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Symptoms of depression in people with impaired glucose metabolism or Type 2 diabetes mellitus: The Hoorn Study

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Abstract

Objective To study the prevalence and risk factors of depressive symptoms, comparing subjects with normal glucose metabolism (NGM), impaired glucose metabolism (IGM) or Type 2 diabetes mellitus (DM2).

Research design and methods Cross-sectional data from a population-based cohort study conducted among 550 residents (276 men and 274 women) of the Hoorn region, the Netherlands. Levels of depressive symptoms were measured using the Centre for Epidemiologic Studies Depression Scale (CES-D score ≥ 16). Glucose metabolism status was determined by means of fasting and post-load glucose levels.

Results The prevalence of depressive symptoms in men with NGM, IGM and DM2 was 7.7, 7.0 and 15.0% ($P = 0.19$) and for women 7.7, 23.1 and 19.7% ($P < 0.01$), respectively. Depression was significantly more common in women with IGM [odds ratio (OR) = 3.60, 95% confidence interval (CI) = 1.57 to 8.28] and women with DM2 (OR = 3.18, 95% CI = 1.31 to 7.74). In men, depression was not associated with IGM (OR = 0.90, 95% CI = 0.32 to 2.57) and non-significantly more common in DM2 (OR = 2.04, 95% CI = 0.75 to 5.49). Adjustment for cardiovascular risk factors, cardiovascular disease and diabetes symptoms reduced the strength of these associations.

Conclusions Depressive symptoms are more common in women with IGM, but not men. Adjustment for cardiovascular risk factors, cardiovascular disease and diabetes symptoms partially attenuated these associations, suggesting that these variables could be intermediate factors.

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Keywords depression, epidemiology, prevalence, risk factors, Type 2 diabetes

Abbreviations CES-D, Centre for Epidemiologic Studies Depression Scale; DM2, Type 2 diabetes mellitus; HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; IGM, impaired glucose metabolism; IMT, intima-media thickness; NGM, normal glucose metabolism; OGTT, oral glucose tolerance test; WHO, World Health Organization

Introduction

Diabetes and depression are both common diseases. There are currently more than 171 million people with diabetes, mostly Type 2 diabetes mellitus (DM2), worldwide [2]. It is estimated that this number will rise to 366 million in 2030 [1,2]. An estimated 121 million people currently suffer from depression and about 6% of men and 10% of women will experience a depressive episode in any given year [3]. Evidence from the past decades strongly suggests that diabetes and depression are associated. Approximately 10–15% of patients with diabetes mellitus meet criteria for co-morbid major depression [4,5]. Interestingly, depression is also a risk factor for development of diabetes mellitus [6,7]. Knol *et al.* concluded that non-diabetic adults with depression have a 30% increased risk for DM2 [8]. Moreover, depression also contributes to poor self-care and adherence to medical treatment, higher symptom burden [9], higher glycated haemoglobin (HbA_{1c}) [10], more diabetes complications [11,12] and increased healthcare use and costs in patients with diabetes [13,14].

In concert with the increasing number of people with diabetes, the number of people with impaired glucose metabolism

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(pre-diabetes) is also rising rapidly [15]. Given the close association of depression with DM2 and the rising numbers of both DM2 and people with impaired glucose metabolism, it is logical to study whether this association also exists in persons with pre-diabetes. This could shed light on the underlying mechanisms explaining the observed association between depression and metabolic abnormalities. Until recently, the prevalence of depression among different groups of glucose metabolism was not known.

Knol *et al*. were the first to study the prevalence of depression in people with impaired fasting glucose [16]. They found that impaired fasting glucose was not associated with depressive symptoms, while diagnosed DM2 was associated with an increased prevalence of depressive symptoms. The authors stated important limitations such as the use of self-report to define diagnosis of DM2 and the possible lack of generalizabillity because of the relatively young age (mean age 39.4 years) of the study population. Knol *et al*. did not report the association between groups of different glucose metabolism and depression for men and women separately. There is evidence that this association is stronger for women with DM2 compared with men and it is hypothesized that this may be because of differences in oestrogen levels [17].

The actual prevalence and risk factors of depressive symptoms in normal glucose metabolism subjects, impaired glucose metabolism (pre-diabetes) subjects and patients with DM2 for both men and women separately, is currently unknown. Such knowledge is relevant from a clinical perspective as pre-diabetes is increasingly common. Moreover, depression is an established risk factor for cardiovascular disease.

We therefore analysed cross-sectional data from the Hoorn Study, a population-based cohort study, to investigate the prevalence and risk factors of depression in a group of elderly adults, comparing subjects with normal glucose metabolism with subjects with impaired glucose metabolism (pre-diabetes) and patients with DM2 and analysing men and women separately.

Research design and methods

Subjects

The Hoorn Study is a population-based cohort study on DM2 in the general Dutch population that started in 1989 and has been described in detail previously [18]. In summary, it consisted of 2484 men and women aged 50–75 years at baseline, selected from the population register of the middle-sized Dutch town of Hoorn. In 2000–2001, a third examination was performed of surviving participants who gave their permission to be re-contacted. We invited all participants who had diabetes, as determined by a 75-g oral glucose tolerance test (OGTT) or by diabetes treatment ($n = 176$) at the second examination of the entire cohort in 1996–1998 [19]. We also invited random samples of participants who had normal glucose metabolism ($n = 705$) or impaired glucose metabolism ($n = 193$) in 1996–1998. Of 1074 individuals invited, 648 persons (60.3%) participated. The main reasons for not participating in the 2000–2001 follow-up examination are described elsewhere

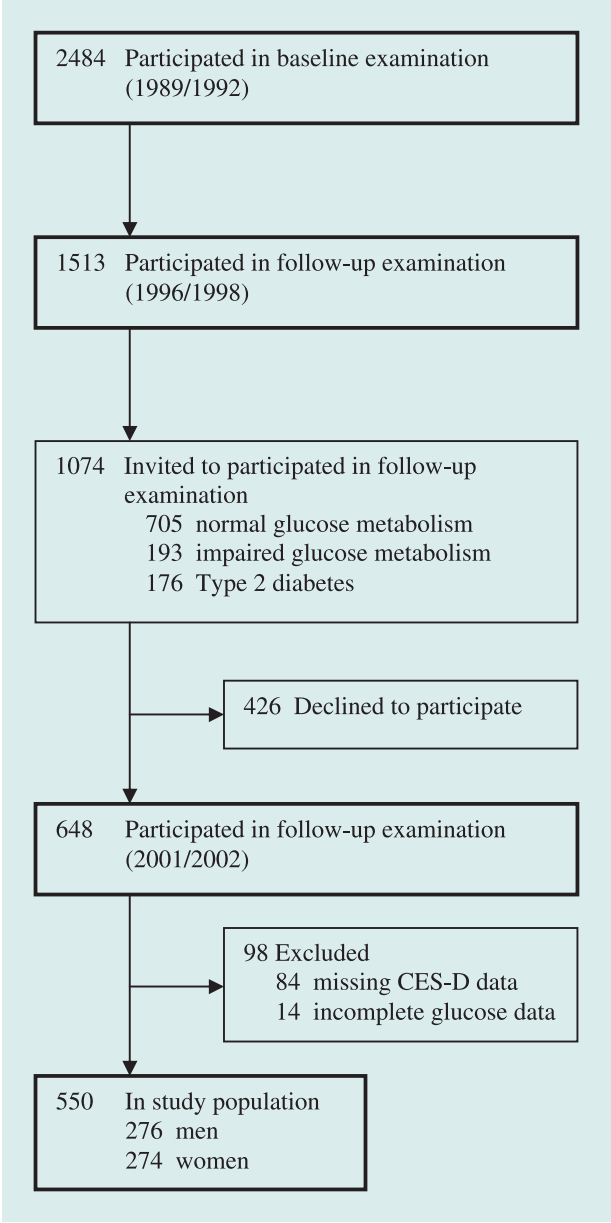

FIGURE 1 Flow chart of the study population at baseline and follow-up examinations. CES-D, Centre for Epidemiologic Studies Depression Scale.

[20]. For the present study, cross-sectional data of the 2000–2001 follow-up examination were analysed. Of the 648 participants, 84 individuals were excluded because of missing symptoms of depression data. Another 14 individuals were excluded because glucose metabolism data were incomplete. Therefore, our final study cohort consisted of 550 subjects; 276 men and 274 women (Fig. 1). The study protocol was approved by the Ethical Review Committee of the VU University Medical Center and all participants gave written informed consent.

Depressive symptoms

Levels of depressive symptoms were measured using the 20-item Centre for Epidemiologic Studies Depression Scale (CES-D

score ≥ 16) [21]. The Dutch translation of this instrument has good psychometric properties and satisfactory criterion validity [22]. The overlap between depression and symptoms of physical illness appeared to be minimal in several studies. The CES-D measures the frequency of symptoms of depression over the past 7 days. The CES-D total score can range from 0 to 60. The generally used cut-off score of 16 and above was used to identify respondents with clinically significant levels of depression [22].

Demographic and cardiovascular variables

Data were collected during the medical examination that was carried out at the Diabetes Research Centre in Hoorn. Information about age, sex, smoking and education level (low vs. middle and high level) was assessed by means of a questionnaire. Participants were not aware of their metabolic status prior to completing either the CES-D or the Type 2 Diabetes Symptom Checklist. Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest. Fasting and 2-h post-load plasma glucose were measured with the hexokinase method (Roche Diagnostics, Mannheim, Germany). Glucose metabolism status was defined according to the World Health Organization (WHO) 1999 criteria, i.e. fasting plasma glucose ≥ 7.0 mmol/l on two separate occasions or a plasma glucose level ≥ 11.1 mmol/l 2 h after the glucose load [23]. HbA_{1c} was determined by ion-exchange high-performance liquid chromatography with Modular Diabetes Monitoring System (Bio-Rad, Veenedaal, the Netherlands). Serum total cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides were measured by enzymatic techniques (Boeringer-Mannheim, Mannheim, Germany).

Systolic and diastolic blood pressure were determined at the right upper arm, after 5 min rest in seated participants, with a random-zero sphygmomanometer (Hawksley-Gelma, Lancing, UK). Blood pressure was calculated as the mean of two measurements. Individuals were considered to be hypertensive if they had a diastolic blood pressure ≥ 90 mmHg and/or a systolic blood pressure ≥ 140 mmHg and/or they were taking antihypertensive medication. Carotid intima-media thickness (IMT) was determined by ultrasonography, using previously described techniques [24]. Subjects were classified as having albuminuria if they had an albumin : creatinine ratio > 2.0 mg/mmol. Ischaemic heart disease was defined as the presence of Minnesota codes 1-1, 1-2, 1-3, 4-1, 4-2, 4-3, 5-1, 5-3 or 7-1, respectively, on the electrocardiogram recording.

Diabetes symptoms

People with pre-diabetes may experience symptoms of diabetes. This may contribute to the development of depression. To measure diabetes symptom distress, we used the revised version of the Type 2 Diabetes Symptom Checklist [25], which refers to the month preceding the visit. The presence of diabetes-related symptoms is measured as Yes/No and, if the respondent answers Yes, the perceived burden was scored on a 5-point Likert-scale from 0 ('not at all') to 4 ('extremely'). The Type 2 Diabetes Symptom Checklist consists of 34 symptom items covering eight dimensions: hyperglycaemic (four items), hypoglycaemic (three items), polyneuropathic pain (four items), polyneuropathic sensory (six items), psychological fatigue (four items), psychological cognitive distress (four items), cardiovascular (four items) and ophthalmological (five items) symptoms. The eight sub-scale scores are calculated by summating the item scores, divided by the number of items of that dimension. The Type 2 Diabetes Symptom Checklist total score is calculated by summation of all item scores divided by 34. Higher scores indicate more symptom distress. The scales of the Type 2 Diabetes Symptom Checklist appeared to have satisfactory reliability [26,27].

Statistical analysis

All analyses were performed separately for men and women because of the statistically significant effect modification by sex of the relations under condition. Descriptive data (means, standard deviation and percentage) of subjects with normal glucose metabolism, impaired glucose metabolism and DM2 are presented for men and women separately. Differences in study sample characteristics for the three groups of glucose metabolism status by sex were examined using analyses of variance for continuous variables and χ^2-tests for categorical variables. Next, analyses were carried out to contrast the data on depressive symptoms (CES-D score ≥ 16), comparing subjects with impaired glucose metabolism or detected DM2 with normal glucose metabolism subjects. In analyses pertaining to depressive symptoms, crude and adjusted odds ratios with 95% confidence intervals were calculated. Logistic regression analyses were used to study whether depression symptom severity was significantly associated with demographic variables (age and low education). Moreover, we were interested in the potential intermediating effects of cardiovascular diseases, cardiovascular risk factors and diabetes symptoms on the relationship between glucose status and depression. Therefore, we tested whether adjustment for cardiovascular risk factors (triglycerides, HDL cholesterol, total cholesterol, waist circumference, hypertension and smoking), cardiovascular disease (carotid IMT, myocardial infarction and ischaemic heart disease) and diabetes symptoms (hyperglycaemic, cardiovascular, neuropathic pain, sensibility and ophthalmological) changed the association between glucose status and depression. In these analyses, we excluded three of the eight diabetes symptoms dimensions (hypoglycaemic, psychological fatigue and cognitive distress) from the model (Model 4) because these scales contain depressive/anxiety/irritability symptoms that are also used in the depression outcome parameter. For all statistical testing, we used two-sided hypothesis testing with an alpha level of < 0.05. Statistical analyses were performed using the SPSS 11.5 software package for Windows (SPSS Inc., Chicago, IL, USA).

Results

Participants

Descriptive data (means, standard deviation and percentage) of the demographic and clinical variables of the subjects with normal glucose metabolism (NGM), impaired glucose

Table 1 Characteristics of the study participants by sex and glucose status

	Men				Women			
	NGM	IGM	DM2	*P*	NGM	IGM	DM2	*P*
N	130	86	60	—	130	78	66	—
Age (years)	69.1 ± 5.9	69.1 ± 6.1	70.9 ± 6.4	0.131	68.0 ± 6.0	70.4 ± 5.9	72.1 ± 7.1	< 0.001
Low education (%)	42.3	40.7	32.2	0.408	45.4	57.3	61.3	0.072
Fasting plasma glucose (mmol/l)	5.5 ± 0.4	6.1 ± 0.5	8.0 ± 1.9	< 0.001	5.4 ± 0.4	6.1 ± 0.5	7.9 ± 2.2	< 0.001
HbA_{1c} (%)	5.7 ± 0.4	5.8 ± 0.4	6.8 ± 1.0	< 0.001	5.7 ± 0.4	5.9 ± 0.3	6.8 ± 0.9	< 0.001
Triglycerides (mmol/l)	1.3 ± 0.6	1.5 ± 0.7	1.9 ± 1.0	< 0.001	1.2 ± 0.6	1.6 ± 0.8	1.9 ± 0.9	< 0.001
HDL cholesterol (mmol/l)	1.3 ± 0.4	1.3 ± 0.3	1.1 ± 0.3	< 0.001	1.7 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	< 0.001
Total cholesterol (mmol/l)	5.4 ± 1.0	5.5 ± 1.0	5.2 ± 1.0	0.089	6.1 ± 0.9	6.1 ± 1.1	5.9 ± 1.0	0.343
Waist circumference (cm)	96 ± 9	100 ± 10	102 ± 10	< 0.001	86 ± 10	95 ± 11	98 ± 12	< 0.001
Hypertension (%)	59.2	65.1	88.3	< 0.001	54.6	79.5	92.3	< 0.001
Smoking (%)	22.3	29.1	10.0	0.022	12.3	15.4	10.8	0.693
Carotid IMT (mm)	0.86 ± 0.19	0.89 ± 0.18	0.93 ± 0.19	0.092	0.80 ± 0.15	0.87 ± 0.15	0.91 ± 0.15	< 0.001
Myocardial infarction (%)	10.1	7.1	9.1	0.749	3.1	6.4	6.7	0.422
Ischaemic heart disease (%)	31.8	32.9	38.2	0.696	33.1	39.7	50.0	0.082

Data are %, means ± SD. *P* = *P*-values based on one-way ANOVA for continuous variables and χ^2-tests for categorical variables.
DM2, Type 2 diabetes mellitus (World Health Organization 1999 criteria); HbA_{1c}, glycated haemoglobin; HDL, high-density lipoprotein; IGM, impaired glucose metabolism; IMT, intima-media thickness; NGM, normal glucose metabolism; SD, standard deviation.

Table 2 Prevalence (%) and odds ratios for elevated levels of depressive symptoms (CES-D score ≥ 16) by sex with impaired glucose metabolism or Type 2 diabetes subjects compared with normal glucose metabolism subjects

		n	% (*n*)	Unadjusted OR (95% CI)*	Model 1 OR (95% CI)†	Model 2 OR (95% CI)‡	Model 3 OR (95% CI)§	Model 4 OR (95% CI)¶
Men	NGM	130	7.7 (10)	Referent	Referent	Referent	Referent	Referent
	IGM	86	7.0 (6)	0.90 (0.32–2.57)	0.90 (0.31–2.58)	0.78 (0.26–2.35)	0.83 (0.23–2.95)	0.89 (0.28–2.90)
	DM2	60	15.0 (9)	2.04 (0.76–5.49)	1.95 (0.71–5.34)	1.05 (0.32–3.39)	1.26 (0.36–4.43)	1.52 (0.47–4.94)
	R^2			2%	5%	13.6%	14.3%	25.8%
Women	NGM	130	7.7 (10)	Referent	Referent	Referent	Referent	Referent
	IGM	78	23.1 (18)	3.60 (1.57–8.28)	3.04 (1.28–7.21)	2.55 (1.00–6.49)	3.48 (1.35–8.95)	2.21 (0.87–5.60)
	DM2	66	19.7 (13)	3.18 (1.31–7.74)	3.18 (1.26–8.02)	2.52 (0.86–7.33)	2.83 (0.93–8.61)	2.76 (1.01–7.50)
	R^2			7.3%	9.6%	12.6%	13.6%	25.8%

*The unadjusted odds ratios.
†Model 1: adjusted for age and low education.
‡Model 2: adjusted for age, low education and cardiovascular risk factors (triglycerides, HDL cholesterol, total cholesterol, waist circumference, hypertension and smoking).
§Model 3: adjusted for age, low education and cardiovascular diseases (carotid intima-media thickness and ischaemic heart disease).
¶Model 4: adjusted for age, low education and diabetes symptoms (hyperglycaemic, cardiovascular, neuropathic pain, sensibility and ophthalmological).
CES-D, Centre for Epidemiologic Studies Depression Scale; CI, confidence interval; DM2, Type 2 diabetes mellitus (World Health Organization 1999 criteria); IGM, impaired glucose metabolism; NGM, normal glucose metabolism; OR, odds ratio.

metabolism (IGM) or DM2 subjects are presented stratified by sex in Table 1. There were 550 subjects, 276 men (50.2%) and 274 women, aged 69.5 ± 6.3 years (mean ± SD). Of those, 309 subjects were between 60 and 69 years of age (56.2%), 196 subjects were between 70 to 79 years of age (35.6%) and 45 subjects were between 80 and 87 years old (8.2%). Fasting plasma glucose, HbA_{1c}, triglycerides, HDL cholesterol, waist circumference and hypertension in both sexes were significantly associated with deteriorating glucose metabolism when tested for a linear trend. Likewise, smoking in men and age and carotid IMT in women were positively associated with impaired glucose metabolism status.

Prevalence of depressive symptoms

The prevalence of depressive symptoms in the whole group was 12% [men 9.1% ($n = 25$) and women 15.0% ($n = 41$)]. The prevalence of depressive symptoms in men with NGM, IGM and DM2 was 7.7, 7.0 and 15.0% ($P = 0.19$) and for women was 7.7, 23.1 and 19.7% ($P < 0.01$), respectively (Table 2).

Risk factors

In the unadjusted logistic regression analysis, the odds for higher levels of depressive symptoms was three-fold in women with IGM (OR = 3.60, 95% CI = 1.57 to 8.28) or DM2 (OR = 3.18, 95% CI = 1.31 to 7.74) (Table 2). In contrast, in men depression was not associated with IGM (OR = 0.90, 95% CI = 0.32 to 2.57), whereas men with DM2 had a doubled risk for depression (OR = 2.04, 95% CI = 0.75 to 5.49), although this was not statistically significant.

In men, the association between DM2 and depressive symptoms did not substantially change when adjusting for age and low education (only 4% lower). However, in men with DM2, the odds ratio dropped considerably after adjusting for cardiovascular risk factors (Model 2; 48% reduction) or the presence of cardiovascular disease (Model 3; 38% reduction) and to a lesser degree after adjustment for diabetes symptoms (Model 4; 25% reduction). However, this data should be interpreted with caution because none of the presented odds ratios for men reached statistical significance.

In women, when adjusting for age and low education (Model 1), the odds ratios for IGM and DM2 were only slightly attenuated and remained significant. The odds ratio for the association between IGM or DM2 and depression dropped after adjustment for cardiovascular risk factors (Model 2; 29% reduction in IGM, 21% reduction in DM2), cardiovascular disease (Model 3; 3% reduction in IGM, 11% reduction DM2) or diabetes symptoms (Model 4; 39% reduction in IGM, 13% reduction DM2).

Discussion

To our knowledge, this is the first population-based study that determined the prevalence and risks for depressive symptoms in different groups of glucose metabolism for men and women separately, using diagnostic criteria for diabetes (i.e. OGTT). We observed that the prevalence of depressive symptoms was higher in women with IGM and DM2 compared with NGM. In men, depressive symptoms were not associated with IGM, whereas men with DM2 had a doubled risk for depression, although this was not statistically significant. Interestingly, adjustment for cardiovascular risk factors, cardiovascular diseases and diabetes symptoms lowered these odds ratios considerably, suggesting that these variables could be intermediate factors.

The observation that IGM was not associated with increased depression in men, in contrast to women with IGM, was unexpected and is difficult to explain. It is conceivable that the results are as a result of selection bias, for example, because male participants with depression were less willing to participate in the study. Our finding that the prevalence of depressive symptoms is not higher in men with IGM and diabetes is consistent with the finding of the Caerphily prospective cohort study, which showed that insulin resistance was not associated with depression in middle-aged men [28]. The results in the men are also consistent with recent results of Knol *et al*., who found that an increased level of depressive symptoms was not more common in men and women with impaired fasting glucose [16]. In another study, we found only weak associations between depressive symptoms and insulin resistance, which did not differ among different glucose metabolism subgroups or between men and women [29]. The fact that HbA_{1c} was similar in subjects with NGT and IGT speaks against the possibility that hyperglycaemia is responsible for the association between depressive symptoms and different states of glucose tolerance. Thus, it could be speculated (while ruling out insulin resistance and hyperglycaemia) that cardiovascular risk factors (or factors of the metabolic syndrome) combined with readiness to report symptoms may be more important for high depressive symptoms than diabetes-related metabolic variables.

Cardiovascular disease is one of the most common complications of diabetes. The review de Groot *et al*. concluded that cardiovascular disease is associated with an increased risk for depression [11]. Furthermore, in an earlier study using data of the Longitudinal Aging Study Amsterdam, we have found that the prevalence of increased depressive symptoms was not increased in patients with diabetes only, while it was increased in diabetes patients who had co-morbid disease, in particular those with cardiovascular disease [30]. We found only partial attenuation of the association between glucose metabolism and depression by cardiovascular disease (or its risk factors) and diabetes symptoms. We therefore believe that the prevalence of depression in women with IGM could be related to other, unmeasured confounders, such as being widowed or the burden of having other co-morbid disease(s).

The results of the present study, demonstrating partial attenuation of the association between glucose metabolism and depression by cardiovascular disease (or its risk factors) and diabetes symptoms suggest that other mechanisms, in addition to the burden of disease, might also play a role. Some plausible alternative mechanisms include, for example, dysregulation of the hypothalamic–pituitary–adrenal axis and the sympathetic nervous system [31–33], sex steroid hormone levels [34], the role of polyunsaturated fatty acids [35], low grade inflammation [36,37] or vitamin D deficiency [38–40]. More research is needed with regard to factors underlying these biological mechanisms.

Several strengths of our study should be emphasized. First, we used gold-standard assessment to determine glucose metabolism status by means of fasting glucose and post-load glucose levels, based on the OGTT and using the WHO 1999 diagnostic criteria. Second, the precise assessment of the cardiovascular variables, especially carotid IMT determined by ultrasonography, and myocardial infarction and ischaemic heart disease defined by using electrocardiogram recording. Third, the Hoorn Study is conducted in a population-based cohort. Finally, the outcomes are presented separately for men and women because of the effect modification by sex.

Our study also has several limitations. First, our results should be interpreted with caution because of the relative

small numbers with elevated levels of depression per glucose group. Second, our depression assessment was based on self-report, using the CES-D rather than a gold-standard diagnostic psychiatric interview. However, the CES-D is a widely used, well-validated measure for depressive symptoms, particularly suited for large-scale epidemiological studies, both in the general population and in diabetes patients [41]. Third, the present study has a cross-sectional design, thus we cannot infer causality between depression and either pre-diabetes or diabetes. Finally, the present study was limited to a Dutch Caucasian elderly population. It is not clear whether the relationship between depression, glucose metabolism and cardiovascular risk factors is consistent across different racial, ethnic and age groups.

In conclusion, our study suggests that depressive symptoms are more common in women with IGM and DM2. In men, depression was not associated with IGM but non-significantly increased in DM2. Adjustment for cardiovascular risk factors, cardiovascular diseases and diabetes symptoms attenuated these associations, suggesting that these factors could play an intermediate role in the aetiology of depression in diabetes, or even explain why depressed people are at increased risk for DM2. Type 2 diabetes, IGM and depression are increasingly common conditions [1,2,15]. A high level of depressive symptoms is not only associated with increased risk for diabetes and cardiovascular disease, but also with increased mortality [42–44].

Our findings need to be replicated. Moreover, further well-designed prospective research is needed: (i) to test whether depression in IGM is associated with an increased risk for developing DM2 and cardiovascular disease in women; (ii) to disentangle the complex causal relationships between (the onset of) depressive symptoms, glucose metabolism status and cardiovascular disease; and (iii) to clarify its mechanisms.

Competing interests

None to declare.

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