Acta Neuropsychiatrica

cambridge.org/neu

Leptin and leptin receptor gene polymorphisms and depression treatment response

Ida-Maria Tavast[1], Anssi Solismaa[1,2], Leo-Pekka Lyytikäinen[3], Nina Mononen[3], Eeva Moilanen[4], Mari Hämäläinen[4], Terho Lehtimäki[3] and Olli Kampman[1,2,5,6,7]

[1]Department of Psychiatry, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [2]Department of Psychiatry, The Pirkanmaa Wellbeing Services County, Tampere, Finland; [3]Department of Clinical Chemistry, Tampere University Hospital and Fimlab Laboratories and Finnish Cardiovascular Research Center-Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; [4]The Immunopharmacology Research Group, Faculty of Medicine and Health Technology, Tampere University and Tampere University Hospital, Tampere, Finland; [5]Department of Psychiatry, Department of Clinical Sciences (Psychiatry), Faculty of Medicine, University Hospital of Umeå, Umeå University, Umeå, Sweden; [6]Department of Clinical Medicine (Psychiatry), Faculty of Medicine, University of Turku, Turku, Finland and [7]Department of Psychiatry, The Wellbeing Services County of Ostrobothnia, Vaasa, Finland

Original Article

Cite this article: Tavast I-M, Solismaa A, Lyytikäinen L-P, Mononen N, Moilanen E, Hämäläinen M, Lehtimäki T, and Kampman O. (2025) Leptin and leptin receptor gene polymorphisms and depression treatment response. *Acta Neuropsychiatrica*. **37**(e38), 1–8. doi: 10.1017/neu.2024.43

Received: 30 April 2024
Revised: 16 July 2024
Accepted: 22 July 2024

Keywords:
Depression; genetics; leptin; leptin receptor; treatment outcome

Corresponding author:
Ida-Maria Tavast;
Email: ida-maria.tavast@tuni.fi

Abstract

Objective: Associations between leptin (*LEP*) and leptin receptor (*LEPR*) gene polymorphisms and mood disorders have been found but not yet confirmed in multiple studies. The aim of our study was to study the associations between *LEP* and *LEPR* single nucleotide polymorphisms (SNPs) and treatment response of depression. Associations between leptin levels and depression severity were also investigated. *Methods:* The data included 242 depressed patients in secondary psychiatric care. Symptoms of depression were assessed with the Montgomery–Åsberg Depression Rating Scale (MADRS). Previously found *LEP* and *LEPR* SNPs associated with depression and other mood disorders were studied. Furthermore, all available *LEP* and *LEPR* SNPs were clumped using proxy SNPs to represent gene areas in $r^2 > 0.2$ linkage disequilibrium and their association with treatment response was analysed with logistic regression. *Results:* Two proxy SNPs of *LEPR* gene, rs12564738 and rs12029311, were associated with MADRS response at 6 weeks (p adjusted = 0.024, p adjusted = 0.024). SNPs from previous studies were not associated with MADRS response, but *LEPR* rs12145690 from a previous study was strongly associated with rs12564738 ($r^2 = 0.94$). The positive association between leptin levels and MADRS score at baseline after adjusting with age, sex, body mass index (BMI), Alcohol Use Disorders Identification Test score, and smoking was found ($p = 0.011$). *Conclusion:* Our findings suggest that *LEPR* polymorphisms are associated with depression treatment response. We also found associations between leptin levels and depression independently of BMI. Further studies and meta-analyses are needed to confirm the significance of found SNPs and the role of leptin in depression.

Highlights

- The study identified significant associations between leptin receptor gene (*LEPR*) polymorphisms rs12564738 and rs12029311 and the treatment response of depression, indicating their potential role in predicting treatment outcomes.
- A positive association was found between leptin levels and depression severity, independent of body mass index (BMI), suggesting that leptin could be a marker for depression severity.
- Previously identified single nucleotide polymorphisms in *LEP* and *LEPR* genes did not show significant associations with depression treatment response in this study, highlighting the need for further research to clarify these genetic relationships.

Significant outcomes

- *LEPR* polymorphisms rs12564738 and rs12029311 are associated with depression treatment response.
- An association between leptin levels and depression severity was found independently of BMI.

Limitations

- Sample size was relatively limited.
- The sample included patients with harmful alcohol use.
- There was variation in the onset of depression and previous treatments between patients.

Introduction

Major depressive disorder (MDD) is a common psychiatric illness with a global prevalence of around 5 % (Ferrari *et al.*, 2013). It is one of the most significant contributors to disability globally (Atun, 2015). Depression is a multifactorial disorder, and its ethiology and pathophysiology are not fully understood. Depression is associated with obesity, and they may have shared biological mechanisms, such as the dysregulation of leptin (Milaneschi *et al.*, 2019).

Leptin is a 167 amino acid protein (16 kDa) encoded by the leptin gene (*LEP)* on chromosome 7 and primarily secreted from white adipose tissue in proportion to the percentage of body fat (Münzberg & Morrison, 2015). Leptin is best known for its role in the regulation of energy homeostasis by reducing energy intake and increasing energy consumption (Farr *et al.*, 2015). Leptin binds to leptin receptors (*LEPR*) encoded by the *LEPR* gene on chromosome 1 (Endomba *et al.*, 2020). Leptin receptors are located in different parts of the body, including the central nervous system, where leptin receptors have been found in hypothalamic and thalamic regions, hippocampus, amygdala, substantia nigra, cortex, brainstem, cerebellum, and some other brain regions (Erichsen *et al.*, 2022).

In the central nervous system, leptin modulates stress adaptation and the control of energy homeostasis via the hypothalamic-pituitary-adrenal (HPA) axis (Roubos *et al.*, 2012). Hyperactivation of the HPA axis is associated with MDD (Pariante & Lightman, 2008). Leptin also regulates neural plasticity, especially in brain regions related to depression, by affecting neuronal morphology and hippocampus synaptic transmission and by working as a neurotrophic factor via brain-derived neurotrophic factor (Ge *et al.*, 2018), which has been linked to depression and antidepressant effects (Castrén & Monteggia, 2021). In animal studies, leptin has reduced depressive behaviour caused by chronic unpredictable stress and had antidepressant effects (Lu *et al.*, 2006; Garza *et al.*, 2012). However, studies with humans have thus far been controversial reporting both increased and decreased leptin levels in depressed patients (Zou *et al.*, 2019); thus, leptin has not been identified as a biomarker for depression. Furthermore, acute alcohol use reduces plasma leptin levels, whereas chronic alcohol use may increase leptin levels (Bach *et al.*, 2021). Smoking is associated with lower leptin levels (Shaheen *et al.*, 2023).

Leptin resistance has also been suggested to be associated with depression and explain the relationship between depression and obesity (Lu, 2007; Yamada *et al.*, 2011). *LEP* and *LEPR* polymorphisms are one factor that can cause leptin resistance (Liu *et al.*, 2018). Mutations in the *LEP* gene may also lead to a reduced leptin levels, as well as alterations in its production (Socol *et al.*, 2022). Some genetic studies have investigated the association between leptin polymorphism and addictions, depression, and other mental disorders, but the impact of these polymorphisms has not yet been verified. Short variants (<208bp) of the *LEP* gene D7S1875 short tandem repeat marker are potential risk factors for depression (Kapoor *et al.*, 2009). *LEPR* gene variant rs1137101 is linked to high leptin concentrations but no association has been found between the *LEPR* gene variant rs1137101 and depressive symptoms (Reis *et al.*, 2015). Certain genetic polymorphisms of the leptin gene (rs10487506, rs4731423, rs2278815, rs4731426, rs12706832, rs11763517, and rs3828942) are risk factors for antidepressant treatment resistance in depressed patients (Kloiber *et al.*, 2013). In addition, an association has been found between the *LEPR* gene rs1171276 variant and a higher suicide risk (Acikel *et al.*, 2020), as well as between *LEPR* gene variants (rs1137100, rs12145690, rs8179183) and better treatment response in bipolar disorder (Chang *et al.*, 2022).

The aim of this study is to study associations between depression treatment response and *LEP* and *LEPR* variants by analysing all available single nucleotide polymorphism (SNP) variations in these genes and examining the polymorphisms found in previous studies separately. The secondary aim was to investigate the association between leptin levels and depression severity. These findings could help in developing tools to predict treatment response in depression and provide new information about the genetic mechanisms between leptin and depression.

Patients and methods

Study design and participants

The study protocol is registered in ClinicalTrials.gov with an identifier NCT02520271 (Ostrobothnia Depression Study [ODS], 2016). From 2009 to 2013, 242 patients were included in the study from one psychiatric hospital ward and from five psychiatric outpatient clinics located in the South Ostrobothnia Hospital District of Finland with a population of 200,000. Patients had depressive symptoms and comorbid problems such as anxiety, self-destructiveness, insomnia, or alcohol or other substance use. Beck Depression Inventory (BDI, version 1A) (Beck *et al.*, 1996) was used to screen patients and at least moderately depressed patients were recruited (BDI score ≥17). Two-thirds of patients had a recurrent depression. Patients who had primary psychotic disorders (ICD-10 codes F20-29) or organic brain disease or brain damage were excluded from the study. The local ethics committee approved the study, and all participants gave a written informed consent.

Diagnostic and symptom assessments were performed at baseline and included Mini International Neuropsychiatric Interview 5.0 (MINI) (Sheehan *et al.*, 1998), BDI-21 and Montgomery–Åsberg Depression Rating Scale (MADRS) (Montgomery & Asberg, 1979). Alcohol use was evaluated using the Alcohol Use Disorders Identification Test (AUDIT) (Babor *et al.*, 2001) and timeline follow-back (Sobell *et al.*, 1986) about alcohol amounts per week and duration of harmful drinking. Other substance use during the past 12 months and self-reported smoking status were also assessed. Blood samples were collected for laboratory tests. The patients were weighted, and their length was measured by a study nurse.

All patients received Behavioural Activation Therapy (Cuijpers *et al.*, 2023) for up to 6 months, and patients with substance abuse received additional motivational interview. The study protocol did not provide specific instructions for medication except medication dosing regimen if MADRS score was over 19 points at baseline. In the follow-up visits at 6 weeks and 6 months, the severity of depression was assessed with MADRS, and alcohol use was

https://doi.org/10.1017/neu.2024.43 Published online by Cambridge University Press

assessed with AUDIT. Laboratory tests were measured at baseline and at 6 months. Treatment response was determined as at least a 50% reduction with the MADRS scale (Nierenberg & DeCecco, 2001).

Laboratory analyses

Venous blood samples were collected from each patient at baseline and at 6 months. All samples were collected in the morning to control for daily changes in circulating leptin. The serum was centrifugated and stored at the temperature of –80°C before the analysis. Leptin levels were measured by enzyme-linked immunosorbent assay with commercial reagents (R&D Systems, Abingdon Science Park, UK). The lowest standard and inter-assay coefficient of variation was 15.6 pg/ml and 3.6% for leptin.

Genotyping and imputation

QIAamp DNA Blood Midikit and an automated biorobot M48 extraction (Qiagen, Hilden, Germany) were used to extract genomic DNA from peripheral blood leukocytes. The genotyping of samples was performed by using an Illumina Infinium HumanCoreExome-12 DNA Analysis Beadchip version 1, following the manufacturer's instructions at Helmholtz Zentrum, München, Germany. The quality was controlled by the following filters: GenTrain score < 0.20, GenCall score < 0.15, sample and an SNP call rate <0.95, excess heterozygosity, Hardy–Weinberg equation P value $< 10^{-6}$, cryptic relatedness (pi-hat > 0.2), multidimensional scaling, and gender check. Imputation was done by using SHAPEIT v2 in haplotype phasing and IMPUTE2 v.2.3.2 and 1000 Genomes Phase I integrated variant set haplotypes as a reference in genotype imputation. Well-imputed SNPs had info ≥ 0.3.

Statistical methods

The distribution of the variables was explored using the normal Q–Q plot and Kolmogorov–Smirnov test. Two-variable associations between age, baseline MADRS, sex, smoking, baseline AUDIT score, and body mass index (BMI) were explored with correlation tests, t-tests, and Mann–Whitney U-tests. Associations between baseline MADRS and baseline leptin serum levels were analysed with Pearson correlation tests and linear regression models. Leptin serum level distribution was skewed; therefore, a logarithmic transformation was also used. We conducted chi-squared tests to examine differences in treatment response rates by gender at 6 weeks and 6 months. For changes in MADRS scores, we used the Mann–Whitney U-test at 6 weeks due to non-normal distribution and a t-test at 6 months for normally distributed data. The correlations between independent variables used in the regression models were tested with Spearman correlation coefficients. The variation in serum leptin level was analysed with a linear regression model with age, baseline MADRS, sex, smoking, baseline AUDIT score and BMI as explanatory variables.

Based on a literature search on SNPs in *LEP* and *LEPR* related to depression with the following terms: "leptin" and "depression" and "genetics", statistically significant SNPs found in the earlier studies were selected. The following SNPs from the *LEP* gene were included in this study: rs10487506, rs4731423, rs2278815, rs4731426, rs12706832, rs11763517, and rs3828942 and SNPs from the *LEPR* gene: rs1171276, rs1137100, rs12145690, and rs8179183 (Kloiber *et al.*, 2013; Acikel *et al.*, 2020; Chang *et al.*, 2022). The association of these SNPs with treatment response was studied using logistic regression and linear regression models, with MADRS response and MADRS score change, respectively, at 6 weeks and 6 months as dependent variables and age, sex, BMI, baseline AUDIT score, smoking, and selected SNPs separately as covariables. As the original studies did not account for alcohol use, the same analyses were also performed excluding patients with AUDIT > 10. To account for multiple testing, p-values were adjusted with false discovery rate (FDR).

Lastly, genetic associations between treatment response and all available *LEP* and *LEPR* SNPs were studied. Proxy SNPs were calculated to represent gene areas in $r^2 > 0.2$ linkage disequilibrium. Analyses were performed with both logistic regression and linear regression models, with MADRS response and MADRS score change, respectively, at different timepoints as dependent variables and age, sex, BMI, baseline AUDIT score, smoking, and SNPs one at a time as covariables. P-values were FDR-adjusted. For assessing collinearity between explanatory variables, a threshold of $r \geq 0.5$ was used.

All analyses were performed with R version 4.1.1 (R Core Team, 2021).

Results

Characteristics of the study population are presented in Table 1. Baseline AUDIT score and smoking were correlated significantly (Spearman $r = 0.39$, $p < 0.0001$). Men had markedly higher baseline AUDIT score compared to women (15.1 ± 10.6 vs. 7.93 ± 8.30, Mann–Whitney U-test $p < 0.0001$). Men had slightly higher baseline MADRS scores than women (24.5 ± 6.4 vs. 22.3 ± 6.8, t-test $p = 0.012$). Patients who smoked had higher MADRS scores than those who did not (24.4 ± 5.8 vs. 21.2 ± 7.0, t-test $p = 0.0012$). There was no difference in smoking between men and women ($\chi^2 = 2.72$, $p = 0.10$). BMI had a strong correlation with serum leptin levels ($r = 0.72$, $p < 0.0001$). Mean serum levels of leptin in women and men were 31.0 ± 24.2 and 10.4 ± 10.9, respectively (t-test $p < 0.0001$). Age was not correlated with serum leptin levels ($r = 0.11$, $p = 0.10$). A diagnosis of diabetes was present in 5.8% ($n = 14$) of the patients. There was no significant association between diabetes and baseline MADRS scores (t-test, $p = 0.13$) or serum leptin levels (t-test, $p = 0.93$). There were no differences in treatment response rates by gender at 6 weeks or 6 months (χ^2, $p = 0.44$ and $p = 0.60$, respectively) nor were there differences in MADRS point reduction by gender at 6 weeks (Mann–Whitney U-test, $p = 0.84$) or 6 months (t-test, $p = 0.51$).

No correlation between baseline MADRS and baseline leptin serum levels was found (Pearson $r = 0.041$, $p = 0.56$). Baseline MADRS score was associated with leptin serum level in a linear regression model adjusted with age, sex, smoking, baseline AUDIT score, and BMI (Table 2). None of the explaining factors used in the model had a correlation (Spearman) of 0.5 or higher with each other.

In the logistic regression model explaining MADRS response at 6 weeks and at 6 months with age, sex, BMI, AUDIT score, smoking, and selected SNPs from previous studies as covariables, no SNP was statistically significant after adjusting the p-value (Tables 3 and 4). Due to the strong correlation between BMI and leptin levels, leptin was not included in the regression analysis to avoid multicollinearity. Excluding patients with AUDIT score > 10 had no substantial effect on the results.

In linear regression models explaining MADRS score change at 6 weeks or at 6 months with age, sex, BMI, AUDIT score, smoking,

https://doi.org/10.1017/neu.2024.43 Published online by Cambridge University Press

Table 1. Characteristics of the study population

	Baseline	6 weeks	6 months	12 months	24 months
N with MADRS available (% of baseline)	226	182 (80.5 %)	148 (65.5 %)	118 (52.2 %)	66 (29.2 %)
Sex	39.8 % male 60.2 % female	40.1 % male 59.9 % female	37.2 % male 62.8 % female	31.4 % male 68.6 % female	33.3 % male 66.7 % female
Age mean ± SD years	38.57 ± 12.10	39.01 ± 12.16	39.82 ± 12.01	40.02 ± 12.13	41.50 ± 12.57
MADRS score mean ± SD	23.16 ± 6.70	16.99 ± 8.06	13.26 ± 8.73	9.86 ± 7.72	8.05 ± 7.66
BMI mean ± SD kg/m^2	28.22 ± 6.67		28.90 ± 6.74		
Smoking %	53.4 %		46.9 %	44.9 %	41.5 %
AUDIT mean ± SD	10.71 ± 9.88		7.48 ± 7.41	6.19 ± 6.51	6.45 ± 7.24
Serum leptin level mean ± SD µg/l	22.98 ± 22.44		26.09 ± 22.36		

MADRS, Montgomery–Åsberg Depression Rating Scale; BMI, body mass index; AUDIT, Alcohol Use Disorders Identification Test.

Table 2. Linear regression model with leptin serum level as dependent variable and age, baseline MADRS score, sex, smoking, baseline AUDIT score and BMI as covariables

	B	z	p
Age	−0.0041	−1.086	0.28
MADRS (baseline)	0.020*	2.59	**0.011**
Sex (female)	1.13	11.57	<**0.001**
Smoking (yes)	−0.20	−2.010	**0.047**
AUDIT (baseline)	0.0040	0.78	0.44
BMI	0.12	16.40	<**0.001**

MADRS, Montgomery–Åsberg Depression Rating Scale; AUDIT, Alcohol Use Disorders Identification Test; BMI, body mass index.
*Positive estimate (B) means that patients with higher MADRS score had a higher serum leptin level.

and selected SNPs from previous studies as covariables, no SNP was statistically significant.

When analysing all available LEP and LEPR SNPs, two proxy SNPs of *LEPR* gene, rs12564738 and rs12029311, were associated with MADRS response at 6 weeks in a logistic regression model adjusted with age, sex, BMI, AUDIT score, and smoking (Table 5, Figure 1).

Discussion

In this study, two proxy SNPs in *LEPR* gene, rs12564738 and rs12029311, were associated with treatment response at 6 weeks. The significant SNPs from previous studies were not associated with depression treatment response in our study. In addition, we found an association between baseline depression severity and leptin levels after adjusting with age, sex, BMI, AUDIT score, and smoking.

After analysing all available variations in *LEP* and *LEPR* genes, two *LEPR* polymorphisms, rs12564738 and rs12029311, were associated with MADRS response at 6 weeks. There are no previous publications on these polymorphisms. *LEPR* polymorphism rs12564738 is an upstream transcript variant and transforms $C > G$ or $C > T$ in the upstream of the *LEPR* gene. Rs12029311 is an intron variant of the *LEPR* gene and transforms $G > A$ or $G > T$ in the *LEPR* gene. These proxy SNPs represent a larger number of polymorphisms, and it is possible that detected effect comes through other polymorphisms connected to these SNPs. We searched previous publications on SNPs that were strongly connected to these proxy SNPs with $r^2 > 0.8$. Rs3790435 was associated with metabolically unhealthy obesity in children (Abaturov & Nikulina, 2021) and with obstructive sleep apnoea risk (Li *et al.*, 2019). Rs1327118 was associated with a decreased risk of type 2 diabetes in men and increased systolic and diastolic blood pressure and decreased HDL cholesterol levels in women (Zhang *et al.*, 2018). Rs12145690 was associated with better treatment response of bipolar disorder (Chang *et al.*, 2022) and with plasma leptin levels in women (Ortega-Azorín *et al.*, 2019). It was also one of the SNPs we analysed separately in our study. The effect of rs12145690 was the largest compared to other SNPs, but it did not reach statistical significance in our data. However, it was strongly connected ($r^2 = 0.94$) to proxy SNP rs12564738 which was associated with MADRS response at 6 weeks in our study. Further meta-analyses are needed to confirm the significance of rs12145690.

https://doi.org/10.1017/neu.2024.43 Published online by Cambridge University Press

Table 3. Logistic regression model explaining MADRS response at 6 weeks and at 6 months with age, sex, BMI, AUDIT score, smoking, and selected SNPs from previous studies as covariables

		MADRS response at 6 weeks				MADRS response at 6 months			
	Previous publication	B	*t*	*p*	p adj.*	B	*t*	*p*	p adj.*
rs10487506	(Kloiber *et al.*, 2013)	0.25	0.68	0.49	0.72	−0.073	−0.20	0.84	0.97
rs4731423	(Kloiber *et al.*, 2013)	0.37	1.04	0.30	0.69	0.20	0.56	0.57	0.90
rs2278815	(Kloiber *et al.*, 2013)	0.36	1.01	0.31	0.69	0.21	0.61	0.54	0.90
rs4731426	(Kloiber *et al.*, 2013)	0.36	1.01	0.31	0.69	0.21	0.61	0.54	0.90
rs12706832	(Kloiber *et al.*, 2013)	0.19	0.54	0.59	0.72	0.31	0.91	0.36	0.90
rs11763517	(Kloiber *et al.*, 2013)	0.23	0.56	0.58	0.72	0.47	1.19	0.23	0.90
rs3828942	(Kloiber *et al.*, 2013)	−0.089	−0.23	0.82	0.82	−0.15	−0.41	0.68	0.94
rs1171276	(Acikel *et al.*, 2020)	−0.34	−0.43	0.66	0.73	−0.14	−0.15	0.88	0.97
rs1137100	(Chang *et al.*, 2022)	0.46	1.25	0.21	0.69	0.0083	0.024	0.98	0.98
rs12145690	(Chang *et al.*, 2022)	0.75	1.86	0.063	0.69	0.31	0.81	0.42	0.90
rs8179183	(Chang *et al.*, 2022)	−0.51	−0.84	0.40	0.72	−1.015	−1.67	0.095	0.90

MADRS, Montgomery–Åsberg Depression Rating Scale.
*FDR-adjusted *p*.

Table 4. Logistic regression model explaining MADRS response at 6 weeks and at 6 months with age, sex, BMI, smoking, and selected SNPs from previous studies as covariables excluding patients with AUDIT > 10

		MADRS response at 6 weeks				MADRS response at 6 months			
	Previous publication	B	*t*	*p*	p adj.*	B	*t*	*p*	p adj.*
rs10487506	(Kloiber *et al.*, 2013)	0.19	0.56	0.57	0.81	−0.29	−0.93	0.35	0.65
rs4731423	(Kloiber *et al.*, 2013)	0.27	0.84	0.40	0.74	−0.014	−0.048	0.96	0.998
rs2278815	(Kloiber *et al.*, 2013)	0.26	0.83	0.41	0.74	−0.00091	−0.0030	0.998	0.998
rs4731426	(Kloiber *et al.*, 2013)	0.26	0.83	0.41	0.74	−0.00076	−0.0025	0.998	0.998
rs12706832	(Kloiber *et al.*, 2013)	0.14	0.43	0.67	0.81	0.042	0.14	0.89	0.998
rs11763517	(Kloiber *et al.*, 2013)	0.17	0.48	0.63	0.81	0.74	2.17	**0.030**	0.16
rs3828942	(Kloiber *et al.*, 2013)	−0.11	−0.31	0.76	0.84	−0.36	−1.12	0.26	0.58
rs1171276	(Acikel *et al.*, 2020)	−0.097	−0.13	0.90	0.90	−0.996	−1.26	0.21	0.58
rs1137100	(Chang *et al.*, 2022)	0.30	0.93	0.35	0.74	−0.016	−0.054	0.96	0.998
rs12145690	(Chang *et al.*, 2022)	0.60	1.66	0.098	0.74	0.41	1.19	0.24	0.58
rs8179183	(Chang *et al.*, 2022)	−0.60	−1.19	0.23	0.74	−1.13	−2.24	**0.025**	0.16

MADRS, Montgomery–Åsberg Depression Rating Scale.
*FDR-adjusted *p*.

Based on the literature search, we chose several *LEP* and *LEPR* gene SNPs that have been associated with depression and other psychiatric disorders in previous studies and analysed them separately (Kloiber *et al.*, 2013; Acikel *et al.*, 2020; Chang *et al.*, 2022). In our study, none of these SNPs were associated with depression treatment response at 6 weeks or 6 months after FDR-adjusting the *p*-value. One reason for that could be that the patient material was clinically different in our study compared to previous studies. First, the patients in our sample were recruited from secondary psychiatric care units. Two thirds of our patients suffered from recurrent depression. Most of them had likely been treated in primary care with antidepressants before referring them to specialised health care. Therefore, it is probable that the findings of our study reflect a prolonged state of depression, and it is most likely that our sample included more treatment-resistant patients than the average population. Second, the inclusion criteria were wider in our study than in previous studies. Unlike previous studies, we did not exclude patients with harmful alcohol use. Chronic alcohol consumption might elevate plasma leptin levels, while acute alcohol use reduces plasma leptin concentration (Bach *et al.*, 2021). However, we were able to take alcohol users into account in our models, and we did our analyses also excluding patients with AUDIT scores >10, which had no substantial effect on the results.

As a secondary finding, we found an association between high leptin levels and depression severity independently of BMI. In line with our result, few studies have found an association between high leptin levels and depression severity (Cernea *et al.*, 2019; Syk *et al.*,

https://doi.org/10.1017/neu.2024.43 Published online by Cambridge University Press

Table 5. Proxy SNPs after clumping of all available LEP and LEPR SNPs and their association with MADRS response at 6 weeks in a logistic regression model adjusted with age, sex, BMI, AUDIT score and smoking

SNP	Effect allele	Gene	Location	Chromosome	MAF	B	*z*	*p*	p.adj
rs12564738	C	LEPR	Upstream transcript variant	1	0.44	0.94	2.86	**0.0043**	**0.024**
rs12029311	G	LEPR	Intron variant	1	0.075	−1.80	−2.85	**0.0043**	**0.024**
rs61090190	G	LEPR	Intron variant	1	0.060	1.82	1.92	0.055	0.20
rs9436740	A	LEPR	Intron variant	1	0.23	−0.65	−1.46	0.14	0.35
rs77980027	T	LEPR	Intron variant	1	0.083	−0.63	−1.24	0.22	0.35
rs6687148	T	LEPR	Intron variant	1	0.054	−1.0047	−1.22	0.22	0.35
rs28954118	A	LEP	3'-UTR variant	7	0.051	−1.028	−1.39	0.16	0.35
rs11585329	G	LEPR	Intron variant	1	0.095	0.55	0.90	0.37	0.51
rs148099962	T	LEPR	Intron variant	1	0.11	0.54	0.80	0.42	0.52
rs4731427	C	LEP	Intron variant	7	0.086	−0.17	−0.30	0.77	0.84
rs10157915	T	LEPR	Intron variant	1	0.052	−0.076	−0.083	0.93	0.93

SNP, single nucleotide polymorphism; LEPR, leptin receptor; LEP, leptin.

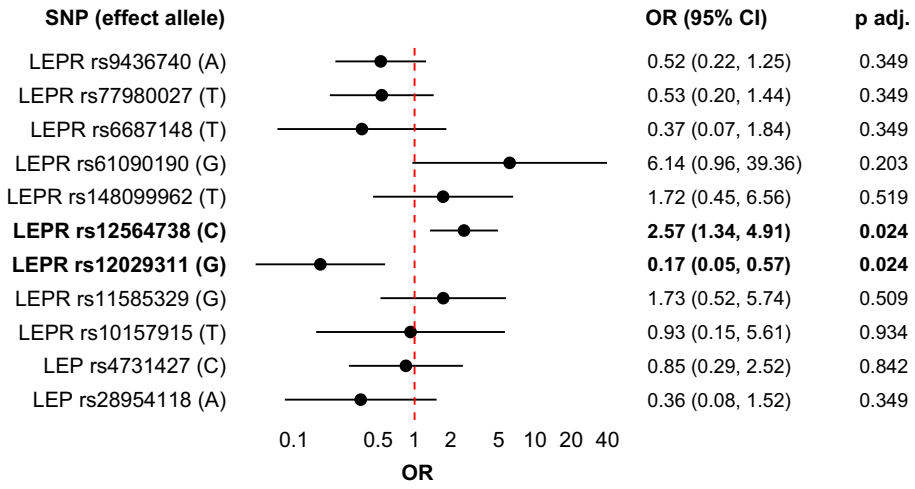

Figure1. Forest plot of odds ratios (OR) from logistic regression examining treatment response at 6 weeks for clumped LEPR and LEP SNPs, adjusted for age, sex, BMI, AUDIT score, and smoking, including effect alleles and FDR-adjusted *p*-values. OR > 1: for each additional effect allele (going from 0 to 1 or 1 to 2), the odds of treatment response increase by the factor of the OR. OR < 1: for each additional effect allele, the odds of treatment response decrease by the factor of the OR.

2019; Takekawa *et al.*, 2019; Wittekind *et al.*, 2022). One study found that high leptin levels were associated only with somatic symptoms of depression but not cognitive symptoms or all symptoms of depression (Chirinos *et al.*, 2013). Morris *et al.* found that adiposity mediated the association between leptin and depression severity, and the association was not significant after controlling for BMI. In their subgroup analyses, low leptin levels associated with depression severity in normal-weight patients while in overweight patients were high leptin levels associated with more severe depression (Morris *et al.*, 2012).

Previous case-control studies have yielded inconsistent results regarding the leptin levels in depression and have been limited by small sample sizes and clinical heterogeneity. Some studies have found lower leptin levels in depressed patients than in healthy controls (Kraus *et al.*, 2001; Jow *et al.*, 2006; Yang *et al.*, 2007), while other studies have reported higher leptin levels in depressed patients than controls (Esel *et al.*, 2005; Gecici *et al.*, 2005; Cizza *et al.*, 2012). Two latest meta-analysis did not find a significant association between leptin levels and depression (Carvalho *et al.*, 2014; Cao *et al.*, 2018). Large studies by Milaneschi *et al.* suggested that leptin is only associated with MDD in connection with increased neurovegetative symptoms such as appetite and weight (Milaneschi *et al.*, 2017; Milaneschi *et al.*, 2017). Furthermore, a previous study using the same cohort as the present study found that baseline leptin levels were higher in women, with more notable changes over a 6-month follow-up compared to men, highlighting significant gender differences (Archer *et al.*, 2018).

The positive association between leptin levels and depression severity is inconsistent with leptin's antidepressant effects observed in preclinical studies (Lu *et al.*, 2006). Leptin resistance may explain this discrepancy (Lu, 2007; Yamada *et al.*, 2011). The main mechanisms of leptin resistance are disorders of the blood-brain barrier transport, competitive inhibition of leptin, mutations of leptin receptor (*LEPR*), and impairment of the leptin cellular signalling (Liu *et al.*, 2018). The previous data indicate that reduced leptin signalling rather than low leptin levels is associated with depression (Milaneschi *et al.*, 2014). Obesity is connected to high leptin levels and the development of leptin resistance (Considine

https://doi.org/10.1017/neu.2024.43 Published online by Cambridge University Press

et al., 1996). However, there is also evidence that leptin resistance is linked to depression regardless of obesity status (Cernea *et al*., 2019).

There were certain limitations in our study. First, the sample size was relatively limited. Second, we used a Fisher's method (*p*-values) instead of Bayesian statistics when we examined SNPs from previous studies. The real-world setting of the study was both a strength and a limitation. As mentioned earlier, the inclusion criteria were wide, and we did not exclude alcohol or other substance users. The use of antidepressants was not standardised, and the patients had different medications. In practice, patients with depression do have common alcohol and substance use and different medications, so the results are well generalisable to patient populations in secondary psychiatric health care. We were also able to take smoking, weight, and the use of alcohol into account in our models. Another limitation of our study is the absence of measurements for soluble leptin receptor levels. The inclusion of these measurements would have enabled the calculation of the Free Leptin Index, a surrogate marker of leptin resistance. Future studies should consider incorporating soluble leptin receptor levels to provide a more comprehensive analysis of leptin resistance.

In conclusion, we found an association between two *LEPR* proxy SNPs, rs12564738 and rs12029311, and depression treatment response. We also found that leptin is associated with depression severity regardless of BMI. Further studies and meta-analyses are needed to confirm the significance of these SNPs and the role of leptin in depression.

Acknowledgements. Ms. Terhi Salonen is warmly acknowledged for her excellent technical assistance.

Author contributions. Olli Kampman contributed to planning and designing the original study and data collection. Ida-Maria Tavast and Anssi Solismaa planned the present study. Leo-Pekka Lyytikäinen, Nina Mononen, and Terho Lehtimäki provided the genotyping of the patients. Eeva Moilanen and Mari Hämäläinen provided the design and practice of the other laboratory analyses for the study. Ida-Maria Tavast and Anssi Solismaa planned and conducted the statistical analyses with Leo-Pekka Lyytikäinen participating in the genetic analyses. Ida-Maria Tavast and Anssi Solismaa drafted the article. All authors revised the article and have approved the article.

Financial support. This study was supported by the Academy of Finland (grant number 356405) for T.L., EU Horizon 2020 (grant number 848146) for To Aition, Competitive State Research Financing of the Expert Responsibility area of Tampere University Hospital (PIRHA) (grant number X51001), and state research funding (VTR).

Competing interests. None.

Ethical standard. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Abaturov A and Nikulina A (2021) Obesity in children with leptin receptor gene polymorphisms. *Acta Medica (Hradec Kralove, Czech Republic)* **64**(3), 158–164.

Acikel SB, Eroglu C, Ugras Dikmen A and Kurar E (2020) The association between leptin receptor polymorphism and suicidal behaviour in depressed adolescents. *International Journal of Psychiatry in Clinical Practice. Taylor and Francis Ltd* **24**(2), 120–126.

Archer M, Niemelä O, Hämäläinen M, Moilanen E, Leinonen E and Kampman O (2018) The effects of adiposity and alcohol use disorder on adipokines and biomarkers of inflammation in depressed patients. *Psychiatry Research* **264**, 31–38.

Atun R (2015) Transitioning health systems for multimorbidity. *The Lancet* **386**(9995), 721–722.

Babor, T. F., Higgins-Biddle, J. C., Saunders, J. B. and Monteiro, M. G. (2001). The Alcohol Use Disorders Identification Test Guidelines for Use in Primary Care. World Health Organization, Department of Mental Health and Substance Dependence. http://apps.who.int/iris/bitstream/10665/67205/1/WHO_MSD_MSB_01.6a.pdf. Accessed February 23, 2024.

Bach P, Koopmann A and Kiefer F (2021) The impact of appetite-regulating neuropeptide leptin on alcohol use, alcohol craving and addictive behavior: A systematic review of preclinical and clinical data. *Alcohol and Alcoholism* **56**(2), 149–165.

Beck AT, Steer RA, Ball R and Ranieri W (1996) Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *Journal of Personality Assessment* **67**(3), 588–597.

Cao B, Chen Y, Brietzke E, Cha D, Shaukat A, Pan Z, Park C, Subramaniapillai M, Zuckerman H, Grant K, Mansur RB and McIntyre RS (2018) Leptin and adiponectin levels in major depressive disorder: A systematic review and meta-analysis. *Journal of Affective Disorders* **238**(October), 101–110.

Carvalho AF, Rocha DQC, McIntyre RS, Mesquita LM, Köhler CA, Hyphantis TN, Sales PMG, Machado-Vieira R and Berk M (2014) Adipokines as emerging depression biomarkers: A systematic review and meta-analysis. *Journal of Psychiatric Research* **59**, 28–37.

Castrén E and Monteggia LM (2021) Brain-derived neurotrophic factor signaling in depression and antidepressant action. *Biological Psychiatry* **90**(2), 128–136.

Cernea S, Both E, Huțanu A, Șular FL and Roiban AL (2019) Correlations of serum leptin and leptin resistance with depression and anxiety in patients with type 2 diabetes. *Psychiatry and Clinical Neurosciences* **73**(12), 745–753.

Chang HH, Hsueh YS, Cheng YW and Tseng HH (2022) A longitudinal study of the association between the LEPR polymorphism and treatment response in patients with bipolar disorder. *International Journal of Molecular Sciences. MDPI* **23**(17), 9635.

Chirinos DA, Goldberg R, Gellman M, Mendez AJ, Gutt M, McCalla JR, Llabre MM and Schneiderman N (2013) Leptin and its association with somatic depressive symptoms in patients with the metabolic syndrome. *Annals of Behavioral Medicine* **46**(1), 31–39.

Cizza G, Ronsaville DS, Kleitz H, Eskandari F, Mistry S, Torvik S, Sonbolian N, Reynolds JC, Blackman MR, Gold PW, Martinez PE, Federici M and for the P.O.W.E.R. (Premenopausal, Osteopenia/Osteoporosis, Women, Alendronate, Depression) Study Group (2012) Clinical subtypes of depression are associated with specific metabolic parameters and circadian endocrine profiles in women: The power study. *PloS one* **7**(1), e28912.

Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ and Bauer TL (1996) Serum immunoreactive-leptin concentrations in normal-weight and obese humans. *New England Journal of Medicine* **334**(5), 292–295.

Cuijpers P, Karyotaki E, Harrer M and Stikkelbroek Y (2023) Individual behavioral activation in the treatment of depression: A meta analysis. *Psychotherapy Research* **33**(7), 886–897.

Endomba FT, Tankeu AT, Nkeck JR and Tochie JN (2020) Leptin and psychiatric illnesses: Does leptin play a role in antipsychotic-induced weight gain? Lipids in health and disease. *BioMed Central Ltd* **19**(1), 22.

Erichsen JM, Fadel JR and Reagan LP (2022) Peripheral versus central insulin and leptin resistance: Role in metabolic disorders, cognition, and neuropsychiatric diseases. *Neuropharmacology* **203**, 108877.

Esel E, Ozsoy S, Tutus A, Sofuoglu S, Kartalci S, Bayram F, Kokbudak Z and Kula M (2005) Effects of antidepressant treatment and of gender on serum leptin levels in patients with major depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* **29**(4), 565–570.

Farr OM, Gavrieli A and Mantzoros CS (2015) Leptin applications in 2015: What have we learned about leptin and obesity? *Current Opinion in Endocrinology, Diabetes & Obesity* **22**(5), 353–359.

Ferrari AJ, Somerville AJ, Baxter AJ, Norman R, Patten SB, Vos T and Whiteford HA (2013) Global variation in the prevalence and incidence of major depressive disorder: A systematic review of the epidemiological literature. *Psychological Medicine* **43**(3), 471–481.

https://doi.org/10.1017/neu.2024.43 Published online by Cambridge University Press

Garza JC, Guo M, Zhang W and Lu XY (2012) Leptin restores adult hippocampal neurogenesis in a chronic unpredictable stress model of depression and reverses glucocorticoid-induced inhibition of GSK-3B2;/B2;-catenin signaling. *Molecular Psychiatry* **17**(8), 790–808.

Ge T, Fan J, Yang W, Cui R and Li B (2018) Leptin in depression: A potential therapeutic target. *Cell Death & Disease* **9**(11), 1096.

Gecici O, Kuloglu M, Atmaca M, Tezcan AE, Tunckol H, Emül HM and Ustundag B (2005) High serum leptin levels in depressive disorders with atypical features. *Psychiatry and Clinical Neurosciences* **59**(6), 736–738.

Jow G-M, Yang T-T and Chen C-L (2006) Leptin and cholesterol levels are low in major depressive disorder, but high in schizophrenia. *Journal of Affective Disorders* **90**(1), 21–27.

Kapoor M, Kapur S, Mehra S, Dube U, Sharad S and Sidhu S (2009) Genetic variation in D7S1875 repeat polymorphism of leptin gene is associated with increased risk for depression: A case-control study from India. *Depression and Anxiety* **26**(9), 791–795.

Kloiber S, Ripke S, Kohli MA, Reppermund S, Salyakina D, Uher R, McGuffin P, Perlis RH, Hamilton SP, Pütz B, Hennings J, Brückl T, Klengel T, Bettecken T, Ising M, Uhr M, Dose T, Unschuld PG, Zihl J, Binder E, Müller-Myhsok B, Holsboer F and Lucae S (2013) Resistance to antidepressant treatment is associated with polymorphisms in the leptin gene, decreased leptin mRNA expression, and decreased leptin serum levels. *European Neuropsychopharmacology* **23**(7), 653–662.

Kraus T, Haack M, Schuld A, Hinze-Selch D and Pollmächer T (2001) Low leptin levels but normal body mass indices in patients with depression or schizophrenia. *Neuroendocrinology* **73**(4), 243–247.

Li J, Yang S, Jiao X, Yang Yunyun, Sun H, Zhang M, Yang Yunxiao, Qin Y and Wei Y (2019) Targeted sequencing analysis of the leptin receptor gene identifies variants associated with obstructive sleep apnoea in Chinese han population. *Lung* **197**(5), 577–584.

Liu J, Yang X, Yu S and Zheng R (2018) The leptin resistance. *Advances in Experimental Medicine and Biology* **1090**, 145–163.

Lu X-Y (2007) The leptin hypothesis of depression: A potential link between mood disorders and obesity? *Current Opinion in Pharmacology* **7**(6), 648–652.

Lu X-Y, Kim CS, Frazer A and Zhang W (2006) Leptin: A potential novel antidepressant. *Proceedings of the National Academy of Sciences of the United States of America* **103**(5), 1593–1598.

Milaneschi Y, Lamers F, Bot M, Drent ML and Penninx BWJH (2017) Leptin dysregulation is specifically associated with major depression with atypical features: Evidence for a mechanism connecting obesity and depression. *Biological Psychiatry* **81**(9), 807–814.

Milaneschi Y, Lamers F, Peyrot WJ, Baune BT, Breen G, Dehghan A, Forstner AJ, Grabe HJ, Homuth G, Kan C, Lewis C, Mullins N, Nauck M, Pistis G, Preisig M, Rivera M, Rietschel M, Streit F, Strohmaier J, Teumer A, Van der Auwera S, Wray NR, Boomsma DI, Penninx BWJH and for the CHARGE Inflammation Working Group and the Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium (2017) Genetic association of major depression with atypical features and obesity-related immunometabolic dysregulations. *JAMA Psychiatry* **74**(12), 1214–1225.

Milaneschi Y, Simmons WK, van Rossum EFC and Penninx BW (2019) Depression and obesity: Evidence of shared biological mechanisms. *Molecular Psychiatry* **24**(1), 18–33.

Milaneschi Y, Sutin AR, Terracciano A, Canepa M, Gravenstein KS, Egan JM, Vogelzangs N, Guralnik JM, Bandinelli S, Penninx BWJH and Ferrucci L (2014) The association between leptin and depressive symptoms is modulated by abdominal adiposity. *Psychoneuroendocrinology* **42**, 1–10.

Montgomery SA and Asberg M (1979) A new depression scale designed to be sensitive to change. *British Journal of Psychiatry* **134**(4), 382–389.

Morris AA, Ahmed Y, Stoyanova N, Hooper WC, De Staerke C, Gibbons G, Quyyumi A and Vaccarino V (2012) The association between depression and leptin is mediated by adiposity. *Psychosomatic Medicine* **74**(5), 483–488.

Münzberg H and Morrison CD (2015) Structure, production and signaling of leptin. *Metabolism: Clinical and Experimental. W.B* **64**(1), 13–23.

Nierenberg AA and DeCecco LM (2001) Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: A focus on treatment-resistant depression. *The Journal of Clinical Psychiatry* **62**(Suppl 16), 5–9.

Ortega-Azorín C, Coltell O, Asensio EM, Sorlí JV, González JI, Portolés O, Saiz C, Estruch R, Ramírez-Sabio JB, Pérez-Fidalgo A, Ordovas JM and Corella D (2019) Candidate gene and genome-wide association studies for circulating leptin levels reveal population and sex-specific associations in high cardiovascular risk mediterranean subjects. *Nutrients* **11**(11), 2751.

Ostrobothnia Depression Study (ODS) (2016) A naturalistic Follow-up Study on Depression and Related Substance Use Disorders. https://clinicaltrials.gov/ct2/show/NCT02520271. Accessed May 18, 2023.

Pariante CM and Lightman SL (2008) The HPA axis in major depression: Classical theories and new developments. *Trends in Neurosciences* **31**(9), 464–468.

R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/. Accessed February 24, 2024.

Reis TC, Silva RRV, Pena GG, Domingos PLB, Pereira CS, Farias LC, Santos SHS, Jones KM, De Paula AMB, Rodrigues Neto JF, Velásquez-Meléndez G and Guimarães ALS (2015) Sex, age and smoking, but not genetic variation in LEPR (rs1137101), are associated with depressive symptoms. *Psychiatric Genetics* **25**(3), 137–138.

Roubos EW, Dahmen M, Kozicz T and Xu L (2012) Leptin and the hypothalamo-pituitary-adrenal stress axis. *General and Comparative Endocrinology* **177**(1), 28–36.

Shaheen N, Shaheen A, Diab RA, Saad AM, Abdelwahab OA, Soliman S, Hefnawy MT, Ramadan A, Meshref M and Nashwan AJ (2023) Association of serum leptin and ghrelin levels with smoking status on body weight: A systematic review and meta-analysis. *Frontiers in Psychiatry* **14**, 1296764.

Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R and Dunbar GC (1998) The mini-international neuropsychiatric interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *The Journal of clinical psychiatry* **59**(Suppl 20), 22–33.

Sobell MB, Sobell LC, Klajner F, Pavan D and Basian E (1986) The reliability of a timeline method for assessing normal drinker college students' recent drinking history: Utility for alcohol research. *Addictive Behaviors* **11**(2), 149–161.

Socol CT, Chira A, Martinez-Sanchez MA, Nuñez-Sanchez MA, Maerescu CM, Mierlita D, Rusu AV, Ruiz-Alcaraz AJ, Trif M and Ramos-Molina B (2022) Leptin Signaling in Obesity and Colorectal Cancer. *International Journal of Molecular Sciences* **23**(9), 4713.

Syk M, Ellström S, Mwinyi J, Schiöth HB, Ekselius L, Ramklint M and Cunningham JL (2019) Plasma levels of leptin and adiponectin and depressive symptoms in young adults. *Psychiatry Research* **272**, 1–7.

Takekawa D, Kudo T, Saito J, Kimura F, Nikaido Y, Sawada K, Yasui-Furukori N and Hirota K (2019) Higher plasma leptin and lower C-peptide levels are associated with depression: A cross-sectional study. *Journal of Affective Disorders* **243**, 70–74.

Wittekind DA, Kratzsch J, Biemann R, Mergl R, Riedel-Heller S, Witte V, Villringer A and Kluge M (2022) Association between self-rating depression scores and total ghrelin and adipokine serum levels in a large population-based sample. *Frontiers in Psychiatry* **13**, 891325.

Yamada N, Katsuura G, Ochi Y, Ebihara K, Kusakabe T, Hosoda K and Nakao K (2011) Impaired CNS leptin action is implicated in depression associated with obesity. *Endocrinology* **152**(7), 2634–2643.

Yang K, Xie G, Zhang Z, Wang C, Li W, Zhou W and Tang Y (2007) Levels of serum interleukin (IL)-6, IL-1beta, tumour necrosis factor-alpha and leptin and their correlation in depression. *Australian & New Zealand Journal of Psychiatry* **41**(3), 266–273.

Zhang L, Qin Y, Liang D, Li L, Liang Y, Chen L, Tong L, Zhou J, Li H and Zhang H (2018) Association of polymorphisms in LEPR with type 2 diabetes and related metabolic traits in a Chinese population. *Lipids in health and disease* **17**(1), 2.

Zou X, Zhong L, Zhu C, Zhao H, Zhao F, Cui R, Gao S and Li B (2019) Role of leptin in mood disorder and neurodegenerative disease. *Frontiers in Neuroscience* **13**, 378.

https://doi.org/10.1017/neu.2024.43 Published online by Cambridge University Press