=84 005)					
No. (%)	69 148 (82.3)	1152 (1.4)	126 (0.2)		13 579 (16.2)
Age, mean (SD)	48.3 (15.0)	58.5 (15.5)	64.9 (16.3)	<0.001	46.8 (15.0)
Marital status, n (%)				0.070	
Married/registered partnership	41 460 (59.1)	680 (59.1)	63 (50.0)		7195 (53.1)
Other	27 602 (39.9)	471 (40.9)	63 (50.0)		6356 (46.9)
Education, n (%)				<0.001	
Basic education	17 614 (31.0)	431 (48.4)	50 (64.9)		4854 (36.0)
Upper secondary education	22 627 (39.8)	294 (33.0)	20 (26.0)		4735 (35.1)
Tertiary education	16 547 (29.1)	165 (18.5)	7 (9.1)		3897 (28.9)
Serum glucose, mmol/L, mean (SD)	5.1 (0.7)	8.6 (0.8)	13.8 (2.4)	<0.001	–
Serum total cholesterol, mmol/L, mean (SD)	5.7 (1.2)	6.1 (1.3)	6.3 (1.3)	<0.001	6.0 (1.3)
Current smoker	20 562 (29.7)	301 (26.1)	22 (17.5)	0.002	4986 (36.7)
Systolic blood pressure, mean (SD)	129.8 (21.1)	141.3 (24.1)	152.8 (24.6)	<0.001	130.8 (21.4)
BMI, mean (SD)	25.7 (4.4)	27.4 (5.1)	31.2 (6.2)	<0.001	24.7 (4.2)
Obesity	10 670 (15.5)	307 (27.7)	57 (52.3)	<0.001	1452 (10.7)
Time since last meal, mean (SD)	1.9 (1.4)	1.0 (1.1)	1.6 (1.3)	<0.001	2.2 (1.5)
Endpoints, n (%)					
Acute myocardial infarction	1637 (2.4)	66 (5.7)	13 (10.3)	<0.001	472 (3.5)
Stroke	2187 (3.2)	96 (8.3)	19 (15.1)	<0.001	573 (4.2)
Cardiovascular death	1983 (2.9)	109 (9.5)	22 (17.5)	<0.001	539 (4.0)
All cause death	5850 (8.5)	243 (21.1)	49 (38.9)	<0.001	1614 (11.9)
Men (n=75 726)					
No. (%)	61 853 (81.7)	1692 (2.2)	216 (0.3)		11 965 (15.8)
Age, mean (SD)	49.6 (15.0)	57.5 (14.3)	57.7 (14.1)	<0.001	46.0 (13.9)
Marital status, n (%)				<0.001	
Married/cohabitant	39 098 (63.4)	1235 (73.1)	135 (62.5)		6652 (55.8)
Other	22 338 (36.3)	454 (26.9)	81 (37.5)		5275 (44.2)
Education, n (%)				<0.001	
Basic education	11 448 (24.6)	423 (35.8)	62 (42.5)		3494 (29.4)
Secondary education	21 161 (45.4)	465 (39.3)	56 (38.4)		4509 (37.9)
Tertiary education	13 965 (30.0)	294 (24.9)	28 (19.8)		3887 (32.7)
Serum glucose, mmol/L, mean (SD)	5.3 (0.8)	8.7 (0.8)	13.9 (2.5)	<0.001	–
Serum total cholesterol, mmol/L, mean (SD)	5.8 (1.1)	5.9 (1.1)	6.1 (1.2)	<0.001	6.0 (1.2)
Current smoker	17 910 (29.0)	553 (32.7)	66 (30.6)	<0.001	4533 (37.9)
Systolic blood pressure, mean (SD)	136.3 (17.8)	144.7 (21.0)	149.0 (21.1)	<0.001	136,5 (16.7)
BMI, mean (SD)	26.3 (3.4)	27.2 (4.0)	29.3 (5.0)	<0.001	25.5 (3.3)
Obesity	8239 (13.4)	369 (22.1)	85 (41.2)	<0.001	1070 (9.0)
Time since last meal, mean (SD)	2.0 (1.5)	1.0 (1.1)	1.6 (1.5)	<0.001	2.3 (1.6)
Endpoints, n (%)					
Acute myocardial infarction	3394 (5.5)	145 (8.6)	21 (9.7)	<0.001	821 (6.9)
Stroke	2498 (4.0)	131 (7.7)	23 (10.7)	<0.001	590 (4.9)
Cardiovascular mortality	2360 (3.8)	130 (7.7)	25 (11.6)	<0.001	510 (4.3)

Continued

Table 1 Continued

	Casual blood glucose level at baseline				
	Normal (<7.8 mmol/L)	Borderline (7.8–11.0 mmol/L)	High (>11.0 mmol/L)	P value*	Missing†
All-cause mortality	7267 (11.8)	398 (23.5)	61 (28.2)	<0.001	1614 (13.5)

Number of missing: marital status: 573 (0.4%), education: 28 698 (18.0%), cholesterol: 259 (0.2%), systolic blood pressure: 427 (0.3%), BMI: 774 (0.5%), smoking: 1697 (1.1%), and time since last meal: 7967 (5.0%).
*Test for trend by comparing participants with normal, borderline, and high casual blood glucose. Regress for continuous variables and logit/ologit for categorical variables.
†Persons with missing data on casual glucose level (before imputation).
BMI, body mass index.

with men (table 3). The stronger HRs were especially apparent for subsequent risk of AMI for high glucose versus normal glucose with a multivariable-adjusted HR of 1.79 (95% CI 1.03 to 3.12) for women compared with 1.14 (95% CI 0.74 to 1.75) for men. Interaction tests for effect modification by sex were not significant for any of the endpoints.

Results from analyses stratified by age (<65 and ≥65 years) are presented in online supplemental table S3. In participants younger than 65 years of age, we found an increased risk of a stroke (HR 1.77; 95% CI 1.01 to 3.09), cardiovascular mortality (HR 2.66; 95% CI 1.45 to 4.89), and all-cause mortality (HR 1.68; 95% CI 1.07 to 2.56) when we compared those with high versus normal glucose levels. In participants aged 65 years and above, we observed a 60%–70% increased risk of all four endpoints for participants with high compared with normal glucose levels. Similar results, except for AMI, were found for participants aged 65 years and above with a borderline glucose level. Interaction tests for effect modification by age group were not significant for any of the endpoints.

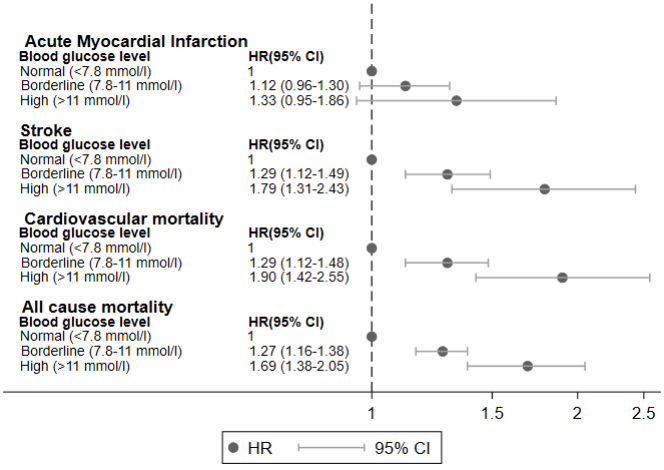

Figure 1 Casual blood glucose and risk of fatal or nonfatal acute myocardial infarction, stroke, cardiovascular mortality and all-cause mortality in 159 731 Norwegian men and women, followed up to 12.7 years (imputed data). All analyses adjusted for age, sex, cholesterol, systolic blood pressure, BMI, time since last meal, smoking, education and marital status. BMI, body mass index.

CONCLUSIONS

The results of the current study indicate that casual blood glucose level is a significant predictor of CVD and mortality among community-dwelling adults without a known diagnosis of diabetes. A linear increasing risk per 1 mmol/L increase in glucose level among participants with both normal and borderline glucose levels was found for AMI, stroke, and cardiovascular as well as all-cause mortality. The analyses also revealed higher relative risk estimates for all four endpoints in women compared with men, although not significantly higher. Furthermore, no clear pattern was found when stratifying the analyses by age group (<65 versus ≥65 years).

Comparison with other studies

Limited evidence is available on the association between casual blood glucose level and future CVD risk. In the current study, subjects without diagnosed diabetes but with blood glucose levels higher than normal, as well as borderline glucose levels below the diagnostic threshold for diabetes, were found to be at increased risk of CVD and mortality. The associations remained but were weaker after multivariable adjustment for other CVD risk factors. The mechanism behind the association between glucose level and future CVD remains uncertain, but results from in vitro and animal studies have suggested that, together, increased glucose levels, free fatty acids, and insulin resistance lead to, for example, oxidative stress and activation of protein kinase C isoform, which may further result in vasoconstriction, inflammation, and thrombosis.[18 19]

The results of the current study are consistent with the meta-analysis by Levitan *et al*,[20] who analyzed 38 prospective observational studies and identified hyperglycemia in persons without a diagnosis of diabetes as a risk marker for CVD. They did, however, include studies with different measures of blood glucose (postload glucose, casual glucose, fasting glucose, or hemoglobin A1c), of which only four studies used casual blood glucose. A meta-analysis from 2011 that included a variety of study designs found no evidence of an association between casual blood glucose level and CVD.[21] A later study by Imano *et al*[22] from 2012 observed an increased risk of coronary heart disease in individuals with borderline and high glucose levels. This study did have a notably smaller

Table 2 HRs with 95% CIs per 1 mmol/L increase in casual glucose levels from Cox proportional hazards models* with glucose analyzed as a continuous variable with and without linear splines in 159 731 Norwegian men and women, followed up to 12.7 years (imputed data)

		HR (95% CI) for model with linear splines with three knots			HR (95% CI) for model without linear splines
Events/no.		<7.8 mmol/L (normal)†	7.8–11.0 mmol/L (borderline)†	>11.0 mmol/L (high)†	All groups combined†
Acute myocardial infarction	6569/159 731	1.03 (1.00 to 1.07)	1.01 (0.92 to 1.12)	1.06 (0.96 to 1.18)	1.03 (1.01 to 1.06)
Stroke	6117/159 731	1.03 (1.00 to 1.07)	1.16 (1.06 to 1.28)	0.98 (0.89 to 1.09)	1.05 (1.03 to 1.07)
Cardiovascular mortality	5678/159 731	1.06 (1.02 to 1.10)	1.11 (1.01 to 1.22)	1.04 (0.95 to 1.13)	1.07 (1.04 to 1.09)
All-cause mortality	17,096/159 731	1.05 (1.03 to 1.08)	1.13 (1.07 to 1.19)	1.00 (0.94 to 1.06)	1.06 (1.05 to 1.08)

*Adjusted for age, sex, cholesterol, systolic blood pressure, BMI, time since last meal, smoking, education and marital status.
†HR per mmol/L increase in casual glucose levels with 95% CI.
BMI, body mass index.

study population (n=7332) than ours (n=1 59 731), and it only included individuals aged 40–69 years of age. Similar results were also found in the study by Kadowaki *et al*[23] from 2008, which analyzed more than 450 000 men and women aged 30 years and above.

In the current study, we also found a linear increasing risk per 1 mmol/L increase in glucose level among participants with both normal and borderline glucose levels for all four endpoints. This is in accordance with two Asian studies from 2008 and 2016.[23 24] Thus, the use of casual glucose measurements in general practice might be an important marker for further follow-up to identify people at risk of diabetes and CVD many years before diagnosis. Such early identification of high-risk individuals can delay the development of diabetes and its complications. Nevertheless, few previous studies have examined the association between casual blood glucose levels and CVD risk in large community-based studies, which was the motivation for conducting the current study.

Differences between men and women

When looking at differences in CVD risk between the sexes, the risk estimates tended to be higher for all endpoints among women than among men in subjects with borderline or high glucose levels. These results are consistent with previous studies[20 22] and indicate that hyperglycemia may be a stronger CVD risk factor among women than among men. The manifestations of CVD vary between the sexes, and it is well known that CVD risk among individuals with diabetes varies between the sexes.[25 26] Women appear to be more susceptible to hyperglycemia than men, and hyperglycemia may be associated with different CVD risk factors among women than among men.[20 27] Extensive statistical adjustment for CVD risk factors does not seem to explain the observed sex differences, which may suggest that hyperglycemia cancels out some of the protective effect of female sex as regards CVD risk.[20] Nevertheless, it is well known that men develop CVD at a younger age and have a higher risk of developing coronary heart disease than women.[28] When using relative effect measures such as HRs, the differences between men and women will be exaggerated because the same absolute risk increase will result in a higher relative risk increase among women. Also, in the current study, there were few individuals with high glucose level and we can therefore not rule out that the different effect of glucose level on CVD risk between the sexes would change if we had a larger study sample and thereby more statistical power.

Age differences

There is a lack of studies examining the association between casual blood glucose and future risk of CVD in older individuals. Only one[29] of the four studies assessing casual glucose in the meta-analysis from 2004[20] included participants aged 65 years and above and that study had a short follow-up period (<5 years), fewer than 3000 study participants and no statistical adjustment for CVD risk factors. The study by Imano *et al* from 2012 included men and women aged 40–60 years,[22] while Kadowaki *et al*[23] included participants aged 30 years and above. None of these three studies looked at potential age differences in relation to CVD risk with increasing glucose level. The Chinese study from 2016 by Bragg *et al*[24] found a more or less similar risk of CVD mortality and major occlusive vascular disease in those with high glucose levels aged 35–59, 60–69, and 70–79 years, although with some indication of stronger associations with CVD risk among the youngest. Moreover, it has been found that, while those aged 51–60 years with diabetes have approximately a 2.5-fold higher risk of coronary heart disease than those without diabetes, those aged 31–40 years with diabetes have an approximately 17 times higher risk than individuals without diabetes.[30] Furthermore, a study from the USA found that young (18–39 years of age) and middle-aged (40–64 years of age) individuals have substantially

Table 3 Casual blood glucose and risk of incidence of fatal or non-fatal acute myocardial infarction and stroke and cardiovascular and all-cause mortality in 159 731 Norwegian men and women, followed up to 12.7 years, stratified by sex (imputed data)

		Baseline casual blood glucose level		
Events/no.		**<7.8 mmol/L (normal)**	**7.8–11.0 mmol/L (borderline)**	**>11.0 mmol/L (high)**
Acute myocardial infarction				
Women	2188/84 005			
Adjusted HR (95 % CI)*		1 (ref.)	1.37 (1.07 to 1.76)	1.98 (1.14 to 3.44)
Adjusted HR (95% CI)†		1 (ref.)	1.30 (1.02 to 1.68)	1.79 (1.03 to 3.12)
Men	4381/75 726			
Adjusted HR (95% CI)*		1 (ref.)	1.13 (0.95 to 1.35)	1.33 (0.87 to 2.03)
Adjusted HR (95% CI)†		1 (ref.)	1.05 (0.88 to 1.26)	1.14 (0.74 to 1.75)
Stroke				
Women	2875/84 005			
Adjusted HR (95% CI)*		1 (ref.)	1.46 (1.17 to 1.81)	2.18 (1.38 to 3.45)
Adjusted HR (95% CI)†		1 (ref.)	1.39 (1.11 to 1.73)	1.93 (1.21 to 3.05)
Men	3242/75 726			
Adjusted HR (95% CI)*		1 (ref.)	1.33 (1.12 to 1.60)	1.87 (1.24 to 2.83)
Adjusted HR (95% CI)†		1 (ref.)	1.23 (1.03 to 1.47)	1.66 (1.09 to 2.53)
Cardiovascular mortality				
Women	2653/84 005			
Adjusted HR (95% CI)*		1 (ref.)	1.53 (1.25 to 1.87)	2.17 (1.40 to 3.35)
Adjusted HR (95% CI)†		1 (ref.)	1.48 (1.22 to 1.81)	1.99 (1.29 to 3.07)
Men	3025/75 726			
Adjusted HR (95% CI)*		1 (ref.)	1.25 (1.04 to 1.51)	1.98 (1.33 to 2.93)
Adjusted HR (95% CI)†		1 (ref.)	1.16 (0.97 to 1.40)	1.81 (1.21 to 2.70)
All-cause mortality				
Women	7756/84 005			
Adjusted HR (95% CI)*		1 (ref.)	1.29 (1.13 to 1.47)	1.89 (1.42 to 2.52)
Adjusted HR (95% CI)†		1 (ref.)	1.27 (1.12 to 1.45)	1.83 (1.36 to 2.46)
Men	9340/75 726			
Adjusted HR (95% CI)*		1 (ref.)	1.29 (1.17 to 1.44)	1.64 (1.27 to 2.12)
Adjusted HR (95% CI)†		1 (ref.)	1.27 (1.14 to 1.41)	1.59 (1.22 to 2.08)

*Adjusted for age and time since last meal.
†Adjusted for age, cholesterol, systolic blood pressure, BMI, time since last meal, smoking, education and marital status.
BMI, body mass index.

higher glycemic levels than older adults.[10] In the current study, there was no clear effect modification by age for the association between glucose level and subsequent CVD and mortality. For AMI, the association was only significant for high glucose levels among those 65 years and older, while the association with cardiovascular mortality was most pronounced among those younger than 65 years of age. For strokes and all-cause mortality, only small differences were found between the two age groups with slightly stronger associations among those younger than 65 years. There was no significant interaction effect between age group and glucose for any of the endpoints, but given the small number of individuals and endpoints in the highest glucose category, this could be a consequence of low power. Taken together, these findings may imply that the association between casual blood glucose and future risk of CVD is strongest among the youngest, although no firm conclusions can be drawn based on currently available research.

Strengths and weaknesses

The strength of the current study includes its community-based cohort design and its use of information on glucose level and subsequent risk of CVD and mortality to conduct a large study of men and women without a known diagnosis of diabetes. We were able to investigate differences according to sex and age group and to adjust for the effect of several CVD risk factors. Some

limitations also need to be addressed. First, this study was based on one single blood glucose measurement and not two, which is recommended in clinical guidelines. Thus, the results may not accurately reflect an individual's usual or longer term glucose and thereby indicate values over the diagnostic threshold. Moreover, no information was available about subsequent diabetes diagnoses among those with borderline or high glucose levels, and we were therefore unable to examine whether the increased CVD risk among these individuals was mediated by diabetes. There may also be individuals with undiagnosed diabetes at baseline. Second, by using casual glucose level, we had information on both fasting and non-fasting individuals, and although only 0.2% of the study population reported that it had been more than 7 hours since their last meal, it may not be suitable to categorize these individuals according to the same glucose categories as non-fasting participants. Compared with fasting glucose levels, casual levels may have larger intraindividual and interindividual variations due to the influence of sampling time (eg, time since last meal).[24] Also, previous studies have shown that both HbA1c and fasting blood glucose independently predict CVD.[31–33] However, Hemoglobin A1c (Hba1c) and blood glucose measure different aspects of glucose metabolism; HbA1c measures chronic glycemia, while blood glucose reflects glucose at the time of sampling. These two measures therefore identify different individuals at risk of CVD. Casual glucose has the advantage of lower costs and higher feasibility. Third, we imputed missing values for the main exposure variable: casual blood glucose. For the majority of the participants with missing glucose levels, the values were missing completely at random, because one of the regional health surveys in CONOR did not include measurement of glucose. For the remaining participants with missing values, it is reasonable to assume them to be missing at random given the other cardiovascular risk factors included in the model. We therefore do not believe that the imputation could have introduced any substantial bias. Lastly, there were considerable differences in baseline characteristics across categories of glucose levels and even though we have adjusted for confounding by using multiple regression, we cannot rule out that the associations found in the current study may be due to residual confounding because of imbalance between categories. The observed associations between continuous glucose and CVD risk within the normal and borderline range of glucose is however less prone to residual confounding caused by failure to reach covariate balance.

In conclusion, the current study found an association between elevated casual blood glucose level, even within the range of normal and borderline levels, and future CVD and mortality among adults without a known diagnosis of diabetes. These findings point to the importance of early identification of individuals at risk of diabetes and subsequent CVD. Screening for casual blood glucose levels also among those who are not suspected of having diabetes may be important from a public health viewpoint.

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