Insulin Resistance and Depressive Symptoms in Young Adult Males: Findings From Finnish Military Conscripts

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Objective: To investigate whether the association between insulin resistance (IR) and depressive symptoms is present already in young adult males. The association between IR and depression has been poorly studied, although the existence of a connection of Type II diabetes with depression is well established. We previously demonstrated at epidemiological level in two groups of men aged 31 years and 61 to 63 years that IR is linked with depressive symptoms. **Methods:** In a cross-sectional study, involving 1054 healthy Finnish male military conscripts of about 19 years of age, IR was defined through homeostasis model assessment (HOMA-IR). The severity of the depressive symptoms was evaluated through a Finnish modification of the 13-item Beck Depression Inventory (R-BDI). Moderate-to-severe depressive symptoms were said to be present, if the R-BDI score was ≥8, and mild depressive symptoms were present if the R-BDI score was 5 to 7. **Results:** After adjusting for confounders, moderate-to-severe depressive symptoms increased the risk for IR, as defined by the highest decile of the HOMA-IR, up to 2.8-fold (odds ratio = 2.8; 1.2–6.5). Mild depressive symptoms were not significantly associated with IR. **Conclusions:** In young adult males, co-occurring strictly defined IR seems to be positively associated with current moderate-to-severe depressive symptoms. **Key words:** depressive symptoms, homeostasis model assessment, insulin resistance, males.

cAMP = cyclic adenosine monophosphate; **CI** = confidence interval; **HOMA** = homeostasis model assessment; **HPA** = hypothalamus-pituitary-adrenal; **GR** = glucocorticoid receptor; **IR** = insulin resistance; **OR** = odds ratio; **PKA** = protein kinase A; **R-BDI** = Finnish modification of the 13-item Beck Depression Inventory.

INTRODUCTION

The association between Type II diabetes and depression has recently become a matter of considerable research interest (1). Yet, the association between depression and insulin resistance (IR), representing an important fundamental metabolic defect in Type II diabetes, has been sparsely studied (2). However, some studies, based mainly on clinical datasets, have pointed to a positive association between IR and depression despite numerous methodological limitations (2–4). A positive association between IR and depressive symptoms was also reported in a population-based study of subjects aged 61 to 63 years (5). Very recently, investigations based on data from a Birth Cohort in Northern Finland showed that there even existed an association between IR and depressive symptoms in males aged 31 years, and that the strength of the association increased in line with tightening the definition of IR (6). There are, however, also reports that suggest that IR is not associated with depression and that IR may even provide protection against depression (7,8). Thus, the few population-based investigations (5–8) present conflicting findings with regard to an association between IR and depression. There is consequently an apparent need to solve this issue. The aim of the present study was to explore, by using data from military conscripts, whether or not the association under debate was already noticeable in young adult males. Secondly, we investigated, whether this putative association would be dependent on the severity of IR as had been observed earlier in studies with older men (6).

MATERIALS AND METHODS

Study Sample

In Finland, all young men, 19 years of age, are drafted into military service lasting 6 to 12 months. About 85% of the male population completes the service (9). Our study population was collected in January and July 2005 from two consecutive intake groups for military service at Sodankylä Jaeger Brigade, Finland. All male conscripts (n = 1467) were invited to participate in the present study and 79% of them (n = 1160) attended. The mean ± standard deviation (SD) age of these conscripts was 19.2 ± 1.0 years (range 18–28 years), and all of them were White.

At the beginning of their military service, conscripts were asked to complete a questionnaire on their depressive symptoms and, in addition, their smoking habits, alcohol use, and physical activity as well as education. The study protocol included each conscript's weight and height as well as waist circumference measured midway between the lowest rib and the iliac crest. Blood samples for the determination of fasting serum insulin as well as fasting plasma glucose were taken by physicians and trained medical assistants after an overnight fast. Plasma and serum samples were separated from blood by centrifuging at 1500 g for 15 minutes. Then, plasma and serum samples were immediately frozen at −20°C. The study protocol was approved by the Ethics Committee of Lapland Central Hospital, Rovaniemi, Finland.

Assessment of Dependent Variable

Fasting plasma levels of glucose were measured in the laboratory of Oulu's Deaconess Institute by using commercially available hexokinase assay (Konelab analyzers, Thermo Electron Oy, Vantaa, Finland). Fasting serum insulin levels were determined by AxSYM Insulin assay (Abbott Laboratories, Abbott Park, Illinois) in the laboratory of the National Public Health Institute, Oulu.

IR was ascertained by the homeostasis model assessment (HOMA-IR) (10). IR, using the World Health Organization cut-off point, was defined as the highest quartile of the HOMA-IR of our study population (11). Additionally, the highest decile of the HOMA-IR was used to explore whether a more strictly defined IR associated more strongly with depressive symptoms.

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Assessment of Independent Variable

Depressive symptoms were assessed by a Finnish modification of the 13-item Beck Depression Inventory (R-BDI) (12–14), which is based on the 13-item Beck Depression Inventory (15), which in turn is a shortened version of an originally 21-item questionnaire designed by Beck and colleagues (16). The R-BDI has earlier been validated with regard to the Finnish population by Raitasalo (12), and the psychometric properties of the Finnish 13-BDI version have been reported to be totally adequate for use with youths (14). The R-BDI consists of statements showing increasing intensity of depressive emotions and cognitions, scored with 0 to 3 points each; thus, the total R-BDI score ranges from 0 to 39. Based on the total score of the R-BDI, the severity of depressive symptoms was categorized as follows: 0–4 = nondepressed; 5–7 = mild depressive symptoms; 8–15 = moderate; and ≥16 = severe depressive symptoms (13–15). In the statistical analyses, moderate-to-severe depressive symptoms were pooled together due to the small number of cases displaying severe depressive symptoms ($n = 6$).

Assessment of Confounding Variables

In previous studies, obesity (17,18), alcohol consumption (19,20), smoking (19,21), and education (22) as well as physical inactivity (23,24) have been shown to be associated with IR/disturbances in glucose metabolism and depression. Therefore, waist circumference, alcohol consumption, smoking, and education as well as physical inactivity were used as potential confounding variables in multivariate regression analyses.

Information on the frequencies of beer, wine, and other spirit consumptions as well as statements on the usual amounts of each alcoholic drink per one drinking occasion was requested in the questionnaire. For each type of drink (the alcohol percentages of which were turned into amounts of pure alcohol consumed), the frequency of alcohol use was proportioned to 365 days. The average amount of pure alcohol (g/day) was calculated as follows: pure alcohol (g) at any one time × frequency of alcohol use (1/day). Alcohol consumption was categorized as abstainers/light drinkers (<15 g of pure alcohol/day), moderate drinkers (15–40 g/day), and heavy drinkers (>40 g/day) (25).

Smoking habits were also assessed through the above-mentioned questionnaires by posing the following question: "Are you currently smoking?" with six alternatives to the answer. For the purpose of the present study, the answers of this question were dichotomized into regularly smoking (i.e., smoking on 7 days/5–6 days/2–4 days a week) versus occasionally smoking (i.e., smoking once a week/occasional smoker/nonsmoker).

Physical activity was assessed by posing the following question: "How often do you train physically so that it makes you breathless and sweat at least mildly?" with six alternatives to the answer. In this study, exercise habits were categorized as physically active (exercising daily/4–6 times/2–3 times a week) versus physically inactive (exercising once a week, 2–3 times a month, a few times a year, none due to injury or illness).

Education was dichotomized according to the information provided by the conscripts as compulsory (basic) and post compulsory (upper secondary and tertiary) level (26). In the statistical analyses, the third category comprised those with missing information on this issue.

Statistical Methods

Differences in categorical variables between subgroups were investigated by Pearson's χ^2 test. Analysis of variance was used to compare the trend in the means of continuous variables across the severity of depressive symptoms. HOMA-IR, insulin, glucose, and alcohol intake variables were logarithmically transformed. Of those, who attended the present study, information on depressive symptoms was available from 1130 conscripts. The total variable information in multivariable analyses was available in 1054 subjects.

The generalized additive model (GAM) with binomial error and logit link was used to provide a graphic representation of the relationship between IR and R-BDI total score (27). Logistic regression analyses were also used to explore the association between IR and depressive symptoms (as defined above) adjusting for the potential confounding variables. Because there is evidence that IR is a state-dependent metabolic abnormality in cases of depressive disorders, suggesting that depression would cause IR (3), IR was used as a dependent variable in our analyses. Results are presented by using crude and adjusted odds ratios (OR) and their 95% confidence intervals (CIs). Statistical analyses were performed using the SAS (version 8.02) for Windows (SAS Institute, Inc., Cary, North Carolina). Furthermore, GAM analyses as well as graphic representations were carried out by the "R Development Core Team" (28).

RESULTS

In the young male military conscripts of our study material, mild and moderate-to-severe depressive symptoms were present in 7.1% and 4.6%, respectively. HOMA-IR values increased (i.e., IR increased) in line with the increased severity of depressive symptoms as assessed by R-BDI (p value for trend, $p < .05$). Detailed information on the conscripts' physical and behavioral characteristics is given in Table 1.

A graphic representation of the relationship between IR and R-BDI total scores is presented in Figure 1. The curves obtained using GAM by adjusting for waist circumference, alcohol consumption, current smoking, physical inactivity, and education level show a statistically significant association between R-BDI total score and IR, when IR is defined by the highest decile of the HOMA-IR.

Also, as defined by the highest decile of the HOMA-IR, moderate-to-severe depressive symptoms increased the risk of IR up to 2.9-fold (OR = 2.9; 95% CI = 1.4–5.9). Regarding mild depressive symptoms, the corresponding OR was 1.3 (0.6–2.7). With IR defined by the WHO cut-off point (i.e., the highest quartile of the HOMA-IR), the corresponding ORs with regard to mild and moderate-to-severe depressive symptoms were 1.5 (0.9–2.5) and 1.4 (0.8–2.7), respectively. The prevalences of IR in nondepressed as well as in mild and moderate-to-severe depressive symptoms, according to highest decile and quartile of HOMA-IR, are presented in Figure 2. After adjusting for waist circumference, alcohol consumption, current smoking, physical inactivity, and education level, moderate-to-severe depressive symptoms increased the risk of developing IR (as defined by the highest decile of the HOMA-IR) up to 2.8-fold (OR = 2.8; 1.2–6.5).

DISCUSSION

The major finding of this study was that co-occurring strictly defined IR (i.e., the highest decile of the HOMA-IR) was positively associated with current moderate-to-severe depressive symptoms in young adult males, and that the corresponding significant association was also observed when depressive symptoms (i.e., R-BDI total score) were analyzed as a continuous variable. Thus, in addition to our earlier findings (5,6), we were now able to demonstrate that a positive association between depressive symptoms and IR existed at epidemiological level in three different age groups of Finnish males. Earlier, we found that concomitant IR, assessed by the 21-item BDI (16), was positively associated with depressive symptoms in a population-based study of subjects aged 61 to 63 years (5), and with current severe depressive symptoms, defined by Hopkins' Symptom Checklist-25, in young adult males aged 31 years (6). Our findings are also in line with earlier reports that were based on clinical samples and

TABLE 1. Characteristics of Young Male Military Conscripts With No, Mild, and Moderate-to-Severe Depressive Symptoms According to the Finnish Modification of the 13-Item Beck Depression Inventory (R-BDI)

	Total (n = 1130)	Depressive Symptoms			p
		No (n = 997)	Mild (n = 81)	Moderate-to- Severe (n = 52)	
HOMA-IR[a]	1.1 (0.7, 1.9)	1.1 (0.7, 1.8)	1.2 (0.7, 2.1)	1.3 (0.7, 2.3)	.047
Highest 25th percentile	24.1%	23.3%	31.2%	30.0%	.180
Highest 10th percentile	9.6%	8.9%	10.4%	22.0%	.009
Fasting insulin (mU/l)	4.8 (3.0, 7.8)	4.7 (2.9, 7.5)	5.1 (3.0, 8.7)	5.4 (3.1, 9.3)	.060
Fasting glucose (mmol/l)	5.2 (4.8, 5.6)	5.2 (4.8, 5.6)	5.2 (4.7, 5.6)	5.3 (4.7, 5.9)	.234
Waist circumference	81.8 (10.4)	81.4 (9.9)	84.1 (10.8)	86.5 (14.9)	<.001
Current smokers[b]	44.6%	43.9%	42.5%	61.5%	.041
Alcohol intake (g/day)	9.5 (2.4, 37.7)	9.3 (2.4, 35.5)	10.3 (2.0, 52.5)	16.3 (4.5, 58.6)	.006
Light drinkers	65.6%	66.7%	63.8%	48.1%	.001
Moderate drinkers	28.0%	27.9%	25.0%	34.6%	
Heavy drinkers	6.4%	5.4%	11.2%	17.3%	
Physical inactivity[c]	35.5%	32.7%	51.9%	65.4%	<.001
Education					.091
Basic	8.1%	7.3%	14.8%	11.5%	
Secondary	72.6%	73.4%	67.9%	63.5%	
Not known	19.4%	19.3%	17.3%	25.0%	

Means (SD), geometric means (SD range), or percentages.

[a] HOMA-IR = homeostasis model assessment for insulin resistance (10).

[b] Current smoking was dichotomized as regular smokers (i.e., smoking on 7 days/5–6 days/2–4 days a week) versus occasional smokers (i.e., smoking once a week/occasional smoker/nonsmoker).

[c] Exercise habits were dichotomized as physical activity (exercising daily/4–6 times/2–3 times a week) versus physical inactivity (exercising once a week, 2–3 times a month, few times a year, none due to injury or illness).

had shown that patients with depression often exhibited IR (2,3). However, we attach particular importance to the findings of the present study because they show that the association under debate can already be detected in seemingly healthy young adult males, as long as they exhibit moderate-to-severe depressive symptoms.

Our findings are in contradiction to some earlier epidemiological studies that reported an inverse (7) or no (8) association between depression and IR. However, one of the earlier studies (7) involved only female subjects. Thus, it seems to us that the association between IR and depression could be different in males and females, and that therefore gender should be taken into account in future studies on this issue. The contradictory findings between our present as well as our earlier studies (5,6) with a prospective cohort study on middle-aged men from Wales (8) warrants closer scrutiny, in which also age and ethnicity should be considered.

With regard to the confounding variables used in our study, our results are in agreement with previous investigations (18,20,21,24), in which obesity, smoking, alcohol consumption, and physical inactivity were shown to be associated with depression. However, with regard to the educational status, our results are not in line with those of the earlier literature (22), because we did not find any independent association between education and depressive symptoms. But we must bear in mind that individuals with diagnosed depression are temporarily excused from military service and this could have weakened the association between educational level and depressive symptoms in our study population.

The strengths of our study were that it was based on a relatively large epidemiological database of young adult Finnish males. In addition, our sample was genetically highly homogeneous.

Limitations of our study were that the data regarding HOMA-IR and R-BDI were collected cross-sectionally. Further, the R-BDI does not provide a specific depression diagnosis like structured clinical interviews. A possible limitation was also that the data on depressive symptoms were collected from newly recruited military conscripts. Strict disciplinary rules, physical workload, and adaptation to a new environment may lead to higher rates of self-reported depressive symptoms under these conditions. Consequently, our finding with regard to depressive symptoms might depict a nonspecific stress reaction. However, it seems worth noting that the prevalence of at least mild depressive symptoms in our sample of male conscripts was of about the same magnitude as that found in the nonmilitary population of young adult Finnish men (29). The presence of severe depressive symptoms is, however, considered to be underrepresented in our sample, because military service is postponed in call-ups for physical examination in men with known major depression. Due to the small number of young men with severe depressive symptoms, however, separate statistical analyses, focusing on them alone, were not feasible. Finally, our results cannot be generalized beyond the gender and ethnicity represented in this study.

The precise etiology of IR in depressed persons has remained unknown, but it has been suggested to be multifactorial (3). Hypothalamus-pituitary-adrenal (HPA) hyperactivity,

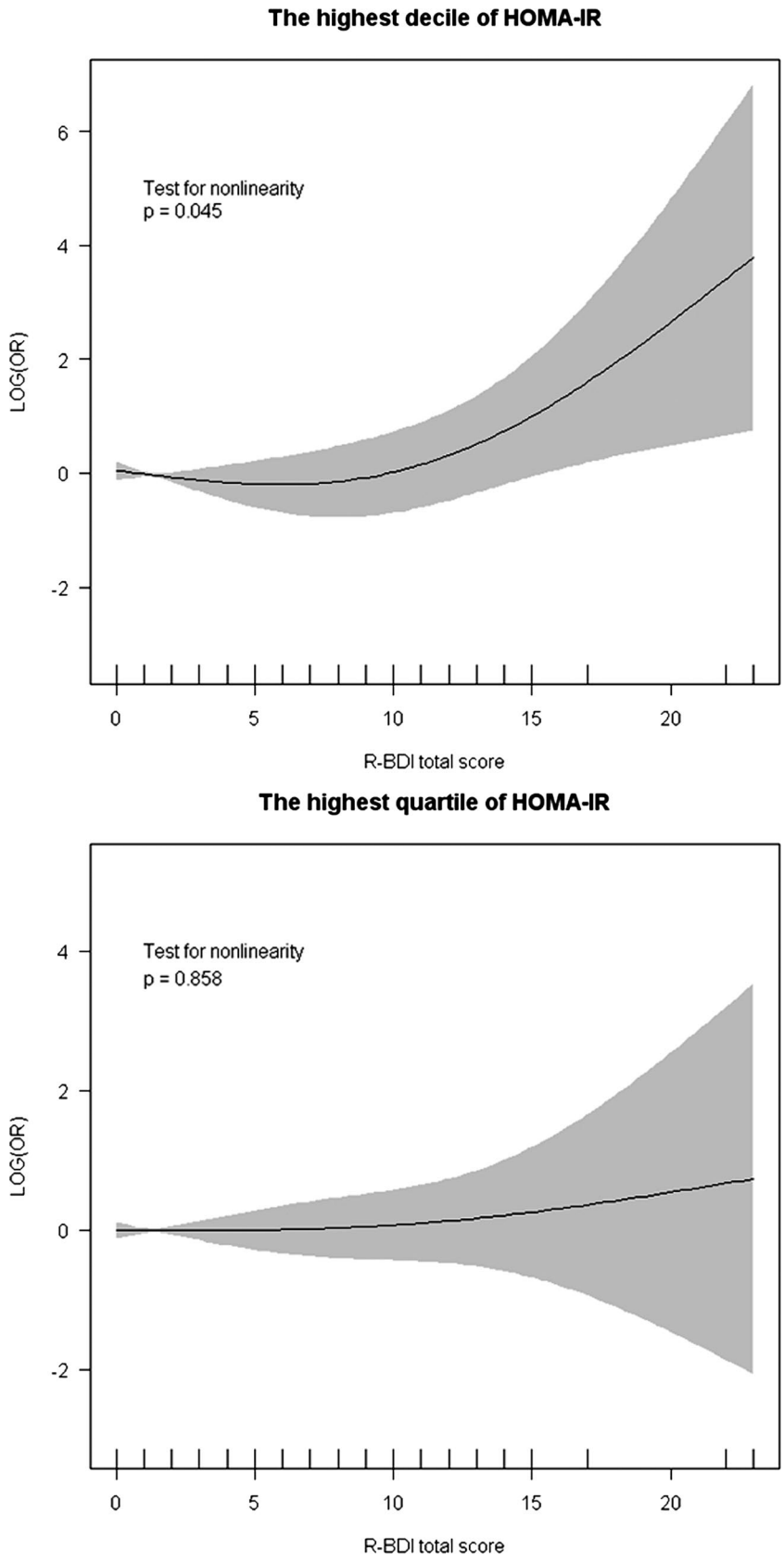

Figure 1. Relative odds (logarithmic scale) on insulin resistance (the highest decile and quartile of homeostasis model assessment for insulin resistance (HOMA-IR)), by R-BDI (the Finnish modification of the 13-item Beck Depression Inventory) total score. The shaded area is the 95% confidence interval of the relative odds curve.

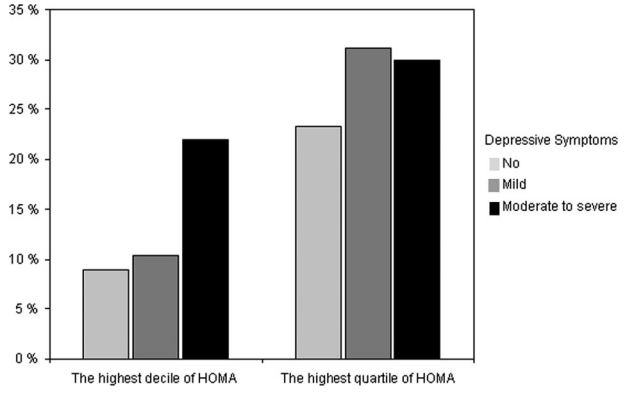

Figure 2. Prevalence of insulin resistance in connection with no depressive symptoms as well as mild and moderate-to-severe depressive symptoms according to highest decile and quartile of homeostasis model assessment for insulin resistance (HOMA-IR) in young male military conscripts.

genetic mechanisms, and disturbances in the serotonin system have been confirmed as potential biological mechanisms behind the association (3). In addition, chronic low-grade inflammation is also frequently associated with both depression (3) and IR (30) and thus could serve as a potential pathophysiological mechanism underlying the association.

Regarding causality, there is evidence that IR is a state-dependent metabolic abnormality in cases of depressive disorders, suggesting that depression would cause IR (3). Conversely, IR may be involved in the pathogenesis of depression (3). In the present study, causality could not be investigated and remains to be further studied. We speculate that there might also be reciprocal causality between these two conditions. If so, IR could at least partly be prevented by treating or preventing the outbreak of depression. Such measures would be of considerable benefit to public health.

One of the most frequently studied areas in depression is the HPA axis (31). Although a considerable amount of evidence points to a dysregulation of the HPA axis during depressive episodes, most often characterized by hyperactivity of the HPA axis, the highly variable nature of the system itself causes difficulties in obtaining definitive answers on this matter of HPA axis and depression (32). Variations due to circadian and monthly rhythms are difficult to take into consideration in any study. Further, studies based purely on baseline glucocorticoid measurements lack the methodology to measure changes in the feedback loop; for example, the responsiveness of the HPA axis as reviewed by Swaab and colleagues (32). However, increased levels of glucocorticoids have been proven to cause defects in insulin signaling, culminating in insulin resistance (33). As such, a clear and simple hypothesis for the state-dependent connection between depression and IR can be formulated: hypercortisolism, itself state-dependent in depression (34), would then directly exacerbate IR in a state-dependent fashion. This would seem to be an alluring and simple hypothesis. On the other hand, there also exist studies, in which underactivity of the HPA axis has been shown to be associated with atypical depression as reviewed by Kasckow and associates (35).

A closer look at the dysfunction of the HPA axis in depression focuses attention on impaired glucocorticoid receptor (GR) function as an important issue (31) and one of the suggested mechanisms for impaired GR function is a reduced activity of the cyclic adenosine monophosphate (cAMP) dependent protein kinase A (PKA) cascade. Studies on antidepressants suggest that cAMP and increased PKA activity play important roles as mediators of the therapeutic effects, and additional work has shown that depressed patients exhibit decreased cAMP-dependent PKA activity (31). Yet, insulin is known to decrease both cAMP and PKA activity intracellularly (36). In diabetic and also hyperinsulinemic (but normoglycemic) primates, basal PKA activity is significantly reduced (37). Thus, it seems reasonable to hypothesize that an increase in insulin levels could be to the detriment of GR function through reduced PKA activity, resulting in depression. Consequently, a bidirectional link between depression and IR seems very probable, with the possibility of a vicious cycle during depressive episodes.

In summary, concomitant strictly defined IR seems to be positively associated with current depressive symptoms in young adult males. Further investigations are, however, needed to examine whether our findings can be confirmed in young males other than Finnish military conscripts. If our findings were to be confirmed in other cross-sectional settings, investigations on temporality and direction of the association between IR and depression in prospectively followed cohort settings would be highly desirable.

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