The association of hyperglycaemia and insulin resistance with incident depressive symptoms over 4 years of follow-up: The Maastricht Study

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Abstract

Aims/hypothesis Depression is twice as common in individuals with type 2 diabetes as in the general population. However, it remains unclear whether hyperglycaemia and insulin resistance are directly involved in the aetiology of depression. Therefore, we investigated the association of markers of hyperglycaemia and insulin resistance, measured as continuous variables, with incident depressive symptoms over 4 years of follow-up.

Methods We used data from the longitudinal population-based Maastricht Study (n = 2848; mean age 59.9 ± 8.1 years, 48.8% women, 265 incident depression cases, 10,932 person-years of follow-up). We assessed hyperglycaemia by fasting and 2 h post-load OGTT glucose levels, HbA1c and skin autofluorescence (reflecting AGEs) at baseline. We used the Matsuda insulin sensitivity index and HOMA-IR to calculate insulin resistance at baseline. Depressive symptoms (nine-item Patient Health Questionnaire score ≥10) were assessed at baseline and annually over 4 years. We used Cox regression analyses, and adjusted for demographic, cardiovascular and lifestyle risk factors.

Results Fasting plasma glucose, 2 h post-load glucose and HbA1c levels were associated with an increased risk for incident depressive symptoms after full adjustment (HR 1.20 [95% CI 1.08, 1.33]; HR 1.25 [1.08, 1.44]; and HR 1.22 [1.09, 1.37] per SD,

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respectively), while skin autofluorescence, insulin sensitivity index and HOMA-IR were not (HR 0.99 [0.86, 1.13]; HR 1.02 [0.85, 1.25]; and HR 0.93 [0.81, 1.08], per SD, respectively).

**Conclusions/interpretation** The observed temporal association between hyperglycaemia and incident depressive symptoms in this study supports the presence of a mechanistic link between hyperglycaemia and the development of depressive symptoms.

**Keywords** Depression · Depressive symptoms · Epidemiology · Hyperglycaemia · Insulin resistance · Population-based cohort study · Type 2 diabetes mellitus

**Abbreviations**
- IGM: Impaired glucose metabolism
- ISI: Insulin sensitivity index
- MDD: Major depressive disorder
- NGM: Normal glucose metabolism
- PHQ-9: Nine-item Patient Health Questionnaire
- ROS: Reactive oxygen species
- SAF: Skin autofluorescence

**Introduction**

The prevalence of depression is nearly doubled in individuals with type 2 diabetes as compared with the general population, with prevalence rates of 6.5% to 33% [1]. Comorbid depression in type 2 diabetes is associated with impaired quality of life [2], worse self-care, suboptimal blood glucose levels and an increased risk for macro- and microvascular complications, mortality [3] and dementia [4]. In addition, their co-occurrence has an adverse economic impact with increased healthcare costs and decreased work productivity [5]. Furthermore, depression appears to be highly persistent and/or recurrent in type 2 diabetes [6]. Although there is evidence for a bidirectional association between type 2 diabetes and depression, the exact nature and the aetiological direction of the relationship remain unknown [1].

Hyperglycaemia and insulin resistance are key features of type 2 diabetes, and have been proposed as underlying mechanisms involved in the aetiology of depression [7]. Both fluctuations in plasma glucose and prolonged hyperglycaemia may be involved in the development of depression. The brain is particularly vulnerable to fluctuations in plasma glucose levels because neurons do not possess an active glucose transporter. As a consequence, high extracellular glucose levels lead to high intracellular glucose levels. The resulting
biochemical changes, for instance the formation of reactive oxygen species (ROS) or AGEs, and accumulation of the resulting damage over the years, may lead to neuronal damage and/or disturbances of the hypothalamic–pituitary–adrenal axis, which eventually may lead to depression [7]. However, current evidence on the temporality of these associations remains scarce. A recent meta-analysis of prospective studies found an association between prevalent diabetes and incident depression but not between impaired glucose metabolism (IGM) or newly diagnosed type 2 diabetes and incident depression, compared with normal glucose metabolism (NGM) [8]. However, numbers for incident depression with IGM [9–11] or newly diagnosed type 2 diabetes were relatively small [10–13] and thus confidence intervals were large, and all studies used categorical instead of continuous values of glucose metabolism.

With regard to insulin resistance, only four prospective studies examined the association with incident depression. One study found an association [14], while the others did not [15–17]. However, these studies have important methodological limitations, such as a single follow-up assessment of depression [14, 16, 17], inclusion of only men [15] or only elderly men [14], a small study population [17] or a small number of incident depression cases [14].

In summary, there is a need for methodologically well-conducted prospective studies to assess whether hyperglycaemia and insulin resistance are temporally related to the development of depression. Therefore, the aim of this study was to examine the associations of markers of hyperglycaemia and insulin resistance measured as continuous variables with incident clinically relevant depressive symptoms within the population-based Maastricht Study. In addition, we assessed whether these associations were independent of demographic, cardiovascular and lifestyle risk factors, or differed between women and men. We hypothesised that hyperglycaemia and higher levels of insulin resistance are independently associated with incident clinically relevant depressive symptoms, and that these associations are similar in women and men.

Methods

Study population and design The Maastricht Study is an observational population-based cohort study. The rationale and methodology have been described previously [18]. In brief, the study focuses on the aetiology, pathophysiology, complications and comorbidities of type 2 diabetes and is characterised by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status, with an oversampling of individuals with type 2 diabetes, for reasons of efficiency. The present report includes baseline data from 3124 participants, who completed the baseline survey between November 2010 and September 2013. Figure 1 gives an overview of the study design. The baseline examinations of each participant were performed within a time window of 3 months. Follow-up data were only available for depression data and were available in 91.9%, 85.4%, 79.9% and 71.4% of the participants with available baseline data at, respectively, 1, 2, 3 and 4 years of follow-up. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare, and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Figure 2 shows the flowchart of the study population. From the initial 3451 participants we excluded individuals with other types of diabetes than type 2 diabetes (n = 41). For the cross-sectional analyses we included participants with available hyperglycaemia, insulin resistance and nine-item Patient Health Questionnaire (PHQ-9) data at baseline (n = 3124). For the longitudinal analyses, we excluded participants with clinically relevant depressive symptoms at baseline (PHQ-9 score ≥10, n = 139) or without any follow-up PHQ-9 data (n = 137) to investigate the associations with newly developed depressive symptoms during follow-up, resulting in a study population of 2848 participants with an average follow-up duration of 3.8 ± 1.0 years.

Hyperglycaemia Markers of hyperglycaemia were measured at baseline. Participants, except those who used insulin (as endogenous insulin production is limited), underwent a standardised 2 h 75 g OGTT to determine fasting and 2 h post-load blood glucose levels after an overnight fast. For safety reasons, participants with a fasting glucose level above 11.0 mmol/l, as determined by a finger prick, did not undergo the OGTT (n = 42). Venous fasting and 2 h post-load plasma glucose levels were measured by the enzymatic hexokinase method on two automatic analysers, the Beckman Synchron LX20 (Beckman Coulter, CA, USA) for samples obtained between November 2010 and April 2012, and the Roche Cobas 6000 (Roche Diagnostics, Mannheim, Germany) for samples obtained thereafter. Glucose metabolism status was defined according to the World Health Organization 2006 criteria as NGM, prediabetes (fasting glucose 6.1–7.0 mmol/l or 2 h post-load blood glucose 7.8–11.1 mmol/l) or type 2 diabetes (fasting blood glucose ≥7.0 mmol/l or 2 h post-load blood glucose ≥11.1 mmol/l, or used oral glucose-lowering medication or insulin) [19]. Type 1 diabetes and other types of diabetes were determined by use of a clinical interview. HbA1c was determined in fasting venous blood samples by ion-exchange high performance liquid chromatography [18].
Skin autofluorescence (SAF) was measured with the AGE Reader (DiagnOptics Technologies, Groningen, the Netherlands), which is a desktop device that uses ultraviolet light to excite autofluorescence in human skin tissue to estimate the level of AGE accumulation in the skin, as described elsewhere [20].

**Insulin resistance** Insulin resistance was assessed by the Matsuda insulin sensitivity index (ISI) and the HOMA-IR [21] as baseline only. The ISI was calculated as suggested by DeFronzo and Matsuda [22]:

$$\text{ISI} = \frac{10,000}{(G_0 \times I_0 \times G_{\text{mean}} \times I_{\text{mean}})^{1/2}},$$

where $G$ and $I$ represent plasma glucose (mmol dl$^{-1}$) and insulin (mU l$^{-1}$) concentrations, respectively, and ‘0’ and ‘mean’ indicate fasting value and mean value during OGTT.

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**Fig. 1** Study design

**Fig. 2** Flowchart of study population. *Missing data on covariates are not mutually exclusive*
respectively. The reciprocal (i.e., 1/ISI) was used to reflect insulin resistance as a risk factor. The ISI is strongly correlated ($r = 0.73$, $p < 0.0001$) with the rate of whole-body glucose disposal during the euglycaemic insulin clamp [23].

HOMA-IR was calculated with the HOMA2 calculator version 2.2.3 for Windows [24]. HOMA-IR is the most widely used and validated surrogate marker of insulin resistance and corresponds reasonably well to clamp-derived measures of insulin sensitivity [25]. Neither measure was calculated for participants receiving insulin treatment ($n = 169$); as endogenous insulin levels will be close to zero, ISI and HOMA-IR calculations will result in zero as well.

**Depressive symptoms** Depressive symptoms were assessed by a validated Dutch version of the PHQ-9 [26] both at baseline and during annual follow-up over 4 years. The PHQ-9 is a self-administered questionnaire that assesses the presence of the nine symptoms for the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for a major depressive disorder (MDD) [27] on a four-point Likert-scale ranging from 0, ‘not at all’, to 4, ‘nearly every day’. When one or two items were missing, the total score was calculated as $9 \times \left( \frac{\text{total points}}{9} - \text{number of missing items} \right)$ and rounded to the nearest integer. When more items were missing, the total score was scored as missing.

A cut-off score of $\geq 10$ is most often used as a dichotomous scoring system for defining clinically relevant depressive symptoms, with sensitivity and specificity of, respectively, 88% and 78% [28]. Online PHQ-9 questionnaires were completed annually during a follow-up period of 4 years. Prevalent depressive symptoms were defined as clinically relevant depressive symptoms at baseline (PHQ-9 $\geq 10$). Incident depressive symptoms were defined as no depressive symptoms at baseline (PHQ-9 <10) and presence of clinically relevant depressive symptoms on at least one follow-up moment (PHQ-9 $\geq 10$). In addition, at baseline only, current and lifetime diagnosis of MDD was assessed by the Mini-International Neuropsychiatric Interview (MINI) [29].

**General characteristics and covariates** General characteristics and covariates were measured at baseline. Educational level (low, intermediate, high), partner status (partner/no partner), history of CVD, smoking status (never, current, former), alcohol consumption (none, low, high), physical activity and Mediterranean diet score were assessed by questionnaires [18]. We measured height, weight, waist circumference, office blood pressure, plasma lipid profile, eGFR (in ml min$^{-1}$ 1.73 m$^{-2}$) and 24 h urinary albumin excretion (twice). Urinary albumin excretion was defined as normal (<15 mg/24 h), microalbuminuria (15 to <30 mg/24 h) or macroalbuminuria ($\geq 30$ mg/24 h). Medication use was assessed in a medication interview where generic name, dose and frequency were registered. More details about these general characteristics and covariates are provided in the electronic supplementary material (ESM) methods.

**Statistical analysis** All statistical analyses were performed by use of the Statistical Package for Social Sciences (version 25.0; IBM, Chicago, Illinois, USA). General characteristics of the study population were evaluated using independent $t$ tests, Mann–Whitney $U$ tests or $\chi^2$ tests. Negative binomial and logistic regression analyses were used to investigate the cross-sectional associations of markers of hyperglycaemia and insulin resistance per SD with, respectively, depressive symptoms and clinically relevant depressive symptoms. We used Cox proportional regression analyses to assess the association of markers of hyperglycaemia and insulin resistance per SD with incident depressive symptoms (PHQ-9 $\geq 10$), with time-in-study as time axis. Participants were censored at the date of the event or, in case of attrition, the last available date of follow-up, whichever came first. Hazard ratios indicate the increased risk for incident depressive symptoms per SD higher marker of hyperglycaemia or insulin resistance.

We performed complete case analyses in which associations were adjusted for potential confounders in four models: model 1, crude; model 2, adjusted for demographic confounders (age, sex and educational level); model 3, additionally adjusted for cardiovascular risk factors (waist circumference, office systolic blood pressure, blood pressure-lowering medication, total-to-HDL-cholesterol ratio, lipid-modifying medication, eGFR and history of CVD); and model 4, additionally adjusted for modifiable lifestyle-related risk factors (smoking behaviour and alcohol use). We also investigated whether there was an interaction with sex in the fully adjusted model.

Several additional analyses were performed. To study whether the associations were driven by the oversampling of individuals with diagnosed type 2 diabetes, we additionally adjusted for type 2 diabetes, and excluded participants with type 2 diabetes from the analyses. To reduce potential misclassification of participants with subthreshold depression (MDD but low PHQ-9 scores due to remission or treatment), we performed the following sensitivity analyses: first, we additionally adjusted for use of antidepressant medication at baseline; second, we excluded participants who used antidepressant medication at baseline; and third, we excluded participants who had an MDD diagnosis at baseline. To restrict analyses to ‘de novo’ depression, we excluded participants who had a lifetime MDD diagnosis at baseline. We also applied stricter rules on the follow-up data, allowing no or a maximum of one missing follow-up measurement. Furthermore, we additionally adjusted for physical activity and Mediterranean diet score, as these data were missing in more participants. Finally, we replaced office systolic blood pressure with 24 h ambulatory systolic
blood pressure, waist circumference with BMI and total-to-HDL-cholesterol ratio with triacylglycerols. A two-sided p value <0.05 was considered statistically significant.

### Results

#### General characteristics of the study population

During 10,932 person-years of follow-up, 265 (9.3%) participants developed clinically relevant depressive symptoms (PHQ-9 ≥10; average
follow-up time of 2.5 ± 1.2 years), which yields an incidence rate of 24 cases per 1000 person-years. Participants not included in the analyses (\(n = 603\)) were statistically significantly younger, had a lower level of education, less often had a partner, had higher levels of hyperglycaemia and insulin resistance, and had a worse

| Model | Prevalent depressive symptoms | \(p\) value | Prevalent clinically relevant depressive symptoms (PHQ-9 ≥10) | \(p\) value |
|-------|-------------------------------|------------|-----------------------------------------------------------|------------|
|       | Rate ratio (95% CI)           |            | OR (95% CI)                                               |            |
|       |                               |            |                                                           |            |
|       | Markers of hyperglycaemia     |            |                                                           |            |
|       | Fasting plasma glucose (per 1 SD) |            |                                                           |            |
| Model 1 | 1.08 (1.04, 1.12)          | <0.001     | 1.30 (1.15, 1.46)                                         | <0.001     |
| Model 2 | 1.15 (1.10, 1.20)          | <0.001     | 1.41 (1.25, 1.60)                                         | <0.001     |
| Model 3 | 1.08 (1.03, 1.13)          | 0.001      | 1.17 (1.00, 1.36)                                         | 0.045      |
| Model 4 | 1.07 (1.02, 1.12)          | 0.008      | 1.13 (0.97, 1.32)                                         | 0.130      |
|       | 2 h post-load glucose (per 1 SD) |            |                                                           |            |
| Model 1 | 1.04 (1.00, 1.08)          | 0.074      | 1.19 (1.01, 1.41)                                         | 0.042      |
| Model 2 | 1.10 (1.05, 1.15)          | <0.001     | 1.35 (1.13, 1.61)                                         | 0.001      |
| Model 3 | 1.03 (0.98, 1.09)          | 0.298      | 1.06 (0.84, 1.33)                                         | 0.619      |
| Model 4 | 1.02 (0.97, 1.08)          | 0.407      | 1.05 (0.84, 1.33)                                         | 0.656      |
|       | HbA1c (per 1 SD)            |            |                                                           |            |
| Model 1 | 1.12 (1.07, 1.16)          | <0.001     | 1.42 (1.26, 1.61)                                         | <0.001     |
| Model 2 | 1.18 (1.13, 1.23)          | <0.001     | 1.54 (1.35, 1.75)                                         | <0.001     |
| Model 3 | 1.11 (1.06, 1.16)          | <0.001     | 1.30 (1.11, 1.52)                                         | 0.001      |
| Model 4 | 1.08 (1.03, 1.13)          | 0.002      | 1.21 (1.03, 1.42)                                         | 0.022      |
|       | SAF (per 1 SD)              |            |                                                           |            |
| Model 1 | 1.03 (0.99, 1.08)          | 0.122      | 1.18 (1.00, 1.39)                                         | 0.051      |
| Model 2 | 1.11 (1.06, 1.16)          | <0.001     | 1.43 (1.19, 1.72)                                         | <0.001     |
| Model 3 | 1.07 (1.02, 1.13)          | 0.004      | 1.31 (1.07, 1.60)                                         | 0.009      |
| Model 4 | 1.04 (0.99, 1.09)          | 0.152      | 1.18 (0.95, 1.45)                                         | 0.129      |
|       | ISI (per SD)               |            |                                                           |            |
| Model 1 | 1.04 (1.00, 1.09)          | 0.056      | 1.16 (0.93, 1.45)                                         | 0.182      |
| Model 2 | 1.10 (1.05, 1.15)          | <0.001     | 1.29 (1.02, 1.63)                                         | 0.033      |
| Model 3 | 1.02 (0.96, 1.07)          | 0.598      | 0.89 (0.69, 1.15)                                         | 0.363      |
| Model 4 | 1.01 (0.96, 1.07)          | 0.621      | 0.88 (0.68, 1.14)                                         | 0.323      |
|       | HOMA-IR (per SD)            |            |                                                           |            |
| Model 1 | 1.07 (1.02, 1.12)          | 0.004      | 1.20 (1.02, 1.42)                                         | 0.032      |
| Model 2 | 1.12 (1.07, 1.17)          | <0.001     | 1.28 (1.08, 1.53)                                         | 0.005      |
| Model 3 | 1.03 (0.97, 1.09)          | 0.345      | 0.95 (0.75, 1.20)                                         | 0.665      |
| Model 4 | 1.02 (0.96, 1.08)          | 0.485      | 0.93 (0.73, 1.18)                                         | 0.561      |

Total number of participants included in model 1: \(n = 3121\) (fasting plasma glucose); \(n = 2920\) (2 h post-load glucose); \(n = 3115\) (HbA1c); \(n = 2959\) (SAF); \(n = 2709\) (ISI); and \(n = 2814\) (HOMA-IR)

Number of prevalent depression cases in model 1: \(n = 138\) (fasting plasma glucose); \(n = 113\) (2 h post-load glucose); \(n = 139\) (HbA1c); \(n = 131\) (SAF); \(n = 101\) (ISI); and \(n = 110\) (HOMA-IR)

Model 1: crude
Model 2: adjusted for age, sex and educational level. Data missing, \(n = 60\) (fasting plasma glucose)
Model 3: additionally adjusted for waist circumference, office systolic blood pressure, antihypertensive medication, total-to-HDL-cholesterol ratio, lipid-modifying medication and history of CVD. Additional missing data, \(n = 128\) (fasting plasma glucose)
Model 4: additionally adjusted for smoking behaviour and alcohol use. Additional missing data, \(n = 97\) (fasting plasma glucose)

\(a\) The reciprocal was used for the ISI (1/ISI)
Markers of insulin resistance

Markers of hyperglycaemia

Table 3

| Model | Incident depressive symptoms (PHQ-9 ≥10) HR (95% CI) | p value |
|-------|-------------------------------------------------------|---------|
| Markers of hyperglycaemia | | |
| Fasting plasma glucose (per 1 SD) | | |
| Model 1 | 1.35 (1.25, 1.46) | <0.001 |
| Model 2 | 1.33 (1.22, 1.45) | <0.001 |
| Model 3 | 1.21 (1.09, 1.34) | <0.001 |
| Model 4 | 1.20 (1.08, 1.33) | 0.001 |
| 2 h post-load glucose (per 1 SD) | | |
| Model 1 | 1.32 (1.18, 1.47) | <0.001 |
| Model 2 | 1.29 (1.14, 1.45) | <0.001 |
| Model 3 | 1.26 (1.09, 1.46) | 0.002 |
| Model 4 | 1.25 (1.08, 1.44) | 0.003 |
| HbA1c (per 1 SD) | | |
| Model 1 | 1.44 (1.32, 1.57) | <0.001 |
| Model 2 | 1.40 (1.27, 1.53) | <0.001 |
| Model 3 | 1.28 (1.15, 1.43) | <0.001 |
| Model 4 | 1.22 (1.09, 1.37) | 0.001 |
| SAF (per 1 SD) | | |
| Model 1 | 1.15 (1.02, 1.30) | 0.019 |
| Model 2 | 1.12 (0.99, 1.28) | 0.075 |
| Model 3 | 1.06 (0.93, 1.22) | 0.401 |
| Model 4 | 0.99 (0.86, 1.13) | 0.831 |
| Markers of insulin resistance | | |
| ISI (per SD) | | |
| Model 1 | 1.22 (1.05, 1.43) | 0.010 |
| Model 2 | 1.21 (1.03, 1.42) | 0.018 |
| Model 3 | 1.03 (0.86, 1.23) | 0.748 |
| Model 4 | 1.03 (0.86, 1.23) | 0.783 |
| HOMA-IR (per SD) | | |
| Model 1 | 1.19 (1.06, 1.34) | 0.003 |
| Model 2 | 1.19 (1.05, 1.34) | 0.006 |
| Model 3 | 0.99 (0.84, 1.17) | 0.962 |
| Model 4 | 0.98 (0.83, 1.15) | 0.766 |

Associations of hyperglycaemia with incident depressive symptoms

Table 3 shows the associations of markers of hyperglycaemia with incident depressive symptoms. Fasting plasma glucose, 2 h post-load glucose and HbA1c levels were associated with an increased risk for incident depressive symptoms after full adjustment (HR 1.20 [95% CI 1.08, 1.33]; HR 1.25 [1.08, 1.44] and HR 1.22 [1.09, 1.37] per SD, respectively). SAF was not associated with incident depressive symptoms (HR 0.99 [0.86, 1.13] per SD). No interactions were found with regard to sex for fasting plasma glucose (p-interaction = 0.981), 2 h post-load glucose (p-interaction = 0.234) and HbA1c (p-interaction = 0.686). There was an interaction with sex for SAF (p-interaction = 0.031); however, associations were not significant in stratified analyses for men (HR 1.13 [0.94, 1.37] per SD) or women (HR 0.83 [0.67, 1.02] per SD).

Associations of insulin resistance with incident depressive symptoms

Table 3 shows the associations of insulin resistance with incident depressive symptoms. A lower ISI and a higher HOMA-IR were associated with an increased risk for incident depressive symptoms after adjustment for age, sex and educational level (HR 1.21 [1.03, 1.42] and HR 1.19 [1.05, 1.34] per SD, respectively). After additional adjustment for cardiovascular risk factors, these associations were attenuated (HR 1.03 [0.86, 1.23] and HR 0.99 [0.84, 1.17] per SD, respectively). These attenuations were mainly caused by waist circumference (model 2 additionally adjusted for waist circumference: HR 1.04 [0.87, 1.24] and HR 1.02 [0.87, 1.19] per SD, respectively). No interaction with regard to sex was found for ISI (p-interaction = 0.589) and HOMA-IR (p-interaction = 0.621).

Additional analyses

Results of additional analyses are shown in Table 4. Additional adjustment for type 2 diabetes, and excluding participants with type 2 diabetes from the analyses, did not materially change the associations. As expected, additional adjustment for type 2 diabetes attenuated the associations, but HRs remained directionally similar.
Table 4 Additional analyses for associations of markers of hyperglycaemia with incident depressive symptoms

| Model | Incident clinically relevant depressive symptoms (PHQ-9 ≥10) HR (95% CI) | p value |
|-------|-------------------------------------------------------------------------|---------|
| Fasting plasma glucose (per 1 SD) | | |
| Model 4 | 1.20 (1.08, 1.33) | 0.001 |
| Model 5: model 4 + type 2 diabetes | 1.12 (0.99, 1.27) | 0.085 |
| Model 6: model 4 excl. type 2 diabetes (excluded data n = 683) | 1.35 (0.81, 2.25) | 0.255 |
| Model 7: model 4 + antidepressant medication | 1.20 (1.08, 1.33) | 0.001 |
| Model 8: model 4 excl. antidepressant users (missing data n = 152) | 1.18 (1.05, 1.33) | 0.006 |
| Model 9: model 4 excl. baseline MDD (excluded data n = 150) | 1.19 (1.06, 1.33) | 0.003 |
| Model 10: model 4 excl. lifetime MDD (excluded data n = 897) | 1.06 (0.87, 1.29) | 0.580 |
| Model 11: model 4 + physical activity (missing data n = 160) | 1.19 (1.07, 1.33) | 0.002 |
| Model 12: model 4 + Mediterranean diet (missing data n = 123) | 1.18 (1.06, 1.32) | 0.002 |
| Model 13: model 4 replacing office SBP for 24 h SBP (missing data n = 294) | 1.19 (1.06, 1.33) | 0.003 |
| Model 14: model 4 replacing waist circumference for BMI | 1.21 (1.09, 1.34) | <0.001 |
| Model 15: model 4 replacing total-to-HDL-cholesterol ratio for triacylglycerols | 1.17 (1.05, 1.30) | 0.004 |
| 2 h post-load glucose (per 1 SD) | | |
| Model 4 | 1.25 (1.08, 1.44) | 0.003 |
| Model 5: model 4 + type 2 diabetes | 1.16 (0.93, 1.45) | 0.192 |
| Model 6: model 4 excl. type 2 diabetes (excluded data n = 539) | 1.19 (0.78, 1.83) | 0.419 |
| Model 7: model 4 + antidepressant medication | 1.27 (1.10, 1.47) | 0.001 |
| Model 8: model 4 excl. antidepressant users (missing data n = 132) | 1.26 (1.08, 1.47) | 0.003 |
| Model 9: model 4 excl. baseline MDD (excluded data n = 143) | 1.23 (1.05, 1.44) | 0.009 |
| Model 10: model 4 excl. lifetime MDD (excluded data n = 840) | 1.18 (0.94, 1.49) | 0.163 |
| Model 11: model 4 + physical activity (missing data n = 153) | 1.22 (1.04, 1.42) | 0.014 |
| Model 12: model 4 + Mediterranean diet (missing data n = 116) | 1.24 (1.06, 1.44) | 0.006 |
| Model 13: model 4 replacing office SBP for 24 h SBP (missing data n = 274) | 1.23 (1.05, 1.44) | 0.008 |
| Model 14: model 4 replacing waist circumference for BMI | 1.25 (1.08, 1.44) | 0.002 |
| Model 15: model 4 replacing total-to-HDL-cholesterol ratio for triacylglycerols | 1.21 (1.04, 1.40) | 0.015 |
| HbA1c (per 1 SD) | | |
| Model 4 | 1.22 (1.09, 1.37) | 0.001 |
| Model 5: model 4 + type-2 diabetes | 1.14 (1.00, 1.31) | 0.057 |
| Model 6: model 4 excl. type-2 diabetes (excluded data n = 684) | 1.23 (0.82, 1.83) | 0.318 |
| Model 7: model 4 + antidepressant medication | 1.23 (1.10, 1.38) | <0.001 |
| Model 8: model 4 excl. antidepressant users (missing data n = 152) | 1.18 (1.03, 1.34) | 0.017 |
| Model 9: model 4 excl. baseline MDD (excluded data n = 150) | 1.21 (1.07, 1.37) | 0.003 |
| Model 10: model 4 excl. lifetime MDD (excluded data n = 894) | 1.08 (0.87, 1.33) | 0.486 |
| Model 11: model 4 + physical activity (missing data n = 160) | 1.25 (1.11, 1.41) | <0.001 |
| Model 12: model 4 + Mediterranean diet (missing data n = 123) | 1.20 (1.06, 1.35) | 0.004 |
| Model 13: model 4 replacing office SBP for 24 h SBP (missing data n = 294) | 1.23 (1.08, 1.41) | 0.002 |
| Model 14: model 4 replacing waist circumference for BMI | 1.23 (1.10, 1.38) | <0.001 |
| Model 15: model 4 replacing total-to-HDL-cholesterol ratio for triacylglycerols | 1.20 (1.07, 1.35) | 0.002 |
| SAF (per 1 SD) | | |
| Model 4 | 0.99 (0.86, 1.13) | 0.831 |
| Model 5: model 4 + type-2 diabetes | 0.94 (0.85, 1.11) | 0.606 |
| Model 6: model 4 excl. type-2 diabetes (excluded data n = 658) | 0.87 (0.72, 1.05) | 0.154 |
| Model 7: model 4 + antidepressant medication | 1.00 (0.87, 1.15) | 0.975 |
| Model 8: model 4 excl. antidepressant users (missing data n = 147) | 1.01 (0.87, 1.18) | 0.852 |
| Model 9: model 4 excl. baseline MDD (excluded data n = 145) | 1.01 (0.87, 1.17) | 0.876 |
| Model 10: model 4 excl. lifetime MDD (excluded data n = 854) | 1.00 (0.81, 1.25) | 0.985 |
Adjustments to reduce potential misclassification of participants with subthreshold depression did not materially change our results. Furthermore, applying stricter rules on the follow-up data, allowing no or a maximum of one missing follow-up measurement for the control participants, did not materially change our results (data not shown).

Similar strengths of the associations were found after additional adjustment for physical activity or Mediterranean diet score. Furthermore, our results were not materially changed by replacing office systolic blood pressure with 24 h ambulatory systolic blood pressure, replacing waist circumference with BMI or replacing total-to-HDL-cholesterol ratio with triacylglycerols.

**Discussion**

This population-based study demonstrates that fasting plasma glucose, 2 h post-load glucose and HbA1c were associated with incident depressive symptoms, with an increased risk of ~20% per SD higher level of hyperglycaemia markers. These associations were independent of demographical, cardiovascular and lifestyle-related risk factors, and were similar in women and men. The association of insulin resistance with incident depressive symptoms was explained by cardiovascular risk factors (waist circumference). Our results suggest that hyperglycaemia precedes the development of depression, and may be directly involved in its aetiology.

Our finding that hyperglycaemia is associated with incident depressive symptoms corroborates and further extends previous evidence of an association between type 2 diabetes and incident depression [30], and provides additional evidence that hyperglycaemia as such may be involved in the development of depression. This is in line with results of a large-scale cross-sectional study that showed an association between both diagnosed and undiagnosed diabetes and higher prevalence of depression [31]. Although a previous meta-analysis concluded that hyperglycaemia is unlikely to be causally related to incident depressive symptoms [8], this study did not investigate a linear contribution of hyperglycaemia to the incidence of depression.

Several pathophysiological pathways may explain the association between hyperglycaemia and incident depression. Hyperglycaemia is associated with generalised microvascular dysfunction [32], which may consequently lead to cerebral small vessel disease and subsequent depression [33]. Indeed, a recent meta-analysis showed that cerebrovascular damage was associated with incident depression [34]. Optimising blood glucose levels is the most effective therapy to prevent the development of microvascular complications in type 2 diabetes, and could potentially also contribute to preventing or slowing down the development of depressive symptoms. Alternatively, suboptimal blood glucose levels may also identify those individuals at high risk for depression. Furthermore, hyperglycaemia has been associated with low-grade inflammation [35], which in turn has been associated with cerebrovascular damage [36] and incident depression as well [37]. In support of this potential mechanism, several studies have shown that treatment resistance to antidepressants is associated with low-grade inflammation [38] and that anti-inflammatory therapy may be beneficial to individuals with depression [39]. Moreover, hyperglycaemia may activate the polyol pathway which induces oxidative stress, increases lipid peroxidation and imbalances the generation of ROS [40]. These processes may lead to apoptosis in the brain, which may eventually lead to depression via shrinkage of specific brain structures (atrophy) [41]. This assumption is supported by a stronger association between oxidative stress and depression in individuals with IGM and type 2 diabetes than in those with NGM [42]. Furthermore, previous studies have assumed that diabetes may increase risk of depression because of disease burden [8]. However, disease burden alone may be not sufficient to explain the association between hyperglycaemia and incident depression, since 65% of the
association remained after additional adjustment for type 2 diabetes. In addition, the suggestion that somatic symptoms may explain this association is unlikely, as a previous study of our group has shown that affective and somatic symptoms do not differ between individuals with and individual without type 2 diabetes [46].

We found no association between SAF and incident depressive symptoms, although earlier cross-sectional analyses in a smaller dataset (n = 866) from The Maasstricht Study did show an association between higher SAF and prevalent depression [20]. SAF is thought to represent the accumulation of fluorescent AGEs in the skin, but may be a less specific measure of hyperglycaemia, as it also measures other fluorescent proteins in the skin and does not reflect non-fluorescent AGEs [44]. Nevertheless, there are currently no other prospective studies available that have assessed this association. Therefore, this finding warrants replication in other prospective population-based studies in order to draw firm conclusions.

We found that the association of insulin resistance with incident depression was explained by CVD risk factors, in particular central obesity. This is in contrast with results of the Whitehall II Study, the Caerphilly Study and the Pittsburgh Healthy Heart Project, which did not show an association between insulin resistance and incident depression after adjustment for age only [15, 16]. Furthermore, our results contrast with the results of the Health in Men Study, which did show an association between higher insulin resistance and incident depression after adjustment for cardiovascular risk factors including central obesity [14]. However, the Health in Men Study only included older men aged 70–93 years, which hinders direct comparison with our somewhat younger population. There are several explanations for the attenuation of the association between insulin resistance and incident depressive symptoms after adjustment for central obesity. First, central obesity may be on the causal pathway from insulin resistance to depression, which might have resulted in overadjustment. Second, as performing clamps is not feasible in large-scale studies, we used surrogate markers of insulin resistance. These markers moderately reflect hepatic and muscular insulin resistance, which may or may not coincide with cerebral insulin resistance [45]. Consequently, we cannot fully exclude the possibility that cerebral insulin resistance is involved in the development of depression. Third, insulin resistance is less precisely measured than hyperglycaemia. The use of surrogate markers of insulin resistance may have created more noise in the data as compared with the direct markers of hyperglycaemia. Alternatively, hyperglycaemia may be one of the mechanisms linking insulin resistance to depression. Obesity is associated with the development of insulin resistance, but only individuals who lack sufficient insulin secretion to match the degree of insulin resistance will develop type 2 diabetes [46].

The association of hyperglycaemia with an increased risk of depressive symptoms has important clinical implications. First, professionals in diabetes care should be aware of the prevalence of depression, and use diagnostic skills to recognise and treat depression properly. For this, specific guidelines to identify and manage depressive symptoms in diabetes care have been developed [47]. In addition to these guidelines, it is important to distinguish between need for treatment and a high score on a questionnaire [48]. Since depression in individuals with type 2 diabetes is often persistent [6], and is related to suboptimal blood glucose levels [3], early recognition and treatment of depressive symptoms could have a favourable effect on the outcome of both diseases [49]. Considering the high comorbidity of depression and type 2 diabetes, integrated care approaches that treat these conditions jointly need to be implemented in diabetes care.

Strengths of our study include its large sample size and population-based longitudinal design; the oversampling of individuals with type 2 diabetes which results in more variability within the high ranges of hyperglycaemia; the annual assessment of the PHQ-9 to assess depressive symptoms over a 4 year period; the comparable incidence rate of depression to other population-based studies; the use of multiple continuous markers of hyperglycaemia: the extensive assessment of potential confounders; and the execution of several sensitivity analyses.

This study has some limitations. First, there could have been selection and/or attrition bias, which is inherent to prospective population-based studies; individuals with more severe depressive symptoms or with greater comorbidity may have been more likely not to participate or to withdraw, which may have led to an underestimation of the observed associations. Second, the study population was relatively well treated with regard to glucose metabolism, which may mean that the effects of fasting plasma glucose, 2 h post-load glucose and HbA1c on incident depression were suppressed. Estimates of post-load glucose, ISI and HOMA-IR, did not include insulin users, which may have led to an underestimation of the observed findings in more severe type 2 diabetes. Third, the population was mainly of white ethnicity and aged 40–75 years, which should be considered when extrapolating these findings to other populations. Fourth, we measured depressive symptoms with the PHQ-9 questionnaire. High scores on this questionnaire are suggestive for depressive symptoms, but do not necessarily equate with MDD. Finally, because follow-up data were only available for depression data, we could not rule reverse causality; there might be a reciprocal relation in which depression may also lead to hyperglycaemia.
Conclusion

In conclusion, we showed that higher levels of hyperglycaemia were associated with incident depressive symptoms in a population-based setting, independent of major demographical, cardiovascular and lifestyle risk factors. The association of insulin resistance with incident depressive symptoms was dependent on cardiovascular risk factors, in particular, central obesity. These findings establish a temporal relation between hyperglycaemia and incident depressive symptoms, supporting the concept that hyperglycaemia itself is involved in the aetiology of depression, and thus may provide a potential target for the prevention of depression in individuals with and without type 2 diabetes.

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Data availability The data of this study derive from The Maastricht Study, but restrictions apply to the availability of these data, which were used under license for the current study. Data are, however, available from the authors upon reasonable request and with permission of The Maastricht Study management team.

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Contribution statement AFJG, SK, RM, CGS, AO, SJPME, PCD, CDAS, NCS, RMAH, CJIvdk, AW, AK, FRJV and MTS were involved in the design or conduct of the study, the preparation of the manuscript and the decision to submit it for publication, and all verify the accuracy and completeness of the data analyses. AFJG, SK and MTS analysed data and drafted the article. AFJG, SK, RM, CGS, AO, SJPME, PCD, CDAS, NCS, RMAH, CJIvdk, AW, AK, FRJV and MTS commented on the drafts and contributed to writing. AFJG, SK, RM, CGS, AO, SJPME, PCD, CDAS, NCS, RMAH, CJIvdk, AW, AK, FRJV and MTS approved the final version. AFJG is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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