

Depression and Insulin Resistance

Cross-sectional associations in young adults

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OBJECTIVE — To examine the association between depressive disorder and insulin resistance in a sample of young adults using the Composite International Diagnostic Interview to ascertain depression status.

RESEARCH DESIGN AND METHODS — Cross-sectional data were collected from 1,732 participants aged between 26 and 36 years. Insulin resistance was derived from blood chemistry measures of fasting insulin and glucose using the homeostasis model assessment method. Those identified with mild, moderate, or severe depression were classified as having depressive disorder.

RESULTS — The 12-month prevalence of depressive disorder was 5.4% among men and 11.7% among women. In unadjusted models mean insulin resistance was 17.2% (95% CI 0.7–36.0%, $P = 0.04$) higher in men and 11.4% (1.5–22.0%, $P = 0.02$) higher in women with depressive disorder. After adjustment for behavioral and dietary factors, the increased level of insulin resistance associated with depressive disorder was 13.2% (–3.1 to 32.3%, $P = 0.12$) in men and 6.1% (–4.1 to 17.4%, $P = 0.25$) in women. Waist circumference was identified as a mediator in the relationship between depression and insulin resistance, reducing the β coefficient in the fully adjusted models in men by 38% and in women by 42%.

CONCLUSIONS — A positive association was found between depressive disorder and insulin resistance in this population-based sample of young adult men and women. The association seemed to be mediated partially by waist circumference.

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Two recent meta-analyses reported that the odds of depression in people with type 2 diabetes were twice that in people without diabetes (1) and that depressed adults had a 37% increased risk of developing type 2 diabetes (2). Although this evidence suggests a causal relationship between depression and the development of type 2 diabetes, the underlying pathophysiological mechanisms are not clear.

Insulin resistance has been investigated as one of the mechanisms linking depression to diabetes, and different potential pathways can be identified. In 40–60% of people with major depressive

disorder, the hypothalamic-pituitary-adrenal (HPA) axis is hyperactive. Excess circulating cortisol and its disruption of glucoregulatory mechanisms is thought to lead to hyperinsulinemia and insulin resistance, eventually leading to diabetes (3). Alternatively, the relationship between depression and type 2 diabetes may be explained by lifestyle factors associated with depression, including physical inactivity and poor dietary habits that increase the risk of developing insulin resistance. Common to both of these pathways is obesity, which is a significant risk factor for increasing insulin resistance and diabetes. One hypothesis suggests that hy-

peractivity of the HPA axis associated with depression promotes intra-abdominal fat accumulation and there is some support for this in the literature (4).

A small number of cross-sectional population-based studies looking at the association between depression and insulin resistance have reported conflicting results. Some supported a positive association between depression and insulin resistance (5–9), others reported no association (10,11), and one reported an inverse relationship (12). With the exception of two studies reporting findings in young men aged 19 (9) and 31 (8) years, all other studies have been undertaken on older populations. Other methodological limitations of these studies include their reliance on poorly specified measures of depression and their potentially inadequate adjustment for confounding variables.

The key objective of this study was to examine the relationship between depression and insulin resistance in a large population-based sample of young adults aged between 26 and 36 years using the computerized version of the Composite International Diagnostic Interview (CIDI). This is the first study, as far as we are aware, to use a fully structured diagnostic interview to measure depression according to DSM-IV criteria and to examine its association with insulin resistance. We hypothesized that there would be a positive association between depression and insulin resistance and that this association would be explained by the confounding or mediating effects of clinical and behavioral factors and increasing abdominal adiposity.

RESEARCH DESIGN AND METHODS

The data for these cross-sectional analyses were collected in the period 2004–2006 from Australian adults aged 26–36 years as part of the Childhood Determinants of Adult Health (CDAH) study, a longitudinal study of cardiovascular risk factors in the general Australian population. In 2004 this study successfully traced 6,840 (80.5%) original participants of a 1985 Australia-wide survey of health and fitness of 8,498 schoolchildren aged between 7 and 15

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years. The 1985 study used a stratified two-stage sample. The first stage was the selection of schools. These were chosen with a probability proportional to the enrollment numbers of students aged 10 years in primary schools and 14 years in secondary schools. In the second stage, sample groups of boys and girls of each age were drawn, at random, from the total school enrollment. Of those traced, 5,170 (60.8%) were enrolled and provided data for the study. Of these, 2,410 attended one of 34 clinics conducted in major cities and regional centers around Australia.

Participants attended clinics where a variety of biological, physical, socioeconomic, clinical, and psychological parameters were measured after an overnight fast. Analyses were restricted to clinic participants who 1) had complete data for depression, 2) were not pregnant, and 3) had fasting blood glucose and insulin measures ($n = 2,110$). A further 142 participants were excluded from the analysis because their fasting insulin and glucose levels fell outside the recommended range used to calculate insulin resistance using the updated homeostasis model assessment methods (HOMA) (<http://www.dtu.ox.ac.uk>). Additional exclusions because of missing information for one or more study covariates resulted in a final sample size of 1,732 participants. This study was approved by the Southern Tasmanian Health and Medical Human Research Ethics Committee. Written informed consent was obtained from all participants.

Assessment of depression

Depression was assessed using the computerized version of the CIDI, a fully structured diagnostic interview with good reliability and validity (13). The CIDI interview provides current (and lifetime) psychiatric diagnoses according to ICD-10 and DSM-IV criteria and was developed by the World Health Organization. In this study we used 12-month depression determined according to the criteria of the DSM-IV. The CIDI is especially suitable for large epidemiological studies because it can be administered by lay interviewers, does not require outside informants or medical records, and does not assume the presence of a current disorder. The computerized versions of structured interviews offer a number of advantages over standard paper-and-pencil administration including improved standardization of diagnosis, elimination of clinician bias, and high reliability and consistency of administration

(14). Depression status was analyzed as a dichotomous variable. Participants classified as depressed were those experiencing mild, moderate, or severe depressive disorder.

Insulin resistance

Participants had a fasting blood sample drawn at the clinic for biochemical testing. Fasting glucose (millimoles per liter) was measured enzymatically using the Olympus AU5400 automated analyzer. Two methods of insulin determination were used during the follow-up study. Insulin (milliunits per liter) was measured by a microparticle enzyme immunoassay kit (AxSYM; Abbott, Abbott Park, IL) and by electrochemiluminescence immunoassay (Elecsys Modular Analytics E 170; Roche Diagnostics, Mannheim, Switzerland) with interassay standardization. Insulin resistance estimates were derived from blood chemistry measures of fasting insulin and glucose according to the updated homeostasis model assessment (HOMA) methods using the HOMA calculator (<http://www.dtu.ox.ac.uk>). HOMA models are considered appropriate for large-scale epidemiological studies when more sophisticated measures of insulin resistance are impractical.

Demographic measures

A self-administered written questionnaire was used to collect sociodemographic information including age, sex, marital status (married or living as married and single/divorced), highest level of education (school only, vocational training, or tertiary education), and occupation (managers/professionals, white collar, blue collar, or not in the workforce).

Dietary habits

Information about dietary habits was assessed using a modified version of a 127-item food frequency questionnaire (FFQ). The version of the FFQ has been used previously in the Australian 1995 National Nutrition Survey and was based on an existing FFQ developed for the Australian population (15). The FFQ assesses the average number of times the listed food and beverages were consumed over the previous 12 months. For each item participants are asked to choose one of nine response options ranging from "never or less than once a week" to "six or more times per day." Weekly fish intake was assessed from the scores pertaining to the consumption of fish (fresh, fried, canned, or frozen). Daily equivalents

were calculated for each of the FFQ items, assuming that one serving was consumed on each occasion. The number of weekly servings of fish was calculated by summing the average consumption per week for each type of fish. Alcohol consumption was determined from scores pertaining to the consumption of beer (light, medium, and full strength), wine (red, white, and fortified), wine coolers, spirits, and liqueurs. Participants were categorized as drinkers or nondrinkers.

Smoking

Cigarette smoking was ascertained by self-administered questionnaire. Participants were categorized as having never smoked, being a former smoker, or being a current smoker. Current smokers included those who were weekly and daily smokers.

Physical activity

The leisure-time physical activity domain of the International Physical Activity Questionnaire (IPAQ) was used as the measure of physical activity. The IPAQ is a standardized self-report instrument that measures the frequency, duration, and level of intensity of leisure, occupational, commuting, and household/yard activities for the last 7 days. Total weekly minutes spent in moderate and vigorous intensity leisure-time physical activity was calculated by multiplying the frequency and duration of activity participation. The IPAQ has been assessed in two international studies across 12 countries and has been found to have very good levels of repeatability and fair to moderate validity compared with data from accelerometers (16).

Waist circumference

Waist circumference was measured in triplicate at the narrowest point between the lower costal (10th rib) border and the iliac crest using a nonstretch tape measure. Measurements were taken at the end of a normal expiration and recorded to the nearest 0.1 cm. The mean of the three measures is reported.

Medications and polycystic ovary syndrome

Use of antidepressant medication or oral contraceptives and the presence of polycystic ovary syndrome (PCOS) were ascertained as part of a self-administered questionnaire. Participants were asked to respond to "Are you currently taking any medication prescribed by your doctor"

Table 1—Demographic, behavioral, and clinical characteristics of depressed and nondepressed men and women

	Men		P value	Women		P value
	Depressed	Not depressed		Depressed	Not depressed	
n	45	788		105	794	
Age (years)	31.4 ± 2.8	31.1 ± 2.5	0.58	30.7 ± 2.5	30.9 ± 2.7	0.56
Married or living as married	26 (58)	544 (69)	0.11	64 (61)	543 (68)	0.13
Professional/managers	19 (42.2)	489 (62.1)	0.04	46 (43.8)	429 (54)	0.25
Education						
School only	14 (31)	187 (24)	0.21	35 (33)	206 (26)	0.14
Vocational training	19 (42)	288 (36)		29 (28)	201 (25)	
Higher degree	12 (27)	313 (40)		41 (39)	387 (49)	
Smoking						
Never	19 (42)	474 (60)	0.03	47 (45)	462 (58)	0.03
Former	9 (20)	141 (18)		33 (31)	174 (22)	
Current	17 (38)	173 (22)		25 (24)	158 (20)	
Leisure time physical activity						
No physical activity	12 (27)	209 (27)	0.45	37 (35)	175 (22)	0.01
<120 min/week	13 (29)	181 (23)		28 (27)	205 (26)	
120–240 min/week	13 (29)	196 (25)		25 (24)	235 (30)	
>240 min/week	7 (16)	202 (26)		15 (14)	179 (23)	
Current alcohol drinking	43 (96)	721 (92)	0.34	80 (76)	662 (83)	0.07
Frequency of weekly fish consumption	1.5 (0.75–3.0)	1.5 (1.0–2.9)	0.61	1.0 (0–2.0)	1.5 (1.0–3.0)	<0.0001
Waist circumference	92.5 ± 11.5	90.0 ± 10.5	0.12	81.5 ± 14.2	78.0 ± 10.8	0.02
BMI ≥25 kg/m ²	30 (67)	489 (62)	0.54	49 (47)	295 (37)	0.06
Taking antidepressants	9 (20)	9 (1)	<0.0001	33 (31)	20 (2)	<0.0001
Oral contraceptives	NA	NA		14 (13)	177 (22)	0.03
PCOS	NA	NA		12 (11)	41 (5)	0.01
Fasting insulin (mU/l)	7.2 (5.7–11.4)	6.4 (4.7–9.3)	0.07	6.6 (4.7–10.8)	6.0 (4.7–8.4)	0.09
Fasting glucose (mmol/l)	5.2 (5.0–5.6)	5.2 (4.9–5.4)	0.16	4.9 (4.6–5.2)	4.8 (4.6–5.1)	0.33
Insulin resistance	1.04 ± 0.56	0.89 ± 0.57	0.04	0.91 ± 0.42	0.83 ± 0.37	0.02

Data are means ± SD, n (%), or median (interquartile range). NA, not applicable.

with a further prompt to provide the name of the medication and the reason they were taking it. The presence of PCOS was assessed by asking women to respond to the following question; “Has your doctor ever told you that you have polycystic ovaries or PCOS?”

Statistical analysis

Unadjusted characteristics by depressive status were compared separately in men and women using the *t* test, Mann-Whitney *U* test, and χ^2 test for normal, non-normal, and categorical variables, respectively. Means ± SD, medians and interquartile range (IQR), and percentages are reported where appropriate. Insulin resistance was logarithmically transformed for regression modeling.

The association between insulin resistance (outcome) and depressive status (exposure) was assessed using linear regression models. This analytical approach was chosen based on evidence that insulin resistance is a state-dependent metabolic abnormality in individuals with major depressive disorder, suggesting that depres-

sive disorder can cause insulin resistance (17).

Confounding variables identified for inclusion in regression models were smoking, alcohol consumption, physical activity, education, fish consumption, and, in women, PCOS and use of oral contraceptives. All unadjusted and adjusted models were developed separately for men and women. Regression models were constructed to evaluate the effects of possible confounders using the following strategies. Baseline models included terms for age and education; subsequent models examined the inclusion of groupings of additional factors including 1) behavioral factors (smoking and physical activity), 2) dietary factors (alcohol and fish consumption), 3) medications in women, and 4) PCOS. Fully adjusted models retained only those variables that were associated with a ≥15% change in the β coefficient for depressive status upon removal of the variable or were significant independent predictors (*P* < 0.05). Mediation analysis was performed to determine whether antidepressant use

or waist circumference was an intermediate.

RESULTS— Participants’ demographic, clinical, and behavioral characteristics are shown in Table 1. Depressive disorder was present in 5.4% of men and 11.7% of women. A higher proportion of depressed men and women were former or current smokers than nondepressed participants. Depressed women tended to be less physically active than their nondepressed counterparts, to eat less fish, and to have a greater waist circumference. Oral contraceptive use was greater among nondepressed women than among depressed women. A higher proportion of depressed women also reported having PCOS.

Whereas the study sample was derived from a nationally representative sample of children first measured in 1985, only one-third participated in the follow-up in adulthood. Compared with the general Australian population of similar age (25–34 years) (Table 2), this study sample had a higher proportion of profes-

Table 2—Characteristics of study participants compared with the Australian general population

Participant characteristic	CDAH study sample	Australian general population
Current smokers*		
Men	23	34
Women	20	26
Professional/managers		
Men	51.7	40
Women	48.3	35
Overweight and obese†		
Men	62	58
Women	38	35
Antidepressant use	4	3.6
Depression‡		
Men	5.4	5.8
Women	11.7	10.1

Data are %. *Current smokers include those who smoke daily or weekly. †Overweight and obese includes individuals with a BMI ≥ 25 kg/m². ‡Depression assessment for the Australian general population was undertaken using the mood module of the Primary Care Evaluation of Mental Disorders (PRIME-MD) instrument. Scoring to determine depression “caseness” used the PRIME-MD method for detection of DSM-IV diagnoses.

sionals and managers (18). There was a lower proportion of current smokers, and the proportion of participants who were classified as overweight or obese (BMI ≥ 25 kg/m²) was slightly higher for men and women (19). The prevalence of depressive disorder in study participants was similar to that in the general population (20) as was the proportion of participants taking antidepressants (19).

Table 3 shows the results for the regression analysis of depression on insulin resistance in men and women. Before adjustment, insulin resistance was significantly higher among men with depression (17.2%). This association remained largely unchanged after adjustment for demographic, behavioral, and dietary factors. It was markedly reduced after adjustment for antidepressant use (11.3%). In the final fully adjusted model, the mean insulin resistance was 13.2% higher in men with depressive disorder. Factors remaining in the fully adjusted model were age, education, physical activity, smoking, alcohol, and antidepressant use.

Insulin resistance was significantly higher in women with depression in the unadjusted model (11.4%). There was only a slight reduction in the size of association after adjustment for age and edu-

Table 3—Regression of insulin resistance on depression status adjusted for demographic, clinical, and behavioral characteristics in men and women

Models	Ratio of means (95% CI)*	P value
Men (n = 833)		
Unadjusted	1.172 (1.007 – 1.364)	0.04
Model 1 (age and education)	1.163 (0.999 – 1.354)	0.05
Model 1 plus behavioral factors†	1.175 (1.012 – 1.366)	0.03
Model 1 plus dietary factors‡	1.172 (1.008 – 1.362)	0.04
Model 1 plus medications§	1.113 (0.949 – 1.303)	0.19
Fully adjusted model	1.132 (0.969 – 1.323)	0.12
Women (n = 899)		
Unadjusted	1.114 (1.015 – 1.221)	0.02
Model 1 (age and education)	1.100 (1.004 – 1.206)	0.04
Model 1 plus behavioral factors†	1.096 (1.000 – 1.203)	0.05
Model 1 plus dietary factors‡	1.089 (0.999 – 1.196)	0.07
Model 1 plus medications§	1.088 (0.984 – 1.203)	0.10
Model 1 plus PCOS	1.088 (0.993 – 1.193)	0.07
Fully adjusted model	1.061 (0.959 – 1.174)	0.25

Data are ratios of means (95% CI). *Mean insulin resistance of depressed subjects relative to mean insulin resistance of subjects who were not depressed. †Behavioral factors were physical activity and smoking. ‡Dietary factors were alcohol and fish consumption. §Medications were antidepressants and oral contraceptive use (women only). ||Variables remaining in the fully adjusted model for men were age, education, physical activity, smoking, alcohol, and use of antidepressants and for women were age, education, PCOS, fish consumption, and use of antidepressants.

cation (10.0%) and after additional adjustment for behavioral factors (9.6%). There were modest reductions in the association after adjustment for dietary factors (8.9%), oral contraceptive and antidepressant use (8.8%), and PCOS (8.8%). Factors remaining in the fully adjusted model were age, education, PCOS, fish consumption, and antidepressant use.

Inclusion of waist circumference in fully adjusted regression models reduced the β coefficient for depression by 38% in men and 42% in women. No concurrent change in the β coefficient for waist circumference in men or women resulted after removal of depression from the regression model, suggesting that waist circumference is a mediator of the association between depression and insulin resistance.

CONCLUSIONS— In the present study, we examined the association between depression status and insulin resistance among healthy younger adults. To the best of our knowledge this is the first large population-based study including both young men and women to examine this association using a structured diagnostic interview to assess depression according to DSM-IV criteria. In both men and women we found that depressive disorder was significantly related to insulin resistance as indexed by HOMA and that

this relationship remained largely unchanged after adjustment for demographic, behavioral, and dietary factors. This relationship was, however, found to be partially mediated by waist circumference. Similar findings have been reported by Everson-Rose et al. (21) in middle-aged women whereas Pan et al. (6) reported that the odds of insulin resistance associated with depression increased from 1.54 in all participants to 1.65 in overweight and 1.81 in obese men and women, suggestive of effect modification of depression by weight status on insulin resistance. With the exception of these two studies, in the majority of previous studies, positive associations between depression and insulin resistance have remained significant after adjustment for body composition (BMI, waist circumference, or waist-to-hip ratio) (6–9,21).

One of the mechanisms by which depression may contribute to disruptions in glucose metabolism, central adiposity, and ultimately type 2 diabetes is thought to be via activation of the HPA axis. The HPA axis is sensitive to both physical factors such as alcohol and smoking, and psychosocial and socioeconomic factors such as divorce, unemployment, work-related stress, poor education, and poverty. These are thought to provide the basis for conditions such as depression, which is known to activate the HPA axis. Although the HPA axis functions as a pro-

tective mechanism to maintain allostasis, intense chronic activation is believed to lead to permanent derangements of the HPA axis and increased susceptibility to disease. Studies on primates have shown that exposure to moderate psychological stress is followed by a depressive reaction and the development of adverse metabolic indicators, including abdominal fat accumulation and insulin resistance. Similar perturbations in the HPA axis associated with low socioeconomic status and leading to visceral obesity have been reported in humans (22).

Because of the cross-sectional nature of this study, we were not able to determine whether there is a causal relationship between the development of depression and insulin resistance via the mechanisms outlined above. We were also limited by the absence of a measure of HPA activity such as cortisol. We could, however, test the hypothesis that the association between depression and insulin resistance is mediated through abdominal fat. In men and women, we found the association to be partially mediated by waist circumference but not eliminated. A causal association between depression and insulin resistance that is primarily mediated by increases in waist circumference among those with depression cannot therefore be ruled out.

It is also possible that obesity may be casual in the etiology of depression. A recent meta-analysis suggested that although most cross-sectional studies support an association between obesity and depression in women but not men, the overall level of evidence was weak primarily because of a lack of prospective cohort studies (23). The other mechanism by which depression may contribute to disruptions in glucose metabolism and central adiposity is via behavioral factors such as physical inactivity and poor dietary behaviors. In our models we found that these factors did not substantially account for the associations.

Contrary to what was expected, antidepressants did not seem to be an intermediate but rather a confounder. There was moderate attenuation of the β coefficient after adjustment for antidepressants in this study. Whether the antidepressants exert a direct effect on glucose metabolism leading to elevated insulin resistance or whether the effect is mediated via side effects from the medications such as increased appetite and weight gain or sedation remains unclear. A review of the literature (24) suggests that

some antidepressants exert clinically significant effects on metabolism that can be either therapeutic in normalizing glucose homeostasis or have the opposite effect.

A primary point of difference between our study and all prior population-based studies examining the relationship between depression and insulin resistance was the use of the CIDI to determine depression status. Prior studies have used self-report questionnaires to measure either depressive symptoms or depression. Self-report measures of depression do not directly assess clinical diagnostic criteria but rather the presence or absence of emotional symptoms over a specified time period. As observed in a study by Fisher et al. (25), 70% of people with diabetes and high levels of depressive symptoms as assessed using the CES-D were not clinically depressed. Fisher et al. suggested that scores on the CES-D may reflect a more general emotional and diabetes-related distress, rather than a clinical diagnosis of depression. Future research in this area needs to determine whether syndromal depression may be less important than general distress in the depression-insulin resistance-diabetes relationship.

Although this study makes important contributions to the literature, a few limitations should be noted. The temporal relationship between depression and insulin resistance has not been clearly delineated, because the majority of studies, including this one, have been cross-sectional; thus, we are limited in our ability to infer causality in the etiology of depression related to insulin resistance. A second limitation is the possibility of non-response bias, given that analyses were based on only 25% of the original cohort sample. Although the prevalence of obesity in our sample was slightly higher for men and women than in the general population, the 12-month prevalence of depression was similar. Furthermore, the inclusion of a wide distribution of confounders and intermediates suggests that response bias is unlikely and that the results from the study should not be limited in terms of their generalizability. Finally, the inclusion of a young cohort is acknowledged as both a strength and limitation. There is a paucity of studies in this area on younger populations, so this study makes a unique contribution in this way. However, the age range may have limited our findings, given that insulin resistance and diabetes risk become more prevalent with increasing age.

In summary, these results show a sig-

nificant relationship between depressive disorder and greater insulin resistance in young adult men and women. This relationship remained relatively unchanged after adjustment for behavioral and dietary factors but was substantially attenuated and no longer significant after adjustment for waist circumference. The association with depressive disorder may be due to confounding by abdominal adiposity; however, a causal association between depression and insulin resistance mediated by increases in waist circumference among those with depressive disorder is also plausible. Further research should be conducted in an attempt to replicate these findings and clarify the directional nature of these relationships and their underlying mechanisms.

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