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Is depression a risk factor for diabetic foot ulcers? 11-years follow-up of the Nord-Trøndelag Health Study (HUNT)

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ABSTRACT

Aim: To prospectively examine whether depressive symptoms increase the risk of diabetes and a diabetic foot ulcer.
Methods: The Nord-Trøndelag Health Study (HUNT) is a community-based longitudinal study. The Hospital Anxiety and Depression Scale (HADS-D subscale) assessed depressive symptoms. We followed individuals with complete HADS-D data from HUNT2 (1995–97) and assessed whether they reported diabetes with or without a history of diabetic foot ulcer (DFU) in HUNT3 (2006–08) ($n = 36{,}031$). Logistic regression was used to investigate the effect of depressive symptoms on subsequent development of diabetes and of DFU.
Results: Unadjusted odds for reporting diabetes at follow-up was higher among individuals who reported a HADS-D score ≥ 8 at baseline (OR 1.30 95% CI, 1.07–1.57) than among those reporting a lower score. After adjusting for age, gender and BMI, this association was no longer significant. The odds of developing a DFU was almost two-fold (OR = 1.95 95% CI, 1.02–3.74) for those reporting a HADS-D score of 8–10, and 3-fold (OR = 3.06 95% CI, 1.24–7.54) for HADS-D scores ≥ 11, compared to HADS-D scores < 8, after adjusting for age, gender and serum glucose.
Conclusions: Symptoms of depression at baseline are associated with an increased risk of a diabetic foot ulcer in a dose response manner during this 11-year follow-up.

1. Introduction

Individuals with depression have a moderately increased risk of developing type 2 diabetes (Knol et al., 2006). The reverse is also found (Demakakos, Pierce, & Hardy, 2010; Nouwen et al., 2010; Rotella & Mannucci, 2013), individuals with diabetes have an increased risk of developing depression, suggesting a bidirectional association between the two conditions (Chen, Chan, Chen, Ko, & Li, 2013; Golden et al., 2008; Mezuk, Eaton, Albrecht, & Golden, 2008; Pan et al., 2010). Depression is commonly associated with suboptimal HbA_{1c} (Lustman et al., 2000) and adverse health outcomes including an increased all-cause and cardiovascular mortality (Dooren, 2013).

Individuals with both diabetes and depression are at increased risk of developing clinically relevant micro- and macrovascular complications relative to individuals with diabetes but without depression (Lin et al., 2010). The effect of combined depression and diabetes on the development of complications has been shown to be multiplicative in older Mexican Americans (Black, Markides, & Ray, 2003). Other studies, mostly with relatively short observation periods (Black et al., 2003; Golden et al., 2008; Gonzalez et al., 2010; Lin et al., 2010; Williams et al., 2010) have also found that major depression is an independent risk factor for the development of foot ulcers among persons with diabetes (Gonzalez et al., 2010; Williams et al., 2010).

Although depression has been associated with both diabetes and diabetic foot ulcers (DFU), no large community-based cohort studies of European Caucasians have examined the association between depression and these outcomes over an extended time-period. The purpose of this analysis was to examine whether symptoms of depression increases the risk of developing diabetes, and subsequently the risk of developing a DFU during an 11 year follow-up.

The HUNT Study (HUNT2) afforded an excellent opportunity to investigate these research questions in a large, population-based sample of Caucasian men and women with and without diabetes at baseline.

2. Subjects: materials and methods

2.1. Study setting and sample

The Nord-Trøndelag Health Study (HUNT) is a community-based study including residents of Nord-Trøndelag county aged ≥20 years

Conflict of Interest: The authors declare that they have no conflict of interests.

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surveyed in 1995–97 (HUNT2) and 2006–08 (HUNT3); attendance rates were 69.5% and 54.1%, respectively. HUNT2 and HUNT3 were approved by the Norwegian Data Inspectorate and the Regional Committee for Medical and Health Research Ethics. Participation was voluntary, and each participant signed a consent form. Further details on the recruitment procedures have been published elsewhere (Krokstad et al., 2013).

The HUNT2 questionnaire (Q1) included the question "Do you have or have you had diabetes?" Those who responded negatively were classified as not having diabetes (Midthjell, Holmen, Bjørndal, & Lund-Larsen, 1992). Those who responded affirmatively were classified as having diabetes and were invited to a follow-up appointment (74.8% of these participated). The follow-up appointment involved a diabetes-specific questionnaire, and a fasting blood sample was drawn and analyzed for glucose, C-peptide, and GAD antibodies to assess diabetes classification.

The depression subscale (HADS-D) of the Hospital Anxiety and Depression Scale was used to assess depressive symptoms (Bjelland, Dahl, Haug, & Neckelmann, 2002; Iversen et al., 2009; Zigmond & Snaith, 1983). This subscale includes seven questions on general depressive symptoms during the past week. HADS was originally designed for symptom screening in hospital settings, and therefore excludes items that could be attributed to somatic illness to reduce the likelihood of false positive cases among individuals with somatic diseases (Zigmond & Snaith, 1983). Each item is scored from 0 to 3, the maximum score of 21 indicating the highest symptom load. We imputed missing items for individuals who had responded to at least five of the HADS-D questions (Zigmond & Snaith, 1983). This was done by multiplying the obtained score by 7/5 if five of the seven questions were answered and by 7/6 if six questions were answered. The HADS-D has previously been shown to have good psychometric properties in the HUNT2 study (Mykletun, Stordal, & Dahl, 2001). "Caseness" of depression is usually defined by a score of 8 or above on the HADS-D (Bjelland et al., 2002). To enhance the specificity of identifying depression, a cut-off point of 11 is also used (Zigmond & Snaith, 1983).

Among participants who completed the HADS-D in the general questionnaire in HUNT2 (baseline), 60,696 reported to not have diabetes and 1,771 to have diabetes (Fig. 1). The diabetes-specific questionnaire included the question: "Have you had a foot ulcer that required more than three weeks to heal?" Those who answered affirmatively on this question in HUNT2 were excluded (n = 147). Information on persons who died (n = 8,944) or were not living in the Nord-Trøndelag county (n = 240) during the follow up period was obtained from the Norwegian Population Registry using the unique 11-digit personal identification number assigned to each Norwegian resident. Twenty-six percent (16,372/62,467) of the HUNT2 cohort did not participate in HUNT3. Those with missing information on diabetes or diabetic foot ulcer in HUNT3 (n = 693) and participants reporting not having diabetes any more (n = 40) were excluded (Fig. 1).

2.2. Follow-up

The follow-up sample included cohort members who also participated in HUNT3 about 11 years after HUNT2 and who answered the question "Do you have or have you had diabetes?" Those who responded affirmatively to this question were classified as having diabetes and were given a diabetes-specific questionnaire (83.3% responded) with the question "Have you had a foot ulcer that required more than three weeks to heal?" Those who answered no to this question were classified as having diabetes *without* a DFU (n = 1,331), while those who responded yes were classified as having diabetes *with* a DFU (n = 84). A total of 34,616 individuals reported not to have diabetes at HUNT3. HADS-Depression was investigated as predictor of developing diabetes among participants without diabetes in HUNT2 (n = 35,667), and was investigated as predictor of developing a diabetic foot ulcer among those with diabetes at HUNT2 and/or HUNT3 (n = 1,415) (Fig. 1).

2.3. Clinical characteristics

On enrollment in HUNT2 the participants completed the baseline questionnaire which included information on angina pectoris, myocardial infarction and stroke; those who responded affirmatively to at least one of these items were defined as having cardiovascular disease. In addition, subjects reported whether they used antidepressant agents (yes/no). Height and weight were measured, and body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Non-fasting blood samples were drawn, and serum glucose was measured using an autoanalyzer (Hitachi Biocore Systems, Thornhill, ON, Canada) at Levanger Hospital. In HUNT3 participants with diabetes also reported in which year they had been first diagnosed.

2.4. Statistical analyses

Descriptive statistics with mean (standard deviation) and proportion were tabulated, and t-tests and χ^2 tests were used to compare baseline characteristics between subgroups. The HADS-D scale was either dichotomized with a cut-off point of 8, or categorized as a three level variable: < 8; 8–10 and ≥11. Logistic regression analyses were performed to estimate the effect of depressive symptoms, measured by HADS-D, on the odds of having developed diabetes at follow-up and to estimate the effect of depressive symptoms on reporting a DFU during the follow up period. Logistic regression analyses were also performed to adjust for and estimate the effect of the covariates age (continuous) and gender. In addition, BMI (as a continuous variable) was included as a covariate in the logistic regression analyses with diabetes at follow-up as the outcome; serum glucose was used as a covariate when estimating the effect of depressive symptoms on the report of a DFU during the follow up period. Effect estimates are presented as odds ratios (OR) with 95% CI.

Variable selection for the multivariable modeling was made *a priori*. A history of cardiovascular disease was not included in the multiple logistic regression analyses since we did not know whether individuals had developed cardiovascular disease before or after they got diabetes or a DFU. Sensitivity analyses were performed with depression status alternatively defined as symptoms of depression (HADS-D score ≥8) and/or use of antidepressant medication to avoid misclassification of persons with medically treated depression in remission as non-depressed (Rubin et al., 2005). Analyses were also performed using HADS-D as a continuous variable. Statistical significance was set as $p < 0.05$, and analyses were conducted using SPSS version 20.0.

3. Results

Table 1 presents baseline characteristics of the analysis sample (n = 36,031; 45% men, mean age 47 years, range 20–90). A HADS-D score ≥8 at baseline was reported by 3,325 (9.2%) participants, 6.8% had a score of 8–10 and 2.4% of 11 or above. Compared to participants with scores <8, those with depressive symptoms were older (50.7 years vs. 46.3 years, $p < 0.001$) and more likely to be male (44.6% with a HADS-D score <8 and 46.8% with a HADS-D score ≥ 8, $p = 0.02$).

At HUNT3, 3.9% (1,415/36,031) reported diabetes (Fig. 1). The median duration of diabetes among those developing diabetes (n = 1,051) during the 11 years was 5.0 years (range 0–12 years). Among participants with diabetes at HUNT3 the proportion reporting a DFU was 5.9% (84/1,415), among those with DFU, 21.4% (18/84) had also reported a HADS-D score ≥8 at baseline.

In participants with diabetes at baseline (n = 364; 54% men, mean age 56 years, range 20–84) 12.9% reported a HADS-D score ≥8 (10.2% between 8–10 and 2.7% 11 or above). Comparing men and women