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Insulin resistance and self-rated symptoms of depression in Swedish women with risk factors for diabetes: the Women's Health in the Lund Area study

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Abstract

Previous studies have suggested that depression increases the risk for diabetes and that this may be mediated through insulin resistance. The study aimed to analyze if self-rated symptoms of depression are related to insulin resistance among middle-aged and older Swedish women with features of the metabolic syndrome and being at risk for type 2 diabetes mellitus. We analyzed data from 1047 Swedish women aged 50 to 64 years without a history of diabetes and living in the southern part of Sweden. A variable *self-rated symptoms of depression* (SRSD) was defined by using the Gothenburg Quality of Life instrument. We estimated odds ratios (ORs) to determine whether or not SRSD was associated with the homeostasis model assessment of insulin resistance. The variable SRSD was not associated with insulin resistance. However, it was positively associated with waist-hip ratio (OR, 1.95; 95% confidence interval, 1.28-3.00) and negatively associated with physical exercise (OR, 1.29; 95% confidence interval, 0.99-1.68) after multivariate adjustment. In conclusion, lifestyle factors such as physical inactivity and abdominal obesity, but not insulin resistance, seem to be related to self-rated symptoms of depression in women with risk factors for diabetes mellitus. The relationship between insulin resistance and major depression needs to be further examined.

1. Introduction

There is an ongoing discussion whether or not factors other than obesity and a positive energy balance, such as psychosocial stress or symptoms of depression, contribute to the increasing prevalence of type 2 diabetes mellitus. A Swedish study demonstrated that self-reported low-decision latitude at work and low sense of coherence were associated with type 2 diabetes mellitus [1]. Furthermore, a population-based study in the Netherlands showed that stressful life events were associated with increased risk for type 2 diabetes mellitus [2]. Evidence is accumulating for the hypothesis that the presence of depressive symptoms increases the risk for type 2 diabetes mellitus due to metabolic changes [3].

In some studies, depressed patients with normal glucose tolerance have shown increased insulin resistance as compared with nondepressed control subjects [4,5]. Furthermore, Okamura et al [5] found that the insulin resistance decreased after treatment of depression. Others have, however, found opposite results. In a cross-sectional study of British women, the prevalence of depression was lower in subjects with higher degree of insulin resistance. Lawlor et al [6] speculated that insulin sensitivity may influence tryptophan metabolism, which may explain why women with insulin resistance would be less likely to develop depression, depending on higher levels of serotonin in the central nervous system. Furthermore, a prospective study of almost 15 000 individuals in Helsinki, Finland, showed that a higher degree of insulin sensitivity was associated with an increased risk for suicide [7], which is of special interest as depression is one of the major contributing factors to suicidal behavior [8].

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These contradicting results may mirror a dual relationship between depression and insulin resistance. Both low insulin and high insulin resistance may be associated with depression or depressive symptoms. However, there is a need to distinguish between depression and depressive symptoms. Looking at a population, heterogenic factors may blur associations between depressive symptoms and insulin resistance. For instance, it is not known whether or not there is a relationship between depressive symptoms and insulin resistance in subjects with increased risk to develop type 2 diabetes mellitus. This would be of interest to entangle as the rates of depression and diabetes are increased in both middle-aged and older women.

The current study was a retrospective test on the relationship between self-rated symptoms of depression and insulin resistance in middle-aged and older women with risk markers for diabetes mellitus. These women were included in a Swedish epidemiological investigation on Women's Health in the Lund Area (WHILA). The present study also explored the association between lifestyle factors and symptoms of depression.

2. Patients and methods

2.1. Study population

The population comprised all 10 766 women aged 50 to 64 years living in the Lund area, Southern Sweden, who were invited to participate in the WHILA survey, which took place between 1995 and 2000 and included questionnaires as well as physical and laboratory examinations. In total, 6917 (64.2%) women participated in the study and answered questions concerning medical history, drug treatment, family history of diabetes mellitus and cardiovascular disease, perimenopausal status, education, household working status, and general dietary habits. The Gothenburg Quality of Life (GQL) [9] validated questionnaire on self-rated physical, social, and mental well-being, and subjective physical and mental symptoms were also included in the examination. Furthermore, in the WHILA questionnaire, the participants also reported frequency and intensity of leisure-time physical exercise per week, which was reported as ≤60 or >60 min/wk of jogging or equivalent activities. Smoking was categorized by lifetime consumption of cigarette pack-years, in which 1 "pack-year" corresponded to a consumption of 20 cigarettes per day for 1 year. Subjects were divided into never smokers (<1 pack-year), past smokers, and current smokers (≥1 pack-year for both). Past smokers were those who had stopped smoking at least 1 month before the study. Alcohol intake was defined as the weekly consumption of wine, beer, and spirit converted into gram alcohol and was divided into no consumption, 83 g/wk or less, 84 to 167 g/wk, and 168 g/wk or more. One drink was the same as 1 shot of liquor, 1 glass of wine, or 1 glass of beer (25 cL) and equalized 12 g of alcohol.

The primary physical examination included measurements of body weight, body mass index (BMI; kg/m^2), waist-hip ratio (WHR), and the average of 2 blood pressure recordings in the seated position after 15 minutes of rest. Random blood glucose and serum levels of triglycerides were measured on capillary whole blood (Cholestech LDX-instrument, Cholestech, Hayward, CA). Women with 1 or more risk markers for diabetes, that is, components of the metabolic syndrome, were invited to a separate follow-up where fasting blood samples were drawn. The risk markers for diabetes were BMI ≥30, WHR ≥0.9, systolic blood pressure ≥160 and/or diastolic blood pressure ≥95 mm Hg, random capillary B-glucose ≥8.0 mmol/L, or serum triglycerides ≥2.3 mmol/L, family history of diabetes mellitus, and treatment of hypertension or hyperlipidemia. The baseline design of the study has been described by Lidfeldt et al [10].

In total, 3593 women were positively screened with risk markers for diabetes mellitus, of which 117 had prior known diabetes, 6 have had a stroke, and 11 have had a myocardial infarction during the last year, all of which were thus excluded from the follow-up examination. A total of 2923 women with positive primary screening accepted to undergo the follow-up procedure, of which 1047 were randomly chosen for analysis of insulin resistance.

2.2. Insulin resistance

Fasting venous whole blood glucose was analyzed by using a HemoCue instrument (HemoCue, Ängelholm, Sweden). Hormonal assays were performed using enzyme-linked immunosorbent assay technique for determination of serum levels of fasting insulin (DGR Instrument, Marburg, Germany). Insulin resistance was expressed through the homeostasis model assessment of insulin resistance (HOMA-IR) and calculated by fasting insulin (mIU/L) × fasting glucose (mmol/L)/22.5 [11]. The HOMA-IR, besides being used in continuous form, was also categorized according to quartile values.

2.3. Self-rated symptoms of depression

In the GQL, the women answered with "yes" or "no" regarding whether or not they had different mental conditions during the last 3 months. Self-rated symptoms of depression were subsequently drawn from the GQL and a variable, named *self-rated symptoms of depression* (SRSD), was composed. (The different items that were selected for this variable were, as far as possible, chosen to imitate the criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [*DSM-IV*] [12].)

To be classified as having SRSD the subject had to recognize that they have had periods of feeling depressed during the last 3 months. Furthermore, to be classified as having SRSD the subject must have had at least 1 additional symptom of depression other than periods of feeling depressed. Such additional symptoms included in SRSD were "poor appetite," which corresponds to *DSM-IV*'s "significant weight loss or decrease in appetite"; "trouble sleeping,"

Table 1
Subject characteristics of all women and according to the results of the variable SRSD

	All	SRSD		
		No (n = 1047)	Yes (n = 553)	*P* (n = 494)
Age (y)	56.0 (5.1)	56.4 (5.5)	55.6 (4.7)	.033
Time delay (d)[a]	36.0 (40.0)	35.0 (38.0)	38.0 (41.0)	.023
BMI (kg/m^2)	26.3 (6.4)	26.2 (6.3)	26.5 (6.3)	.118
WHR (cm/cm)	0.8 (0.09)	0.8 (0.09)	0.8 (0.09)	.013
WHR =.90 (n/%)	110/10.5	45/8.1	65/13.2	.007
HOMA-IR	15.4 (15.3)	15.4 (15.3)	15.6 (15.3)	.617
Categories of quartiles (n = 1047) (n/%)				.982
First quartile (≤10.14)	261/24.9	139/25.1	122/24.7	
Second quartile (10.15-15.40)	263/25.1	141/25.5	122/24.7	
Third quartile (15.41-25.45)	262/25.0	137/24.8	125/25.3	
Forth quartile (=25.46)	261/24.9	136/24.6	125/25.3	
Physical exercise (n = 1037) (n/%)				.020
≤60 min/wk	672/64.8	336/61.5	336/68.4	
>60 min/wk	365/35.2	210/38.5	155/31.6	
Smoking habits (n = 1046) (n/%)				.322
Never	694/66.3	377/68.3	317/64.2	
Past	200/19.1	97/17.6	103/20.9	
Current	152/14.5	78/14.1	74/15.0	
Alcohol consumption (n = 998) (n/%)				.876
None	293/29.4	158/29.9	135/28.7	
Low (≤83 g/wk)	538/53.9	280/53.0	258/54.9	
Moderate (84-167 g/wk)	125/12.5	69/13.1	56/11.9	
High (=168 g/wk)	42/4.2	21/4.0	21/4.5	

Values are presented as median (IQR) and percentage.
[a] Difference in days between the primary screening and the follow-up examination.

which corresponds to *DSM-IV*'s "insomnia or hypersomnia"; "general fatigue," which corresponds to *DSM-IV*'s "fatigue or loss of energy"; and "I have had problems concentrating," which corresponds to *DSM-IV*'s "diminished ability to think or concentrate." Some of the diagnosis criteria according to *DSM-IV* were, however, not included in GQL ("markedly diminished interest or pleasure"; "feelings of worthlessness or excessive or inappropriate guilt"; "psychomotor agitation or retardation"; and "recurrent thoughts of death/suicidal ideation/suicidal plans/suicidal attempt").

2.4. Statistical analysis

Values are given as median (interquartile range [IQR]). The Mann-Whitney *U* test and Pearson χ^2 test were used for analyses of differences between groups regarding continuous and categorical variables. Multiple logistic regression analyses (backward, likelihood ratio) were performed to identify factors possibly associated with SRSD. Beside HOMA-IR, variables that in the bivariate analyses were significantly associated ($P = .20$) to each of the dependent variables were included in the separate regression models. A *P* value of less than .05 was considered significant. All statistical analyses were performed using SPSS 11.5 for Windows (SPSS, Chicago, IL).

3. Results

3.1. All women analyzed for insulin resistance

Table 1 shows subject characteristics of all women. The median age (IQR) was 56.0 years (5.1 years), with a BMI of 26.3 kg/m^2 (6.4 kg/m^2), a WHR of 0.8 (0.09 cm/cm), and HOMA-IR of 15.4 (15.3). The delay between the primary screening and follow-up blood test was 36.0 days (40.0 days).

Table 2
Multivariate regression risk analysis on women according to SRSD

	SRSD	
	OR (95% CI)	*P*
Age (y)	0.95 (0.91-0.99)	.013
Time delay (d)[a]	1.00 (1.00-1.00)	.209
BMI (kg/m^2)	0.97 (0.74-1.27)	.801
WHR (cm/cm)	1.95 (1.28-3.00)	.002
HOMA-IR		
Categories of quartiles (n = 1047) (n/%)		
First quartile (≤10.14)	1.0	
Second quartile (10.15-15.40)	0.95 (0.66-1.37)	.787
Third quartile (15.41-25.45)	0.90 (0.63-1.30)	.579
Forth quartile (=25.46)	0.96 (0.67-1.37)	.808
Physical exercise (n = 1037) (n/%)		
≤60 min/wk	1.29 (0.99-1.68)	.062
>60 min/wk	1.0	
Smoking habits (n = 1046) (n/%)		
Never	1.0	
Past	1.22 (0.87-1.71)	.244
Current	1.11 (0.76-1.61)	.594
Alcohol consumption (n = 998) (n/%)		
None	1.0	
Low (≤83 g/wk)	1.12 (0.83-1.51)	.455
Moderate (84-167 g/wk)	0.88 (0.57-1.35)	.549
High (=168 g/wk)	1.03 (0.53-2.00)	.940

The result of the Hosmer-Lemeshow goodness-of-fit test for SRSD was 0.124.
[a] Difference in days between the primary screening and the follow-up examination.

3.2. Self-rated symptoms of depression

Table 1 presents subject characteristics of women in relation to SRSD. Women having SRSD were younger (55.6 vs 56.4 years, $P = .033$), had a longer time delay from primary to secondary screening (38 vs 35 days, $P = .023$), had a WHR of 0.90 cm/cm or higher to a greater extent (13.2% vs 8.1%, $P = .007$), and performed less physical exercise (≤60 min/wk, 68.4% vs 61.5%; $P = .020$) than women who reported no such symptoms. No differences were found between the 2 groups regarding BMI, HOMA-IR, smoking habits, or alcohol consumption (Table 1).

Multiple logistic regression analysis revealed a negative association between having SRSD and age (odds ratio [OR], 0.95; 95% confidence interval [CI], 0.91-0.99; $P = .013$) and a positive association between SRSD and WHR (OR, 1.95; 95% CI, 1.28-3.00; $P = .002$), and a tendency for a positive association between SRSD and low degree of physical exercise (OR, 1.29; 95% CI, 0.99-1.68; $P = .062$) (Table 2).

4. Discussion

In the present study, insulin resistance was not related to SRSD in the GQL among middle-aged and older women at risk for diabetes. However, lifestyle factors associated with diabetes mellitus and the metabolic syndrome, such as abdominal obesity and exercise, were significantly associated with self-rated symptoms of depression. This suggests that these common lifestyle factors, associated with both diabetes mellitus and depression, may increase the risk for these women to develop depression or diabetes mellitus.

Our observation of a positive association between SRSD and abdominal obesity (WHR), but not for general obesity (BMI), is in accordance with other studies [13-15]. This may mirror an increased hypothalamic-pituitary-adrenal axis activity with elevated cortisol levels in the subjects with symptoms of depression. Increased cortisol levels may cause elevated lipoprotein activity in abdominal adipose tissue and low lipolytic activity, which may induce insulin resistance [16].

There was also a positive association between increased physical exercise and absence of self-rated symptoms of depression. This is in line with findings of risk of depression among physically active and sports players [17]. Furthermore, aerobic exercise has been observed to reduce depressive symptoms in major depression [18,19]. One biological explanation for this could be that physical exercise up-regulates brain-derived neurotrophic factor [20-22], which seems to play an important role in depression [23,24]. For instance, brain-derived neurotrophic factor has been reported to influence the growth and survival of serotonin neurons [25]. This leads to the hypothesis that mentally healthy people might prevent the development of depression by the same mechanism. However, an alternative explanation is that people exercise more when they are feeling better.

One general objection to the WHILA study could be that blood samples were collected later than the answers about depressive symptoms [10]. For practical reasons it was not possible to collect information about each respondent's history of depressive symptoms during the period between primary screening and blood sample collection. However, the finding that this time delay did not remain significant in multivariate analysis indicates that this does not influence the interpretation of our results. A more important limitation may be the inclusion criteria, as the variable SRSD did not cover all the diagnosis criteria included in *DSM-IV*'s major depressive disorder. The constructed variable SRSD is not validated, and the results need to be interpreted with caution. There is also a possibility of a statistical type II error as the variable SRSD was significantly associated with factors known to be associated with insulin resistance such as WHR and physical inactivity.

The general conclusion of the current study is that self-related symptoms of depression are not related to insulin resistance among middle-aged and older women at risk for type 2 diabetes mellitus, but to common lifestyle factors, such as abdominal obesity and physical inactivity. It is possible that a psychiatric evaluation could reveal other relations between depressive symptoms, insulin resistance, and lifestyle factors. The relationship between insulin resistance and major depression needs to be further examined. It would also be of interest to further study whether or not abdominal obesity and physical inactivity are associated with other major biological mechanisms related to resilience to develop depression.

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References

[1] Agardh EE, Grill V, Efendic S, et al. Work stress and low sense of coherence is associated with type 2 diabetes in middle-aged Swedish women. Diabetes Care 2003;26:719-24.

[2] Mooy JM, De Vries H, Grootenhuis PA, et al. Major stressful life events in relation to prevalence of undetected type 2 diabetes. Diabetes Care 2000;23:197-201.

[3] Talbot F, Nouwen A. A review of the relationship between depression and diabetes in adults: is there a link? Diabetes Care 2000;23:1556-62.

[4] Chiba M, Suzuki S, Hinokio Y, et al. Tyrosine hydroxylase gene microsatellite polymorphism associated with insulin resistance in depressive disorder. Metabolism 2000;49:1145-9.

[5] Okamura F, Tashiro A, Utumi A, et al. Insulin resistance in patients with depression and its changes during the clinical course of depression: minimal model analysis. Metabolism 2000;49:1255-60.

[6] Lawlor DA, Smith GD, Ebrahim S. Association of insulin resistance with depression: cross sectional findings from the British women's heart and health study. BMJ 2003;327:1383-4.

[7] Golomb BA, Tenkanen L, Alikoski T, et al. Insulin sensitivity markers: predictors of accidents and suicides in Helsinki Heart Study screenees. J Clin Epidemiol 2002;55:767-73.
[8] Mann JJ, Apter A, Bertolote J, et al. Suicide prevention strategies: a systematic review. JAMA 2005;294:2064-74.
[9] Tibblin G, Tibblin B, Peciva S, et al. "The Göteborg quality of life instrument"—an assessment of well-being and symptoms among men born 1913 and 1923: methods and validity. Scand J Prim Health Care 1990;1:33-8.
[10] Lidfeldt J, Nerbrand C, Samsioe G, et al. A screening procedure detecting high-yield candidates for OGTT. The Women's Health in the Lund Area (WHILA) study: a population based study of middle-aged Swedish women. Eur J Epidemiol 2001;17:943-51.
[11] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28: 412-9.
[12] American Psychiatric Association. Diagnostic and statistical manual of mental disorder. 4th ed. Washington (DC): American Psychiatric Association; 1994.
[13] Rosmond R, Björntorp P. Psychiatric ill-health of women and its relationship to obesity and body fat distribution. Obes Res 1998;6:338-45.
[14] Lapidus L, Bengtsson C, Hällström T. Obesity, adipose tissue distribution and health in women—result from a population study in Gothenburg, Sweden. Appetite 1989;12:25-35.
[15] Wing RR, Matthews KA, Kuller LH. Waist to hip ratio in middle-aged women: associations with behavioral and psychosocial factors and with changes in cardiovascular risk factors. Arterioscler Thromb 1991;11:1250-7.
[16] Rebuffé-Scrive M, Krotkiewski M, Elfversson J, et al. Muscle and adipose tissue morphology and metabolism in Cushing's syndrome. J Clin Endocrinol Metab 1988;67:1122-8.
[17] Paffenbarger RS, Lee I-M, Leung R. Physical activity and personal characteristics associated with depression and suicide in American college men. Acta Psychiatr Scand 1994;377:16-22.
[18] Babyak M, Bluementhal JA, Herman S, et al. Exercise treatment for major depression: maintenance of therapeutic benefit at 10 months. Psycosom Med 2000;62:633-8.
[19] Dunn AL, Trivedi MH, Kampert JB, et al. Exercise treatment for depression: efficiency and dose response. Am J Prev Med 2005; 28:1-8.
[20] Huang AM, Jen CJ, Chen HF, et al. Compulsive exercise acutely upregulates rat hippocampal brain-derived neurotrophic factor. J Neural Transm 2006;113:803-11.
[21] Vaynman S, Gomez-Pinilla F. License to run: exercise impacts functional plasticity in the intact and injured central nervous system by using neurotrophins. Neurorehabil Neural Repair 2005; 19:283-95.
[22] Berchtold NC, Chinn G, Chou M, et al. Exercise primes a molecular memory for brain-derived neurotrophic factor protein induction in the rat hippocampus. Neuroscience 2005;133:853-61.
[23] Angelucci F, Brenè S, Mathé AA. BDNF in schizophrenia, depression and corresponding animal models. Mol Psychiatry 2005;10:345-52.
[24] Karege F, Perret G, Bondolfi G, et al. Decreased serum brain-derived neurotrophic factor levels in major depressed patients. Psychiatry Res 2002;109:143-8.
[25] Mattson MP, Maudsley S, Martin B. A neural signaling triumvirate that influences ageing and age-related disease: insulin/IGF-1, BDNF and serotonin. Ageing Res Rev 2004;3:445-64.