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THE IMPACT OF THE BURDEN OF CHRONIC ILLNESS UPON DEPRESSION IS INFLUENCED BY A POLYMORPHISM IN THE SEROTONIN TRANSPOTER GENE

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BACKGROUND

Evidence suggests that **5-HTTLPR**, a polymorphism in the promoter region of *SLC6A4,* the gene that encodes for the serotonin transporter (5-HTT), could **moderate the association between stress and depression** [1,2] although a recent meta-analysis provided conflicting evidence [3]. It is also well known that **depression is frequent among patients with long-term medical conditions** (LTCs).

Resilience refers to a dynamic process that moderates the negative effects of stress and promotes adaptation, optimism and acceptance [4]. Although a small number of studies have shown a link between the 5-HTTLPR polymorphism and resilience, to the best of our knowledge no studies have investigated whether an interaction between 5-HTTLPR polymorphism and resilience **could influence** the association of stress (e.g., a chronic physical illness) with depression.

OBJECTIVE

To test whether the presence of depression in people with one or two co-occurring LTCs is influenced by the 5-HTTLPR polymorphism and whether resilience levels mediate this relationship.

DATA AND METHODS

Data were collected during the baseline assessment of the prospective study **ASSERT-DEP: "Assessing and enhancing resilience to depression in people with long term medical conditions in the era of the current Greek social and financial crisis".**

The present **cross-sectional study** took place between 09/2015 and 03/2016. Among **366 patients with diabetes, COPD, and rheumatic diseases** attending specialty clinics or the emergency department and **128 people without LTCs** recruited from the hospital staff, we tested whether the 5-HTTLPR polymorphism could influence depressive symptom severity **(PHQ-9)** and the presence of probable depression **(PHQ-9>10)**, after adjusting for socio-demographic variables. Analyses were repeated with ***resilience*** **(RS-14)** and its **interactions** as additional covariates, in linear and binary logistic hierarchical regression models.

DNA was isolated from whole blood samples and amplified with polymerase chain reaction (PCR) and the PCR products were separated by electrophoresis in a 3% agarose gel. **Two allele variants were identified** based on PCR fragment sizes: **long (L, 530bp) and short (S, 426bp)**. The sample was split into three groups based on 5-HTTLPR genotypes: **L/L, L/S, and S/S**. Genotype and allele frequencies (L: 0.58, S: 0.42) were in Hardy-Weinberg equilibrium ($\chi^2(1)=0.78$, $p>0.05$) and in agreement with previous findings [2].

RESULTS

There were **no significant differences in genotype frequencies** across gender, age, marital status, education, health/disease, number of LTCs, or across disease type.

PHQ-9 scores were significantly correlated with age, sex, education, and marital status, and these variables were included as covariates.

RS-14 scores were significantly correlated with PHQ-9 scores ($r=-0.315$, $p<0.001$) and the number of LTCs ($r=-0.108$, $p=0.023$).

To investigate interactive effects, an **interaction term (RS-14 x number of LTCs)** was produced after standardization of the raw scores of the variables (i.e. converted to z-scores).

A. Depressive symptom severity (PHQ-9 scores) (Fig. 1)

Homozygous L-carriers (LL) without long-term medical conditions (LTCs) presented **similar PHQ-9 scores** with LL patients with one or two co-occurring LTCs (p=0.317).

On the contrary, **S-carriers (LS-SS) with one** (p=0.020) **or two co-occurring LTCs** (p=0.004) presented **higher PHQ-9 scores** compared with S-carriers without LTCs.

Addition of resilience scores as measured by the RS-14 **weakened the significance of the polymorphism** in the sample with two LTCs (from p=0.004 to p=0.016).

B. Probable Depression (PHQ-9 ≥ 10) (Table 1)

With PHQ-9>10 as dependent variable, the odds of being diagnosed with probable depression **among LL homozygous were similar across all samples** (p=0.647).

On the contrary, **among S-carriers**, the odds (95% CI) of being diagnosed with probable depression **were 2.8** (1.1-7.8; p=0.041) **for people with one LTC and 6.9** (1.7-27.1; p=0.006) **for those with two LTCs**, compared with people without LTCs.

Addition of RS-14 **rendered the contribution of the number of LTCs non-significant** (p=0.107), and this mediation effect was more prominent in **S-carriers with two LTCs** (p=0.073).

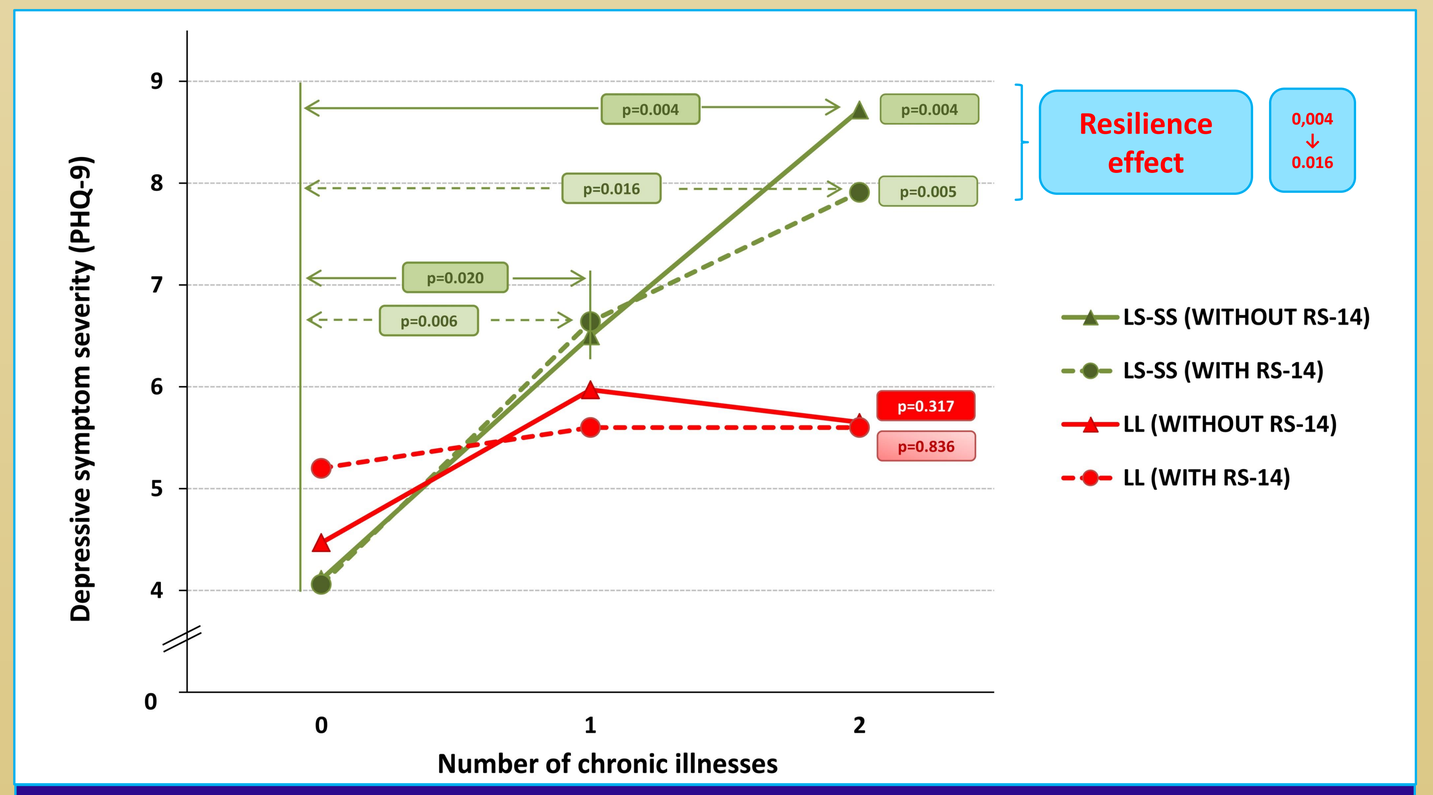

Figure 1. Resilience weakens the effects of the 5-HTTLPR polymorphism on PHQ9, in patients with 2 LTCs

Table 1. Hierarchical Multiple Regression Analyses with dependent variable: Probable Depression (PHQ-9 ≥10)

Independent variables	Step 1		Step 2	
	Odd ratios (95% CI)	p	Odd ratios (95% CI)	p
L/L Homozygous (N=148)				
Age	1.0 (.93-1.01)	.106	1.0 (.92-1.01)	.114
Sex	2.0 (.77-5.09)	.155	2.0 (.72-5.27)	.186
Education	0.4 (.19 - .92)	.031	0.4 (.19 - .98)	.044
Divorced/Widowed/Separated (R)	0.3 (.08 - .99)	.049	0.2 (.07 - .90)	
Number of medical illnesses		.647		.834
One	1.8 (.47-7.19)	.378	1.5 (.35-6.61)	.564
Two co-occurring LTCs	1.4 (.16-11.9)	.764	1.8 (.18-17.6)	.615
Resilience (RS-14)	-		0.9 (.91 - .98)	.007
Interaction RS-14 x Nb of LTCs	-		1.0 (.54-1.77)	.993
Nagelkerke R square	0.176		0.260	
S-carriers (N=298)				
Age	0.9 (.94 - .99)	.024	0.9 (.94 - .99)	.012
Sex	1.0 (.58-2.05)	.792	1.1 (.57-2.21)	.736
Education	0.5 (.29 - .76)	.002	0.5 (.28 - .79)	.005
Divorced/Widowed/Separated (R)	0.5 (.21-1.24)	.141	0.5 (.18-1.17)	.104
Number of medical conditions		.022		.107
One	2.8 (1.1-7.79)	.041	3.0 (1.03-8.6)	.042
Two co-occurring LTCs	6.9 (1.7-27.1)	.006	4.0 (.87-18.3)	.073
Resilience (RS-14)	-		0.9 (.92 - .98)	.001
Interaction RS-14 x Nb of LTCs	-		0.6 (.37 - .87)	.010
Nagelkerke R square	0.152		0.261	

LIMITATIONS

Present findings should be interpreted in the context of some limitations:

1. Since our patient sample included patients with different LTCs we could not adjust for the severity of underlying illnesses.
2. Notwithstanding the robust psychometric properties of the PHQ-9 as a screening tool for depression among patients with LTCs, a positive screen does not substantiate a diagnosis of depression.
3. The cross-sectional design precludes causal inferences.

CONCLUSIONS

Present results confirm the few previous findings reporting that the 5-HTTLPR, polymorphism moderates the association between stress and depression in people with somatic illnesses [5].

Our study also provides new findings, as we found that the effect of the 5-HTTLPR polymorphism is stronger in patients with two co-occurring LTCs, and that resilience levels may mediate this association.

STUDY IMPLICATIONS

Although future prospective studies are warranted to confirm our findings, psychotherapy trials targeting resilience hold promise for both prevention and amelioration of depressive symptoms in vulnerable people with somatic illnesses.

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