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Haemoglobin A1C, fasting glucose and future risk of elevated depressive symptoms over 2- years follow up in the English Longitudinal Study of Ageing

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Abstract

Background—The cross-sectional association between impaired glucose/diabetes and depression is inconsistent. We examined the longitudinal associations between diabetes, indicators of glucose metabolism and depressive symptoms over 2 years follow up.

Methods—Participants were 4338 men and women from the English Longitudinal Study of Ageing, a prospective study of community dwelling older adults (aged 62.9 ± 9.0 yrs, 45.2% men). Depressive symptoms were assessed at baseline and 2 years follow up using the 8 item CES-D scale. Haemoglobin A1C levels, fasting glucose and other biological and behavioural risk factors were also assessed at baseline.

Results—Approximately 11.5% of the sample were categorised with elevated depressive symptoms at follow up (a score ≥ 4 on the CES-D). There was an association between A1C and depressive symptoms at follow up (per unit increase, odds ratio [OR]= 1.17, 95% CI, 1.03 – 1.33) after adjustment for age and baseline CES-D. Cross-sectionally, the probability of depressive symptoms increased with increasing HbA1c levels until the value of 8.0% after which there was a plateau (p[curve]=0.03). Compared to those with normal fasting glucose, participants with diabetes (confirmed through self report or elevated fasting blood glucose) at baseline had elevated risk of depressive symptoms at follow up (OR=1.52, 95% CI, 1.01 – 2.30) after adjusting for depressive symptoms at baseline, behavioural and socio-demographic variables, adiposity and inflammation.

Conclusions—These data suggest that poor glucose metabolism and diabetes are risk factors for future depression in older adults. There was no evidence of a U-shaped association.

Keywords

diabetes; depressive symptoms; ageing; psychobiology; Haemoglobin A1C

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Author contributions

MH had full access to the data, and takes responsibility for the integrity and accuracy of the results. All authors contributed to the concept and design of study, drafting and critical revision of the manuscript.

Conflict of interest

None of the authors have any competing interests to declare.

Introduction

Depression and diabetes are both major public health concerns in the elderly population. For example, approximately 10% of adults in England aged 75 yrs and above have been diagnosed with diabetes (Shelton, 2008). Clinically significant levels of depression are also apparent in 11% – 25% of the general elderly population (Wancata *et al.* 2006). However, the determinants of mental health remain poorly understood.

The hypothesised association between diabetes and depression is theoretically feasible because depression could result from the biochemical changes directly caused by diabetes, its treatment, or from the distress associated with living with diabetes and its often debilitating consequences. For example, preliminary evidence found brain abnormalities, such as reduced white matter volume and enlarged cerebrospinal fluid space, in obese adolescents with type II diabetes, which might result from a combination of subtle vascular changes and glucose abnormalities (Yau *et al.* 2010). A common causal pathway for depression and diabetes is also a possibility, with early factors, such as low birth weight and childhood adversity predisposing individuals to both obesity/type 2 diabetes (de Lauzon-Guillain *et al.* 2010; Thomas *et al.* 2008) and depression (Colman *et al.* 2007). However, based on existing evidence the association between diabetes/glucose control and depression is contentious. Patients with diabetes tend to demonstrate a higher prevalence of depression than their diabetes-free counterparts (Ali *et al.* 2006, Mezuk et al. 2008), although the existing evidence is inconsistent with regards to the associations between glucose control and depression (Georgiades et al. 2007; Icks *et al* 2008; Adriaanse *et al.* 2008; Chida & Hamer 2008; Golden *et al.* 2008; Rhee *et al.* 2008; Holt *et al.* 2009; Kivimaki *et al.* 2009; Gale *et al.* 2010; Fisher *et al.* 2010). Some studies suggest a non-linear association between the two conditions. In the US Multi-Ethnic Study of Atherosclerosis, for example, individuals with impaired fasting glucose or undiagnosed diabetes had lower risk of incident depression than both non-diabetic individuals and patients with treated diabetes (Golden *et al.* 2008). A study from the British Whitehall II cohort reported greater levels of depression in participants with very high and very low fasting glucose (Kivimaki *et al.* 2009). These curvilinear associations were not, however, replicated in the Vietnam Experience study (Gale *et al.* 2010). Gaining a better insight into the association between diabetes and depression is therefore crucial as elevated depression risk at both low and high glucose levels would have important implications for prevention and treatment.

Previous studies have largely utilised a cross-sectional design. With the exception two prospective studies (Golden *et al.* 2008; Pan *et al.* 2010) that have indicated bi-directional associations between diabetes and depression, it is impossible to identify the direction of association from previous cross-sectional work. In order to simplify the interpretation of what is a potentially important relationship, we used data from the English Longitudinal Study of Ageing (ELSA), a prospective cohort study of older individuals. Previous analyses from ELSA have demonstrated an associated between depressive symptoms and incident diabetes (Demakakos *et al.* 2010). The aim of the present study was to examine the association of diabetes, levels of fasting glucose, and haemoglobin A1C at baseline, with new cases of elevated depressive symptoms arising over two years follow up. We used haemoglobin A1C because this biomarker has recently been highlighted as a gold standard indicator of diabetes risk (The International Expert Committee, 2009).

Methods

Study sample and procedures

ELSA is an ongoing cohort study that contains a nationally representative sample of the English population living in households (see ELSA user guide). The original ELSA cohort

consists of men and women born on or before 29 February 1952. The sample was drawn from households that have participated in Health Survey for England (HSE) in 1998, 1999, and 2001. HSE recruits participants using multistage stratified probability sampling with postcode sectors selected at the first stage and household addresses selected at the second stage.

For the purposes of the present analyses data collected at wave 2 (2004-05) were used as the baseline, when clinical information was first gathered. Follow up data were collected two years later (2006-07). A total of 7666 participants attended the wave 2 (baseline) clinical assessment although 1230 did not attend the follow up, and a further 2098 of them were excluded because of missing biological data (n=1651) or incomplete data on other measures (n=447), leaving a final sample size of 4338 individuals (aged 62.9 ± 9.0 yrs, 45.2% men). Missing biological data was mainly because participants did not consent to give blood or were ineligible (participants with clotting and bleeding disorders, or taking anti-coagulant medication). In comparison with the overall sample, the sub-group used in the present analyses were slightly younger (62.9 vs. 63.8 yrs, $p<0.001$), from higher socioeconomic status groups (e.g., 35.4% vs. 27.8%, $p<0.001$, from managerial/professional level), had a lower prevalence of longstanding illness/disability (50.4% vs. 58.1%, $p<0.001$), and better health behaviours including lower rates of smoking (13.2% vs. 17.9%, $p<0.001$) and greater physical activity (32.6% vs. 23.4%, $p<0.001$, vigorously active ≥1/wk). In order to account for missing data all analyses were weighted for non-response, which is a standard procedure in order to account for survey non-response and unequal sample selection, thus providing more precise effect estimates (see ELSA User guide). Participants gave full informed consent to participate in the study and ethical approval was obtained from the London Multi-centre Research Ethics Committee.

Measurements

At baseline, data collection consisted of biological, psychosocial, demographic and health related information. Demographic and health-related questions included socioeconomic status as indexed by occupational social class (categorised as: managerial/professional, intermediate, semi routine/routine occupations), cigarette smoking (current or non-smoker), the frequency of participation in vigorous, moderate, and light physical activities (more than once per week, once per week, one to three times per month, hardly ever), frequency of alcohol intake (daily, 5-6/wk, 3-4/wk, 1-2/wk, 1-2/month, once every couple of months, 1-2/year, never) and presence of morbidity (including; doctor diagnosed heart disease, hypertension, diabetes, cancer, neuromuscular conditions, endocrine/metabolic conditions, epilepsy, bronchitis, asthma and other respiratory disorders, and complaints related to the stomach, digestive system, and bowel). Participants were categorised with diabetes if they reported a doctor's diagnosis and/or use of diabetic medication. In addition, participants with diabetes were asked "Do you have sufficient knowledge to manage your diabetes?" and responses were stratified into two groups ("everything or most of what I need to know to manage my condition" and "some or a little of what I need to know"). Depressive symptoms were assessed at baseline and follow up using the 8-item Centre of Epidemiological Studies Depression (CES-D) scale. As in previous studies, we used a score of ≥4 to define cases of elevated depressive symptoms (Steffick 2000).

Nurses collected anthropometric data (weight, height) and blood samples. Blood samples were analysed for C-reactive protein (CRP), cholesterol, and A1C. In a sub-sample of participants we collected fasting blood samples for glucose. The analysis of the blood data was carried out at the Royal Victoria Infirmary (Newcastle-upon-Tyne, UK). Detailed information on the technicalities of the blood analysis, the internal quality control, and the external quality assessment for the laboratory have been described (Graig *et al.* 2006).

Statistical analyses

We calculated odds ratios (OR) and 95% confidence intervals (CI) for the risk of elevated depressive symptoms in relation to A1C using multiple logistic regression. These analyses were performed to examine both the cross-sectional and longitudinal associations. In multivariate models we adjusted for several covariates in a step-wise fashion; Model 1 contained basic variables including age, sex, baseline CES-D score; Model 2 contained behavioural and social covariates including social status, smoking, alcohol, physical activity; Model 3 contained clinical covariates including, self reported diabetes status, CRP, cholesterol, body mass index. This modelling strategy was devised *a priori* based on existing data linking these covariates with diabetes and mental health. In order to examine curvilinear associations we fitted an A1C squared term into the models and calculated the probability of depression by level of AIC based on these models to illustrate the shape of the association. In addition, participants were categorised into diabetes categories, which were used to model risk of depression. Diabetes categories were based on fasting glucose and self report; non-diabetic (fasting glucose <5.6 mmol/l and no self-reported diabetes), impaired fasting glucose (IFG: fasting glucose 5.6-6.9 mmol/l and no self-reported diabetes), and diabetes (fasting glucose ≥7.0 mmol/l, or self reported doctors diagnosis and/or use of diabetes medication). In addition, diabetes status was classified using A1C; non-diabetic (A1C <6%), impaired glucose tolerance (A1C = 6.0 – 6.5%), and diabetes (A1C ≥6.5% or self reported doctors diagnosis and/or use of diabetes medication). All analyses were conducted using SPSS version 14.

Results

Demographics

The proportion of the sample that was classified with elevated depressive symptoms (CES-D≥4) at baseline and follow up was 12.7% and 11.5%, respectively. Participants with depressive symptoms at follow up were older, more likely to be women, smoke, be physically inactive, non-drinkers, and come from lower socio-economic groups (Table 1). In addition, they were more likely to have a diabetes diagnosis and higher A1C, body mass index, and CRP.

Cross sectional associations between diabetes and depressive symptoms

In cross-sectional analyses, A1C (p=0.01) and $[A1C]^2$ (p=0.03) were associated with depressive symptoms, suggesting the presence of a curvilinear association. Between the HbA1c range 4.5% to 9.0%, the probability of depressive symptoms increased with increasing HbA1c levels until the value of 8.0% after which there was a plateau (see Figure 1). The risk of depressive symptoms at baseline was elevated in participants that reported injecting insulin (n=70) (age adjusted odds ratio= 1.84, 95% CI, 1.02-3.34) and in diabetic participants who reported limited knowledge about diabetes management (n=44) (age adjusted odds ratio= 3.19, 95% CI, 1.48-6.89) compared to those with adequate knowledge.

Longitudinal associations between diabetes and depressive symptoms

In longitudinal analyses, A1C was associated with future risk of elevated depressive symptoms after controlling for depressive symptoms at baseline (see Table 2), although there was no evidence of a curvilinear association. The associations appeared to be slightly stronger in men but the sex-A1C interaction term was non-significant (p=0.08). The addition of further covariates to the model attenuated these associations, especially in women. In the fully adjusted model, the association between A1C and depressive symptoms no longer remained statistically significant at conventional levels. The removal of participants reporting depressive symptoms at baseline did not change the results. The other independent

predictors of depressive symptoms in this sample included non-alcohol drinkers (odds ratio= 1.70, 95% CI, 1.17-2.46), physical inactivity (odds ratio= 1.33, 95% CI, 0.97-1.83), lower social status (odds ratio= 1.51, 95% CI, 1.15-2.00), and higher log CRP (odds ratio per unit increase= 1.18, 95% CI, 1.03-1.36).

When we examined the risk of depressive symptoms based on diabetes status (Tables 3a and b), participants with diabetes were at the highest risk of future depression, whether defined using fasting glucose or A1C. Impaired fasting glucose, as defined from fasting blood glucose levels, was not associated with future risk of depressive symptoms (Table 3a). However, impaired glucose tolerance, as defined from A1C was moderately associated with depressive symptoms (Table 3b). There was no statistically significant increased risk of depressive symptoms at follow up (age and baseline depression adjusted odds ratio= 1.20, 95% CI, 0.58-2.51) in participants that reported injecting insulin at baseline. Similarly, there was no association between knowledge about diabetes management and depressive symptoms at follow up (age and baseline depression adjusted odds ratio= 0.94, 95% CI, 0.34-2.58).

Discussion

In the present study we examined the longitudinal association between glucose metabolism and depressive symptoms in a large cohort of older British adults. We showed that A1C was associated with incident elevated depressive symptoms over 2 years follow up, especially in men.

Cross-sectionally, the probability of depressive symptoms increased with increasing HbA1c levels until approximately the value of 8% after which there was a plateau. In longitudinal analyses, we found a modest association between diagnosed diabetes at baseline and depressive symptoms at follow up. The magnitude of this association is comparable to a recent study that employed data from general practices to examine the association between diabetes and subsequent risk of depression (Aarts *et al.* 2009). Injecting insulin and limited knowledge about diabetes management were both associated with greater risk of reporting depressive symptoms at baseline, but these factors did not predict subsequent depression at follow up after taking into account the baseline association. Consistent with cross-sectional findings from other recent studies (Adriaanse *et al.* 2008; Gale *et al.* 2010), participants with impaired glucose metabolism at baseline were at risk of subsequent depression. However, in several other studies impaired glucose tolerance or undiagnosed diabetes was associated with lower risk of depression (Golden *et al.* 2008; Icks *et al.* 2008) or not associated with depression at all (Knol *et al.* 2007; Rhee *et al.* 2008; Holt *et al.* 2009; Aujla *et al.* 2009). Indeed, when we used fasting glucose as an indicator of impaired fasting glucose there was no association with depression. Therefore these discrepancies might possibly be explained by differences in the methods to assess glucose metabolism, and also characteristics of the samples and measures of depression. However, given that the majority of previous studies have been cross-sectional, the prospective nature of our study adds considerably to the current evidence base.

The highest probability of depression was observed at A1C levels of 8 – 9%, which might reflect unrecognised, pre-clinical diabetes and the presence of undiagnosed symptoms. We did not observe increased risk of depressive symptoms among individuals with very low glucose levels. Such an association was previously observed in the Whitehall II cohort (Kivimaki *et al.* 2009), but not in the Vietnam Experience Study, where study participants were, on average, 20 years younger (Gale *et al.* 2010). The reason for this discrepancy was suggested to be a higher prevalence of underlying chronic conditions that potentially relate to low glucose and increased depression risk in Whitehall II. However, the participants in

present study were older than those in both previous studies and we observed no elevation in depression towards the low end of the A1C distribution. Lastly, slightly stronger associations between A1C and depressive symptoms were observed among men, although these sex differences were not statistically significant (p=0.08 for sex interaction). The reasons for this possible sex difference remain unclear and the findings are not consistent with a recent study in women (Pan *et al.* 2010). The mechanisms linking diabetes and depression also remain unclear. Depression could result from the biochemical changes directly caused by diabetes, its treatment, or from the distress associated with living with diabetes and its often debilitating consequences. For example, preliminary evidence found brain abnormalities, such as reduced white matter volume and enlarged cerebrospinal fluid space, in obese adolescents with type II diabetes, which might result from a combination of subtle vascular changes and glucose abnormalities (Yau *et al.* 2010). A common causal pathway for depression and diabetes is also a possibility, with early factors, such as low birth weight and childhood adversity predisposing individuals to both obesity/type 2 diabetes (de Lauzon-Guillain *et al.* 2010; Thomas *et al.* 2008) and depression (Colman *et al.* 2007).

The strengths of this study include the sampling of a large, representative general population-based group, and the well characterised study members which facilitates insights into the role of potential confounding factors, and the prospective element of the study design. The limitations of the present study should also be recognized. Participants retained in our analyses generally reported lower levels of depressive symptoms and better health compared with the overall sample, although the analytic approach that we used accounted for missing data in estimating the association between glucose indicators, diabetes and depression. In fact, weighting for non-response actually had a minimal impact on the results, providing evidence against bias due to selective sample retention. Although the definition of diabetes was not only based on self report but also on objective blood measures, we were unable to differentiate between type I and II. However, it is likely that the majority of cases were type II since this is by far the most prevalent condition in the general adult population.

Conclusions

These data from the English Longitudinal Study of Ageing suggests diabetes is associated with an excess risk of future depressive symptoms in older adults. Considering the totality of data from this study and previous investigations, there seems to be no convincing evidence to support elevated risk of depression at low levels of fasting glucose and A1C. Our findings support the current recommendations of the American Diabetes Association (2008) to screen diabetic patients for depression.

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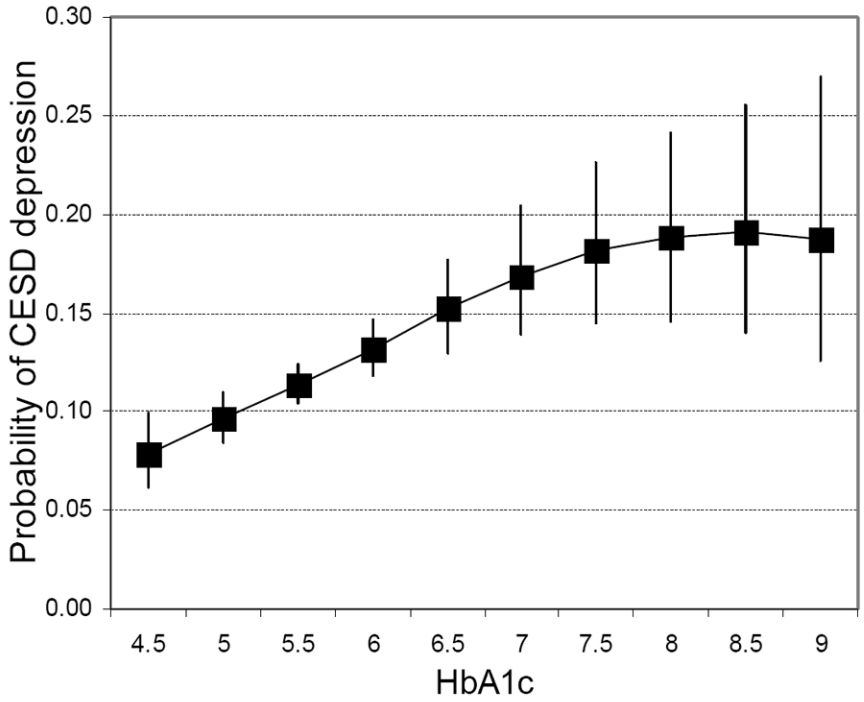

N of CESD cases:

HbA1c≤4%										HbA1c≥9.5%
1	8	98	264	103	19	12	5	5	4	4	3

N of non-cases:

HbA1c≤4%										HbA1c≥9.5%
7	68	928	1964	573	107	57	36	20	15	15	22

Figure 1.

The association between glycated haemoglobin (HbA1C) and probability of elevated depressive symptoms (CES-D≥4) at baseline (N=4338, only HbA1C categories with n>10 shown).

Table 1

Baseline characteristics of participants in relation to depressive symptoms at follow up.

Variable, mean ± SD	Non-depressed (*n*=3840)	Elevated depressive symptoms (*n*= 498)	*P*-value
Age (yrs)	62.8 ± 8.8	64.0 ± 9.9	.004
Men (%)	47.1	30.9	<.001
Managerial/Professional (%)	37.2	21.3	<.001
Current smokers (%)	12.3	20.5	<.001
Physically inactive (%)	15.1	29.9	<.001
Alcohol (% non-drinkers)	7.7	17.7	<.001
Self reported diabetes (%)	6.3	9.2	.01
A1C (%)	5.5± 0.67	5.7± 0.83	<0.001
Body mass index ($kg.m^2$)	27.7± 4.6	28.3± 5.3	.01
Log C-reactive protein	1.18± 0.72	1.40± 0.78	<.001
Cholesterol (mmol/L)	5.95± 1.19	5.98± 1.24	0.58

Table 2

Logistic regression models for HbA1c and risk of future depressive symptoms over 2 yrs follow up in ELSA (n=4338). Cases defined as a score ≥4 on the 8 item CES-D scale

	Model 1 OR (95% CI)	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
All (n=4338, cases=498)			
A1C (per unit)	1.17 (1.03 – 1.33)	1.12 (0.98 – 1.28)	1.08 (0.91 – 1.29)
p-value	0.02	0.09	0.35
Men (n=1961, cases=154)			
A1C (per unit)	1.23 (1.04 – 1.46)	1.19 (0.99 – 1.44)	1.20 (0.95 – 1.52)
p-value	0.02	0.07	0.13
Women (n=2377, cases=344)			
A1C (per unit)	1.14 (0.94 – 1.38)	1.10 (0.90 – 1.33)	0.96 (0.75 – 1.25)
p-value	0.18	0.35	0.78

Model 1 adjusted for age and baseline CES-D score.
Model 2 plus smoking, alcohol intake, physical activity, social status
Model 3 plus C-reactive protein, cholesterol, body mass index, self reported diabetes.

Table 3

a. Association between baseline diabetes status (using fasting glucose)[†] and risk of future depressive symptoms (n= 2930)[*]

	Cases/N	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Non-diabetic	220/2244	1.00	1.00	1.00
IFG	35/385	0.86 (0.57 – 1.30)	0.94 (0.62 – 1.43)	0.92 (0.60 – 1.39)
Diabetic	50/301	1.57 (1.07 – 2.29)	1.55 (1.05 – 2.30)	1.52 (1.01 – 2.30)
p-trend		0.038	0.071	0.08
b. Association between baseline diabetes status (using glycated haemoglobin)[‡] and risk of future depressive symptoms (n= 4338)				
Non-diabetic	397/3712	1.00	1.00	1.00
IGT	46/280	1.53 (1.05 – 2.24)	1.39 (0.94 – 2.04)	1.37 (0.93 – 2.02)
Diabetic	55/346	1.46 (1.02 – 2.07)	1.35 (0.94 – 1.92)	1.36 (0.94 – 1.97)
p-trend		0.016	0.087	0.105

Model 1 adjusted for age and baseline CES-D score.
Model 2 adjusted as model 1 plus for sex, smoking, alcohol intake, physical activity, social status
Model 3 adjusted as model 2 plus for C-reactive protein, cholesterol, body mass index.

[†]Diabetes categories based on fasting glucose and self report; non-diabetic (fasting glucose <5.6 mmol/l and no self-reported diabetes), impaired fasting glucose [IFG] (fasting glucose= 5.6-6.9 mmol/l), diabetic (based on either fasting glucose ≥7.0 mmol/l, self reported doctors diagnosis or use of diabetes medication).

[*]data unavailable in1408 participants.

[‡]Diabetes categories based on A1C values and self report; non-diabetic (A1C <6 % and no self-reported diabetes), impaired glucose tolerance [IGT] (A1C= 6.0 – 6.5 % and no self-reported diabetes), diabetic (based on either A1C >6.5%, self reported doctors diagnosis or use of diabetes medication).