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Duration of diabetes and its association with depression in later life: The Health In Men Study (HIMS)

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ABSTRACT

Objective: To examine if diabetes and duration of diabetes are direct or indirect causes of depression in later life.
Research design and methods: Cross-sectional study of a community-derived sample of 5462 men aged 70–89 years. Men with 'current depression' scored 7 or more on the abbreviated Geriatric Depression Scale (GDS-15), whereas men with 'ever depression' were either currently depressed or reported history or treatment for past depression. The presence of diabetes was established by self-reported history, fasting glucose ≥7 mmol/L (126 mg/dL), or use of insulin or hypoglycemic drugs. Duration of diabetes relied on self-report. Other measured factors included age, place of birth, education, smoking history, and the FRAIL scale.
Results: Diabetes was associated with increased odds ratio (OR) of ever (OR = 1.49, 95%CI = 1.25, 1.76) and current depression (OR = 1.94, 95%CI = 1.15, 2.48). The association between duration of diabetes and risk of current depression was 'J-shaped' with odds ratios of 1.92 (95%CI = 1.44, 2.54), 1.56 (95%CI = 0.89, 2.75), 2.49 (95%CI = 1.16, 5.32) and 3.13 (95%CI = 1.28, 7.63) for <10, 10–19.9, 20–29.9 and ≥30 years of diabetes history compared with older men without diabetes. The strength of these associations was attenuated after the analyses were adjusted for other measured factors, but the shape of the curve did not change. Structural equation modeling showed that frailty mediated some of the association between diabetes duration and depression (about 15%) and was a strong predictor of depression in the sample.
Conclusions: In older men, the association between time lived with the diagnosis of diabetes and the risk of depression is 'J-shaped'. Frailty mediates some of the association between diabetes and depression, although other unmeasured factors are also likely to play a role. The introduction of strategies that are effective at decreasing diabetes-related complications may also contribute to decrease the risk of depression among older men.

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1. Introduction

Several factors are likely to contribute to the causal pathway that leads to the onset of depressive symptoms [1–3], with diabetes featuring prominently among them [4,5]. Interest about the association between diabetes and depression is based, at least in part, on the premise that if the link between diabetes and depression is causal, then the prevention or adequate management of

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diabetes should contribute to reduce the incidence and prevalence of depression in later life.

A systematic review and meta-analysis of 16 observational studies that followed nearly 500,000 people over an average period of 5.8 years found that the odds ratio (OR) of depression was higher among participants with than without diabetes (OR = 1.29, 95% confidence interval = 1.18, 1.40) [6], a finding that replicates that of other systematic reviews and meta-analyses [7,8]. Notwithstanding the consistency of these findings, there is a lingering uncertainty about whether the link between diabetes and depression is truly causal. Tabák et al. have argued that other conditions, such as cardiovascular and chronic respiratory diseases, show a similar pattern of association with depression, and that the link between diabetes and depression may simply reflect the burden caused by a chronic illness [9,10]. In addition, there is no compelling evidence that treatment of diabetes reduces the severity of depressive symptoms or the long-term risk of depression [11,12], although the results of a small 6-week randomised controlled trial comparing metformin with pioglitazone (a medication that increases sensitivity to insulin) for the treatment of women with Polycystic Ovarian Syndrome and depression detected an antidepressant effect in the pioglitazone but not the metformin treated group [13]. More recently, Samaan et al. used data from the EpiDREAM study to investigate the association between presence of a major depressive episode and 20 single-nucleotide polymorphisms (SNPs) linked to increased risk of type-2 diabetes—none of the SNPs were associated with the 12-month prevalence of major depression, although the analyses may have been over adjusted by the inclusion of the body mass index (BMI) [14]. These conflicting results raise questions about the nature of the association between diabetes and depression, and suggest that their connection may not be direct. For example, Moulton et al. have argued that diabetes and depression share biological pathways that modulate inflammation and the hypothalamic–pituitary–adrenal axis response, and that this overlap could be misinterpreted as indicative of a causal relationship [5]. Moreover, currently available evidence indicates that a larger proportion of adults with than without diabetes show evidence of frailty [15], which is characterised by increased exhaustion, decreased physical activity and walking speed, poor grip strength and weight loss [16]. Hence, it seems possible that the purported association between diabetes and depression could be mediated by the presence of frailty, as the latter has also been associated with depression [17].

In this study, we used three complementary approaches to examine the association between diabetes and depression. First, we investigated whether diabetes is cross-sectionally associated with prevalent depression. We then evaluated the association between duration of diabetes and risk of depression and, finally, investigated the impact of frailty on the association between diabetes and depression.

2. Methods

2.1. Study design

This study reports cross-sectional data for a community-derived sample of older men living in the Perth metropolitan region of Western Australia.

2.2. Participants

Participants were older men taking part in the Health In Men Study (HIMS), an ongoing cohort study of a random sample of 12,203 community-dwelling older Western Australians recruited between 1996–1998. Details about the study design have been described elsewhere [18,19]. During 2001–2004 5462 participants completed the second HIMS survey and their ages ranged from 70 to 89 years—they constitute our study sample.

2.3. Outcome: clinically significant symptoms of depression

We used the 15-item version of the Geriatric Depression Scale (GDS-15) to assess symptoms of depression during the second wave of assessment for HIMS [20]. The scale has very good test-retest reliability [21] and total scores of 7 or more are strongly associated with the presence of major depression in later life [20]. Hence, we considered that men with GDS-15 $\geq$ 7 were experiencing clinically significant symptoms of depression at the time of assessment. In addition, we asked participants whether a doctor had previously told them that they had depression, whether they had ever received treatment for emotional problems, or whether they were using antidepressants (information retrieved from list of medications that they were asked to provide at the time of assessment). We used the GDS-15 and the information about past clinical history to assign men to one of the following categories: never depressed, ever depressed (i.e., past history or GDS-15 $\geq$ 7) and current depression (i.e., GDS-15 $\geq$ 7).

2.4. Explanatory variables

Diabetes and duration of diabetes were the exposures of interest in this study. The presence of diabetes was established by asking participants during HIMS wave 1: "Have you ever been told by a doctor that you have diabetes?" (yes/no) and "Have you ever been given advice or treatment for diabetes or sugar trouble?" (yes/no). We considered that participants had diabetes if they replied "yes" to either of these questions, or if they were using insulin or oral hypoglycemic drugs. In addition, we asked our men how old they were when they were first told they had diabetes (in years) and used this information to estimate its duration. During HIMS wave 2, we asked men: "During the past 5 years, have you ever been told for the first time by a doctor that you have diabetes?" (yes/no), and those who answered "yes" or had fasting glucose $\geq$7 mmol/L (blood data available at wave 2 for 4227/5462 participants during wave 2) were considered to have diabetes. This information added 328 cases of diabetes diagnosed between wave 1 and 2 (total number of men with diabetes: 932/5462). For the purposes of this study, we grouped men according to the duration of diabetes: <10 years, 10–19.9 years, 20–29.9 years, and $\geq$30 years. We used this approach due to our inability to accurately measure the duration of illness for participants with less than 10 years of history of diabetes.

Other study measures collected as part of the assessment of participants included age (in years), place of birth (Australia or other), educational attainment (incomplete vs complete high school education), and smoking history (never, past or current). We used the International Academy of Nutrition & Ageing Task Force definition of frailty to guide our assessment of fatigue, resistance, ambulation, illness and loss of weight (the FRAIL Scale, 0/1 for each, maximum score = 5) [16]. The first three items of the scale were derived from questions of the SF-36 Health Survey [22] assessing fatigue (worn out or feeling tired most of the time), resistance (inability to climb a flight of stairs) and ambulation (inability to walk 100 m). We also asked participants if they had ever been told by a doctor that they had (yes/no): arthritis, osteoporosis, angina, stroke, myocardial infarction, heart failure, asthma, chronic bronchitis, emphysema, bowel cancer, prostate cancer, melanoma, other skin cancers, Alzheimer's disease, leg ulcers, Parkinson's disease, thyroid problems or hypertension. Men who acknowledged having 6 or more conditions were ascribed one point for 'illness' on the FRAIL scale. We did not include diabetes in the calculation of our measure of frailty to minimise collinearity. Finally, we assessed changes in

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