Diabetes incidence associated with depression and antidepressants in the Melbourne Longitudinal Studies on Healthy Ageing (MELSHA)

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Objective: Diabetes may be associated with depression and antidepressant medication (ADM) use, but published findings remain equivocal. The authors' aimed to determine the risk of diabetes incidence associated with baseline depression exposures (symptoms and/or ADM use).

Methods: A prospective cohort study *was conducted* in a regionally representative sample of non-institutionalised older Australian people ($N = 1000$, aged $65 +$ year), who were followed up biennially between 1994 and 2004 (attrition was $\approx 24\%$). Analyses excluded participants for prevalent diabetes at baseline, determined by self-report or specific medications. Diabetes incidence was ascertained by first self-report at any follow-up wave. Depression exposures (baseline predictors) were defined by the Psychogeriatric Assessment Scales (PAS) depression scale and ADM use, and classified as: (1) 'symptomatic' (PAS score 5+); (2) 'ADM use'; (3) 'symptomatic or ADM use'; (4) 'symptomatic and no ADM use'; (5) 'asymptomatic (PAS score <5) and ADM use' and (6) 'symptomatic and ADM use'. Covariates were demographic, lifestyle, functional health and chronic disease factors. Cox regressions were used to determined hazard ratios with 95% confidence intervals (HR [95% CI]) for diabetes incidence according to depression exposures, adjusted for significant covariates.

Results: Baseline response rate was 70.3%. Depression predictors of diabetes incidence were 'symptomatic' (2.29 [1.28,4.10]), 'symptomatic or ADM use' (2.13 [1.32,3.44]) and 'symptomatic and no ADM use' (2.38 [1.28,4.45]), after adjustment for significant covariates. Being asymptomatic was not a protective factor among those prescribed antidepressants.

Conclusions: Older people with depressive symptoms are at least twice more likely to develop diabetes than those without depressive symptoms, regardless of antidepressants. Copyright © 2009 John Wiley & Sons, Ltd.

Introduction

Depression is a descriptive syndrome of negative mood states defined by clinical interview or by cut-off scores for self-rated symptoms using psychometric scales. Although highly prevalent among people with diabetes mellitus (diabetes) (Anderson *et al.*, 2001), the temporal order of this association remains unclear. Findings of the most recent systematic review of prospective cohort studies suggest that depression (mostly defined by psychometric scales) significantly increases the risk of developing type 2 diabetes (mostly defined by self-report) by 60% (Mezuk *et al.*, 2008). Several theoretical pathways would qualify depression in the aetiology of diabetes. Cortisol level is inversely associated with glucose control (Oltmanns *et al.*, 2006) and may be elevated among those with depression (Burke *et al.*, 2005). Binge eating disorder is strongly

associated with both diabetes (Goodwin *et al.*, 2003) and depression (Spitzer *et al.*, 1993). While exposure to insufficient physical activity level strongly predicts both incident diabetes (Barr *et al.*, 2006) and depression (Strawbridge *et al.*, 2002). Collectively, this evidence-base conjectures plausible biological and psycho-behavioural pathways causally linking depression with diabetes. Conversely and confounding, uncontrolled (Maraldi *et al.*, 2007) and treated diabetes (Golden *et al.*, 2008) may increase the risk of incident depression, providing evidence of reverse causation.

Experimental studies in depressed people showing effective prevention of incident diabetes or improved blood glucose control after eradicating depression would provide strong evidence of causality. Randomised controlled trials have shown that antidepressant medications (ADM) effectively reduce depressive symptoms during treatment and maintenance in patients with both depression and diabetes, but without concurrent improvement in blood glucose control (Lustman *et al.*, 2000, 2006). Furthermore, recent evidence suggests that ADM use may increase the risk of developing diabetes among those with pre-diabetes (Rubin *et al.*, 2008). This is particularly important knowledge for clinical care of older people, given that they experience the highest burden of chronic disease and prescription medications (Dunstan *et al.*, 2001; Chapman *et al.*, 2005; Simpson *et al.*, 2006). Alternatively, depression may coincidentally co-occur with other chronic diseases, including diabetes, and with declines in functional health, all of which are known to increase with ageing. Previous prospective cohort studies have not comprehensively accounted for these alternative factors, which may help clarify the association between depression and diabetes, whilst there is only one published study to date in *older people* (65 + years) (Carnethon *et al.*, 2007). The authors' of this report aimed to determine whether baseline depression exposures (symptoms and/or ADM use) predicted diabetes incidence during 10 years of follow-up in a regionally representative sample of older Australians, accounting for an extensive list of demographic, lifestyle, functional health and chronic disease covariates.

Methods

Study design and population

The information source for this report was the series of data collections that form the Melbourne Longitudinal Studies on Health Ageing (MELSHA); a 10-year prospective cohort study of older Australian people conducted between 1994 and 2004. The background and methods of the MELSHA have been reported in greater detail (Kendig *et al.*, 1996). The baseline survey for the MELSHA consisted of 1000 people aged 65 years and over living in non-institutional settings. This sample size provided for a minimum detectable relative risk of diabetes incidence >1 of 2.08 and <1 of 0.40 between groups of respondents with and without depression exposure in univariate analyses, assuming 90% sample power; two-tailed test; 5% chance of type 1 error; 10% depression prevalence and 15% diabetes incidence (endpoint) in the reference group. The sampling frame was defined as all residents of private dwellings in metropolitan Melbourne, aged 65 years and over in 1994. The sampling frame was developed from data supplied by the Australian Electoral Commission. A clustered sampling strategy was adopted and the sample excluded people who were living in non-private accommodation, those who could not speak basic English (11.3%), and those who could not be interviewed for health reasons (3%). Excluding these 'out of scope' categories, the response rate for the initial interview was 70.3% (1000/1422), computed as the number of eligible persons with complete data divided by the total number of eligible sampled persons. In comparison with the 1991 Census (which included people in residential care) and the National Health Survey (NHS 1989–1990) the survey population was broadly similar for age (64% *vs.* 58% aged 65–74 years), sex (47% *vs.* 41% men), country of birth (75% *vs.* 67% Australia), marital status (60% *vs.* 55% married), smoker status (9% *vs.* 12% current), and past 12-month hospital admittance (22% *vs.* 21%) characteristics. Overall, the MELSHA cohort at baseline was a representative sample of older people in Melbourne for 1994, apart from those too ill to be interviewed and non-English speaking people.

Data collection

Baseline data collection was conducted by 13 trained interviewers (in order to standardise the interviewing procedure), with 95% of baseline interviews completed during the 7-month period from May to November 1994. Over the 10-year period of the study, participants in the baseline survey were followed up biennially in telephone interviews and by mail in the intervening years (up to 2004). For participants who could not be contacted directly, the tracing procedures relied primarily on next of kin or other individuals

volunteered by participants as key contacts at the time of the baseline interviews. Death records were checked annually to determine mortality, and interview data was collected on approximately 76% of survivors over the study period.

Diabetes incidence (endpoint)

Incident diabetes was determined by first self-reported new 'diabetes' at any biennial follow-up wave, excluding those with prevalent diabetes at baseline. Prevalent diabetes at baseline was determined by self-report or by specific medications used. Prescription medications was determined by interviewers' at the baseline interview who recorded the generic names and dosages of all prescription medications presented by respondents that were, or supposed to have been, taken in the past 2 weeks. Classification of specific use for prescription medications was done by qualitatively assessing product information for these agents from online resources.

Depression exposures (predictors)

The Psychogeriatric Assessment Scales (PAS) depression scale was used to measure depressive symptoms. Participants were asked how they had felt in the past 2 weeks on 12 items, from which symptom scores ranging from 0 to 12 (most severe) were derived. Although PAS scores of 3 or 4 (yielding prevalence estimates of 19.2% and 11.8% respectively) have shown at least 80% screening accuracy for clinical depression (Jorm *et al*., 1995), participants scoring five and above were classified as being 'symptomatic' (yielding a prevalence of 7.4%) to more closely approximate lower national prevalence estimates for depression for persons aged 65 years and over (Australian Bureau of Statistics, 1997). Prescription medications used for depression was determined by inventorying the names of all medications at the baseline interview (described above). Classification into the following depression exposure *versus* non-exposure (reference) subgroups was determined by symptoms and/or ADM use:

(1) 'Symptomatic' (PAS score 5+ regardless of ADM use; corresponding to $n = 73$ of 110 [66%] in Table 1) *versus* 'asymptomatic' (PAS score <5; corresponding to $n = 890$ of 890 [100%] in Table 1]

(2) 'ADM use' (regardless of PAS score) *versus* 'no ADM use'
(3) 'Symptomatic or ADM use' *versus*. 'asymptomatic and no ADM use'
(4) 'Symptomatic and no ADM use' *versus*. 'asymptomatic and no ADM use'
(5) 'Asymptomatic and ADM use' *versus*. 'asymptomatic and no ADM use'
(6) 'Symptomatic and ADM use' *versus*. 'asymptomatic and no ADM use'

Covariates

Demographic and lifestyle. Demographic and lifestyle information were collected using standard question items. Frequencies for walking, exercise, recreation or everyday work at home, and weekly consumption of fruits, vegetables, salads and milk products were used to create composite scores for physical activity and nutrition, respectively. High (*vs*. low) alcohol intake was classified by self-reported 'drinking 3+ alcoholic beverages per day' and 'a few times a week' or more often. Body mass index (BMI) values were derived from measured height (to the nearest 0.5 cm) and weight (to the nearest kg) values, and computed as weight in kilograms divided by height in metres squared. Standard international cut-offs were used to classify healthy weight (BMI 18.5–24.9), underweight (BMI <18.5), overweight (BMI 25–29.9) and obesity (BMI 30+).

Functional health. Independence with activities was assessed using the Instrumental Activities of Daily Living (IADL) sections of the OARS Multidimensional Functional Assessment Questionnaire and the Multi-level Functional Assessment Instrument (Lawton *et al*., 1982). Functional mobility (gait and balance) was assessed using the timed 'get-up and go' test (Mathias *et al*., 1986). Cognitive impairment was assessed using the Organic Brain Syndrome (OBS) scale, which has been shown to correlate well with other PAS for dementia symptoms and confusion states (Elmo Jensen, 1993). Pain was assessed by asking participants 'in the past 12 months how often have you felt pain that is persistent or bothersome or limits your activities'? Visual acuity was assessed using the Snellen chart.

Prevalent chronic disease. Classification of cardiovascular disease (heart attack or myocardial infarction, angina, heart failure or stroke), and high blood pressure was by self-report as have ever been medically diagnosed or by specific medications currently being used, as determined at the baseline interview.

Table 1 Baseline factors according to depression status

Baseline factors (1994)	Depression[a]		χ^2	p-value
	Absent, $n = 890$ n (%)	Present, $n = 110$ n (%)		
Demographic				
Male sex	429 (48)	38 (35)	7.34	0.008
Aged 65–69y	285 (32)	25 (23)	4.56	0.207
Aged 70–74y	294 (33)	38 (35)	—	—
Aged 75–79y	158 (18)	25 (23)	—	—
Aged 80+y	153 (17)	22 (20)	—	—
Married	533 (60)	45 (41)	16.85	0.001
Never married	42 (5)	4 (4)	—	—
Divorced	43 (5)	8 (7)	—	—
Widowed	272 (31)	53 (48)	—	—
Australian ethnicity	658 (74)	85 (77)	5.69	0.125
English ethnicity	96 (11)	7 (6)	—	—
European ethnicity	102 (11)	17 (15)	—	—
Other ethnicity	34 (4)	1 (1)	—	—
Living alone	279 (31)	56 (51)	16.81	0.000
No children	106 (12)	17 (15)	1.14	0.355
Education[b], low	309 (35)	46 (42)	9.21	0.009
Education, medium	266 (30)	41 (37)	—	—
Education, high	315 (35)	23 (21)	—	—
Income (AUD) ≤$264/week	319 (36)	54 (49)	7.66	0.022
Income $265-$341/week	300 (34)	27 (25)	—	—
Income $342/week+	271 (30)	29 (26)	—	—
Lifestyle				
Never smoker	390 (44)	52 (47)	0.71	0.704
Ex-smoker	418 (47)	47 (43)	—	—
Current smoker	82 (9)	11 (10)	—	—
Physical activity[c], low	296 (33)	28 (25)	3.28	0.197
Physical activity, medium	365 (41)	47 (43)	—	—
Physical activity, high	229 (26)	35 (32)	—	—
Social activity, low	197 (22)	37 (34)	7.37	0.024
Social activity, medium	397 (45)	40 (36)	—	—
Social activity, high	296 (33)	33 (30)	—	—
Alcohol intake[d], high	105 (12)	13 (12)	0.00	1.000
Healthy weight (BMI 18.5–24.9)	324 (36)	33 (30)	6.96	0.071
Underweight (BMI <18.5)	19 (2)	1 (1)	—	—
Overweight (BMI 25–29.9)	404 (45)	64 (58)	—	—
Obese (BMI 30+)	143 (16)	12 (11)	—	—
Nutrition[e], low (poor)	224 (25)	55 (50)	34.62	0.000
Nutrition, medium	237 (27)	29 (26)	—	—
Nutrition, high	429 (48)	26 (24)	—	—
Functional health				
IADL, dependent	137 (15)	38 (35)	24.87	0.000
Timed 'get-up and go', (0–8.9 s)	307 (34)	16 (15)	32.55	0.000
Timed 'get-up and go', (9–11 s)	311 (35)	32 (29)	—	—
Timed 'get-up and go', (11.1–40 s)	272 (31)	62 (56)	—	—
Cognitive impairment, none	405 (46)	38 (35)	16.82	0.000
Cognitive impairment, medium	435 (49)	55 (50)	—	—
Cognitive impairment, high	50 (6)	17 (15)	—	—
Pain, none	401 (45)	28 (25)	26.34	0.000
Pain, occasional	294 (33)	35 (32)	—	—
Pain, daily	195 (22)	47 (43)	—	—
Visual acuity, low (poor)	181 (20)	38 (35)	11.97	0.002
Visual acuity, medium	443 (50)	48 (44)	—	—
Visual acuity, high	266 (30)	24 (22)	—	—
Prevalent chronic disease[f]				
Cardiovascular disease	421 (47)	72 (65)	12.90	0.000
Cancer	168 (19)	31 (28)	5.32	0.023
Arthritis	492 (55)	81 (74)	13.48	0.000
Respiratory disease	125 (14)	22 (20)	2.77	0.115
Eye disease	187 (21)	28 (25)	1.15	0.325

(Continues)

Table 1.   (Continued)

Baseline factors (1994)	Depression[a]		χ^2	*p*-value
	Absent, *n* = 890 *n* (%)	Present, *n* = 110 *n* (%)		
Diabetes	144 (16)	30 (27)	8.38	0.005
Gastrointestinal disease	199 (22)	51 (46)	30.09	0.000
High blood pressure	447 (50)	70 (64)	7.05	0.008
Problems with feet or legs	294 (33)	66 (60)	30.90	0.000
High cholesterol	116 (13)	23 (21)	5.07	0.029
Osteoporosis	53 (6)	16 (15)	11.25	0.002

PAS, Psychogeriatric Assessment Scales, depression scale; IADL, Instrumental Activities of Daily Living; BMI, body mass index; AUD, Australian dollars; *p*-values for χ^2 analyses.
[a]Classification by depressive symptoms (PAS score 5+) or antidepressant medication (ADM) use.
[b]Composite scores were based on highest education attained and school leaving age.
[c]Composite scores were derived from self-reported frequency of light and energetic physical activity done in the past 2 weeks.
[d]High classification by self-reported 'drinking 3+ alcoholic beverages per day', and 'a few times a week' or more often, otherwise low.
[e]Composite scores were based on self-reported weekly consumption of fruits, vegetables and salads and milk products.
[f]Classification by self-report as 'ever being diagnosed' or by use of 'specific agents' used to treat the disease (other than 'arthritis', and 'problems with feet or legs', by self-report only).

Classification of cancer (prostate, skin, other growths or cancer), respiratory disease (chronic bronchitis, emphysema or asthma), eye disease (cataracts or glaucoma), diabetes (diabetes or high blood sugar or kidney or bladder problems), gastrointestinal disease (such as ulcer or hernia), high cholesterol and osteoporosis was by self-report as current medically diagnosed conditions or by specific medications currently being used; whereas classification of prevalent arthritis (gout, osteo, rheumatoid or other specified types), and problems with feet or legs was by self-report only.

Statistical analysis

For constructed scales, missing values on component items were pro-rated by the total on the rest of the items. Missing values were imputed in the following manner: items related to each other in content or construct were gathered together, and each item in such a group was regressed on the rest in a list-wise manner. The resulting multiple linear equation was used to fill in missing values on the item being regressed using the (non-missing) scores on the other items; where values were also missing on a predictor in such an imputation equation, the series' mean was used. χ^2 analyses were used to determine significant differences in baseline characteristics between participants with or without depression ('symptomatic or ADM use'). Cox proportional hazards regression analyses were used to determine hazard ratios with 95% confidence intervals (HR 95% CI) for diabetes incidence according to depression predictors

(exposures), and adjusted for significant covariates. Survival time for those classified diabetes incident was ascertained halfway between the wave it first appeared and the preceding wave of data; for those classified diabetes non-incident, censorship date was at their last wave of data. Categorical variables were recoded into pair-wise comparison dummy variables, and reference categories were designated based on *a priori* assumptions for minimum risk. Statistical analyses were completed using SPSS 15.0 (SPSS Inc. Chicago, USA). The following two-stage process was executed for prediction modelling:

(1) Baseline predictors (all factors listed in Table 1) were run singly to predict the endpoint (diabetes incidence), and those with a *p*-value ≥ 0.10 were removed from further analysis.
(2) The remaining successful ($p < 0.10$) baseline predictors were all run together to develop a final model for the endpoint; terms with a partial *p*-value ≥ 0.05 (not $p \geq 0.10$ as in stage one) were omitted, and the best of them only re-entered when the deviance test comparing the initial model to the reduced model yielded a *p*-value < 0.10. This was repeated until a final model was derived with significant predictors, together with deviance test reassurance concerning the omission of non-significant predictors.

RESULTS

Attrition rates at biennial follow-ups were 11.8% for 1996, 21.3% for 1998, 26.5% for 2000, 41.1% for 2002 and 21.2% for 2004. Table 1 presents prevalence

estimates for baseline factors according to depression status. Of 1000 participants, 110 (11%) were classified as depressed, 48 (44%) of whom had been prescribed ADM, 37 (34%) of whom were asymptomatic (PAS score <5) and 11 (10%) of whom remained symptomatic (PAS score 5+). At *p*-value <0.001, prevalence estimates were significantly higher among depressed than non-depressed participants for living alone, nutrition low (poor), IADL dependent, timed 'get-up and go' 11.1–40 s (poor), cognitive impairment high, pain daily, cardiovascular, arthritis, gastrointestinal disease and problems with feet or legs. At *p*-value between <0.01 and 0.001, prevalence estimates were significantly higher among depressed than non-depressed participants for female sex, unmarried, education low, visual acuity low and diabetes, high blood pressure and osteoporosis. At *p*-value between <0.05 and 0.01, prevalence estimates were significantly higher among depressed than non-depressed participants for income low, social activity low, cancer and high cholesterol.

Table 2 presents HRs for diabetes incidence during 10 years of follow-up according to baseline depression predictors. Several depression exposures significantly predicted diabetes incidence in both univariate and final multivariate models. 'Symptomatic' increased the risk for incident diabetes by 145% in the univariate analysis, and by 129% in the final model after adjustment for divorced (HR 2.01, *p* = 0.021); timed 'get-up and go' 11.1–40 s (HR 1.57, *p* = 0.013); social activity medium (HR 1.43, *p* = 0.029) and for problems with feet or legs (HR 1.35, P = 0.078). 'ADM use' increased the risk for incident diabetes in

the univariate analysis (HR 2.02, *p* = 0.041), but the conferred risk was attenuated in the multivariate analysis (HR 1.68, *p* = 0.093). 'Symptomatic or ADM use' increased the risk for incident diabetes by 123% in the univariate analysis, and by 113% in the final model after adjustment for divorced (HR 1.83, *p* = 0.046); timed 'get-up and go' 11.1–40 s (HR 1.75, *p* = 0.001) and social activity medium (HR 1.44, *p* = 0.023).

Compared with 'asymptomatic and no ADM use', 'symptomatic and no ADM use' increased the risk for incident diabetes incidence by 134% in univariate analysis, and by 138% in the final model after adjustment for divorced (HR 1.86, *p* = 0.043); timed 'get-up and go' 11.1–40 s (HR 1.72, *p* = 0.002) and social activity medium (HR 1.45, *p* = 0.022); but no significant associations were found for 'asymptomatic and ADM use' or 'symptomatic and ADM use' exposures. Findings indicate that 'symptomatic' was the depression exposure that most reliably predicted incident diabetes, over and above other significant covariate predictors—the strongest of which was timed 'get-up and go' 11.1–40 s.

DISCUSSION

This report presents findings of a 10-year prospective cohort study in a regionally representative sample of older Australians aimed at determining whether depression exposures predicted diabetes incidence. Findings indicate that several depression exposures at least doubled the risk of developing diabetes, and are

Table 2 Hazard ratios for diabetes incidence during 10-years follow-up according to baseline depression exposures (predictors)

Baseline depression predictors (1994)	Exposed	Non-exposed	Univariate			Final		
	Diabetes incidence[a] (n = 155/826)		z	HR	(95% CI)	z	HR	(95% CI)
	Cases (per 1000 PYs)							
Symptomatic *versus* asymptomatic	13 (83.6)	142 (34.8)	3.09	2.45	(1.39,4.34)	2.78	2.29	(1.28,4.10)
ADM use *versus* no ADM use	9 (71.6)	146 (35.6)	2.05	2.02	(1.03,3.97)	1.68	1.80	(0.91,3.57)
Symptomatic or ADM use *versus* asymptomatic and no ADM use	20 (74.5)	135 (34.1)	3.35	2.23	(1.40,3.58)	3.11	2.13	(1.32,3.44)
Asymptomatic and no ADM use (ref)	—	135 (34.1)	—	1	—	—	1	—
Symptomatic and no ADM use	11 (76.9)	—	2.71	2.34	(1.27,4.33)	2.72	2.38	(1.28,4.45)
Asymptomatic and ADM use	7 (61.8)	—	1.59	1.86	(0.87,3.97)	1.40	1.73	(0.80,3.73)
Symptomatic and ADM use	2 (160.6)	—	2.01	4.23	(1.04,17.28)	1.43	2.83	(0.68,11.85)

z, asymptotic *z*-score; PYs, person-years; HR, hazard ratios with 95% confidence intervals (CI); ADM, antidepressant medication; Symptomatic (PAS score 5+); Asymptomatic (PAS score <5); PAS, Psychogeriatric Assessment Scales, depression scale.
Final, model adjusted for significant demographic, lifestyle, functional health, and prevalent chronic disease predictors (presented in the results text).
[a]Remaining sample size after excluding those with prevalent diabetes at baseline.

consistent with (and about 50–80% higher than) those reported previously (Mezuk *et al.*, 2008). Point estimates for conferred risk were reliable for 'symptomatic' exposures regardless of ADM use, and were not substantially modified after adjustment for significant covariate predictors, except for 'symptomatic and ADM use' which only contained two cases of incident diabetes, and therefore unreliable (Table 2).

There was no evidence that being 'asymptomatic' among those prescribed antidepressants (reflecting treatment response) was protective against developing diabetes compared to those remaining 'symptomatic'. To our knowledge, this is the first cohort study to have investigated the joint effects of depressive symptoms and ADM use on diabetes risk, which may explain why there are equivocal findings for ADM use in the published literature (Knol *et al.*, 2007, 2009; Rubin *et al.*, 2008). Although none of those in the 'ADM use' groups were prescribed selective serotonin reuptake inhibitors, experimental studies in dogs have shown that intraportally infused fluvoxamine increases hepatic glucose uptake (glycogen concentration) and improves glucose control (Moore *et al.*, 2004). Such therapeutic benefits in humans for other SSRI agents are lacking (Lustman *et al.*, 2000, 2006). More prospective research is needed to ascertain whether effective management of depression prevents the development of diabetes in older people, and whether there are differential effects on diabetes risk according to specific therapeutic agents.

It is possible that the increased risk of diabetes incidence associated with depression may have been due to several 'intermediate' factors not accounted for in the present study. Depression may have caused increases in hypothalamic-pituitary-adrenal activity, resulting in elevated circulating cortisol levels. Cortisol stimulates the release of glucose and other energy providing molecules into the blood, and if chronic would likely cause hyperglycaemia and lead to the development of diabetes.

Depression, and associated chronically elevated cortisol, is hypothesised to stimulate greater consumption of pleasurable, energy-dense foods ('comfort foods') to alleviate symptoms (Dallman *et al.*, 2003). Consumption of energy-dense foods is a predictor of diabetes incidence independent of weight status (Wang *et al.*, 2008). Snacking behaviour is highly prevalent among older people, and associated with higher consumption of energy-dense foods than non-snacking behaviour (Zizza *et al.*, 2007). Therefore, snacking behaviour and higher consumption of comfort foods among those with depression may play an important role in the development of diabetes.

Depression was significantly associated with poor functional health factors particularly with the 'timed get-up and go' test (Table 1), and likely reflects low skeletal muscle mass and strength, both of which are important factors for improving glucose control (Brooks *et al.*, 2007). Muscle mass decreases with age, and most precipitously among those 65 years and over (Atlantis *et al.*, 2008), which may have occurred more among those with than without depression. Therefore substantial and toxic decreases in muscle mass may also mediate the association between depression and increased risk of diabetes incidence.

Future studies should further explore interactions between depression and ADM use (by specific therapeutics), and intermediate factors such as hypothalamic-pituitary-adrenal activity, muscle mass and strength, and consumption of energy-dense 'comfort foods', glucose control and subsequent risk of diabetes incidence. Research into intermediate causal pathways between depression exposures and diabetes incidence are needed to identify important additional intervention targets for prevention.

Strengths and limitations

Principle strengths of this report include the representative sample of older Australians, and the low aggregate attrition rate for determining diabetes incidence. Further, information was collected by trained interviewers, medication use was accurately inventoried, depression was defined using a clinically validated psychometric and by ADM use, classification of most chronic diseases was by self-report as well as by specific medications, and functional health was assessed using validate questionnaires and an objective test ('get-up and go' test). Limitations commonly found among cohort studies include biases due to self-report measures, responder compliance (particularly for the 2002 follow-up wave), and to misclassification of depression, chronic disease and other baseline factors.

In conclusion, older people with depressive symptoms were at least twice more likely to develop diabetes than those without depressive symptoms during 10-years of follow-up. Point estimates for increased risk were consistent for 'symptomatic' exposures regardless of ADM use, and were not substantially modified after adjustment for significant covariate predictors. Being 'asymptomatic' may not be a protective factor among those prescribed antidepressants. Future research is needed to identify intermediate pathways linking depression exposures with diabetes risk, to identify preventive intervention targets.

> **Key points**
>
> - Older people with depressive symptoms are at least twice more likely to develop diabetes than those without depressive symptoms, regardless of antidepressants.
> - Being 'asymptomatic' may not be a protective factor among those prescribed antidepressants.
> - Future research is needed to identify intermediate pathways linking depression with diabetes risk, to identify preventive intervention targets.

Conflict of interest

There are no conflicts of interest to declare.

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