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Article (Published Version)

Pols, Alide Danielle, Adriaanse, Marcel C, van Tulder, Maurits W, Heymans, Martijn W, Bosmans, Judith E, van Dijk, Susan E and van Marwijk, Harm W J (2018) Two-year effectiveness of a stepped-care depression prevention intervention and predictors of incident depression in primary care patients with diabetes type 2 and/or coronary heart disease and subthreshold depression; data from the Step-Dep cluster randomized controlled trial. BMJ Open, 8 (10). e020412 1-10. ISSN 2044-6055

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Two-year effectiveness of a stepped-care depression prevention intervention and predictors of incident depression in primary care patients with diabetes type 2 and/or coronary heart disease and subthreshold depression: data from the Step-Dep cluster randomised controlled trial

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ABSTRACT

Introduction Major depressive disorders (MDD), diabetes mellitus type 2 (DM2) and coronary heart disease (CHD) are leading contributors to the global burden of disease and often co-occur.

Objectives To evaluate the 2-year effectiveness of a stepped-care intervention to prevent MDD compared with usual care and to develop a prediction model for incident depression in patients with DM2 and/or CHD with subthreshold depression.

Methods Data of 236 Dutch primary care patients with DM2/CHD with subthreshold depression (Patient Health Questionnaire 9 (PHQ-9) score ≥6, no current MDD according to the Mini International Neuropsychiatric Interview (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria)) who participated in the Step-Dep trial were used. A PHQ-9 score of ≥10 at minimally one measurement during follow-up (at 3, 6, 9, 12 and 24 months) was used to determine the cumulative incidence of MDD. Potential demographic and psychological predictors were measured at baseline via web-based self-reported questionnaires and evaluated using a multivariable logistic regression model. Model performance was assessed with the Hosmer-Lemeshow test, Nagelkerke’s $R^2$ explained variance and area under the receiver operating characteristic curve (AUC). Bootstrapping techniques were used to internally validate our model.

Results 192 patients (81%) were available at 2-year follow-up. The cumulative incidence of MDD was 97/192 (51%). There was no statistically significant overall treatment effect over 24 months of the intervention (OR 1.37; 95% CI 0.52 to 3.55). Baseline levels of anxiety, depression, the presence of >3 chronic diseases and stressful life events predicted the incidence of MDD (AUC 0.80, IQR 0.79–0.80; Nagelkerke’s $R^2$ 0.34, IQR 0.33–0.36).

Conclusion A model with 4 factors predicted depression incidence during 2-year follow-up in patients with DM2/CHD accurately, based on the AUC. The Step-Dep intervention did not influence the incidence of MDD. Future depression prevention programmes should target patients.

Strengths and limitations of this study

- This study provides a prediction model of incident major depressive disorder (MDD) in patients with diabetes mellitus type 2 and/or coronary heart disease with subthreshold depression, which could assist healthcare providers in its detection and facilitate targeting indicated prevention to highest-risk patients.
- Only predictors that are readily available or easily obtained in practice were used in the multivariable model, which enhances the practical use of the model.
- This study had a relatively long follow-up and outcomes were frequently measured, whereas dropout rates were relatively low and missing values imputed.
- The relatively small study population might have caused overoptimism of the prediction model, but an internal validation procedure with bootstrapping techniques showed that this risk was minor.
- Data were derived from a randomised controlled trial, but statistically non-significant intervention effects for incident MDD at both 12 and 24 months follow-up justify using the Step-Dep population as a cohort.
with these 4 predictors present, and aim to reduce both anxiety and depressive symptoms. 

**Trial registration number** NTR3715.

**INTRODUCTION**

Depression is a major and increasing contributor to the global burden of disease, whereas coronary heart disease (CHD) and diabetes mellitus type 2 (DM2) rank among the leading causes of morbidity and mortality worldwide. Comorbid depression in patients with DM2 and/or CHD is common and has detrimental effects on self-care and medication adherence, quality of life and health status and increases healthcare costs and mortality. Despite its negative impact, many cases of depression go unrecognised in primary care, especially in patients with chronic diseases like DM2 and/or CHD. Additionally, about one-third of those recognised and treated does not respond to current approaches, and over half of those who experience a first onset of a major depressive episode will experience one or more recurrences.

Given the significant burden of disease of depression, its poor recognition and the limited effect of current treatment options for it, it would be of great value if incident cases could be averted by early detection and preventive treatment of patients at risk (“indicated prevention”). Meta-analyses have shown that preventive psychological interventions can overall reduce the incidence of major depressive disorder (MDD) in comparison to control groups. Offering preventive psychological interventions in a stepped-care format could be an efficient approach, as patients start with minimally intensive evidence-based treatments and only those who do not improve adequately step up to a treatment of higher intensity. Recently, we conducted a randomised controlled trial (RCT) in which we evaluated whether a pragmatic nurse-led stepped-care programme was effective in reducing the incidence of MDD at 12 months of follow-up in comparison with usual care among patients with DM2 and/or CHD and subthreshold depression (Step-Dep). Subthreshold depression entails clinically relevant depressive symptoms without fulfilling the criteria for MDD and is a known important risk factor for depression. We demonstrated that the Step-Dep intervention was not superior to usual care and the overall cumulative incidence of MDD was lower than expected after 1 year. However, it may be possible that the follow-up period was too restricted to demonstrate the potential health benefits of the stepped-care programme over usual care, or the presence of subthreshold depression alone posed a lower than expected prior risk of MDD in our DM2 and/or CHD population.

Identifying additional major risk factors of incident depression in patients with DM2 and/or CHD might facilitate targeting indicated prevention to patients with highest risk, but also potentially aid in its detection. In patients with DM2, several longitudinal studies have been conducted to determine risk factors for comorbid incident depression. However, these studies have rendered heterogeneous results, due to small patient samples (<80 at follow-up), analyses of single factors only, the use of mixed samples of type 1 diabetes and DM2, patients with either no MDD at baseline or both with and without depression at baseline and differences across community, primary care and secondary care settings. In patients with CHD, the only available longitudinal data are derived from studies in patients with acute coronary syndrome followed-up after hospital discharge. Predictors that were repeatedly identified in DM2 or CHD studies were: depression severity at baseline, history of depression, female sex and baseline anxiety levels. However, data of patients with both DM2 and CHD, non-acute CHD or within primary care settings are scarce. The goal of the present study was twofold: (1) to evaluate the 2-year effectiveness of a nurse-led stepped-care intervention to prevent MDD as compared with usual care (Step-Dep); and to (2) develop a prediction model for incident depression during 2-year follow-up in primary care patients with DM2 and/or CHD and subthreshold depression.

**METHODS**

**Design**

Data of the Step-Dep cluster RCT were used. Step-Dep was conducted in 27 general practitioner (GP) practices in 3 regions in the Netherlands (Amsterdam, Leiden and Twente), between January 2013 and November 2016, including recruitment and 2 years of follow-up. A statistician blinded to the characteristics of the GP practices performed the randomisation of GP practices using a computer-generated list of random numbers. Randomisation was done at the level of the GP practice, which corresponds to the participating practice nurse, to avoid contamination between the treatment groups, and was stratified for size (less or more than 5000 patients). The study was performed in accordance with the declaration of Helsinki (2008) and the Dutch Medical Research involving Human Subjects Act (WMO). The protocol was approved (NL39261.029.12, registration number 2012/223), and registered in the Dutch Trial Register (NTR3715 http://www.trialregister.nl/trialreg/admin/rctview.asp?TC=3715). The evaluation of predictors of incident depression were not prespecified in designing the study. Further details on the methods and design of the Step-Dep study have been published elsewhere.

**Patient and public involvement**

Patients were not involved in determining the design, the recruitment to or conduct of the study. The medical ethics committee of the VU University Medical Centre assessed the burden of the intervention and participation in the study in general as acceptable for patients. The burden of and satisfaction with the intervention were assessed in a process evaluation with 15 patients. All patients are...
thanked in the acknowledgements section. Results of the study will be disseminated by letter to all participants.

Patients

Included patients were aged 18 years or more who had an International Classification of Primary Care (ICPC) diagnosis of DM2 and/or CHD and had subthreshold depression identified by screening. Patients with a Patient Health Questionnaire 9 (PHQ-9; range 0–27 with higher scores indicating more severe depressive symptoms) score of 6 or higher, and no MDD according to the Mini International Neuropsychiatric Interview (MINI), were considered to have subthreshold depression. Exclusion criteria were cognitive impairment, psychotic illnesses, a terminal illness, the use of antidepressant medication, a history of suicide attempt(s), loss of significant other in the past 6 months, visual impairment, current pregnancy, bipolar disorder, borderline personality disorder or any difficulties completing written questionnaires or visiting the primary care centre. A total of 236 patients gave informed consent to participate.

Outcome measure

The outcome measure used was an incident depression (yes/no) defined as a PHQ-9 score of ≥10 at minimally one moment during follow-up (measured at 3, 6, 9, 12 and 24 months after baseline). The PHQ-9 is a widely used and validated instrument that performs well in patients with chronic medical illnesses both as dichotomous diagnosis of major and minor depression and a continuous severity score. A cut-off of ≥10 has been shown to be the optimum cut-off for major depression, also in this patient group. PHQ-9 was self-reported with web-based or written questionnaires. When these web-based or written questionnaires were not completed, the PHQ-9 was administered by telephone by trained research assistants, blinded to randomisation status.

Potential predictors

The selection of the potential predictors was based on a thorough literature search. Predictors of incident depression that were identified in multiple studies in patients with DM2 or CHD and are routinely available or easily obtained in daily GP practice were used. Additionally, we chose the presence of multiple chronic diseases and stressful life events although they were identified in single studies only, as these were also indicated as causes of depression by patients and practice nurses in semi-structured interviews as part of the process evaluation of Step-Dep (Pols, submitted) and age.

Apart from GP information system-derived data on sex, age and ICPC diagnosis of DM2 and/or CHD, demographics and psychological factors were measured at baseline via web-based (or written if preferred) self-reported questionnaires. To take possible effects of the intervention into account, we included randomisation status in the selection models as well. Patients in the intervention arm were offered a stepped-care prevention programme, and patients in the control arm received care as usual during 1 year. The stepped-care intervention consisted of 4 sequential but flexible treatment steps, each lasting 3 months: (1) watchful waiting, (2) guided self-help, (3) problem solving treatment and (4) referral to a GP. After each step, patients with a persisting PHQ-9 score of 6 or more were offered the next treatment step of the intervention. Baseline depression levels were measured with the PHQ-9. Baseline anxiety levels were measured with the Hospital Anxiety and Depression Scale Anxiety (HADS-A; range 0–21 with higher scores indicating more severe anxiety). History of depression and stressful life events were self-reported using a subset of the Diagnostic Interview Schedule. Number of comorbid chronic illnesses was measured using the self-reported Dutch Questionnaire Chronic Illnesses. This was dichotomised using the median in our sample: 3 or less versus more than 3 chronic diseases.

Statistical analyses

The 2-year effectiveness of the intervention on the primary and secondary outcomes was analysed according to the intention to treat principle. Generalised estimating equations were used for binary outcome variables, and linear mixed models for longitudinal data were used for continuous outcome variables. For each outcome, an overall effect over time and separate effects at different time points were estimated by taking time into account as a categorical variable (with 5 categories: 0–3 months, 3–6 months, 6–9 months, 9–12 months and 12–24 months of follow-up). The main analyses consisted of fully corrected models that were corrected for baseline values of the respective outcome and additionally included the covariates gender, age and any other possible confounding variable on which the treatment groups differed at baseline (marital status, employment status, level of education, coexistence of DM2 and CHD, alcohol use, number of depressive episodes in history and age of onset of depression), based on absolute baseline differences judged by the researchers rather than statistical testing. For these analyses, STATA V.14 was used.

Missing data were imputed using multiple imputation according to the multivariate imputation by chained equations algorithm in SPSS V.23. For the imputations, missing at random was assumed. Variables that were associated with missing data and variables that were associated with the outcome were identified and included in the imputation model. Also, all variables in the analysis model (potential predictors and outcome) were included. The number of imputed datasets was 25 based on the proportion of cases with incomplete measurements, 24%. The subsequent analyses were performed on pooled data according to Rubin’s rules.

Prediction model

We created a multivariable logistic regression model in SPSS V.23 from the baseline variables estimating the probability of having at least one major depression (PHQ ≥10)
during the 2-year assessment. To calculate the number of potential predictors for developing the prediction model, we used the criterion of 10 events per variable. Continuous variables were checked for linearity with the outcome using spline regression curves and linearity was confirmed. All variables were entered into the logistic model and tested for statistical significance in the presence of the total set of predictors. Subsequently, the least significant predictor (p value >0.157, as recommended in the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement,50 Wald statistic) was removed, and the model was refit (backward selection). Randomisation status was maintained in the model. This was repeated until we reached a statistical model that only included statistically significant predictors. This process was repeated with p values of 0.05. We also compared the results with complete case analysis (CCA), that is, all patients with missing data were excluded from the analyses.

We checked the performance of the model with regard to the goodness of fit (Hosmer-Lemeshow test), the explained variation and the discriminative ability of the model. The Nagelkerke’s $R^2$ explained variation is the extent to which the outcome can be predicted by the predictors in the model in current data sets. The discriminative ability is reflected by the area under the receiver operating characteristics curve (AUC). Bootstrapping techniques were used to internally validate our model, that is, to simulate the performance with respect to the explained variance and the AUC in comparable patient data sets.51 After that, we calculated the linear predictor of the bootstrapped model with an adjusted intercept and regression coefficients corrected for the shrinkage factor. Performance measures were assessed in each imputed data set and results were summarised using median values.52 All analyses were done with SPSS V.23.0 and R software.

RESULTS

Participants

The baseline characteristics of the study population are presented in table 1. Of the 236 patients included in Step-Dep, 192 patients (81%) completed 2 years of follow-up. A flowchart of participants through the first 12 months of the Step-Dep study has been published elsewhere.20 At 24 months of follow-up, 18 additional patients dropped out (2 for unknown motives, 7 due to time considerations, 4 were deceased, 3 too frail and 2 unable to contact). We compared the baseline characteristics of patients with missing data to those without. Patients with missing data were more often living alone (61% vs 41%), but no other differences between these groups were found.

There was no statistically significant overall treatment effect over 24 months of the intervention (OR 1.37; 95% CI 0.52 to 3.55), nor at any of the time points. There were no significant differences in PHQ-9 scores between the study groups at any time point and the course of PHQ-9 scores over time did not differ significantly between the groups. Results are shown in table 2. The statistically non-significant intervention effects for incident MDD at both 12 months20 and 24 months of follow-up justify using the Step-Dep population as a cohort.

Prediction model

The cumulative incidence during 2-year follow-up was 97/192 (51%). The multivariable models using $p=0.05$ and $p=0.157$50 were identical. The final model consisted of 4 predictors: level of anxiety, level of depression, presence of more than 3 chronic diseases and having suffered a stressful life event in the past year. This model performed well (Hosmer-Lemeshow test $p=0.12$ and median of pooled Nagelkerke’s $R^2$ explained variance 0.34 IQR 0.33–0.36) with good discriminative properties (median of the pooled AUC 0.80, IQR 0.79–0.80). In a CCA with $p=0.05$, the same predictors remained. In a CCA using $p=0.157$,50 the categorical variable DM2/CHD/both also remained.

The risk of an incident MDD during 2 years of follow-up more than doubled when either more than 3 chronic diseases were present or a patient had suffered a stressful life event in the past year. Both higher depression and anxiety levels at baseline increased the risk of MDD with each incremental point on the PHQ-9 of the HADS scales, respectively. One point higher on the PHQ-9 at baseline resulted in a 1.37 higher risk of developing MDD during 2 years, compared with 1.13 for increasing anxiety levels. With regard to the internal validation of the model, the calibration slope (or shrinkage factor to correct regression coefficients of the original model) was 0.92 IQR 0.91–0.92, the median explained variance was 31% IQR 0.29–0.32 and the AUC 0.78 IQR 0.77–0.78. This means that after corrections for overoptimism, both the performance and discriminative properties of the model remained good. Results are shown in table 3.

DISCUSSION

This study showed that the Step-Dep intervention was not more effective than usual care in the prevention of MDD at 2 years of follow-up. The risk of incident MDD during 2 years of follow-up among patients with DM2 and/or CHD and subthreshold depression was increased by higher baseline levels of anxiety and depression, the presence of more than 3 chronic diseases and having suffered a stressful life event in the past year. This risk was not influenced by a stepped-care intervention aimed at preventing MDD.

Our findings have to be viewed in the context of strengths and limitations of this study. Strengths are its relatively long follow-up with frequent outcome measurements and low dropout rates. In addition, missing values were imputed using multiple imputation techniques. We only used predictors that are readily available or easily obtained in practice, which enhances the practical use.
of the model in primary care consultations. Furthermore, testing a multivariable model instead of single factors appointed only the most relevant predictors, which rendered a simple model that is manageable in its use. There were limitations to this study. First, the study population was relatively small, which might have caused overoptimism of the prediction model. This means that it predicts the outcome better in the sample used to develop the model than in new samples, potentially restricting its external validity. However, an internal validation procedure with bootstrapping techniques showed that this risk was minor. Second, we used data derived from a RCT instead of a cohort, which potentially limits the generalisability of our results. Third, we evaluated a limited number of predictors in this study and genetic and other biological risk indicators, for example, were not included. This was due to the relatively small population size and our preselection criteria for potential predictors: predictors had to be both identified before in multiple studies and easily obtainable in GP practice. Finally, in this study, the use of the PHQ-9 with a cut-off score of 10 or more rendered a higher cumulative incidence of depression than the MINI. This could be explained by the fact that the PHQ-9 was measured more frequently than the MINI. Also, the PHQ-9 was self-reported instead of administered with a diagnostic interview by a trained research assistant. However, it is possible that depression was sometimes overdiagnosed with the PHQ-9 due to potential overlap.

| Table 1 Patients’ baseline characteristics at baseline in intervention group, care as usual group and total sample |
|-----------------------------------------------|
| Characteristics | Total sample (n=236) | Intervention (n=96) | Care as usual (n=140) |
|-----------------------------------------------|
| Female | 107/236 (45.3) | 42/96 (43.8) | 65/140 (46.4) |
| Age, mean (SD) | 67.5 (10.0) | 67.8 (9.2) | 67.3 (10.5) |
| Stressful life event | 112/210 (53.3) | 48/89 (53.9) | 64/121 (52.9) |
| Positive history of depression | 113/210 (53.8) | 54/89 (60.7) | 59/121 (48.8) |
| ICPC diagnosis (diabetes mellitus type 2 (DM2) and/or coronary heart disease (CHD)) |  |
| DM2 | 88/236 (37.3) | 38/96 (39.6) | 50/140 (35.7) |
| CHD | 86/236 (36.4) | 36/96 (37.5) | 50/140 (35.7) |
| DM2 and CHD | 62/236 (26.3) | 22/96 (22.9) | 40/140 (28.6) |
| More than 3 chronic diseases | 98/210 (46.7) | 38/89 (42.7) | 60/121 (49.6) |
| PHQ-9 at baseline, mean (SD) | 9.4 (3.2) | 9.5 (3.1) | 9.3 (3.2) |
| Anxiety HADS, mean (SD) | 6.5 (3.8) | 6.9 (3.7) | 6.3 (3.9) |
| Depression HADS, mean (SD) | 6.5 (3.8) | 6.9 (3.9) | 6.1 (3.7) |
| Marital status |  |
| Married/living together | 122/220 (55.5) | 55 (61.1) | 67/130 (51.5) |
| Single/divorced/widowed | 98/220 (44.5) | 35 (38.9) | 63/130 (48.5) |
| Both parents born in the Netherlands | 186/220 (84.5) | 74/90 (82.2) | 112/130 (86.2) |
| Rural residential area | 99/236 (41.9) | 42 (43.8) | 57/140 (40.7) |
| Unemployed/sick | 26/220 (11.8) | 12/90 (13.3) | 14/130 (10.8) |
| Level of education |  |
| Low | 89/220 (40.5) | 33/90 (36.7) | 56/130 (43.1) |
| Average | 60/220 (27.3) | 22/90 (24.4) | 38/130 (29.2) |
| High | 71/220 (32.3) | 35/90 (38.9) | 36/130 (27.7) |
| Current smoker | 39/219 (17.8) | 16/90 (17.8) | 23/129 (17.8) |
| Alcohol use above norm | 63/219 (28.8) | 29/90 (32.2) | 34/129 (26.4) |
| Exercise under norm | 141/219 (64.4) | 56/90 (62.2) | 85/129 (65.9) |
| BMI, mean (SD) | 28.9 (6.1) | 29.4 (6.8) | 28.5 (5.6) |
| Locus of control, mean (SD) | 7.9 (4.2) | 8.3 (4.2) | 7.6 (4.1) |
| Social support, mean (SD) | 36.3 (9.2) | 35.8 (9.0) | 36.7 (9.5) |
| Dysthymia | 13/236 (5.5) | 6/96 (6.3) | 7/140 (5.0) |
| Onset of depression after age of 55 | 101/210 (48.1) | 38/89 (42.7) | 63/121 (52.1) |

Numbers are percentages unless stated otherwise.
BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; ICPC, International Classification of Primary Care; PHQ-9, Patient Health Questionnaire-9.
## Table 2  Results of the mixed model and GEE long-term effectiveness analyses

| Cumulative incidence of depression (n/N) % | Intervention | Care as usual | Corrected analyses* | Crude analyses |
|------------------------------------------|--------------|---------------|---------------------|---------------|
|                                          |              |               | OR (95% CI)         | P values      | OR (95% CI) | P values |
| Baseline                                 | 0            | 0             | 0.82 (0.19 to 3.51) | 0.79          | 0.90 (0.32 to 2.50) | 0.84     |
| T6                                      | (5/84) 6.0   | (10/125) 8.0  | 1.44 (0.46 to 4.47) | 0.53          | 1.20 (0.49 to 2.92) | 0.70     |
| T12                                     | (9/82) 11.0  | (12/118) 10.2 | 1.23 (0.50 to 3.02) | 0.66          | 1.11 (0.51 to 2.44) | 0.79     |
| T24                                     | (13/77) 16.9 | (17/105) 16.2 | 1.37 (0.52 to 3.55) | 0.52          | 1.11 (0.49 to 2.49) | 0.80     |
| Overall effect                           | na           | na            | na                  | na            | na           | na        |

| PHQ mean (SD)                            | Intervention | Care as usual | Corrected analyses* | Crude analyses |
|------------------------------------------|--------------|---------------|---------------------|---------------|
|                                          |              |               | B (95% CI)          | P values      | B (95% CI) | P values |
| Baseline                                 | 9.53 (3.14)  | 9.28 (3.23)   | −0.39 (–1.52 to 0.74) | 0.50          | −0.03 (–1.17 to 1.11) | 0.96     |
| T3                                      | 6.68 (4.55)  | 6.58 (4.21)   | −0.37 (–1.50 to 0.76) | 0.52          | −0.17 (–1.30 to 0.95) | 0.76     |
| T6                                      | 6.10 (4.43)  | 6.12 (4.41)   | −0.48 (–1.62 to 0.65) | 0.40          | −0.40 (–1.53 to 0.73) | 0.49     |
| T9                                      | 6.28 (4.31)  | 6.46 (4.51)   | −0.09 (–1.20 to 1.02) | 0.88          | −0.03 (–1.13 to 1.07) | 0.96     |
| T12                                     | 6.60 (5.23)  | 6.29 (4.46)   | 0.00 (–1.18 to 1.19) | 0.88          | 0.02 (–1.15 to 1.19) | 0.97     |
| T24                                     | 5.81 (4.76)  | 5.15 (4.33)   | 0.29 (–1.15 to 0.58) | 0.52          | −0.13 (–0.99 to 0.73) | 0.77     |
| Overall effect                           | na           | na            | na                  | na            | na           | na        |

| Perceived recovery (%)                   | Intervention | Care as usual | Corrected analyses* | Crude analyses |
|------------------------------------------|--------------|---------------|---------------------|---------------|
|                                          |              |               | OR (95% CI)         | P values      | OR (95% CI) | P values |
| Baseline                                 | na           | na            | 0.78 (0.42 to 1.45) | 0.44          | 0.64 (0.36 to 1.15) | 0.14     |
| T3                                      | 40.3%        | 49.5%         | 1.46 (0.79 to 2.69) | 0.23          | 1.15 (0.65 to 2.02) | 0.64     |
| T6                                      | 48.8%        | 45.5%         | 1.47 (0.79 to 2.75) | 0.22          | 1.30 (0.74 to 2.30) | 0.91     |
| T9                                      | 55.0%        | 48.7%         | 1.04 (0.56 to 1.92) | 0.91          | 0.91 (0.51 to 1.61) | 0.74     |
| T12                                     | 55.6%        | 58.1%         | 2.38 (1.21 to 4.67) | 0.01          | 2.04 (1.08 to 3.87) | 0.03     |
| T24                                     | 68.0%        | 57.1%         | 1.32 (0.87 to 2.00) | 0.19          | 1.10 (0.75 to 1.62) | 0.61     |
| Overall effect                           | na           | na            | na                  | na            | na           | na        |

| HADS-A mean (SD)                          | Intervention | Care as usual | Corrected analyses* | Crude analyses |
|                                          |              |               | B (95% CI)          | P values      | B (95% CI) | P values |
| Baseline                                 | 6.91 (3.74)  | 6.25 (3.90)   | −0.27 (–1.13 to 0.60) | 0.54          | −0.13 (–1.00 to 0.74) | 0.76     |
| T3                                      | 6.35 (4.04)  | 6.29 (3.97)   | −1.04 (–1.91 to –0.18) | 0.02          | −1.04 (–1.91 to –0.18) | 0.02     |
| T6                                      | 5.70 (4.10)  | 6.63 (4.00)   | −0.49 (–1.35 to 0.38) | 0.27          | −0.45 (–1.31 to 0.42) | 0.31     |
| T9                                      | 6.16 (4.24)  | 6.03 (4.04)   | −0.50 (–1.37 to 0.38) | 0.27          | −0.43 (–1.31 to 0.44) | 0.33     |
| T12                                     | 5.77 (4.69)  | 5.83 (3.99)   | −0.59 (–1.50 to 0.31) | 0.20          | −0.48 (–1.38 to 0.43) | 0.30     |
| T24                                     | 5.45 (4.46)  | 5.06 (3.90)   | −0.59 (–1.23 to 0.06) | 0.08          | −0.52 (–1.17 to 0.13) | 0.12     |
| Overall effect                           | na           | na            | na                  | na            | na           | na        |

| HADS-D mean (SD)                          | Intervention | Care as usual | Corrected analyses* | Crude analyses |
|                                          |              |               | B (95% CI)          | P values      | B (95% CI) | P values |
| Baseline                                 | 6.93 (3.87)  | 6.11 (3.73)   | −0.26 (–1.12 to 0.60) | 0.55          | −0.29 (–1.15 to 0.56) | 0.51     |
| T3                                      | 6.14 (4.16)  | 6.21 (3.87)   | −0.22 (–1.07 to 0.64) | 0.62          | −0.32 (–1.18 to 0.53) | 0.46     |
| T6                                      | 5.82 (3.79)  | 5.75 (4.03)   | −0.21 (–1.06 to 0.65) | 0.63          | −0.24 (–1.09 to 0.61) | 0.58     |
| T9                                      | 6.36 (4.04)  | 6.07 (4.08)   | −0.41 (–1.27 to 0.46) | 0.36          | −0.50 (–1.36 to 0.36) | 0.26     |
| T12                                     | 6.09 (4.20)  | 6.11 (4.22)   | −0.41 (–1.30 to 0.48) | 0.37          | −0.48 (–1.37 to 0.41) | 0.29     |
| T24                                     | 5.59 (4.66)  | 4.92 (3.90)   | −0.30 (–0.94 to 0.33) | 0.35          | −0.37 (–1.00 to 0.26) | 0.25     |
| Overall effect                           | na           | na            | na                  | na            | na           | na        |

*Corrected for: baseline values of the outcome, age, gender, marital status, employment status, level of education, coexistence of DM2 and CHD, alcohol use, number of depressive episodes in history and age of onset of depression. The baseline value of the outcome is not added as an extra variable in the corrected analyses of the overall effects since it is already incorporated in the crude overall analyses. GEE, generalised estimating equations; HADS-A, Hospital Anxiety and Depression Scale-Anxiety; HADS-D, Hospital Anxiety and Depression Scale-Depression; na, not applicable; PHQ-9, Patient Health Questionnaire-9.
of (somatic) symptoms of the chronic disease and those of depression.

In a previous publication, we have hypothesised the causes for the lack of effect of the Step-Dep intervention as compared with care as usual in preventing incident MDD at 12 months of follow-up, which we assume also explain the lack of effect at 24 months of follow-up. In summary, a first explanation could be that subthreshold depression was potentially overdiagnosed in our population, whereas stepped-care may be more effective in patients with more severe symptoms. Second, fewer patients than expected were treated with the more intensive treatment steps. This was partly caused by the fact that a considerable proportion of patients did not want to start one or more of the treatment steps. This may indicate that our programme did not sufficiently match their need for care. Furthermore, this was in part due to the low PHQ-9 scores of 6.7 on average at 3 months after baseline measurements, which made only a relatively small proportion of the patients eligible for more intensive treatment steps. The drop in PHQ-9 scores between baseline and 3 months of follow-up in both groups exceeded the expectations of spontaneous recovery alone. It is unlikely that either of the groups received any specific treatment during this period. The Step-Dep programme entailed an initial period of watchful waiting and Dutch primary care clinical guidelines recommend a similar waiting period before starting treatment for subthreshold depression. Additionally, screening for depression alone does not change the management of depression in primary care. We argue that the decrease in depressive symptoms may partly be caused by attention, regression to the mean or patients’ self-insight into their mental symptoms and problems. Finally, depressive and anxiety symptoms slightly improved over time in both groups, possibly indicating that usual care is already of reasonable quality and, therefore, the room for improvement for new interventions over usual care may be limited.

We observed a remarkable drop between baseline and 3 months in the PHQ-9, but not for the HADS-D. We can only speculate about this difference in drop between PHQ-9 and HADS-D at 3 months. Currently, we have no solid explanation for this difference. There is a possibility of a statistical artefact. The PHQ-9 is made to align with Diagnostic and Statistical Manual of Mental Disorders diagnostic symptoms of depression irrespective of the comorbid presence of physical conditions, while the HADS-D should be robust for physical illnesses and perhaps measures a broader construct (for instance, ‘I can laugh and see the funny side of things’). We do think that the different sensitivity of these instruments may have minimal implications, if at all, for the intervention algorithm of the Step care approach. In the Step-Dep effectiveness study, we used the MINI, the PHQ-9, the HADS-D and HADS-A to look at the differences in incident major depression and depression and anxiety levels, respectively. All instruments used are valid and reliable. We found no statistically significant differences at any time point nor a statistically significant difference in the course of incident MDD or depression and anxiety symptom levels over time between the groups. In other words, the slope of the different outcomes over time was virtually the same.

Our multivariable model consisted of 4 predictors of MDD incidence. First, baseline depression severity level is the most frequently found and often strongest predictor of incident depression in other studies in patients with DM2 or CHD. In line with these findings, in our model, a clinically relevant baseline difference in depressive symptoms of 5 points on the PHQ-9 translated to an almost 5 times increased risk of developing a MDD during 2 years. This factor was used as a continuous variable in which the severity level predicts the occurrence of a depressive episode, which supports the concept of a gradual risk of depression. Second, the anxiety level at baseline was an important predictor of MDD. Anxiety has been frequently appointed as an important risk factor for depression in DM2 and CHD populations. Predictors are not necessarily aetiological factors. Nonetheless, as anxiety is also known for its high comorbidity with depression, the assumption that reducing anxiety will have a positive effect on depressive symptoms and MDD incidence seems defendable. Third, the risk the

| Predictor                        | RC | OR  | 95% CI       | P value |
|----------------------------------|----|-----|--------------|---------|
| Female sex                       | –  | –   | –            | –       |
| Age                              | –  | –   | –            | –       |
| Somatic disorder                 | –  | –   | –            | –       |
| DM2                              | –  | –   | –            | –       |
| CHD                              | –  | –   | –            | –       |
| DM2 and CHD                      | –  | –   | –            | –       |
| History of depression            | –  | –   | –            | –       |
| Baseline depression scores       | 0.32| 1.37| 1.20 to 1.55 | 0.00    |
| Baseline anxiety scores          | 0.12| 1.13| 1.02 to 1.25 | 0.01    |
| Stressful life event in past year| 0.74| 2.10| 1.02 to 4.32 | 0.04    |
| >3 chronic illnesses             | 0.78| 2.19| 1.12 to 4.25 | 0.02    |
| Randomisation status I versus C  | 0.14| 1.15| 0.58 to 2.29 | 0.68    |

An OR >1 reflects a higher probability the outcome an incident depression and an OR <1 reflects a lower probability compared with the reference category. OR estimated after multiple imputation (n=25 data sets) with p value of 0.157. Linear predictor corrected after bootstrapping = –4.1147 + 0.131*Randomisation status + 0.7167*<3 chronic illnesses + 0.680*stressful life event in past year + 0.1118*baseline anxiety scores + 0.2868*baseline depression scores. CHD, coronary heart disease; DM2, diabetes mellitus type 2; p.p.i., per point increase; RC, regression coefficient.
occurrence of stressful life events poses has been demonstrated before in patients with CHD. Although most of our knowledge on the role of stressful life events as predictors of depression cover a short period of time, more recent research has shown their long-term risk. This would imply that healthcare providers should not only be temporarily alert on the negative influence on mental health of stressful life events, but should also be aware of deferred effects. Fourth, the presence of more than 3 chronic diseases was identified as a predictor of MDD in our study, in concordance with results in a DM2 population of Fisher et al. Interestingly, the presence of either DM2, CHD or both was not a predictor in our study, which suggests that these patients are at the same risk of incident depression. As all included patients in Fisher’s and our study had at least one chronic disease, a discrimination between the predictive values of no chronic disease versus only one versus multiple chronic diseases could not be made. The specific importance of an increased number of diseases as opposed to the risk of a chronic disease has also been demonstrated previously in a primary care population with subthreshold depression and several elderly populations. Why the number of diseases would matter in itself can perhaps be understood from findings from qualitative interviews. Step-Dep patients explained that chronic diseases indirectly lead to depression, as they diminish future perspectives and cause disability (Pols, submitted), which might be subjective to a certain ‘threshold’ burden of disease. Finally, in contrast to findings in multiple other studies, female sex and a history of depression did not predict incident MDD in our study. These factors were also not univariately associated with incident depression in our data. A history of depression was self-reported in our study. Perhaps patients over-reported this, as it was not required that they received treatment for this depressive episode, which might explain the lack of a univariate correlation with incident depression.

The model rendered in this study had good discriminative properties with an AUC of 0.80 with the use of only 4 predictors that are relatively easily obtained by the GP. This makes this prediction model practically viable. It could assist as a tool to both improve the (early) recognition of depression in primary care patients with DM2 and/or CHD and indicate which patients need further care. As chronic care in the Netherlands is being delegated more and more to primary care practice nurses, such a tool might prove useful in their and the GPs’ regular check-ups. In practice, this would not only entail that in patients with DM2 and/or CHD, GPs and practice nurses standardly inquire about symptoms of depression and anxiety during regular checkups, but also that in those with multiple chronic diseases next to their DM2 or CHD, who suffered a recent stressful life event, the presence and course of depressive and anxiety symptoms are assessed and monitored over time with, for example, the PHQ-9 and HADS. Whenever depressive or anxiety symptoms are clinically severely elevated or significantly deteriorate over time, treatment should be offered according to the patients’ need for care. By reducing both depressive and anxiety symptoms, perhaps MDD and its negative consequences can be averted.

Future research should focus on the external validation to test the generalisability of our results, for example, on patients with DM2 and/or CHD without subthreshold depression, or outside the Dutch setting. Subsequently, studies are required to investigate the influence of the prediction model on decision making and patient outcomes. Consecutively, future research should evaluate whether the suggested enhanced vigilance strategies in combination with depression prevention programmes that only target those with all 4 indicated predictors present and aim to reduce both anxiety and depressive symptoms are cost-effective.

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Acknowledgements The authors would like to thank Marcella van der Linden, Lucca Wedder and Mieke Schlattmann for their contribution in the data collection for this study and Jos Twisk for his help in the long-term effectiveness analyses. We also would like to thank all the participating general practices and the research networks of general practitioners (ANH, THOON and LEON) for their participation and collaboration in the implementation and execution of the study. Furthermore, this study has been possible thanks to all Step-Dep participants.

Contributors ADP constructed the design of this study, performed all statistical analyses and drafted the manuscript. MCA, MWvT and HWJvM constructed the design of the study and revised the manuscript. JEB and SEvD constructed the design of the Step-Dep study and revised the manuscript. MWH collaborated on the statistical analyses and revised the manuscript. The final manuscript was read and approved by all authors.

Funding This study is funded by ZonMw, the Netherlands Organisation for Health Research and Development (project number 80-82310-97-12110).

Competing interests None declared.

Patient consent Not required.

Ethics approval The study was performed in accordance with the declaration of Helsinki (2008) and the Dutch Medical Research Involving Human Subjects Act (WMO). The protocol was approved by the medical ethics committee of the VU University Medical Centre (NL.39261.029.12, registration number 2012/223), and registered in the Dutch Trial Register (registration number 3715).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Full data set and statistical code is available from the corresponding author.

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REFERENCES
1. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:2011–30.
2. WHO. World health statistics 2017: monitoring health for the SDGs, 2017.
3. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. J Affect Disord 2012;142 Suppl:S8–21.
4. Rüdisch B, Németh B. Epidemiology of coronary artery disease and depression. Biol Psychiatry 2003;54:227–40.
5. Lin EH, Katon W, Von Korff M, et al. Relationship of depression and diabetes self-care, medication adherence, and preventive care. Diabetes Care 2004;27:2154–60.
6. Gehr A, Haas D, Pippin S, et al. Depression and medication adherence in outpatients with coronary heart disease. Arch Intern Med 2005;165:2508–13.
7. Ali S, Stone M, Skinner TC, et al. The association between depression and health-related quality of life in people with type 2 diabetes: a systematic literature review. Diabetes Metab Res Rev 2010;26:75–89.
8. Rutledge T, Vaccarino V, Johnson BD, et al. Depression and cardiovascular health care costs among women with suspected myocardial ischemia: prospective results from the WISE (Women's Ischemia Syndrome Evaluation) Study. J Am Coll Cardiol 2009;53:176–83.
9. Bomsjas JE, Adriaanse MC. Outpatient costs in pharmacologically treated diabetes patients with and without a diagnosis of depression in a Dutch primary care setting. BMC Health Serv Res 2012;12:46.
10. Katon W, Lin EH, Von Korff M, et al. Integrating depression and chronic care disease among patients with diabetes and/or coronary heart disease: the design of the TEAMcare study. Contemp Clin Trials 2010;33:312–22.
11. Sullivan M, O’Connor P, Feehey P, et al. Depression predicts all-cause mortality in patients with diabetes. Curr Diabetes Rev 2012;8:1708–15.
12. Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 2009;374:609–19.
13. National Collaborating Centre for Mental Health. Depression in adults with a chronic physical health problem. The NICE Guideline of Treatment and Management, 2010.
14. Chisholm D, Sanderson K, Ayuso-Mateos JL, et al. Reducing the global burden of depression: population-level analysis of intervention cost-effectiveness in 14 world regions. Br J Psychiatry 2004;184:393–403.
15. Cuipiers P, van Boxtel A, Smit F, et al. Preventing the onset of depressive disorders: a meta-analytic review of psychological interventions. Am J Psychiatry 2008;165:1272–80.
16. van Zoonen K, Buntrock C, Ebert DD, et al. Preventing the onset of major depressive disorder: a meta-analytic review of psychological interventions. J Affect Disord 2014;163:19–29.
17. Bower P, Gilbody S. Stepped care in psychological therapies: access, effectiveness and efficiency. Narrative literature review. Br J Psychiatry 2005;186:11–17.
18. van Dijk SE, Pols AD, Adriaanse MC, et al. Cost-effectiveness of a stepped-care intervention to prevent major depression in patients with type 2 diabetes mellitus and/or coronary heart disease and subthreshold depression: design of a cluster-randomized controlled trial. BMC Psychiatry 2013;13:128.
19. Davidson SK, Harris MG, Dowrick CF, et al. Mental health interventions and future major depression among primary care patients with subthreshold depression. J Affect Disord 2015;177:65–73.
20. Pols AD, van Dijk SE, Bomsjas JE, et al. Effectiveness of a stepped-care intervention to prevent major depression in patients with type 2 diabetes mellitus and/or coronary heart disease and subthreshold depression: a pragmatic cluster randomized controlled trial. PLoS One 2017;12.
21. Bot M, Poutier F, Ormel J, et al. Predictors of incident major depression in diabetes outpatients with subthreshold depression. Diabet Med 2010;27:1295–301.
22. Pibirner-Okanovic M, Begic D, Peros K, et al. Psychosocial factors contributing to persistent depressive symptoms in type 2 diabetic patients: a Croatian survey from the European Depression in Diabetes Research Consortium. J Diabetes Complications 2008;22:246–53.
23. Badawi G, Pagé V, Smith KJ, et al. Self-rated health: a predictor for the three year incidence of major depression in individuals with Type II diabetes. J Affect Disord 2013;145:100–5.
24. Fisher L, Skaff MM, Mullan JT, et al. A longitudinal study of affective and anxiety disorders, depressive affect and diabetes distress in adults with Type 2 diabetes. Diabet Med 2008;25:1096–101.
25. Katon W, Russo J, Lin EH, et al. Depression and diabetes: factors associated with major depression at five-year follow-up. Psychosomatics 2005;46:570–7.
26. Nefs G, Poutier F, Denollet J, et al. The course of depressive symptoms in primary care patients with type 2 diabetes: results from the Diabetes, Depression, Type D Personality Zuidoost-Brabant (DIAZoDB) Study. Diabetologia 2012;55:608–16.
27. Doyle F, McGee H, Delaney M, et al. Depressive vulnerabilities predict depression status and trajectories of depression over 1 year in persons with acute coronary syndrome. Gen Hosp Psychiatry 2011;33:224–31.
28. Spijkerman TA, van den Brink RH, Jansen JH, et al. Who is at risk of post-MI depressive symptoms? J Psychosom Res 2005;58:425–32.
29. Pedersen SS, Denollet J, van Gestel YR, et al. Clustering of psychosocial risk factors enhances the risk of depressive symptoms 12-months post percutaneous coronary intervention. Eur J Cardiovasc Prev Rehabil 2008;15:203–9.
30. Ossola P, Paglia F, Pelosi A, et al. Risk factors for incident depression in patients at first acute coronary syndrome. Psychiatry Res 2015;228:446–53.
31. Kang HJ, Stewart R, Bae KY, et al. Predictors of depressive disorder following acute coronary syndrome: Results from K-DEPACS and ESDEPACS. J Affect Disord 2015;181:1–8.
32. Kroenke K, Spitzer RL. The PHQ-9: a new depression diagnostic and severity measure. Psychiatr Ann 2002;32:509–18.
33. Lammers F, Jonkers CC, Bosma H, et al. Summed score of the Patient Health Questionnaire-9 was a reliable and valid method for depression screening in chronically ill elderly patients. J Clin Epidemiol 2008;61:679–87.
34. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl 20):22–33.
35. Van Viet LM, De Beurs E. Het Mini Internationaal Neuropsychiatricisch Interview (MINI): Een kort gestructureerd diagnosticisch psychiatrisch interview voor DSM-IV en ICD-10-stoornissen. Tijdschr Psychiatr 2007;49:393–7.
36. Meader N, Mitchell AJ, Chew-Graham C, et al. Case identification of depression in patients with chronic physical health problems: a diagnostic accuracy meta-analysis of 113 studies. Br J Gen Pract 2011;61:808–20.
37. Moriarty AS, Gilbody S, McMillan D, et al. Screening and case finding for major depressive disorder using the Patient Health Questionnaire (PHQ-9): a meta-analysis. Gen Hosp Psychiatry 2015;37:567–76.
38. van der Zwaan GL, van Dijk SEM, Adriaanse MC, et al. Diagnostic accuracy of the Patient Health Questionnaire-9 for assessment of depression in type II diabetes mellitus and/or coronary heart disease in primary care. J Affect Disord 2016;190:68–74.
39. Spinlhoven F, Ormel J, Sloecker PP, et al. A validation study of the Hospital Anxiety and Depression Scale (HADS) in different groups of Dutch subjects. Psychol Med 1997;27:363–70.
40. Robins LN. National institute of mental health diagnostic interview schedule. Arch Gen Psychiatry 1981:38:381–9.
41. Kriegsman DM, Penninx BW, van Eijk JT, et al. Self-reports and general practitioner judgment on the presence of chronic diseases in community dwelling elderly. A study on the accuracy of patients’ self-reports and on determinants of inaccuracy. J Clin Epidemiol 1996;49:1407–17.
42. Twisk J. Different methods to analyse the results of a randomized controlled trial with more than one follow-up measurement. In: van Montfoort K, Oud J, ed. Developments in statistical evaluation of clinical trials, 2014:177–93.
43. McCulloch CE NJ. Generalized linear mixed models. Encyclopedia of biostatistics: John Wiley & Sons, 2005.
44. Twisk JW. Applied longitudinal data analysis for epidemiology: a practical guide: Cambridge University Press, 2013.
45. Ali S, Stone MA, Peters JL, et al. The prevalence of co-morbid depression in adults with type 2 diabetes: a systematic review and meta-analysis. Diabetologia 2006;49:1185–73.
46. Comijs HC, Nieuwesteeg J, Kok R, et al. The two-year course of late-life depression: results from the Netherlands study of depression in older persons. BMC Psychiatry 2015;15:1.
47. de Boer MR, Waterlander WE, Kuiper LD, et al. Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate. Int J Behav Nutr Phys Act 2015;12:4.
48. Van Buren S, Groothuis-oudshoorn K, mice: Multivariate Imputation for Mental Health. John Wiley & Sons, 2005.
49. Van Buuren S, Groothuis-oudshoorn K, mice: Multivariate Imputation for Mental Health. John Wiley & Sons, 2005.
50. Collins GS, Rittsma JB, Altman DG, et al. Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): The TRIPOD Statement. Eur J Clin Pharmacol 2015;67:1142–51.
51. Heymans MW, Van Riet LS, Knol DL, et al. Variable selection under multiple imputation using the bootstrap in a prognostic study, BMC Medical Research Methodology 2007;10:1–10.
52. Marshall A, Altman DG, Holder RL, et al. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol* 2009;9:57.

53. Reddy P, Philpot B, Ford D, et al. Identification of depression in diabetes: the efficacy of PHQ-9 and HADS-D. *Br J Gen Pract* 2010;60:e239–45.

54. Cuijpers P, Koole SL, van Dijke A, et al. Psychotherapy for subclinical depression: meta-analysis. *Br J Psychiatry* 2014;205:268–74.

55. van’t Veer-Tazelaar PJ, van Marwijk HW, van Oppen P, et al. Stepped-care prevention of anxiety and depression in late life: a randomized controlled trial. *Arch Gen Psychiatry* 2009;66:297–304.

56. Depressie N. M44 NHG-standaard depressie. *Huisarts&Wetenschap* 2012;55:252–9.

57. Gilbody S, Sheldon T, House A. Screening and case-finding instruments for depression: a meta-analysis. *CMAJ* 2008;178:997–1003.

58. Moons KGM, Royston P, Vergouwe Y, et al. Prognosis and prognostic research: what, why, and how? *BMJ* 2009;338:b375.

59. Kendler KS, Karkowski LM, Prescott CA, et al. Stressful life events and major depression: risk period, long-term contextual threat, and diagnostic specificity. *J Nerv Ment Dis* 1998;186:661–9.

60. Assari S, Lankarani MM. Stressful life events and risk of depression 25 years later: race and gender differences. *Front Public Health* 2016;4:49.

61. Cuijpers P, Smit F, Willemsse G. Predicting the onset of major depression in subjects with subthreshold depression in primary care: a prospective study. *Acta Psychiatr Scand* 2005;111:133–8.

62. Vink D, Aartsen MJ, Schoevers RA. Risk factors for anxiety and depression in the elderly: a review. *J Affect Disord* 2008;106:29–44.

63. Steyerberg EW, Moons KG, van der Windt DA, et al. Prognosis Research Strategy (PROGRESS) 3: prognostic model research. *PLoS Med* 2013;10:e1001381.