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REVISIONES

Excess weight and depression associated with serotonin transporter gene polymorphism (5-HTTLPR): a systematic review

Exceso de peso y depresión asociados al polimorfismo del gen transportador de la serotonina (5-HTTLPR): Una revisión sistemática

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ABSTRACT:

Background: Excess weight and depression have been studied due to the high prevalence in the population, the evidence indicates that there is a bidirectionality of origin and development of these diseases. Additionally, genetic load has been significantly associated in these diseases, an example is the polymorphism of the promoter region of the serotonin transporter gene (5-HTTLPR), studies report that this genetic factor can condition and aggravate the symptoms present in both conditions.
Objective: Collect, review, and analyze published studies of the relationship between 5-HTTLPR polymorphism for the development of depression in overweight-obese people.
Methods: Using the PRISMA checklist guidelines, a systematic search was performed in the databases: PubMed, Scopus, Web of Science (Science Citation Index Expanded and Social Sciences Citation Index) and EBSCO (Academic Search Complete, Fuente Académica and MedicLatina). The Web 3.0 platform: Critical Reading Files was used to analyze the quality of the studies
Results: Seven studies were included, which provided evidence of the relationship between 5-HTTLPR polymorphism, depression and increased BMI / overweight-obesity.
Conclusion: The evidence analyzed shows that the 5-HTTLPR polymorphism is linked to the development and symptoms of depression and obesity. Information that health personnel must consider in order to carry out treatments and care plans according to the needs of individuals with these conditions.

Key words: Genetic Factor; 5-HTTLPR Polymorphism; Depression; Overweight; Obesity.

RESUMEN:

Introducción: El exceso de peso y la depresión han sido objeto de estudio por su elevada prevalencia en la población, la evidencia refiere que existe una bidireccionalidad de origen y desarrollo entre éstas enfermedades. Además, la carga genética se ha asociado significativamente en estas enfermedades, un ejemplo es el polimorfismo de la región promotora del gen transportador de la serotonina (5-HTTLPR), estudios reportan que este factor genético puede condicionar y agravar los síntomas presentes de ambas condiciones.

Objetivo: Recopilar, revisar y analizar estudios publicados de la relación que existe entre polimorfismo 5-HTTLPR para el desarrollo de la depresión en personas con sobrepeso-obesidad.
Métodos: Por medio de los lineamientos del checklist de PRISMA se realizó una búsqueda sistemática en las bases de datos: PubMed, Scopus, Web of Science (Science Citation Index Expanded y Social Sciences Citation Index) y EBSCO (Academic Search Complete, Fuente Académica y MedicLatina). La plataforma Web 3.0: Ficheros de Lectura Crítica se utilizó para analizar la calidad de los estudios.
Resultados: Se incluyeron siete estudios, los cuales aportaron evidencia de la relación entre el polimorfismo 5-HTTLPR, la depresión y el aumento de IMC/sobrepeso-obesidad.
Conclusión: La evidencia analizada demuestra que el polimorfismo 5-HTTLPR está ligado al desarrollo y síntomas de la depresión y obesidad. Información que debe considerar el personal de salud para poder realizar tratamientos y planes de cuidado acorde a las necesidades de los individuos con estas condiciones.

Palabras Clave: Factor Genético; Polimorfismo 5-HTTLPR; Depresión; Sobrepeso; Obesidad.

INTRODUCTION

Overweight and obesity (OW-OB) are defined as an abnormal or excessive accumulation of body fat that can be detrimental to health [(1)]. In the last three decades its prevalence has increased alarmingly, which represents a great challenge for the prevention and early diagnosis of OW-OB and the analysis of the behaviors that lead to its appearance [(2)]. These are pathologies of a chronic and multifactorial course, for example: genetic, environmental and behavioral factors. An example of these factors is the relationship between OB and depression (DP), which has been studied due to the high prevalence of both conditions in the population, according to studies there is a bidirectionality in the origin and development of these diseases [(3,4)].

DP is a common mental illness that is characterized by low mood, loss of interest or pleasure, decreased energy, feelings of guilt or low self-esteem, sleep or appetite disturbances, and poor concentration [(5)]. One factor related to the development of depressive symptoms is the genetic variation or polymorphism of the region promoting the serotonin transporter gene (5-HTTLPR) [(6)]. A polymorphism is a variation in the sequence of a given DNA site on the chromosomes of individuals in a population [(7)]. In the case of OW-OB and DP, the polymorphism that has been associated is 5-HTTLPR, which has two allelic variants: one long (L) and one short (S) where different studies have related the presence of the S allele with depressive symptoms and a greater vulnerability to develop OW-OB [(8,9)].

On the other hand, in 2016 it was reported that more than 1.9 billion adults 18 years of age or older had OW; of which more than 650 million had OB, it was also reported that 41 million children under 5 years of age were excess weight. In children and adolescents from 5 to 19 years old, the OW-OB increased alarmingly from 4% in 1975 to more than 18% in 2016[(1)]. With respect to DP, it is currently considered one of the 10 most important causes of disability of psychiatric origin and it is predicted that by 2020 it will be the second cause of disability worldwide [(5)]. DP is not only sadness, it is a disease that if left untreated will lead the person suffering from it to a functional decline, it can often be reversed with immediate and adequate treatment. However, if left unchecked, it can accelerate physical, cognitive and social decline, delay recovery from illness and surgery, lead to increased use of medical care, and lead to suicide [(10)].

In the OW-OB and the DP, besides physiological alterations, cerebral morphological alterations have been described in people with OW-OB of diverse age groups [(11,12)]. The

association between OB and DP is so frequent that the presence of a genetically determined tendency predisposing to these pathologies has been suggested; this has not been able to be proven in current genetic studies, in which genetic factors related to a tendency to a high BMI are proven [13].

The increase in OW-OB and DP recorded in recent years shows the importance of incorporating new strategies to reduce the morbidity and mortality caused by these diseases, which occur at younger ages, reducing the quality of life of people who suffer from them. Authors mention [14] the importance of the use of genetics by nursing professionals, as a strategy to provide more personalized care to users. Nursing can use genetics to strengthen areas such as: a) research: genetics and genomics to improve care; b) advocacy for patients who experience genetic testing; c) education to strengthen nursing competencies; d) ethical and legal issues; e) public policy; and f) the role of genetics in the clinic. This will allow nursing professionals to join multidisciplinary teams to conduct research, develop new genetic or follow-up therapies and prevent diseases in families and individuals, originating a new public health and implicitly health professionals committed to the welfare of people [15].

Consequently, there is a need to explore mechanisms to explain the link between the OW-OB and the DP. Due to the above, this work was carried out with the aim of compiling, reviewing and analyzing the results of published studies on the relationship between genetic factors for the development of OW-OB and DP, as well as answering the following research question: Is the polymorphism of the serotonin transporter gene (5-HTTLPR) promoter region associated with the development of DP in people with OW-OB?

METHODS

The guidelines of the PRISMA checklist (Preferred Reporting Items for Systematic Reviews) were followed for this systematic review.

Eligibility criteria

Primary studies were admitted that sought to evaluate the association of the polymorphism of the serotonin transporter gene (5-HTTLPR) region with DP and OW-OB jointly or individually written in English, and Spanish.

Search strategy

To answer the question posed, a systematic search was carried out in the PubMed, Scopus, Web of Science (Science Citation Index Expanded and Social Sciences Citation Index) and EBSCO (Academic Search Complete, Fuente Académica and MedicLatina) databases; the search was conducted during the months of August to October 2019, through an established search strategy (Table 1).

Table 1. Search Strategy

Strategy	Concept
1	Obesity [TIAB]
2	Body mass index [MH]
3	Fat mass [ALL]
4	Obesity/genetics [MH]
5	Obesity/psychology [MH
6	Overweight [MH]
7	OR/ 1-6
6	Overweight [MH]
7	OR/ 1-6
8	Polymorphism, genetic [TIAB]
9	Genetic phenomena [MH]
10	Genetic variation [TIAB]
11	Polymorphism 5 httlpr [TIAB]
12	Serotonin plasma membrane transport proteins [MH]
13	Humans, polymorphisms [ALL]
14	OR 8-13
15	Depression [TIAB]
16	Depressive symptoms [TIAB]
17	Mood disorders/psychology [MH]
18	Mood disorders/genetics [MH]
19	Depression/genetics [MH]
20	OR 15-19
21	7 AND 14 AND 20
Final	("obesity"[Title/Abstract]) OR "body mass index"[MeSH Terms]) OR "fat mass") OR "obesity/genetics"[MeSH Terms]) OR "obesity/psychology"[MeSH Terms]) OR "overweight"[MeSH Terms])) AND ((((("polymorphism, genetic"[Title/Abstract]) OR "genetic phenomena"[MeSH Terms]) OR "genetic variation"[Title/Abstract]) OR "polymorphism 5 httplr"[Title/Abstract]) OR "serotonin plasma membrane transport proteins"[MeSH Terms]) OR "humans, polymorphisms")) AND (((("depression"[Title/Abstract]) OR "depressive symptoms"[Title/Abstract]) OR "mood disorders/psychology"[MeSH Terms]) OR "mood disorders/genetics"[MeSH Terms]) OR "depression/genetics"[MeSH Terms])

Data collection and extraction process

Once the search terms were defined, the final strategy was established and replicated in the various databases. A total of 704 articles were obtained, the EndNote Web bibliographic administrator was used in order to organize the references found and to be able to eliminate duplicated studies. Then an evaluation was made by title and summary of the articles, those not related to the topic of interest were eliminated, and then those articles with relevant information were evaluated in full text in order to obtain the final sample. The procedure described above followed the steps of the PRISMA diagram.

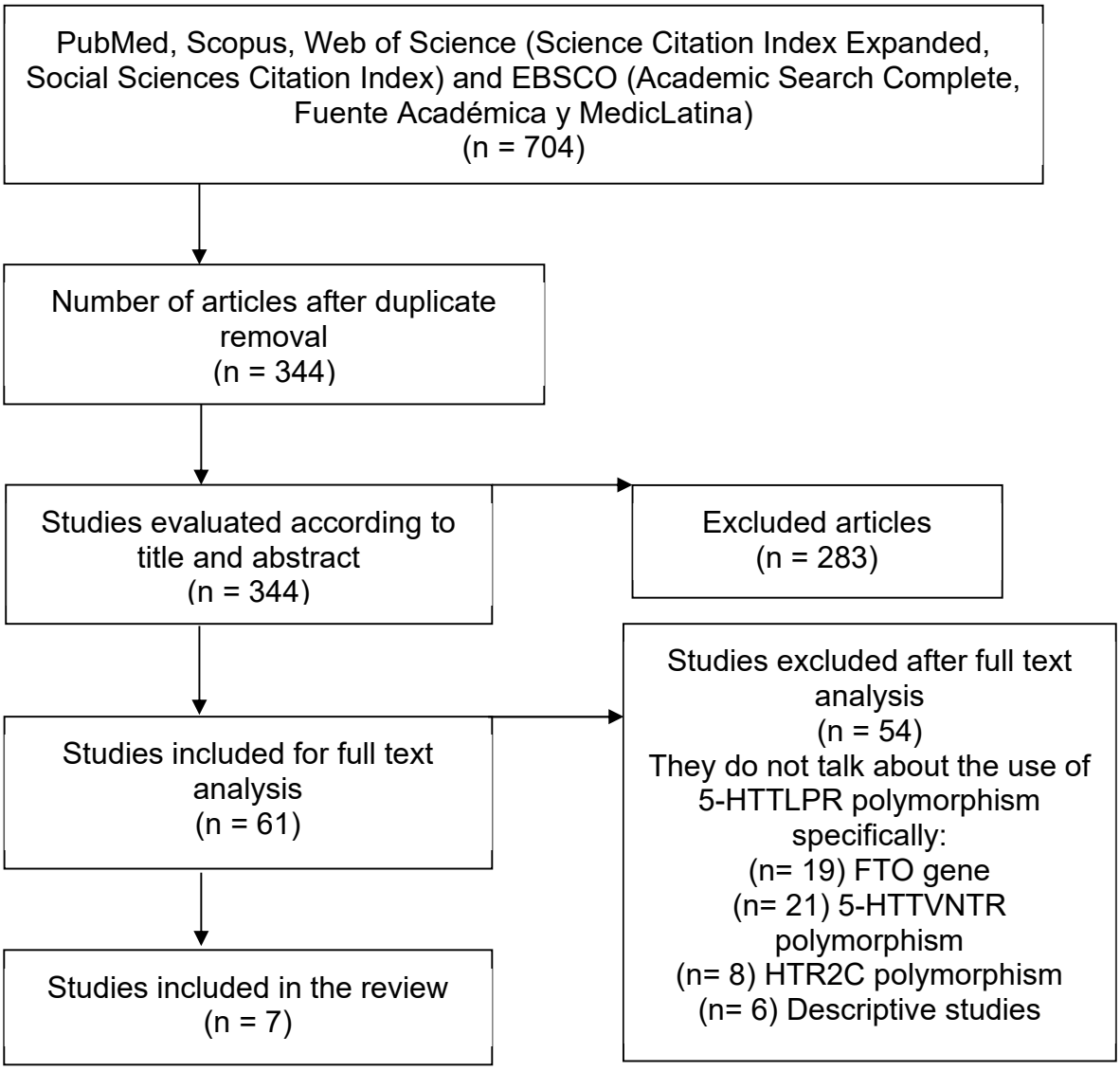
Evaluation of the quality of studies

To analyze the methodological quality of the studies, the Web 3.0 Platform for Critical Reading Files (FLC) was used.

RESULTS

Figure 1 shows the PRISMA diagram describing the study selection process.

Figure 1. PRISMA diagram



Characteristics of the studies

We identified 344 studies that included in their content information related to the topic of interest, 283 of these were discarded because they did not meet the inclusion criteria, subsequently, 61 articles were evaluated in full text, eliminating 53 because they did not discuss the use of the polymorphism of the serotonin transporter gene (5-HTTLPR)

region in relation to DP and OW-OB. Only 7 articles met the inclusion criteria, were evaluated in full text and contained results in relation to the topic of interest.

Summary of results

Primary studies were identified that indicate a correlation between polymorphism of the serotonin transporter gene (5-HTTLPR) promoter region, increased BMI and OB (β = .280, *p* = .033) and with DP (β = .357, *p* < .01), meaning that 5-HTTLPR polymorphism increases the predisposition to weight gain and DP [16]. Likewise, van Strien, Konttinen, Homberg, Engels and Winkens (2016) [17] distinguished correlation between 5-HTTLPR polymorphism and BMI in a longitudinal study in the first measurement and in a measurement after 4 years (T1: r = 110, *p* = 0.01; T2: r = 120, *p* = 0.01), they also obtained significant correlations between DP and BMI (B = 0.18, *p* = .026).

Dias, Muc, Padez, and Manco (2016) [18] studied the relationship between the 5-HTTLPR polymorphism and the risk of OW-OB. Their study was made up of a general sample, a group of athletes and the non-sporting group; in the general sample and in the group doing some physical activity, no association was observed; however, in the group of non-sporting participants, an association was observed between the risk of OW-OB and having the 5-HTTLPR polymorphism (OR [95% CI] = 0. 64 [0.45 - 0.91] *p* = 0.01), suggesting that physical inactivity increases the influence between the polymorphism (5-HTTLPR) and the risk of developing OB.

Borkowska et al. (2015) [19] correlated the genotypic variants of 5-HTTPLR (S/S, S/L and L/L), the BMI and the Beck Depression Inventory (BDI) and the Hamilton Depression Scale (HDRS) used for the detection of DP, finding that the S/S and S/L alleles had a correlation (S/S and BMI *p* = 0. 001; S/S and BDI *p* = 0.001; S/S and HDRS *p* = 0.001; S/L and BMI *p* = 0.001; S/L and BDI *p* = 0.010; S/L and HDRS *p* = 0.001), the scores of the scales for the detection of DP in subjects with the S/S and S/L genotype of 5-HTTLPR were significantly lower compared to the L genotypes. That is, in participants with OB, the S allele of 5-HTTLPR was associated with the development of depressive temperament, while the L allele corresponded to a higher OB and prevalence of DP.

Bielinski et al (2015) [20] identified no significant relationship between BMI and DP, nor in the relationship between 5-HTTLPR genotypes (L/L, S/S and L/S) and BMI (*p* = 0. 85) and with DP using the Beck Depression Inventory (BDI) and the Hamilton Depression Scale (HAM-D) (*p* = 0.660, *p* = .110), that is, it is unlikely that 5-HTTLPR polymorphism is correlated with depressive symptoms in people with OB. However, Fuemmeler et al (2009) [21] analyzed the risk of OW-OB with the 5-HTTLPR genotype with respect to the S allele (OR = 1.94; CI = 1.01 - 3.71; *p* = 0.03; OR = 1.75; CI = 1.07 - 2.85; *p* = 0.03), which means that the S allele of the 5-HTTLPR genotype is a biological risk factor for the development of OB.

Van Strien, Van der Zwaluw and Engels (2010) [22] correlated the 5-HTTLPR phenotype, BMI (r = 120, *p* = .050), DP (r = -.010, *p* = > .050), emotional eating and depressive feelings in a longitudinal study. Both in the first collection and in the second to four years the following results were observed: T1 r = 360 *p* = 0.001; T2 r= 210 p = 0.001. Regression analysis between 5-HTTLPR genotype and depressive feelings about change in emotional eating in the initial model were not significant (B = .31, *p* = .26). However, 5-HTTLPR genotype and depressive feelings (B = -.40, *p* = < .01), the interaction of depressive feelings and 5-HTTLPR and its SS/SL vs LL genotypes were

significantly associated with increased emotional eating (B = .25, $p < .01$). Regression for 5-HTTLPR LL genotypes indicated that depressive feelings were not associated with emotional eating (B = -.19, $p = .11$). That is, the 5-HTTLPR genotype moderated the relationship between depressive feelings and increased emotional eating, since adolescents showed a greater increase in emotional eating if they carried the S allele of 5-HTTLPR.

Table 2 shows the results of the studies included in this review that provide evidence regarding the question of the present review: Is the polymorphism of the serotonin transporter gene (5-HTTLPR) associated with the development of DP in people with OW-OB?

Table 2. Characteristics and Studies' Quality

Reference	Methodology	Population	Results
Abbreviated quote: Schepers & Markus, 2017 *Country:* Netherlands *Quality of evidence:* Media	*Design:* *Correlational* *Objectives:* To investigate whether the S allele of 5-HTTLPR contributes to weight gain in individuals with a high degree of cognitive thinking.	*Number of participants / group:* 827 *students* *Participating features:* 602 were women, the average age of this sample was 21.28 (SD = 2.99).	*Results:* Genotype S of 5-HTTLPR and BMI: β = 0.280, $p = 0.033$ Genotype S of 5-HTTLPR and depressive symptoms β = 0.357, $p < 0.01$
Abbreviated quote: Van Strien et al., 2016. *Country:* Netherlands *Quality of evidence:* High	*Design:* longitudinal *Objectives*: to explore the possible mediating effects of the three eating styles (emotional, external and restricted) on the link between basal depression and future weight gain in a sample of Dutch adults *Period of realization:* 2003-2008	*Number of participants / group:* 592 participants. *Participating characteristics:* 298 men and 294 women T1= the average age of 45.04 (SD = 3.9) and the average BMI was 24.99 (SD = 3.7) 43.2% of the participants had a BMI > 25 and 7.9% had a BMI > 30. T2= (after five years), the	*Results:* Pearson Correlation: 5-HTTLPR and BMI: T1: (r = 110, $p = 0.01$; T2: (r = 120, $p = 0.01$). Depression and BMI: (Beta = 0.18, $p = 0.026$). 5-HTTLPR and depressive symptoms and the change of the BMI by gender. SS-SL alleles in women: Beta (SE): 0.08 (0.23); $p = 0.728$; LL alleles in women: Beta (SE): 0.14 (0.57) $p = 0.804$; SS-SL alleles in men: Beta (SE): 0.36 (0.19) $p = 0.061$; LL alleles in men: Beta (SE): -0.03 (0.28) $p = 0.917$.

		average BMI was 25.26 (SD = 3.4).	Indirect effect of depression on BMI increase was significant.
Abbreviated quote: Dias, Muc & Manco, 2015 *Country:* Portugal *Quality of evidence:* High	*Design:* cross-sectional descriptive correlational study *Objectives*: to investigate the association of polymorphisms in the genes SLC6A4 (5-HTTLPR) and MAOA with overweight (including obesity). *Period of work:* September 2013-February 2014	*Number of participants / group:* 535 *Participating features:* Healthy young adults of Portuguese European descent, 225 men and 310 women aged 17-36	*Results:* Association of 5-HTTLPR polymorphisms with risk of overweight/obesity in the sample of young Portuguese adults*:* *General Sample:* OR (95% CI) 0.78 (0.58 –1.05) *p* = 0.11 *Sports participants:* OR (95% CI) 1.43 (0.79 – 2.06) *p* = 0.23 *Non-sporting participants:* OR (95% CI) 0.64 (0.45–0.91) *p* = 0.01
Abbreviated quote: Borkowska et al., 2015 *Country:* Poland *Quality of evidence:* High	*Design:* descriptive correlational *Objectives:* The aim of this study was to investigate the influence of a polymorphism in the 5-HTT gene on the types of affective temperament, depressive symptoms and body mass index (BMI) in obese patients.	*Number of participants / group*: 390 *Participating features:* Obese subjects of Polish nationality and Caucasian ethnicity, from 20 to 76 years old. 237 women (20 to 75 years old, mean age 52 years) and 153 men (21 to 76 years old, mean age 53 years) were included.	*Results:* Kendall's partial range correlation Gender vs. BDI and HDRS: τ = .14, *p* = .001 τ = .15, *p* = .001 *Genotype 5-HTTLPR:* S/S, S/L and L/L S/S and BMI *p* = .001 S/S and BDI *p* = .001 S/S and HDRS *p* = .001 S/L and BMI *p* = .001 S/L and BDI *p* = .010 S/L AND HDRS *p* = .001 L/L and BMI *p* > .050 L/L and BDI *p* > .050 L/L and HDRS *p* > .050
Abbreviated quote: Bielinski et al., 2015 *Country:* Poland	*Design:* Descriptive Correlational *Objectives:* To assess the association between polymorphisms related to serotonin-related	*Number of participants / group:* 180 patients between the ages of 18 and 73.	*Results:* Spearman correlation: 1. BMI and depressive symptoms were not statistically significant. 2. Genotypes 5-HTTLPR (L/L, S/S and L/S) and BMI: (*p* = .85).

Quality of evidence: High	genes (5-HT2A and SERT [5-HTTLPR]) and the occurrence of depressive symptoms in obese patients.		3. Genotypes 5-HTTLPR (L/L, S/S and L/S) and depressive symptoms with the BDI and HAM-D scale (p = .110 and .660)
Abbreviated quote: Fuemmeler et al., 2009 *Country:* United States of America *Quality of evidence:* High	*Design:* Longitudinal Cohort *Objectives:* To examine whether depressive symptoms moderate the relationship between candidate genes (SLC6A4 [5-HTTLPR] and MAOA) and obesity. *Period of performance:* April to December 1995; April to August 1996 and August 2001 to August 2002	*Number of participants / group:* 15,197 *Participating features:* The average age in the three waves of data collection was 15.65 (SD = 1.75) years, 16.22 (SD = 1.64) years and 22.96 (SD = 1.77) years, respectively	*Results:* Obesity risk and the SLC6A4 genotype (5-HTTLPR) S/S Allele: OR = 1.94; CI = 1.01-3.71; p = 0.03 Risk of overweight and the genotype SLC6A4 (5-HTTLPR) S/S Allele: OR = 1.75; CI = 1.07-2.85; p = 0.03
Abbreviated quote: Van Strien, Van der Zwaluw & Engels, 2010 *Country:* Netherlands *Quality of evidence:* High	*Design:* longitudinal *Objectives:* To examine the change in emotional eating over 4 years by monitoring reference levels of emotional eating. Hypothesizing that the 5-HTTLPR genotype would act as a moderator, since the relationship between depressive feelings and increased emotional eating would become stronger if adolescents had the short allele 5-HTTLPR. Also, the hypothesis that the moderating effect of the 5-HTTLPR genotype on the relationship between	*Number of participants / group:* 428 Dutch families with two teenage children	*Results:* *Pearson Correlation:* BMI and 5-HTTLPR: r = 120, p = .050 Depression and 5-HTTLPR r = -0.010, p = > .050. Emotional eating and depressive symptoms: T1: r = .360 p = .001 T4: r = 210; p = .001 Regression Analysis The 5-HTTLPR genotype and depressive feelings about the change in emotional eating in the initial model were not significant: (B = .31, p = .26) Genotype 5-HTTLPR and depressive feelings (B= -.40, p < .01). The interaction of depressive feelings and 5-HTTLPR and its SS/SL vs LL genotypes was significantly associated

	depressive feelings and increased emotional eating would be stronger in girls than in boys. *Period of realization:* 4 years		with increased emotional eating (B = .25, *p* < .01). Regression for LL 5-HTTLPR genotypes indicated that depressive feelings were not associated with emotional eating: (B = - .19, *p* = .11).

DISCUSSION

In this review, a systematic search was conducted to identify and analyze existing studies that have addressed the relationship between genetic variation or polymorphism of the serotonin transporter gene (5-HTTLPR) promoter region and its association in the development of DP in people with OW-OB. Seven studies were included that show that the 5-HTTLPR polymorphism is a factor for the development of DP and that it favors the risk in the increase of the BMI and therefore to the development of OW-OB. Based on these results, the review by Heils et al. (1996)[23] highlights that the 5-HTTLPR polymorphism has been associated to psychiatric diseases, depressive disorders, anxiety disorders and in eating disorders and also when the S allele is possessed the functioning is more deficient, which would aggravate the symptomatology.

On the other hand, Solmi et al (2016) [24] in their meta-analysis did not find results that assume an important additive function of the 5-HTTLPR polymorphism for the risk of developing an eating disorder. However, the data provided demonstrate that a possible small effect of the 5-HTTLPR polymorphism (which could be demonstrated only in very large samples), or an interactive effect on ethnic differences, as well as possible environmental risks, stressful and traumatic events, cannot be ruled out, which may interact with the 5-HTTLPR polymorphism to increase the risk of developing eating disorders.

Likewise, Calati, De Ronchi, Bellini and Serretti (2011) [25] in their meta-analysis have found an association between the S allele of the serotonin 5-HTTLPR polymorphism and eating disorders, in particular with anorexia and OB, that is, being a carrier of the 5-HTTLPR polymorphism seems to represent a risk factor. However, Vimaleswara et al (2010) [26] suggest that variants of 5-HTTLPR polymorphism are unlikely to play a major role in OB and mental health-related traits in the general population.

CONCLUSION

Most of the studies included in this review demonstrate that the polymorphism, the genetic variation or polymorphism of the region promoting the serotonin transporter gene (5-HTTLPR) is linked to the development of DP and in turn increases the risk of developing OB. However, they cannot be generalized, since other reviews do not reach a similar consensus and differ with the results described above, so it is recommended that the relationship between 5-HTTLPR polymorphism, DP and excess weight in the population be studied further. It is considered relevant that the nursing professionals know and understand the relationship between genetics and the environment and its

biological and behavioral implications in people, considering ethical and psychosocial aspects so that a successful synergy can occur and that impacts on the improvement of care and expands the options for prevention, diagnosis and treatment of multiple diseases, including DP and excess weight, avoiding health complications.

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