UNIVERSITAT DE BARCELONA

Stressful life events and first-episode psychosis

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The work described in this thesis was performed at the Parc Sanitari Sant Joan de Déu (Sant Boi del Llobregat, Spain), at the Hospital Sant Joan de Déu Infantil (Esplugues del Llobregat, Spain) and at the Department of Personality, Evaluation and Psychological Treatment of Faculty of Psychology, University of Barcelona (Spain).

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Doctoral thesis

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A la meva família

“La vida és un tango”

Lidia Jubany

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Contents

Resum

Actualment, els avenços en la neurociència afectiva i social han demostrat com l'exposició als factors ambientals influeix en l'estructura i la funció del cervell, essent agents actius en la formació del nivell de vulnerabilitat de l'individu. A més, hi ha un interès creixent en la influència de l'estrès en moltes malalties, incloent un primer episodi psicòtic (PEP).

Des del model de vulnerabilitat-estrès (Zubin i Spring, 1977) fins als models actuals de diàtesi-estrès neural (Pruessner et al., 2017), l'esquizofrènia es conceptualitza com un trastorn episòdic en què hi ha vulnerabilitat i estrès a causa de factors biològics i/o ambientals. Això suggereix que probablement els pacients estiguin predisposats a manifestar episodis psicòtics induïts per l'impacte dels factors precipitants, com els esdeveniments vitals estressants (EVEs). En el PEP, és rellevant el paper dels estressors, específicament EVEs, com a factors predisponents o adjuvants a l'aparició de la malaltia. Aquests esdeveniments són circumstàncies que es produeixen en la vida de les persones amb un inici i fi identificables que tenen el potencial d'alterar el seu estat físic o mental actual. Tanmateix, hi ha molt pocs estudis sobre EVEs en pacients amb esquizofrènia i, fins i tot, menys en pacients amb PEP, per la qual cosa és necessari l'estudi en aquestes mostres. Els EVEs poden ser tractats com esdeveniments prodròmics, que juntament amb altres esdeveniments, contribueixen a l'aparició de simptomatologia psicòtica posterior. De fet, és probable que els diferents factors ambientals associats amb l'esquizofrènia puguin estar vinculats a mecanismes subjacents diferents. Diversos estudis han avaluat el paper dels EVEs, però la majoria d'aquests estudis inclouen aquests esdeveniments com a trauma, el que fa que la seva investigació i avaluació sigui més difícil i complicada.

Molts estudis han investigat la relació entre la presència d'EVEs i l'edat, buscant l'etapa vital amb el major nombre d'EVEs i el tipus d'EVEs que es produeixen amb major freqüència en funció de l'edat. Tanmateix, els resultats indiquen que hi ha altres variables implicades en l'augment dels EVEs durant el temps. A més, el grau d'afectació dels EVEs, la probabilitat de la seva aparició i el desenvolupament d'alteracions psicopatològiques varien segons l'edat i els recursos disponibles per a cada subjecte. Un esdeveniment vital ocorregut durant una etapa evolutiva no tindrà el mateix efecte en un individu com el que es produeix en una fase posterior de desenvolupament, pel que és necessari avaluar les conseqüències dels EVEs en el període de desenvolupament de l'individu. L'adolescència i l'edat adulta primerenca són etapes amb grans canvis a nivell familiar, social i biològic. Per tant, la naturalesa canviant d'aquest període evolutiu és important, i els processos de desenvolupament maduratius hi tenen un paper important.

L'etiologia complexa i les manifestacions clíniques heterogènies de la psicosi fan necessari que a més del model de vulnerabilitat-estrès, calgui focalitzar-se en el model d'estadificació clínica i en la intervenció primerenca. Això afavoreix el ràpid accés a l'atenció i el tractament integral en les etapes inicials del trastorn i permet analitzar el paper dels mecanismes psicològics implicats en l'expressió real de símptomes psicòtics en individus amb PEP. Per aconseguir una intervenció primerenca adequada i efectiva dels trastorns psicòtics, calen estudis addicionals per identificar els primers indicadors de la malaltia psicòtica i caracteritzar les fases inicials dels trastorns psicòtics.

Aquesta tesi tenia com a objectiu aconseguir una intervenció primerenca adequada i efectiva en trastorns psicòtics ja que: i) en general, pocs estudis han avaluat específicament els EVEs; ii) cap estudi ha analitzat l'edat d'aparició de PEP en relació amb els EVEs; iii) no hi ha estudis sobre diferències de gènere, historia familiar i simptomatologia psicòtica en relació amb els EVEs; i per últim, iv) no hi ha instruments disponibles per avaluar els EVEs durant el cicle vital.

L'objectiu principal d'aquesta tesi va ser avaluar la relació entre els EVEs i el desenvolupament del PEP. Aquest objectiu es va desenvolupar en tres objectius específics: 1) revisar de forma sistemàtica la literatura disponible dels EVEs i PEP, 2) avaluar l'impacte dels EVEs i la influència de les variables sociodemogràfiques i clíniques sobre l'aparició de PEP, i 3) validar un instrument per mesurar els EVEs en pacients amb PEP i en població sana. Cadascun d'aquests objectius es va associar a un estudi.

El primer objectiu es va plasmar en l'Estudi 1. Aquest estudi fa una revisió de la literatura sobre els EVEs i la seva influència en l'aparició del PEP. Per a la revisió, es van seleccionar els principals estudis sobre EVEs, incloent-hi aspectes clau com l'adolescència, l'afrontament, la resiliència i les diferències ètniques. L'Estudi 1 proporciona una revisió de la literatura en referència als EVEs en relació amb: i) el model de vulnerabilitat a l'estrès, ii) EVEs en pacients amb PEP, iii) EVEs, PEP i adolescència, iv) l'afrontament i la resiliència, i v) Diferències ètniques. Es va realitzar una recerca entre 1980 i 2013 utilitzant PsycINFO, MEDLINE i PSICODOC utilitzant els següents termes: *esdeveniments vitals estressants, adolescència, afrontament, resiliència, esquizofrènia, estrès, primer episodi psicòtic* i *vulnerabilitat*. Es van trobar 289 estudis, dels quals 59 van ser seleccionats per a la seva revisió.

En general, la revisió ressalta la importància de certs factors psicosocials que poden causar un canvi significatiu en la vida de les persones i, en conseqüència, requereixen una resposta d'adaptació. El nucli central és l'adaptació al medi ambient i, en conseqüència, la producció de canvis dinàmics en l'individu. Un exemple és l'efecte dels EVEs, que es consideren factors ambientals que produeixen conflictes, desafiaments i canvis en les persones. L'avaluació integrada dels EVEs, juntament amb altres variables individuals i contextuals, constitueixen una dimensió per a la detecció precoç del PEP com a mitjà de prevenció. Els resultats mostren la necessitat d'un enfocament global a causa dels diferents factors implicats en el PEP.

El segon objectiu es va avaluar a l'Estudi 2, que va analitzar la incidència dels EVEs i l'impacte de les variables sociodemogràfiques (gènere i edat) i clíniques (edat d'aparició del PEP, símptomes psicòtics i història familiar) sobre l'aparició de PEP. Es va utilitzar la Psychiatric Epidemiology Research Interview Life Events Scale la qual va avaluar l'any anterior a l'inici del PEP. Els resultats de l'Estudi 2 van mostrar que només es van trobar diferències significatives segons el sexe per a la categoria d'assumptes judicials en homes adolescents. L'edat d'inici va presentar una correlació negativa significativa amb les categories d'activitats acadèmiques i socials. Per contra, es va trobar una correlació positiva amb la categoria treball i fills. Es va trobar una relació significativa entre la història familiar paterna i les activitats socials, i entre la història familiar materna i les categories acadèmica i amor/matrimoni. Finalment, es va observar una relació inversa entre els símptomes negatius i les categories fills i finances. Els símptomes depressius estaven significativament correlacionats amb la categoria acadèmica.

En general, aquest article mostrava els següents resultats: i) elevada incidència de EVEs en PEP, ii) més EVEs en pacients amb història familiar de trastorns mentals, i per últim, iii) l'edat d'inici del PEP i els símptomes psicòtics s'associen amb la presència dels EVEs.

Els resultats van mostrar la importància dels EVEs durant l'adolescència i van suggerir una clara necessitat de desenvolupar accions preventives per gestionar l'acumulació de l'estrès psicosocial. Els estudis 1 i 2, demostren la necessitat d'avaluar els EVEs durant la vida i considerar l'anàlisi de les característiques rellevants dels EVEs com l'edat del subjecte en el moment de PEP i els nivells d'estrès o impacte emocional.

El tercer objectiu es va avaluar a l'Estudi 3. Es tracta d'un estudi psicomètric centrat en el desenvolupament i la validació del Qüestionari d'Esdeveniments Vitals Estressants (QEVE) en pacients amb PEP i població sana. Els estudis disponibles sobre els EVEs presenten la necessitat d'identificar els EVEs més importants i avaluar les diferents propietats dels EVEs en diferents tipus de mostres (Abad et al., 2000; Lemos et al., 2002). En aquesta tesi, a més d'una mostra PEP, es va incloure una mostra de controls sans per tal d'avaluar els EVEs més influents. La càrrega subjectiva de l'estrès també es va incloure en cada ítem de EVEs ja que l'estrès pot afectar a la seva percepció. Això va conduir al desenvolupament i la validació del QEVE que podia ser útil per identificar quins EVEs havien estat avaluats abans del PEP i avaluar altres variables específiques al llarg de la vida com l'edat en el moment del EVEs i, de forma qualitativa, el nivell d'estrès o impacte emocional.

L'Estudi 3 va consistir en el desenvolupament i la validació del QEVE, on es van descriure aspectes específics de la infància, l'adolescència i l'edat adulta centrats en la presència dels EVEs, l'impacte emocional (nivell d'estrès) i l'edat en la que es va produir l'esdeveniment en la mostra de pacients amb PEP i controls sans. Es va generar un llistat d'ítems i es va avaluar la validesa de contingut. Seguidament, es va analitzar la fiabilitat i validesa de la QEVE: i) anàlisi item-level, ii) fiabilitat intra-rater, i iii) validesa convergent i discriminant. Finalment, es van realitzar l'anàlisi de sensibilitat i especificitat. El qüestionari mostrava bones propietats psicomètriques. Les puntuacions eren fiables i vàlides i, per tant, és un instrument útil per a la mesura i detecció dels EVEs que es produeixen durant el cicle vital en pacients amb PEP, així com amb subjectes sans. Les troballes de l'Estudi 3 suggereixen que el QEVE permet investigar els esdeveniments vitals infantils, adolescents i adults, mesurant l'estrès i l'edat en el moment del EVEs en una escala contínua, sent òptima per a estudis de psicosi. El QEVE també va avaluar la presència i els nivells d'estrès, oferint així un coneixement addicional de l'impacte dels EVEs en la psicosi.

Les dades obtingudes en aquesta tesi proporcionen un coneixement més profund sobre els EVEs i la seva avaluació i detecció, així com la relació d'aquests esdeveniments amb variables i símptomes clínics en una mostra de pacients amb PEP i controls sans.

Aquesta tesi doctoral s'ha centrat en l'estudi dels EVEs i la psicosi. L'objectiu de la identificació dels EVEs en el model de vulnerabilitat-estrès en el continuum de la psicosi pot proporcionar informació sobre l'etiologia d'aquest trastorn i conduir al desenvolupament d'estratègies de prevenció i tractament.

A més, diferents estudis han suggerit que els EVEs tenen un paper important en la precipitació i la recaiguda dels trastorns psiquiàtrics; no obstant això, la relació no és tan senzilla. Hi ha altres vulnerabilitats que poden influir en la precipitació del trastorn, com ara les diferències en el sistema de suport social, habilitats, actituds, creences i característiques de la personalitat (Cohen i Hamrick, 2003; Fumero, Santamaría, i Navarrete, 2009; Pandurangi i Kapur, 1980). Aquests factors poden fer que algunes persones siguin relativament immunes a l'estrès induït per la malaltia i altres que siguin relativament susceptibles, donant lloc al desenvolupament d'un PEP. La gran quantitat de factors desencadenants així com l'ampli període de desenvolupament i la presència de nombrosos factors moderadors de resiliència semblen compatibles amb l'espai psicopatològic que hi ha entre els trets de la personalitat esquizotípica (diferències individuals sanes) i la psicopatologia psicòtica greu. A més, s'ha demostrat que hi ha canvis en el desenvolupament dinàmics en la posició de l'individu al llarg d'aquest continuum hipotètic de risc i resiliència a la psicosi.

Hi ha evidència que els EVEs interactuen amb el PEP i, en conseqüència, la determinació dels EVEs pot ser especialment útil per desenvolupar estratègies per evitar el desenvolupament del PEP. És necessari implementar estratègies que garanteixin la identificació de la psicosi i el tractament en la primera fase, així com aconseguir un control precoç del patiment que la malaltia produeix al pacient i les figures clau dins del seu entorn.

Amb aquest treball proporcionem més proves que la variabilitat dels EVEs pot tenir un paper important en les poblacions PEP i aquest fet és de gran rellevància per a la pràctica dels professionals que es dediquen a detectar, atendre i tractar a persones amb aquesta malaltia .

El treball presentat en aquesta tesi s'emmarca dins del model de vulnerabilitat-estrès i el model d'estadificació clínica, que considera el continu fenotípic que reflecteix un conjunt interactiu entre la diàtesi, els factors psicosocials i els socioculturals.

Actualment, pocs estudis han avaluat els EVEs en aquests tipus de poblacions i hi ha una necessitat d'obtenir una informació més detallada sobre la influència dels EVEs en aquestes poblacions en les quals la genètica i l'estrès tenen un paper rellevant.

Abstract

Nowadays, advances in affective and social neuroscience have shown how the exposure to environmental factors has an impact on the structure and functioning of the brain being thus, active agents in the formation of an individual's level of vulnerability. There is an increasing interest in the influence of stress on many diseases including a first-episode psychosis (FEP).

From the stress-vulnerability model (Zubin & Spring, 1977) to the current models of neural diathesis-stress (Pruessner et al., 2017), schizophrenia is conceptualised as an episodic disorder in which there is vulnerability and stress due to biological and/or environmental factors. This suggests that patients are likely predisposed to manifesting psychotic episodes induced by the impact of precipitating factors, such as stressful life events (SLEs). In FEP, the role of stressors, specifically SLEs, as predisposing factors or adjuvants to the onset of the disease is relevant. These events are circumstances that occur in the lives of people with an identifiable beginning and end which have the potential to alter their current mental or physical status. However, there are very few studies on SLEs in patients with schizophrenia -and even fewer in patients with FEP-, thereby emphasising the need for such studies. SLEs can be treated as prodromal events, which together with other events, contribute to the appearance of later psychotic symptomatology. Indeed, it is likely that the diversity of environmental factors associated with schizophrenia may be linked to an equal number of different underlying mechanisms. Several studies have evaluated the role of SLEs, but most of the studies include these events as trauma, what makes their research and evaluation more difficult and complicated.

Many studies have investigated the relationship between the presence of SLEs and age, seeking the stage of life with the highest number of SLEs and the type of SLEs that most frequently occur based on age. However, the results indicate that other variables are involved in the increase of SLEs over time in addition to age.Moreover, the level of involvement of these SLEs and the probability of their occurrence and the development of psychopathological alterations vary according to the age and resources available to each subject. A life event occurring during an evolutionary stage will not have the same effect on an individual as one which takes place at a later stage of development, thereby making it necessary to evaluate the consequences that SLEs have based on the period of development of the individual. Adolescence and early adulthood are stages with great changes at family, social and biological level. Thus, the changing nature of this evolutionary period is important, with maturational development processes playing an important role.

In addition to the stress-vulnerability model, the complex aetiology and heterogeneous clinical manifestations of psychosis make it necessary to focus on the clinical staging model and on an early intervention. This promotes rapid access to care and to a comprehensive treatment in the initial stages of the disorder, and allows analysis as well of the role of the psychological mechanisms involved in the real-life expression of psychotic symptoms in individuals with FEP. To achieve appropriate and effective early intervention in psychotic disorders, further studies are needed to identify early markers of psychotic illness and characterise the early phases of psychotic disorders.

Abstract

This thesis was aimed at achieving adequate and effective early intervention in psychotic disorders since: i) in general, few studies have specifically evaluated SLEs; ii) no studies have analysed the age of onset of FEP in relation to SLEs; iii) no studies have been found about gender differences, family history and psychotic symptomatology in relation to SLEs; and iv) no instruments are available to assess SLEs along the life cycle.

The main objective of this thesis was to evaluate the relationship between SLEs and the development of FEP. This objective was developed under three specific objectives: 1) to systematically review the literature available on SLEs and FEP, 2) to evaluate the impact of SLEs and the influence of sociodemographic and clinical variables on the appearance of FEP, and 3) to validate an instrument to measure SLEs in FEP and in a healthy population. Each of these objectives was associated with a study.

The first objective was analysed in Study 1. This study reviews the literature on SLEs and their influence on the appearance of FEP. For the review we selected the leading studies on SLEs including key aspects such as adolescence, coping, resilience and ethnic differences. Study 1 provides a review of the literature in reference to SLEs with respect to: i) the stress-vulnerability model, ii) SLEs in patients with FEP, iii) SLEs, FEP and adolescence, iv) coping and resilience, and v) ethnic differences. A search was conducted between 1980 and 2013 using PsycINFO, MEDLINE and PSICODOC using the following terms: *Stressful life events, adolescence, coping, resilience, schizophrenia, stress, first psychotic episode*, and *vulnerability*. A total of 289 studies were found, 59 of which were selected for review.

Overall, the review highlights the importance of certain psychosocial factors which may cause a significant change in subjects' lives and, consequently, require an adaptation response. The central nucleus is the adaptation to the environment and, consequently, the production of dynamic changes in the individual. An example is the effect of SLEs, which is considered an environmental factor that produce conflict, challenge and change in subjects. Integrated assessment of SLEs together with other individual and contextual variables, constitute an approach for the early detection of FEP as a means of prevention. The results show the need for a multiple comprehensive approach because of the different factors involved in the nexus with which FEP is made up.

The second objective was evaluated in Study 2. It analysed the incidence of SLEs and the impact of sociodemographic (gender and age) and clinical variables (age of onset of FEP, psychotic symptoms and family history) on the appearance of FEP. We used the Psychiatric Epidemiology Research Interview Life Events Scale which assessed the year before the onset of FEP. The results of Study 2 showed that significant differences according to gender were only found for the category of legal affairs in adolescent males. Age at onset presented a significant negative correlation with the categories of academic and social activities. By contrast, a positive correlation was found with work and children. A significant relationship was seen between paternal family history and social activities and between maternal family history and academic and love and marriage. Finally, an inverse relationship was observed between negative symptoms and the categories of children and finance. Depressive symptoms were significantly correlated with the category of academic.

Overall this paper showed the following results: i) the high incidence of SLEs in FEP, ii) there are more SLEs in subjects with a maternal/ paternal family history of mental disorders, and iii) the age at onset and psychotic symptoms were associated with the presence of SLEs.

The results showed the importance of SLEs during adolescence and suggested a clear need to develop preventive actions to manage the accumulation of psychosocial stress. Studies 1 and 2, demonstrate the need to assess SLEs along life and consider the analysis of the relevant characteristics of SLEs such as age of the subject at the time of FEP and the levels of stress or of emotional impact.

The third objective was evaluated in Study 3. This was a psychometric study focused on the comparison of the development and validation of the 'Questionnaire of Stressful Life Events' (QSLE)' in patients with FEP with respect to a healthy population. The studies available on SLEs show the need to identify the most important SLEs and evaluate the different properties of SLEs in different types of samples (Abad et al., 2000; Lemos et al., 2002). In this thesis, in addition to a FEP sample, a sample of healthy controls was included in order to assess the most influential SLEs. The subjective burden of stress was also included in each item of SLEs since stress can affect their perception. This led to the development and validation of the QSLE that could be helpful to identify which SLEs should be evaluated before a FEP, and to assess SLEs as well as other specific variables along life such as age at the time of the SLEs, and qualitatively, the level of stress or the emotional impact.

Study 3 involved the development and validation of the questionnaire on SLEs (QSLE), which described specific items of childhood, adolescence, and adulthood focused on the presence of SLEs, emotional impact (stressfulness), and the age at which the event occurred in patients with FEP and healthy controls. An item pool was generated and content validity was evaluated. We then assessed the evidence of the reliability and validity of the QSLE: i) item-level analyses, ii) intra-rater reliability, and iii) convergent and discriminant validity. Lastly, sensitivity and specificity analyses were performed. The questionnaire showed good psychometric properties. The scores were reliable and valid and, thereby this is a useful instrument for the measurement and detection of SLEs that occur during the life cycle in patients with FEP as well as healthy subjects. The findings of Study 3 suggest that the QSLE allows the investigation of childhood, adolescent, and adult life events by measuring stress and the age at the time of the SLEs on a continuous scale, being optimal for psychosis studies. The QSLE also assessed the presence and levels of stress thereby providing additional knowledge of the impact of SLEs on psychosis.

The data obtained in this thesis provide more in depth knowledge regarding SLEs and their evaluation and detection as well as the relationship of these events with clinical variables and symptoms in a sample of patients with FEP and healthy controls.

This doctoral thesis has focused on the study of SLEs and psychosis. The objective of identifying SLEs across the stress-vulnerability model psychosis phenotype continuum may provide insights into the aetiology of this disorder and may lead to the development of strategies for its prevention and treatment.

Furthermore, different studies have suggested that SLEs play an important role in the precipitation and relapse of psychiatric disorders; however, the relationship is not so simple. There are other vulnerabilities that may influence the precipitation of the disorder, such as differences in the social support system, skills, attitudes, beliefs and personality characteristics (Cohen & Hamrick, 2003; Fumero, Santamaría, & Navarrete, 2009; Pandurangi & Kapur, 1980). These factors may make some people relatively immune to disease-induced stress and others relatively susceptible, leading to the development of a FEP. A large number of causative factors as well as the wide developmental time period and the presence of numerous moderating resilience factors seem to be consistent with the psychopathological space between healthy individual differences in schizotypal personality traits and severe psychotic psychopathology. In addition, it has been unveiled that there are dynamic developmental changes in the individual's position along this hypothetic continuum of risk and resilience to psychosis.

There is evidence that SLEs interact with FEP, and consequently, the determination of SLEs might be particularly useful to develop strategies to prevent the development of FEP. There is a need to implement strategies that guarantee the identification of psychosis and treatment in the earliest phase, as well as to achieve early control of the suffering that the disease produces to the patient and the key figures within their environment.

We provide further corroboration that rather than being a correlate of frank psychosis, the variability of SLEs may play an important role in FEP populations and this is of great relevance to the practice of professionals dedicated to detecting, caring for, and treating people with this disease.

The work presented in this thesis is framed within the stress-vulnerability model and the clinical staging model, which considers the phenotypic continuum reflecting a shared interactive set of diathesis, psychosocial and sociocultural factors.

Currently, few studies have evaluated SLEs in these sample types and there is a need to obtain more in depth information on the influence of SLEs in these populations in which genetics and stress play a relevant role.

1. Introduction

This introduction is organised in four subsections. The first is a review of the stress-vulnerability model of schizophrenia. This is the framework of this thesis focused on first-episode psychosis (FEP) and stressful life events (SLEs). The second subsection involves the clinical staging model, which has shown to be useful to establish early subclinical phenomena which, in this thesis, is focused on the clinical stage of FEP. The third section describes FEP including the definition, clinical characteristics and risk factors. Finally, the last subsection describes the dimensions of SLEs with their definition and classification, life cycle (adolescence, stage of change), clinical variables (age at onset of FEP, gender differences, family history and psychotic symptomatology), SLE questionnaires, and SLEs in the population with FEP.

1.1 The stress-vulnerability model of schizophrenia

The stress-vulnerability model (Zubin & Spring, 1977) is one in which the interaction between vulnerability (diathesis), coping ability and stressors determines whether a decline in normal functioning will occur. Psychiatric disorders are consistent with this model, and non-specific environmental factors such as childhood trauma, urbanity, and migration have been implicated. These factors dysregulate the biological pathways involved in response to stress. The stress-vulnerability model postulates the presence of a specific vulnerability which is defined as a basic susceptibility, dimensional feature, that is relatively permanent and lasting and can be precipitated by different environmental factors (see Figure 1).

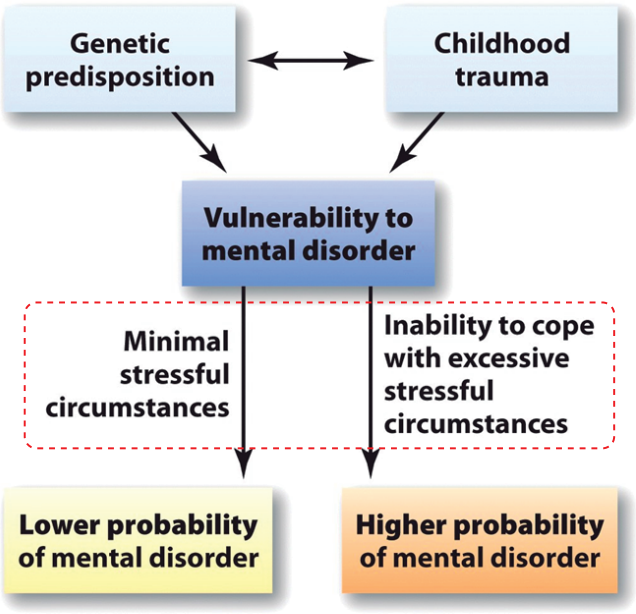

Figure 1. The stress-vulnerability model. [Source: Modified from Norton & Kobusingye, 2013].

Stress and vulnerability are determined early in life by a combination of factors, including genetics, prenatal nutrition and stress, birth complications, and early experiences in childhood (e.g., abuse or the loss of a parent). These factors make up the vulnerability of developing a mental disorder. SLEs are important in the precipitation of disease. On one hand, in patients with few SLEs the probability of developing disease is low while, on the other hand, patients with many SLEs, and therefore an inability to cope with stressful situations, have a higher probability of developing a disease. This is the basic idea; however, other factors are relevant in this process such as coping skills and the resilience of the individual, thereby demonstrating the great variability of these complex models.

According to the stress-vulnerability model in psychosis, stress interacts with pre-existing vulnerability to prodrome triggers and exacerbates the psychosis to the level of a full-blown onset. Stress is defined as any event that challenges a person to adapt and can be induced by internal factors such as maturational changes, toxic substances, infection and physical responses and external factors including bereavement, job promotion, marriage, and daily hassles. It has been hypothesised that additive, or possibly interactive, effects of pre-existing vulnerabilities and external environmental stressors characterise the prodrome (Nuechterlein & Dawson, 1984).

From an evolutionary perspective, when stressors are prolonged by either the stability of a social framework or the recurrence of stressful psychological events, stress response is no longer useful from a physical point of view, and consequently, undesirable effects are produced by the organism. Thus, there is a complex interrelationship between biology and emotions, different forms of personality, feelings and thoughts that can reflect and influence the individual. In addition, vulnerability evolves epigenetically through individual actions and the environment along life, having an important impact from conception to adolescence. In these vital stages, protective and pathogenic factors may appear, such as social support or SLEs that may become relevant to how an individual adapts (Brody, 1981). Indeed, stress is affected by our coping skills, social support, and involvement in meaningful activities.

Currently, advances in affective and social neuroscience have shown how exposure to environmental factors has an impact on the structure and function of the brain, being thus, active agents in the formation of an individual's level of vulnerability.

The stress-vulnerability model is useful to form the framework of this thesis in order to understand the complex interactions between environment, stress and latent sensitivity in the expression of psychotic illness. Environmental and genetic factors contribute and interact amongst themselves in several complex ways to produce vulnerability to phenotypic variance and the risk of developing a disorder (Shah, Tandon, & Keshavan, 2013; van Os, Kenis, & Rutten, 2010; van Os, Krabbendam, Myin-Germeys, & Delespaul, 2005).

Concretely, in the stress-vulnerability model of schizophrenia, vulnerability and FEP are seen as a state-trait, while psychotic symptoms are considered to be provoked by life events or a situation of prolonged stress. However, these symptoms can also be resolved spontaneously without leading to psychosis (Yung & McGorry, 1996). SLEs can be treated as prodromal events, which together with other events, contribute to the appearance of later psychotic symptomatology. Indeed, it is likely that the diversity of environmental factors associated with schizophrenia may be linked to an equal number of different underlying mechanisms. Myin-Germeys et al. (2005) propose that sensitisation in relation to environmental stress can be interpreted according to the hypothesis of dopaminic sensitisation of psychotic symptoms, that is, the hyperresponsiveness of dopaminic neurons to environmental stimuli.

Collip et al. (2007) suggest that in the interaction of epigenetic factors, environmental exposure can induce psychological and/or physiological alterations and, therefore, sensitisation. As a result, environmental exposure facilitates the onset and persistence of psychotic symptoms. On the other hand, Mason et al. (2004) investigated whether knowledge of the family history, obstetric complications, social premorbid functioning, premorbid personality, more recent SLEs, and current symptoms improves the prediction of psychosis in a group of high-risk youths. This study found that half of the participants developed a psychotic disorder and concluded that the most reliable predictor was the presence of schizotypal personality traits. However, the influence of SLEs did not have a significant impact on the development of psychosis. Other studies have highlighted the presence of information processing deficits, anomalies in autonomic reactivity, social competence and coping limitations as potential vulnerability factors in the development of FEP (Nuechterlein & Dawson, 1984). There is also evidence that cumulative stressors increase emotional reactivity in patients with schizophrenia, increasing their vulnerability (Brenner, Böker, Müller, Spichtig, & Würgler, 1987; Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001; Myin-Germeys et al., 2005). Consequently, there is an increased sensitivity in the degree of perception of the sensory and social stimuli (Horan et al., 2005).

Norman and Malla (1993) included 3 types of studies in a review on the relationship between stressors and patients with schizophrenia. The first type of study compared subjects with schizophrenia and other psychiatric patients (e.g., major depression, and anxiety).

They found that 56% of the studies analysed described higher levels of stressors in other psychiatric patients than in those with schizophrenia. The second type of study compared patients with schizophrenia and individuals from the general population and showed that 36% of the studies presented higher levels of stressful events in subjects with schizophrenia than in the general population.

Finally, the third type of study reviewed was related to the time of SLE occurrence and the worsening of symptoms. It was observed that 77% of the studies described high levels of SLEs that were associated with the onset of worsening symptoms. Along this line, one study compared patients with episodes provoked by SLEs with those in whom relapses were not preceded by such events (van Os et al., 1994). At the 3-year follow-up, the first patients received less antipsychotic medication and spent more time in remission, being consistent with the stress-vulnerability model in which patients with less intrinsic vulnerability (requiring less medication and showing better remission of symptoms) require SLEs to trigger a relapse.

In summary, the stress-vulnerability model assumes that the probability of developing a disease depends on the magnitude of biological vulnerability and the influence of the stress that the individual has to face.

Most recent publications have described one more step in the stress-vulnerability model, that is, the updated neural diathesis-stress model (Walker, Mittal, & Tessner, 2008), which is focused on stress neurobiology, including the role of stress and the hypothalamic-pituitary-adrenal (HPA) axis in mental disorders.

Currently the neural diathesis-stress model of schizophrenia has been revisited, considering the complex interplay of vulnerability factors, neurobiological processes and psychosis progression (Pruessner et al., 2017) as shown in Figure 2.

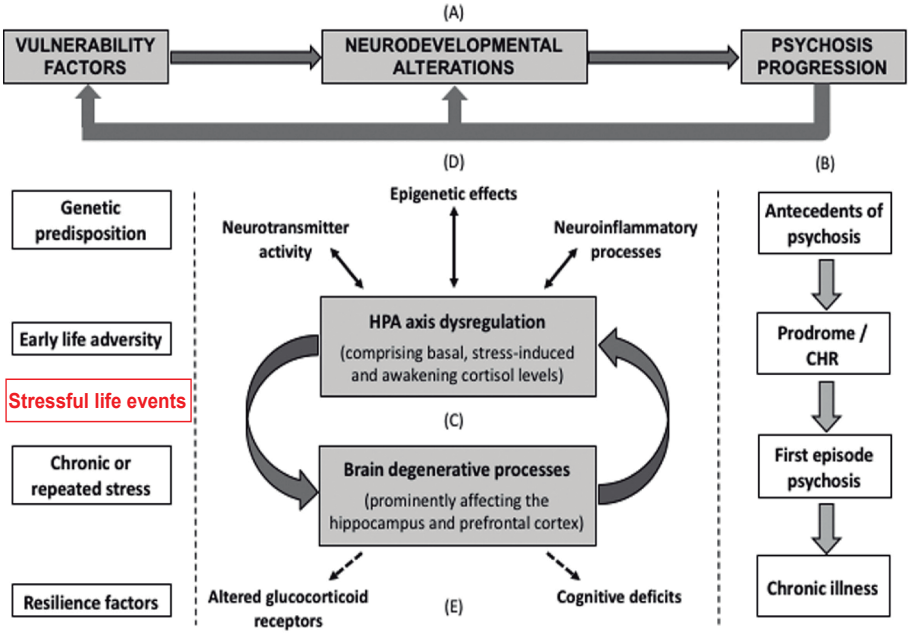

Figure 2. The extended neural diathesis-stress model of schizophrenia. [Source: Modified from Pruessner et al., 2017].

Note: (A) Rightward arrows indicate the contribution of vulnerability factors to neurodevelopmental alterations that predispose the individual to maladaptive responses to later stressors, eventually increasing the risk for psychosis onset. Leftward arrows from psychosis progression illustrate the potential for prodromal/psychotic symptoms to both aggravate the cascade of neurobiological disturbances and further enhance vulnerability. (B) Downward arrows indicate the progression of psychosis from early antecedents to chronic illness. (C) Curved arrows depict the bidirectional cause and effect relationship between HPA axis alterations and degenerative brain processes. (D) Two-way arrows emphasize the complex interactions between the HPA axis and other biological systems. (E) Dashed arrows demonstrate the downstream effects of brain degenerative processes. HPA: hypothalamus-pituitary-adrenal axis; CHR: clinical high risk.

In addition to the stress-vulnerability model, the complex aetiology and heterogeneous clinical manifestations of psychosis make it necessary to focus on clinical staging model and early intervention. This promotes rapid access to care and comprehensive treatment in the initial stages of the disorder, and allows analysis of the role of the relevant psychological mechanisms involved in the real-life expression of psychotic symptoms in individuals with FEP.

1.2. Clinical staging model

In clinical practice, the stress-vulnerability model is used to provide a framework for determining and assessing the factors which have an impact on individuals and facilitate successful intervention. Along this line, the clinical staging model is a flexible system which includes the genetic-environmental interactions involved in the onset and course of psychiatric illness (Insel, 2010). It has shown to be useful for differentiating between early subclinical phenomena and the characteristics observed in patients with a severe clinical disease and chronicity (McGorry, Nelson, Goldstone, & Yung, 2010).

The objective of the clinical staging model is based on the assumption that the longitudinal course of a disease is likely to progress from an at-risk to a prodromal status, and finally to a fully developed disease. The disease progresses through different stages that are characterised by phase-specific clinical manifestations. This model aims to prevent progression to more advanced stages or to promote regression to an earlier stage.

Thus, each stage of the disease and disease progression must be characterised in order to develop preventive interventions. Early detection and prospective evaluation of individuals at-risk for psychotic disorders allows the possible prevention or minimisation of the emergence and course of psychosis (Cannon, Cornblatt, & McGorry, 2007).

From a therapeutic point of view, considering psychotic phenomena as a point of continuum is useful for achieving a strategy based on the risk of continuity and is crucial for identifying targets for future interventions (Cornblatt et al., 2003) and minimising disease chronicity and mortality associated with psychosis (McGorry, Yung, Pantelis, & Hickie, 2009).

Currently, there is no clear consensus regarding the criteria for defining the threshold of onset of a psychotic episode (Yung, Nelson, Thompson, & Wood, 2010). The different stages are defined in relation to the psychopathology and psychosocial functioning of the patients. Table 1 shows the stages from the early phases of psychosis to the development of persistent frank symptoms.

It has been suggested that early and effective management during the critical early years of schizophrenia can improve the long-term outcome of these patients. Early intervention is recommended in cases in which (Mrazek, 1998): i) there is an effective and available 'mechanism' (screening or assessment tools) to detect an illness in an early phase; ii) early intervention will have a positive impact on health outcomes; iii) effective treatment for the illness is available; and iv) effective treatment can be accessed early.

Table 1. Clinical staging model for psychotic and severe mood disorders.

Clinical stage	Definition	Target populations for recruitment	Indicative biological and endophenotypic markers
0	Increased risk of psychotic or severe mood disorder Currently no symptom	First-degree relatives of probands (especially aged 12 to 25 years)	Trait marker candidates and endophenotypes, e.g. Smooth Pursuit Eye Movements, P 50, Niacin sensitivity, Binocular rivalry, Prepulse Inhibition, Mismatch Negativity, Olfactory deficits, etc.
1a	Mild or non-specific symptoms, including neurocognitive deficits of psychosis or severe mood disorder. Mild functional change or decline	Screening of teenage and emerging adult populations; referral by primary care physicians, school counsellors, and self-and family referrals	Trait and state candidates according to sample size.
1b	Ultra high risk (UHR): moderate but subthreshold symptoms, with moderate neurocognitive changes and functional decline (GAF < 70)	Referral by educational agencies, primary care physicians, emergency departments, welfare agencies, drug and alcohol agencies, police and forensic services, and self- and family referrals	Niacin sensitivity, folate status, MRI and MRS changes, HPA axis dysregulation
2	First-episode psychosis (FEP) or severe mood disorder Full threshold disorder with moderate-severe symptoms, neurocognitive deficits and functional decline (GAF 30–50)	Referral by primary care physicians, emergency departments, welfare agencies, specialist care agencies, drug and alcohol services, police and forensic services, and self- and family referrals	Continue with markers of illness state, trait and progression

Note: This table has been reproduced in a modified form. It was originally published in McGorry et al. (2006).

It has been described that early intervention in psychotic disorders has the potential to produce better outcomes during the critical developmental phase of adolescence or early adulthood (Birchwood, McGorry, & Jackson, 1997). To achieve appropriate and effective early intervention in psychotic disorders, further studies are needed to identify early markers of psychotic illness and characterise the early phases of psychotic disorders. This work focuses on the clinical stage of FEP, which is described more in depth in the next section.

1.3. First-episode psychosis

1.3.1. Definition

The development of psychotic symptoms marks the onset of FEP. This stage may be present for a lengthy period of time, but it is only formally addressed when medical attention is sought. The definition of FEP is difficult, since the patients are not homogeneous in terms of clinical presentation, onset and context. FEP is a clinical and research term often used to identify and emphasise special issues which arise when working with this specific population. Operational definitions for FEP fall into three categories (Breitborde, Srihari, & Woods, 2009): i) first treatment contact, ii) duration of antipsychotic medication use, and iii) duration of psychosis. According to this definition, individuals presenting with psychosis in the clinical setting, who have never previously presented with psychosis within the clinical setting, are identified as experiencing their 'first-episode' (Breitborde et al., 2009).

In short, there is no consensus as to the operational definition of individuals with FEP and diagnostic approaches, (e.g., DSM-V; American Psychiatric Association, 2013), with little guidance related to the characterisation of FEP being available. Table 2 presents the current diagnostic criteria for schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V; American Psychiatric Association, 2013). The definition of FEP is only included under 'course specifiers' as 'First episode, currently in an acute episode': First manifestation of the disorder meeting the

defined diagnostic symptoms and time criteria. An “acute episode” is a period in which the symptom criteria are fulfilled.

Table 2. Diagnostic criteria for schizophrenia according to The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

A. Two or more of the following, each present for a significant portion of time during a one-month period, or less if successfully treated. At least one of these must be 1, 2 or 3:

1. Delusions
2. Hallucinations
3. Disorganised speech, e.g. frequent derailment or incoherence
4. Grossly disorganised or catatonic behaviour
5. Negative symptoms, i.e. diminished emotional expression or avolition.

B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas (such as work, interpersonal relations or self-care) is markedly below the level achieved prior to the onset (or when the onset occurs in childhood or adolescence, there is failure to achieve the expected level of interpersonal, academic or occupational functioning).

C. Continuous signs of the disturbance persist for at least six months. This six-month period must include at least one month of symptoms, or less if successfully treated, which meet criterion A (i.e. active-phase symptoms), and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of disturbance may manifest through only negative symptoms, or by two or more symptoms listed in Criterion A which are present in an attenuated form, e.g. odd beliefs and unusual perceptual experiences.

D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either:

1. No major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or
2. If mood episodes have occurred during the active-phase symptoms, they have been present for the minority of the total duration of the active and residual periods of the illness.

E. The disturbance is not attributable to the physiological effects of a substance, e.g. a drug of abuse or a medication, or another medical condition.

F. If there is a history of an autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least one month, or less if successfully treated.

The following course specifiers are only to be used after a one-year duration of the disorder, and if they are not in contradiction to the diagnostic course criteria. Specify if:

- *First episode, currently in an acute episode:* First manifestation of the disorder meeting the defining diagnostic symptoms and time criteria. An “acute episode” is a period in which the symptom criteria are fulfilled
- *First episode, currently in partial remission: “Partial remission”* is a period during which an improvement after a previous episode is maintained, and in which the defining criteria of the disorder are only partially fulfilled
- *First episode, currently in full remission:* “Full remission” is a period after a previous episode, during which no disorder-specific symptoms are present
- *Multiple episodes, currently in an acute episode:* “Multiple episodes” may be determined after a minimum of two episodes, i.e. after a first episode, a remission, and a minimum of one relapse
- *Multiple episodes, currently in partial remission*
- *Multiple episodes, currently in full remission*
- *Continuous:* Symptoms fulfilling the diagnostic symptom criteria of the disorder remain for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course
- *Unspecified*

Specify if with catatonia

The following course specifiers are only to be used after a one-year duration of the disorder, and if they are not in contradiction to the diagnostic course criteria. Specify if:

- *First episode, currently in an acute episode:* First manifestation of the disorder meeting the defining diagnostic symptoms and time criteria. An "acute episode" is a period in which the symptom criteria are fulfilled
- *First episode, currently in partial remission: "Partial remission"* is a period during which an improvement after a previous episode is maintained, and in which the defining criteria of the disorder are only partially fulfilled
- *First episode, currently in full remission:* "Full remission" is a period after a previous episode, during which no disorder-specific symptoms are present
- *Multiple episodes, currently in an acute episode:* "Multiple episodes" may be determined after a minimum of two episodes, i.e. after a first episode, a remission, and a minimum of one relapse
- *Multiple episodes, currently in partial remission*
- *Multiple episodes, currently in full remission*
- *Continuous:* Symptoms fulfilling the diagnostic symptom criteria of the disorder remain for the majority of the illness course, with subthreshold symptom periods being very brief relative to the overall course
- *Unspecified*

Specify if with catatonia

Specify current severity: Severity is rated according to a quantitative assessment of the primary symptoms of psychosis, including delusions, hallucinations, disorganised speech, abnormal psychomotor behaviour and negative symptoms. Each of these symptoms is rated for its current severity (most severe in the last seven days) on a 5-point scale ranging from 0 (not present) to 4 (present and severe).

Note: A diagnosis of schizophrenia can be made without using this severity specifier

1.3.2. Clinical characteristics

Social isolation (Tan, Gould, Combes, & Lehmann, 2014), psychotic symptoms (Velthorst et al., 2013) and functional impairment (Tarbox et al., 2014; Velthorst & de Haan, 2014) may already be present some time before the patient contacts mental health services (prodromal/ premorbid phase). Patients may also present with aggressive and violent or suicidal behaviour (Bakst, Rabinowitz, & Bromet, 2010).

The clinical characteristics of FEP can include hallucinations, delusions and disorganised thinking and behaviour, as well as psychomotor abnormalities (DSM-V; American Psychiatric Association, 2013).

Increasingly negative (Lin et al., 2013; Mahmoodi-Gharaei et al., 2010; Zimmermann et al., 2010) and cognitive symptoms (Chang et al., 2013; MacBeth et al., 2014; Riecher-Rössler et al., 2013) may also be present in this stage.

FEP patients are often distressed by changes in their social patterns and psychotic symptoms (McGlashan & Johannessen, 1996; Wigman et al., 2011). For example, hallucinations and delusions can cause considerable distress and anxiety, mixed with feelings of hopelessness, shame, entrapment and a feeling of being out of control (McGorry, Killackey, & Yung, 2007).

1.3.3. Risk factors

Systematic reviews of epidemiological studies have indicated that the incidence of schizophrenia and related disorders is affected by genetic and environmental factors (March et al., 2008; McGrath, Saha, Chant, & Welham, 2008).

Genetic studies estimate the heritability of schizophrenia to be of approximately 66-83% (Cardno et al., 1999). For instance, studies in twins have suggested that the syndrome has heritability estimates of around 80% (van Os & Kapur, 2009). This high heritability is not only due to the influence of genetic alterations but also environmental effects.

The environmental risk factors linked to a higher likelihood of developing schizophrenia (Khamker, 2015) include: i) history of obstetric and perinatal complications, ii) childhood trauma and abuse, iii) living in a densely populated urban environment, iv) social adversity, and v) cannabis use.

In relation to the first factors, prospective studies have shown that some factors related to the history of obstetric and perinatal complications, such as winter births, as well as older paternal age at conception might account for a small proportion of the incidence of schizophrenia (Brown, 2006; Brown & Susser, 2008; Cannon, Jones, & Murray, 2002; Khashan et al., 2008). With regard to the second factors, childhood trauma and abuse, and parental separation or death during childhood or adolescence (Shah et al., 2013) may be important to consider in this period of vulnerability. During this time in an individual's life, SLEs should also be taken into account as predisposing and mediating factors which may potentially affect the development of mental disorders. Other important risk factor which may increase the risk of the development of schizophrenia in adolescents and young adults is living in a densely populated urban environment. It has been estimated that there is a 30% greater risk of developing schizophrenia among individuals living in an urban environment (Dragt et al., 2012; Krabbendam & van Os, 2005), and social adversity, discrimination or cultural isolation may also have an impact (Boydell et al., 2001; Cantor-Graae & Selten, 2005; Veling et al., 2008; Velthorst et al., 2010).

The last environmental risk factor is substance use, concretely cannabis use during early adolescence (Compton, Broussard, Ramsay, & Stewart, 2011; D'Souza et al., 2005; Henquet et al., 2006; Moore et al., 2007; Sevy et al., 2010). Indeed, between 20% and 60% of patients have a substance use disorder at some stage of the illness (Khamker, 2015).

1.4. Stressful life events

1.4.1. Definition and classification

Among others, SLEs are predisposing and intervening factors which may affect the development of mental disorders. Several studies have evaluated the role of SLEs, but most of these studies include these events as trauma, which makes their research and evaluation more difficult and complicated.

Specifically, at some point in life any event can become stressful, depending on the type of circumstance and how the subject responds or confronts this circumstance (Beards et al., 2013; Tessner, Mittal, & Walker, 2011). Stress is based on the person's evaluation of the disturbance, and without this evaluation, psychological stress would not exist, regardless of the degree of actual danger to the organism (Lazarus, 1993). Initially, stress depends on the quality of the environment and the evaluation of the resources to address the situation. During the course of the stressful episode, individuals continually judge the degree to which their coping efforts are successful.

In the evaluation of the disturbance it must be taken into account whether it is indeed a SLE or not. In addition, these events and the level of social stress are considered factors that interact as characteristics of vulnerability in the development of a psychotic episode (Nuechterlein & Dawson, 1984).

The potentiality of an event is related to the perception of the event and the individual characteristics that determine the degree of vulnerability, that is, the coping strategies available and the contextual cues in which the person is immersed (Canalda and Carbonés, 2005). Therefore, it is important to make qualitative approaches to SLEs, analysing not only their presence or number, but also the type of circumstance and the emotional impact on the individual.

The concept of a life event is complex. It implies that not only psychiatric illnesses are initiated by interactions between the environment and the individual, but also that SLEs may modify this interaction. Cornes (1994) defined SLEs as events that directly or indirectly and subjectively and/or objectively affect individuals and threaten to break their normal daily activities and coping resources.

Understanding how individuals respond to positive and negative environmental influences is important to determine resilience processes and obtain complete characterisation of the aetiology of psychosis. In this regard, stress is often associated with negative events, but positive events and experiences may be stressful as well.

For example, performing well in school, getting a new job, starting a new relationship, or having a baby, all involve some degree of stress. Effective coping enables people to be engaged in interesting, rewarding activities that may involve stress. Coping efforts can make it possible for someone with co-occurring disorders to live a normal life without suffering the negative effects of stress. In general, SLEs can be classified in different ways, but the most common distinction is to differentiate between positive and negative, understanding that their perception depends on the interrelationship of the subject's personal (age, gender, temperament, etc.) and environmental factors (family, school, social support, etc.).

Most studies are on negative SLEs and are related to increased emotional disturbance in children and adolescents since these are stages (especially adolescence) in which many biological, school, social, and family changes take place. Thus, adolescence can be considered a stage of vulnerability (Finlay-Jones & Brown, 1981; Goodyer, Kolvin, & Gatzanis, 1985).

1.4.2. Life cycle: adolescence, stage of change

Several studies have investigated the relationship between the presence of SLEs and age, seeking the stage of life with the highest number of SLEs and the type of SLEs that most frequently occur based on age. Several studies have reported that SLEs increase in older people (Moreno, del Barrio, & Mestre, 1995). However, although Larson and Ham (1993) found the same results for negative SLEs, this was not the case for positive SLEs which were less frequent with age.

These results indicate that other variables are involved in the increase of SLEs over time in addition to age. Other studies have focused on the analysis of the type of SLEs according to age and the need for the events to take place for optimum maturation development. Figure 3 shows an example of a lifeline according to typical SLEs.

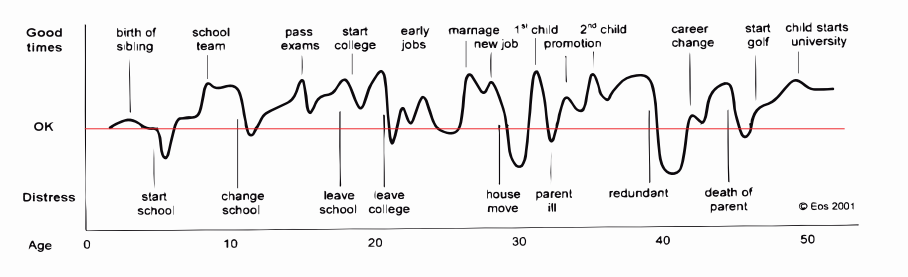

Figure 3. Example of a self-reported lifeline chart of well-being according to typical life events. [Source: Modified from Williams, 1999].

Apart from normative SLEs which take place throughout the life cycle, many SLEs such as family disputes, parental divorce, the death or hospitalisation of a parent may not occur in all children, and these may generate as much or more stress. Nonetheless, the level of involvement of these SLEs and the probability of their occurrence and the development of psychopathological alterations vary according to the age and resources available to each subject. In addition, a life event occurring during an evolutionary stage will not have the same effect on an individual as one which takes place at a later stage of development, thereby making it necessary to evaluate the consequences that SLEs have based on the period of development of the individual.

Adolescence and early adulthood are stages with great changes at the family, social and biological level. Thus, the changing nature of this evolutionary period is important, with maturational development processes playing an important role. During this period sick people do not usually ask for help, or if they do, they are often not properly diagnosed. In addition, a delay in the identification and initiation of appropriate treatment may facilitate the progression of more deteriorating and chronic forms of the disease (Norman & Malla, 2001). Consequently, there is a need to implement strategies that guarantee the identification of psychosis and treatment in the earliest phase, as well as to achieve early control of the suffering that the disease produces to the patient and the key figures within their environment. Adolescence is a vital stage that is characterised by profound transitions. The appearance of numerous and intense changes define this as a stage at which individuals are especially vulnerable to the perception of psychosocial stress. Studies performed in healthy populations indicate that there is a considerable increase in the frequency of SLEs during adolescence (Ge, Lorenz, Conger, Elder, & Simons, 1994). The results available show that the most important SLEs in adolescence are non-normative events, that is, events that are less frequent. According to a review of non-normative events (Jiménez, Menéndez, & Hidalgo, 2008), the death of a parent, divorce of the parents, entry into prison of a family member, pregnancy and parental unemployment were of note among events perceived as SLEs. Among the normative events frequently experienced during adolescence (e.g., preoccupation, social difficulties and daily hassles), those related to the family and peer group are the most common.

With regard to the context of development, the school environment is of note. Lemos (1989) described that individuals likely to develop a psychotic spectrum had presented disturbing behaviours in school. In short, adolescents who later develop a psychological problem of the psychotic type usually exhibit a series of emotional, behavioural, thought and language changes, as well as alterations in personality and social relations before the clinical onset of the disorder (Keshavan, Diwadkar, Montrose, Rajarethinam, & Sweeney, 2005; Yung et al., 2006). In addition to adolescence, it is also important to consider adulthood (Beards et al., 2013) since despite not being a key stage in the onset of FEP, other types of SLEs such as house moving or parental illness may play an important role in the development of psychosis during adulthood. However, few studies on SLEs during adulthood have been performed.

The premorbid adjustment of subjects with FEP, that is the degree of relational, cognitive and behavioural maturity before the onset of the episode, is directly involved in aspects that precede and belong to the disorder such as course, response to treatment and current symptoms (Johnstone, Macmillan, Frith, Benn, & Crow, 1990). In this regard, premorbid adjustment in all psychoses has a potential affect on patient outcome, with altered behaviours in the school and social environment being observed years before the onset of FEP. Thus, a relational deficit is related to the vulnerability of the subject (Stanghellini, 2000).

1.4.3. Clinical variables

1.4.3.1. Age at the onset of first-episode psychosis

Several studies have shown that subjects likely to develop the psychotic spectrum present disturbing behaviours in school, including inappropriate behaviour in class, disciplinary problems, rejection by others, preoccupation, and incapacity to accept criticism (Lemos, 1989). In this sense, the most influential SLEs in adolescence are those related to the academic context and peers (Jiménez et al., 2008). During adolescence there is sensitivity to coping with certain difficulties, the appearance of numerous and intense changes and the new roles expected of them. Overall, data available on the age of FEP onset point to an increase in the frequency of SLEs during early and middle adolescence. However, no studies have correlated the age of onset of FEP with SLEs.

1.4.3.2. Gender differences

The relationship between evaluation and coping with SLEs and gender differences is controversial. In general, there are differences between men and women in the management of the accumulation of stressors. The most recent studies indicate that both genders experience a similar number of difficulties (e.g., SLEs) in their lives (Jiménez et al., 2008; Oliva, Jiménez, Parra, & Sánchez-Queija, 2008). However, the results regarding the emotional impact caused by these events are less conclusive.

In the general population, some studies have not found significant differences in the perception of SLEs between men and women (Kim, Conger, Elder, & Lorenz, 2003; Oliva et al., 2008). However, other authors have confirmed these differences, indicating that women often feel more emotionally affected by the presence of SLEs than men. Women are more likely to experience problems of internalisation, depression and anxiety than men during adolescence, regardless of the country and culture (Abad, Forns, Amador, & Martorell, 2000; Lemos, Vallejo, & Sandoval, 2002). In a study including a FEP population, Pedrós and Tenías (2006) reported that the factor most related to the development of a FEP in women is stress, being drug consumption in men.

In general, studies on gender and SLEs have shown that in relation to masculine gender school is the most frequent area in which disruptive behaviours predominate (Bruyn et al., 2003; Martin and Velarde, 2001). In another study on the relationship between SLEs and schizophrenia (without differentiating between men and women), economic difficulties were found to have a significant influence on the development of FEP (Casado and Vaz, 1998). This review of the gender differences and SLEs in the FEP population demonstrates the need for studies on these variables. Indeed, analysis of the role of gender differences in SLEs can help in the development of future interventions related to gender in the FEP population.

1.4.3.3. Family history and psychotic symptomatology

Regarding family history, one study has shown that approximately 60% of patients with schizophrenia do not have a family history of schizophrenia (Gottesman & Erlenmeyer-Kimling, 2001). In relation to the psychotic symptomatology and SLEs, negative symptoms are a prognostic indicator of poor social and work functioning, as well as a lower quality of life (Fuller, 2002). Clinically, some studies have reported the presence of non-specific prodromal symptoms and primary negative symptoms from 7 and 5 years, respectively, before the onset of clinical manifestations (Häfner, 1995). It is of note that some studies have analysed the relation between family history and psychotic symptomatology in schizophrenia, yet no studies have been carried out in the FEP population.

1.4.4. Questionnaires on stressful life events

Several questionnaires are available on SLEs in depression and anxiety, but there are few on psychosis. In a meta-analysis of life events and psychosis, Beards and colleagues (2013) suggested that differences in life event measurements may account for some of the variations in the findings.

Instruments to assess life events generally fall into two categories: check-lists (Jenkins, Mbatia, Singleton, & White, 2010; Johns et al., 2004; van Nierop et al., 2012) and semi-structured interviews (Al Khani, Bebbington, Watson, & House, 1986; Bebbington et al., 1993; Brown & Birley, 1968; Canton & Fraccon, 1985; Chakraborty, Chatterjee, Choudhary, & Singh, 2007; Day et al., 1987; Dohrenwend et al., 1987; Faravelli, Catena, Scarpato, & Ricca, 2007; Lataster, Myin-Germeys, Lieb, Wittchen, & van Os, 2012; Raune, Kuipers, & Bebbington, 2009). These two categories of instruments present some advantages and disadvantages in the analysis of SLEs. The advantages of interviews are: (1) the questions are structured and asked in a way in which the respondent's answers can be easily categorized, and (2) the interviewer can ensure that the questions are fully understood. In contrast, the disadvantages are: (1) high costs in researcher and participant time as well as in researcher training, (2) the interviewer must adhere to the agreed questions, and (3) they are time consuming. The advantages of checklists are: (1) they are inexpensive, (2) they are easy to administer, and (3) there is good test-retest reliability for the total scores (e.g., Goodman, Corcoran, Turner, Yuan, & Green, 1998; Wittchen, Essau, Hecht, Teder, & Pfister, 1989). The disadvantages of checklists are: (1) they have a small/ modest degree of explained variance according to the relationships of the events with psychopathology and point to other variables, such as social support (Paykel, 2001; Rabkin & Struening, 1976; Sarason, Sarason, Potter, & Antoni, 1985), and (2) the reliability and validity of the traditional inventories are not optimal (Dohrenwend, 2006).

The lack of SLE evaluation instruments available in Spanish is of note. Fernández-Ballesteros, et al. (1987) adapted an SLE questionnaire for adults to Spanish called the PERI-Modified scale (Dohrenwend et al., 1978), and there is a SLE scale for children (6 to 11 years) and adolescents (12 to 18 years). On the other hand, there is a scale that evaluates the development of SLEs during life, albeit related to general health, called the SLE scale (Roohafza et al., 2011). The most recent scales of life events are based on the evaluation of the subjective meaning of psychosis (Bock et al., 2010; Klapheck et al., 2012), and most are focused on the year before FEP. However, there are no instruments for evaluating SLEs along the life cycle.

1.4.5. Stressful life events and first-episode psychosis

Several studies have described the association between SLEs and psychological alterations (Day et al., 1987; Lukoff, Snyder, Ventura, & Nuechterlein, 1984): i) depressive symptoms in adults (Hammen, 2005) and adolescents (Kashani, Vaidya, Soltys, Dandoy, & Reid, 1990; Mghir, Freed, Raskin, & Katon, 1995; Olsson, Nordström, Arinell, & von Knorring, 1999), and ii) symptomatology of anxiety, which show higher levels in the presence of both positive and negative SLEs, although the increase is greater in the presence of the latter (Gothelf, Aharonovsky, Horesh, Carty, & Apter, 2004). However, there are few studies on the relationship between SLEs and FEP.

Research examining the relationship between SLEs and the onset of FEP can be divided into two main groups. The first group of studies consists of those which have found a significant increase in independent SLEs. These events are not influenced or caused by the behaviour of the individuals themselves (e.g., the death of a loved one). Some studies on the aetiology of FEP have shown a higher incidence of SLEs of varying severity over the 3-week interval prior to FEP presentation (Al Khani et al., 1986; Lukoff et al., 1984). In addition, Jones et al. (1993) reported a significant relationship between SLEs and the onset of a psychotic episode. Along the same line, van Os et al. (1994) showed that 51% of patients with FEP had experienced a SLE in the 3 months prior to the onset of FEP. Similarly, in a sample of 41 FEP patients, Raune et al. (2009) found that SLEs were more common in the 3 months before FEP onset compared to the previous 9 months. Likewise, Rusaka and Rancāns (2014) concluded that 44% of patients with acute psychotic disorder had experienced SLEs in the 6 months prior to FEP, while Leff and Vaughn (1980) reported the absence of a relationship between SLEs and the emergence of a FEP.

The second group of studies includes those describing an increase in the number of SLEs before the onset of FEP. From a quantitative point of view, the accumulation of stressors poses a greater threat to adjustment. Cullberg (2003) concluded that a stressful situation cannot be considered a cause of psychosis, but rather a factor of impulse. Canton and Fraccon (1985) showed that subjects with schizophrenia had more SLEs than healthy controls in the areas of work, health, and social/family relationships.

Likewise, patients with schizophrenia experienced more negative, moderate and severe events than healthy controls. However, the occurrence of SLEs is not independent of the influence of the individual's behaviour. Non-independent life events, such as being fired from a job, a divorce or an examination, may reflect the prodromal period of illness or an ongoing psychotic process. Zubin and Spring (1977) identified the processes by which subjects with schizophrenia often have an excess of SLEs called a vital tendency to stress patterns. This predisposition increases the level of stress and influences the time and probability of disease onset (Rabkin, 1980). In relation to the individual perception of tension and symptomatology in patients with FEP, Renwick et al. (2009) indicated that subjects with more depressive symptoms showed higher levels of perceived stress.

Extraordinary or traumatic life events are part of the continuum in psychosis. Bechdolf et al. (2010) noted that subjects at ultra high risk of developing psychosis have a highly predictive history of trauma. Therefore, traumatic experiences lead to greater sensitivity to stress, and this may contribute to the development of FEP under stressful circumstances (Casado and Vaz, 1998; Pruessner et al., 2011). These changes are considered to be more stressful than those related to family or personal situations, such as those related to academic, love and marriage, residence, legal affairs and social activities.

In summary, extensive research has shown a potential relationship between the incidence of psychosis and psychosocial stress exposure (Shah et al., 2015; Tessner, Mittal, & Walker, 2011; Walker & Diforio, 1997): adverse exposures such as traumatic life events (van Os et al., 2010; Wiles et al., 2006), daily hassles (Myin-Germeys et al., 2001; Myin-Germeys & van Os, 2007), or SLEs (Bebbington et al., 2004; Lataster et al., 2012; Morrison et al., 2003) in childhood and adolescence during the weeks preceding a psychotic episode (Raballo et al., 2014; Woodberry et al., 2014). It has been recognized that SLEs are a potent source of distress. The SLE concept fits well within the stress-vulnerability model of schizophrenia and psychosis, and further supports the suggestion that ongoing stressors may play a role in the onset of psychotic disorders. Particularly, SLEs are a source of environmental exposure that has been used in the literature to identify situations or occurrences that bring about a positive or negative change in personal circumstances and/or involve an element of threat (Beards et al., 2013). Some studies have assessed contextual elements of SLEs (Bebbington et al., 1993). For instance, certain types of SLEs, such as dependent and independent events, are associated with the onset of schizophrenia (Brown & Birley, 1968).

Despite the evidence related to the role of major life events and childhood trauma in the development of FEP (Varese et al., 2012; Morgan & Fisher, 2007), there are few studies on environmental exposure to SLEs and how SLEs might influence the onset of a psychotic disorder.

The stress-vulnerability model is the contextual framework of this thesis. This model was used to understand the complex interaction between environment, stress and latent sensitivity in the expression of psychotic illness. Moreover, the clinical staging model and early intervention are related to the psychological mechanisms involved in the expression of psychotic symptoms in FEP individuals.

This thesis was aimed at achieving adequate and effective early intervention in psychotic disorders since: i) in general, few studies have specifically evaluated SLEs; ii) no studies have analysed the age of onset of FEP in relation to SLEs; iii) there are no studies about gender differences, family history and psychotic symptomatology in relation to SLEs; and iv) no instruments are available to assess SLEs along the life cycle.

All of the above is relevant for designing and developing aetiological models of symptom formation and may assist in the development of prophylactic interventions. Hence, the identification of risk and providing early intervention in the early stages of human development are essential in order to follow a normal trajectory of development (Liu, Keshavan, Tronick, & Seidman, 2015).

2. Approach to Work

Currently, the stress-vulnerability model, specifically the neural diathesis-stress model, includes new, redefined definitions of markers and mediators of stress vulnerability in psychosis. These markers may potentially guide future research in the field of stress and psychosis and define treatment strategies and tools to detect the onset of psychosis and the progression of symptoms. Along this line, SLEs are considered to be a mediator factor in this dynamic model. The challenge is to establish the role of SLEs and determine which SLEs affect patients with FEP along their lives before the development of FEP. In addition, it is important to develop valid and reliable evaluation tools for use in the clinical setting.

The aim of the present doctoral thesis was to evaluate the relationship between SLEs and the development of FEP. To our knowledge, this relationship has not been studied to date. Indeed, in depth studies analysing the relationship of SLEs and clinical variables such as gender, age of onset, among others in individuals with FEP are needed as is the development of a questionnaire comparing SLEs in subjects with FEP sample and healthy controls. Furthermore, other specific issues related to the presence of SLEs in subjects with FEP have been included among the objectives of this thesis.

First, a review of the scarce literature on SLEs and their influence on the appearance of FEP was carried out. The search was focused on the stress-vulnerability model, the definition and characteristics of SLEs, adolescence, coping/resilience, ethnic differences, and the relationship between SLEs and patients with FEP.

Second, in the absence of studies analysing SLEs in the population with FEP and other variables, such as age at onset of FEP, psychotic symptoms, and a family history of mental disorder the incidence of SLEs and the influence that sociodemographic variables (gender and age) and clinical variables (age at onset of FEP, psychotic symptoms and family history of mental disorder) have on the appearance of FEP was analysed. In this study, SLEs were analysed with the Psychiatric Epidemiology Research Interview Life Events Scale which assesses the presence or absence of SLEs in the year before the onset of FEP. Many questionnaires on SLEs evaluate only the presence of the event and only the year before the evaluation. Thus, the need to design a new tool to assess SLEs along life taking into account other variables including age at the time of the SLE and the level of stress and emotional impact was evaluated.

Finally, an instrument to measure SLEs which appear along life and the levels of stress involved in a sample of FEP and healthy controls was developed and validated.

In summary, this approach to work will likely advance our understanding of SLEs in relation to the aetiology of psychotic disorders and may help to identify successful tools to detect which the most relevant SLEs in a FEP population. The integrated assessment of SLEs, together with other individual and contextual variables, will allow the screening of FEP as a tool for prevention.

3. Objectives

The main objective of the present thesis was to evaluate SLEs and their relationship with the development of FEP. In order to do this the main objective was divided into three objectives as follows:

1. To review the literature on SLEs and their influence on the appearance of FEP taking into account the definition and characteristics of SLEs, the stress-vulnerability model, adolescence, coping/resilience and ethnic differences.

2. To analyse the incidence of SLEs and the influence of sociodemographic variables (gender and age) and clinical variables (age at onset of FEP, psychotic symptoms and family history) on the appearance of FEP.

3. To develop and validate a psychometric instrument of SLEs (Questionnaire of Stressful Life Events [QSLE]) in patients with FEP and healthy controls.

4. Method

In this thesis, the method was divided into the different studies of the compendium. In addition, in each of the 3 studies, the review, the original article and the development and validation of a questionnaire, the method has been written with a different distribution.

4.1. Study 1

This review included articles on the influence of SLEs on the onset of FEP published from 1980 to 2013. The bibliographic search was performed using the MEDLINE, PsycINFO and PSICODOC databases. Tracking was systematic, exhaustive and structured, taking into account not only the standard documentary studies, but also sources of material not indexed in a standard way or included in bibliographic databases.

The inclusion criteria were related to the following themes: adolescence, coping and resilience, schizophrenia, vulnerability to stress and ethnic differences. The following key words were used in the bibliographic search: *Stressful life events, adolescence, coping, resilience, schizophrenia, stress, first-episode psychosis* and *vulnerability*. A total of 289 studies were found, 59 of which were selected for the review. The selection of articles focused on the SLEs and their relationship with the development of FEP. To discriminate the articles of interest for the study, the abstracts presented by the different databases analysed were read. Those considered to be of interest to the review were selected followed by a more extensive reading of the original articles. Thereafter, articles not related to the review subject were discarded.

Initially, a search using the MEDLINE bibliographic database was performed, using Boolean operators to carry out a more specific search. The descriptors and logical operators were as follows: [psychotic episode AND life events], which appeared in 66 articles, 11 of which were included in the review. In addition, the MEDLINE thesaurus for the term psychotic episode was used to perform a stricter terminological control with the term first-episode psychosis. Fifteen articles were found with the use of the following logical operators: [first-episode psychosis AND life events] [adolescence AND coping] [vulnerability AND schizophrenia], 5 of which were analysed.

With regard to the PsycINFO database, we explored the following descriptors: [life events AND psychotic episode], resulting in 64 articles, 10 of which were used in the study. With the use of the thesaurus related to life events, results on life experiences were found. The use of the thesaurus was also applied to psychotic episode, under which acute psychosis appeared.

A search was made for the following logical operators: [life experiences AND acute psychosis], finding 38 results, 10 of which were included. In addition, we added the following terms to the search: [stress AND first episode psychosis AND vulnerability] achieving 16 results, 3 of which were used. With the following descriptors: [stressful life events and acute psychosis] we obtained 13 results, of which one study was included.

With regard to the PSICODOC database, the following logical operator was found: [schizophrenia AND stress]. In addition, we specified that only articles were sought.

This search obtained 67 results, 11 of which were analysed. A search including [vital events AND schizophrenia], found 3 articles, one of which one was analysed. In addition to the databases mentioned, other sources were also tracked, including journals that publish articles on this specialty (Psicothema, Developmental Psychology, Psychological Bulletin, etc.). Accordingly, 7 articles related to the study subject were found and analysed.

We excluded articles related to psychosis and rehabilitation as well as mental disorders other than FEP or schizophrenia (e.g., post-traumatic stress disorder), untreated psychosis, relapse and treatment (psychological and pharmacological), and risk factors related to drug addiction.

Once the data were obtained, it was structured for use as a source of detailed information. Firstly, the articles analysed were assigned to the following thematic sections: 1) model of stress- vulnerability; 2) SLEs and FEP; 3) adolescence: stage of change; 4) coping, resilience and SLEs; and 5) ethnic differences, SLEs and FEP.

4.2. Study 2

A descriptive, cross-sectional study was carried out in patients consecutively recruited during visits to the public health network.

Participants

The participants were recruited as part of the longitudinal GENIPE study focused on gender differences and clinical variables in FEP patients. FEP subjects who contacted any service at the Parc Sanitari Sant Joan de Déu or child-adolescent mental health centre in the Sant Joan de Déu Hospital and outpatient centres in Barcelona and surrounding areas were included in the study from January 2006 to December 2011. The study sample consisted of 68 patients aged between 13 and 47 years who presented FEP. The inclusion criteria were the same as those of the GENIPE study: two or more psychotic symptoms of schizophrenia criteria A (DSM-V); age between 7 and 65 years, less than 6 months since the first contact with the medical service, and less than one year since the development of symptoms. Patients diagnosed with intellectual disability (Premorbid IQ<70) or traumatic brain injury were excluded from the study. The diagnosis was confirmed based on the criteria for any psychotic disorder, as assessed by the Structured Clinical Interview for DSM-IV (SCID).

Instruments

The assessment was performed by two experienced psychologists at the Parc Sanitari Sant Joan de Déu or child-adolescent mental health centre in the Sant Joan de Déu Hospital.

The evaluators scored over 0.70 in the intraclass correlation coefficient of the instruments prior to the study.

Sociodemographic characteristics and clinical variables were collected using a questionnaire. The Family History-RDC interview (Andreasen, Endicott, Spitzer, & Winoker, 1977) was used to record family data and to analyse the presence of a mental health disorder in first-degree relatives (only parents) in all the sample. The variable included in the analysis was the sum of a family history of mental disorder in both parents (mother/father) separately. Several cohort studies of high-risk (for serious mental disorder) demonstrated the importance of genetic susceptibility (Beards et al., 2013). Indeed, the offspring of mothers with schizophrenia were found to not only have an elevated risk for schizophrenia but also for a range of psychotic, affective, and personality disorders (Mortensen et al., 1999). Thus, we divided family history into maternal and paternal and determined its relationship with SLEs. The Psychiatric Epidemiology Research Interview (PERI-M) Life Events Scale was used to measure SLEs (Dohrenwend, Askenasy, Krasnoff, & Dohrenwend, 1978; Vizcarro, 1984). The presence or absence of different SLEs (positive and negative) was assessed in the FEP sample. The internal consistency of the scale was good. Factorial analysis identified four areas of SLEs: functional discomfort, work-related stress, health problems and relationship problems, with Cronbach's alpha coefficients between 0.73 and 0.77. In addition, there is an adapted version of this scale for adolescent populations (Casullo and Fernández, 2005). In the Spanish version, SLEs were grouped into 8 categories: academic, work, love and marriage, children, residence, legal affairs, finances and social activities.

A total of 102 items are included within these categories, and they are scored according to the presence or absence of each event. The SLEs collected were related to the year before the onset of FEP. Information on clinical variables was obtained through the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987; Peralta & Cuesta, 1994) of psychotic symptomatology, which consists of 30 items (symptoms) scored on a Likert-type scale ranging from 1 (absent) to 7 (extreme). Ratings were obtained for three subscales: positive symptoms, negative symptoms and general psychopathology. The PANSS presented good interobserver and construct validity, internal consistency (Cronbach's alpha of 0.73 for the positive scale, 0.83 for negative and 0.87 for general psychopathology) and adequate test-retest reliability. The intraclass correlation coefficient for the three subscales is around 0.80. The KIDDIE-PANSS (Positive and Negative Syndrome Scale for Children and Adolescents (Fields et al., 1994) scale was used for adolescents from 6–16 years of age. Data on illness severity and psychotic symptomatology were assessed using the Clinical Global Impression-Schizophrenia scale (CGI-S) (Haro et al., 2003) which is a valid and reliable instrument. Given its simplicity, accuracy and clinical validity, the scale is appropriate for use in observational studies and routine clinical practice. We administered this scale to all the sample to measure the severity of positive, negative, cognitive and depressive symptoms. A general illness severity score was also generated. Two measures of psychotic symptomatology and severity were used to reinforce the results with solid instruments of reliability and validity.

All participants were informed about the study aims and methodology and provided signed informed consent to participate. The study was approved by the Sant Joan de Déu Research and Ethics Committee.

Statistical analyses

Statistical analyses of clinical and sociodemographic data were carried out using the SPSS (version 21). The normality assumption tested using the non-parametric Kolmogorov-Smirnov test ($p<0.05$) was not met. As a result, non-parametric tests were used for all the study variables. SLEs were analysed against the different variables. Statistical significance was set at 0.05. Specifically, with respect to the frequencies in the PERI-M (Dohrenwend, Askenasy, Krasnoff, & Dohrenwend, 1978), only SLEs which registered a presence of 15% were described. Means were compared for independent samples using the non-parametric Mann-Whitney U test, which allowed PERI-M scores to be compared according to gender and family history of psychotic episodes. Effect sizes (ES, Cohen's d) were calculated for the PERI-M categories with respect to gender (male/female) and family history (father/mother). The Spearman correlation was used to examine the relationships between different variables. The values for three cases with a paternal family history of FEP were missing as they could not be corroborated in the interview. We could not certify the parental history of mental illness in any case.

4.3. Study 3

The development of the scale and the psychometric properties of the measurements obtained with it are presented in two phases. In phase 1, the item pool, a review of the items, and the establishment of content validity were developed and generated. Phase 2 provides different evidence of the validity of the measures of the scale: psychometric evaluation, sensitivity, and specificity.

Phase 1 was designed to establish the content of and generate the refined items. First, the questionnaire was developed by a group of experts at Parc Sanitari Sant Joan de Déu and Hospital Sant Joan de Déu. Afterwards, the content validity was evaluated by an Expert Survey.

Development and generation of the item pool

Several days of expert consensus meetings at Parc Sanitari Sant Joan de Déu resulted in the generation of the item pool. The experts worked on the definition and consensus of the items to be included in the questionnaire. The first step was to compare and contrast types of checklist approaches for their ability to screen the events of interest and to measure their important characteristics in samples of respondents from relevant populations of interest (FEP). The objective was the occurrence of such events over a lifetime. On identification of this information, the next step was to develop structured, closed questions, the answers to which would provide direct indicators of the nature and severity of the threat posed by the different types of events reported.

Following revision of the feasibility study, the QSLE included 66 items covering SLEs (1) Education (6 items covering problems and changes in the school), (2) Work (14 items covering problems with boss/colleagues, low salary, and changes of shift in workplace), (3) Partner (12 items covering starting to live together with a partner, sexual problems, instability, unfaithfulness, sexual problems), (4) Family (13 items covering child, family relationships), (5) Home (1 item covering change of residence/ leaving home), (6) Legal (6 items covering judicial process, robbery, and physically assault), (7) Finances (2 items covering payment problems), (8) Social (7 items covering friend relationships, illness of close friend, pet death) and (9) Health (5 items covering serious illness, accidents). The domains were assessed based on review questionnaires about life events, such as the PERI Life Events Scale-Modified (Dohrenwend, Askenasy, Krasnoff, & Dohrenwend, 1978), and reports of experiences and personal interviews of experts about life events in patients with FEP. We opted for over-inclusiveness with respect to the number of items, recognizing that a systematic data analysis approach to scale development would result in a smaller psychometric instrument. All items were rated as absence/ presence of the life event, the stress level (1=no stress, 10=maximum stress) and age when the event occurred. The time period covered by the interview was the entire lifetime.

Review of the items and establishment of content validity

In order to evaluate the content validity an Expert Survey was performed. With this survey, the experts determine if an instrument satisfies the extent to which a measurement reflects the specific intended domain of content. An electronic version was used to obtain expert opinion.

This process included questions regarding the background of experts. In addition, we asked about the content of the items. The experts received written instructions to rate each item on a scale of 1 to 5 according to representativeness criteria (whether the item was representative of a life event). Finally, the experts were asked to make comments/suggestions to modify the items. It was considered that an item should be modified if the average of representativeness score was <3, showing that the panel of experts did not consider that the item fitted life events adequately, in accordance with participants' suggestions. These analyses influenced the design of the final version of the QSLE.

Relevance of content

A total of 9 experts in SLEs and FEP participated in the study. The expert panel was 88.9% female and 11.1% male. Of these, 66.7% were psychologists, 22.2% psychiatrists, and 11.1% medical statisticians. The panelists' were from Denmark (22.2%), Italy (22.2%), The Netherlands (22.2%), Spain (22.2%), and Switzerland (11.1%). Regarding their degree of knowledge, 88.9% had knowledge about life events and FEP. Of these, 55.6% performed theoretical analysis and carried out studies on life events and FEP. The Expert Survey reviewed the QSLE. Following their suggestions, a new questionnaire of 54 items was developed. Some items were re-structured in the final version of the QSLE because the experts considered that the information was radically formulated. Other items that experts evaluated as having a score <3 (Items 5, 6, 16, 19, 25, 26, 40, 51, 53, 58, 59, 60, 64 and 65) were eliminated.

Furthermore, the questionnaire was reformulated to enquire about distress rather than anxiety since the experts considered stress to be a more neutral descriptor of psychological burden. Each item is scored according to the occurrence of the item [presence (yes)/absence (no)], and according to the age when the event occurred, scoring the level of stress from 1 to 10, with higher scores being indicative of high stress. With regard to the categories of the QSLE, the experts questioned the purpose of grouping the items into categories, since they considered that some items might be associated with two or more categories. Thus, we decided not to associate the items with categories.

Phase 2 was designed to provide evidence of the evaluation of the psychometric properties of the QSLE. The Standards for Educational and Psychological Testing which was jointly developed by the American Educational Research Association (AERA), American Psychological Association (APA), and the National Council on Measurement in Education (NCME) (2014) provided the conceptual framework for the evaluation and validation of the QSLE.

Participants

The study included 224 people, 102 with FEP and 122 healthy controls from 11-47 years of age ($\bar{x}$=20.02, SD=7.51). The target population was young and adult patients with FEP recruited from the Parc Sanitari Sant Joan de Déu or child-adolescent mental health centre in the Sant Joan de Déu Hospital and outpatient centre.

An FEP was defined as fulfilling the criteria for two or more psychotic symptoms of schizophrenia criteria A (DSM-V) less than 6 months since the first contact with the medical service and less than one year since the development of symptoms. The exclusion criteria were: the diagnosis of intellectual disability, traumatic brain injury, and dementia. Healthy controls were defined as people without a psychotic episode and no history of a FEP in first-degree relatives (mother or father) and were recruited from Parc Sanitari Sant Joan de Déu, School of Sant Josep and School Pedagogium COS in Sant Boi del Llobregat.

Procedure

Participants were informed about the study, and after voluntarily signing the consent form were asked to complete anonymous questionnaires. The study was approved by the Research Ethics Committee of the Parc Sanitari Sant Joan de Déu.

Instruments

Four additional measures were included to characterise the samples and establish relationships with other variables: the Scale of Life Events (PERI-Modified; Dohrenwend, Askenasy, Krasnoff, & Dohrenwend, 1978); the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987); the Clinical Global Impression-Schizophrenia scale (ICG-ESQ; Haro et al., 2003); and the Global Assessment of Functioning Scale (GAF; Hall, 1995).

Data analyses included multiple procedures: a) Item-level descriptive statistics, including item-total correlations; b) items with temporal stability—Cohen's Kappa, Gamma; c) Correlational analyses to assess whether the QSLE significantly correlated with the PERI Modified and other variables (PANSS, ICG-ESQ and GAF); and d) Sensitivity and specificity analyses: the discriminability of the binary items (presence/absence)—chi-square and odds ratios—and sensitivity, specificity, and the AUC of the sum of all the SLEs in the sample of FEP and healthy controls. All analyses were carried out using SPSS version 22 and R version 3.0.3 (2014).

5. Results

5.1. Organisation

As stated previously, the main objective of the present doctoral thesis was to evaluate SLEs and determine their relationship with the development of FEP. In order to do so, it was necessary to operationalise the study into three objectives which are linked to one study or article as shown in Figure 4:

Figure 4. Linking objectives and studies.

The first objective was included in Study 1 and involved SLEs and FEP. Study 1 was entitled Stressful life events and first-episode psychosis. It is a systematic review of the information published on SLEs and their influence on the onset of FEP. The aim of this review was to provide an update and promote further investigation into these events in the context of a stress-vulnerability model.

The second objective was carried out in Study 2, entitled Incidence of stressful life events and influence of sociodemographic and clinical variables on the onset of first-episode psychosis. It is an original article that describes a quantitative analysis of the incidence of SLEs and relevant variables such as gender, age at onset, family history of mental disease and psychotic symptoms in patients with FEP.

The third objective was aimed at developing and validating the 'Questionnaire of Stressful Life Events' (QSLE). It is linked to our third study. Study 3 was entitled 'Development and validation of the Questionnaire of Stressful Life Events (QSLE)'. It is an original article that reports the development, reliability and validation of the questionnaire of SLEs in patients with FEP and healthy controls. It assesses the following aspects of psychometric quality of the instrument: i) the development and generation of the item pool and review of the items and establishment of content validity, ii) the reliability, and, iii) the evidence of the validity of the scale measures: structural evaluation, sensitivity and specificity.

5.2. Publication Compendium

The following includes additional details about the studies which make up the present doctoral thesis, which are presented according to their objectives:

Objective 1:

Study 1: 'Stressful life events and first-episode psychosis'

Authors: Butjosa A, Gómez-Benito J and Ochoa S.

Journal: Psiquiatría Biológica, 2014, 21: 43-58.

Indexed in: Excerpta Medica/EMBASE, IBECS, IME, SCOPUS

Objective 2:

Study 2: 'Incidence of stressful life events and influence of sociodemographic and clinical variables on the onset of first-episode psychosis'

Authors: Butjosa A, Gómez-Benito J, Huerta-Ramos E, Del Cacho N, Barajas A, Baños I, Usall J, Dolz M, Sánchez B, Carlson J, Haro JM, GENIPE group and Ochoa S.

Journal: Psychiatry Research, 2016, 245:108-115

Impact factor: 2.466

Journal Rank in Psychiatry and Mental Health: Q2

Objective 3:

Study 3: 'Development and validation of the Questionnaire of Stressful Life Events (QSLE)'

Authors: Butjosa A, Gomez-Benito J, Myin-Germeys I, Barajas A, Baños I, Usall J, Grau N, Granell L, Sola A, Carlson J, Dolz M, Sánchez B, Haro JM, GENIPE group and Ochoa S.

Journal: Journal of Psychiatric Research, under review

Impact factor: 4.465

Journal Rank in Psychiatry and Mental Health: Q1

5.2.1. Study 1

This paper reviews and updates the literature currently available on SLEs and FEP. The objective of the review was to update and promote further investigation into these events within the context of a stress-vulnerability model (see Annex 1).

First, this article provides a review of the literature in reference to SLEs with respect to: i) the stress-vulnerability model, ii) SLEs in patients with FEP, iii) SLEs, FEP and adolescence, iv) coping and resilience, and v) ethnic differences. A search was conducted between 1980 and 2013 using PsycINFO, MEDLINE and PSICODOC using the following terms: Stressful life events, adolescence, coping, resilience, schizophrenia, stress, first psychotic episode, and vulnerability. A total of 289 studies were found, 59 of which were selected for review.

Overall, the review highlights the importance of certain psychosocial factors which may cause a significant change in subjects' lives and, consequently, require an adaptation response. The central nucleus is the adaptation to the environment and, consequently, the production of dynamic changes in the individual. An example is the effect of SLEs, which are considered environmental factors that produce conflict, challenge and change in subjects.

This results of the review suggest the need for a multiple and integrated approach, taking into account the different factors that are involved in the whole nexus making up a FEP. The results also point out that assessment of SLEs, along with other individual and contextual variables, support an approach for early detection and the need for a prevention tool.

5.2.2. Study 2

The review of the literature of SLEs in the FEP population demonstrated that there are few studies relating SLEs with clinical variables and SLEs and FEP. The framework of SLEs indicates that several mechanisms influence how exposure to external stress factors can affect individuals and increase the risk of psychosis.

Study 2 aims at providing additional empirical knowledge of SLEs in FEP patients by analysing the incidence of certain SLEs and the appearance of FEP and evaluating the influence of different variables such as gender differences, age at onset, family history and psychotic symptomatology on SLEs (see Annex 2).

The results of study 2 showed that significant differences according to gender were only found for the category of legal affairs in adolescent males. Age at onset presented a significant negative correlation with the categories of academic and social activities. By contrast, a positive correlation was found with work and children. A significant relationship was found between paternal family history and social activities and between maternal family history and academic and love and marriage. Finally, an inverse relationship was observed between negative symptoms and the categories of children and finance. Depressive symptoms were significantly correlated with the category of academic.

Overall this paper showed the following results: i) the high incidence of SLEs in FEP, ii) there are more SLEs in subjects with a maternal/ paternal family history of mental disorders, and iii) the age at onset and psychotic symptoms were associated with the presence of SLEs.

This study demonstrates the importance of SLEs during adolescence, a period of constant change and adaptation, and suggests that there is a clear need to develop in depth analyses of SLEs, and preventive actions that promote effective strategies for dealing with the accumulation of psychosocial stress.

5.2.3. Study 3

Studies 1 and 2 highlighted the importance of SLEs as relevant predisposing factors as well as their important relationship with clinical variables (e.g., gender differences, age at onset, family history and psychotic symptomatology) in the FEP population. Both studies indicated the need for the development and validation of a new questionnaire on SLEs, which was the main objective of Study 3 (see Annex 3).

Study 3 involved the development and validation of the questionnaire on SLEs (QSLE), which described specific items of childhood, adolescence, and adulthood focused on the presence of SLEs, emotional impact (stressfulness), and the age at which the event occurred in patients with FEP and healthy controls. An item pool was generated and content validity was evaluated. We then assessed the evidence of the reliability and validity of the QSLE: i) item-level analyses, ii) intra-rater reliability, and iii) convergent and discriminant validity. Lastly, sensitivity and specificity analyses were performed.

Study 3 showed satisfactory psychometric characteristics in a Spanish population. The scores were reliable and valid, thereby making the QSLE a useful instrument for the measurement and detection of SLEs that occur along the life cycle. It should be noted that in the sensitivity and specificity analysis, 18 items had a high relevance in the discrimination capacity between patients with FEP and healthy controls.

The findings of Study 3 suggest that the QSLE allows the investigation of childhood, adolescent, and adult life events by measuring stress and the age at the time of the SLE on a continuous scale, being optimal for psychosis studies. The QSLE also assessed the presence and levels of stress thereby providing additional knowledge of the impact of SLEs on psychosis.

6. Discussion

The framework of the stress-vulnerability model demonstrates the importance of the role of stress in the development process of FEP as a mediating and predisposing factor. There is a complex interplay of vulnerability factors, neurobiological processes and psychosis progression. Therapeutically, psychotic phenomena as a point of continuum is useful for achieving an intervention model based on continuity risk, and it is crucial for identifying targets for future interventions. The role of stress is analysed within this intervention model because of the clear need for evaluation, such as the analysis of SLEs. Figure 5 shows the integrated model of this thesis, demonstrating the valuable role of SLEs and the period of time over which they occur.

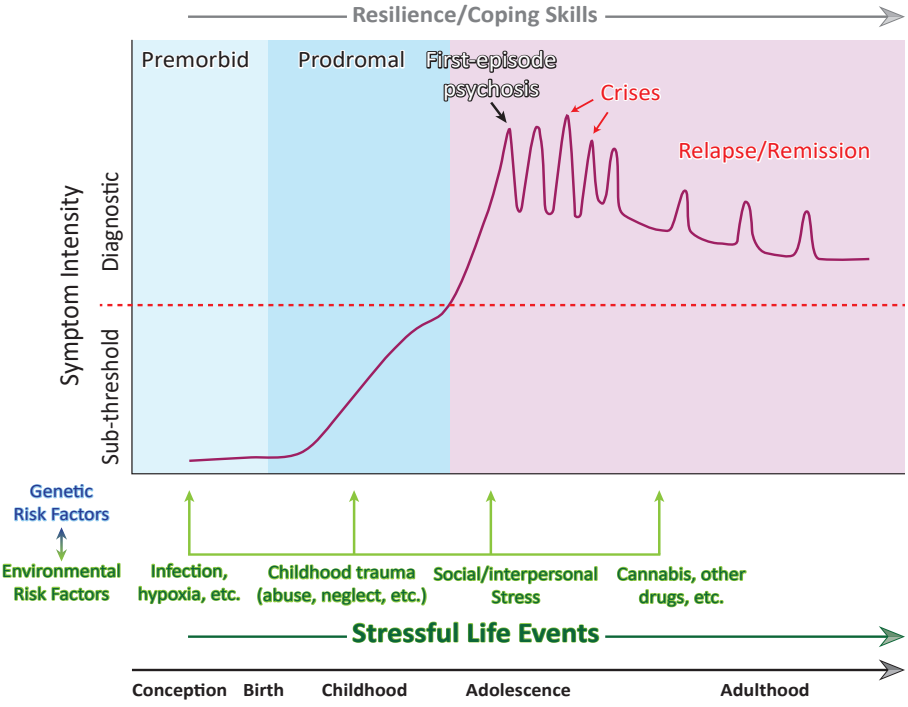

Figure 5. Integrative thesis model of stressful life events and psychosis.

There is an increasing number of studies on psychosis including the evaluation of stress, albeit only in relation to trauma, with few studies evaluating SLEs. Historically, most of the studies of SLEs involve events such as trauma, making the investigation and evaluation more difficult and complicated. Trauma and SLEs are different constructs that can act differently in the continuum of psychosis. For this reason this thesis focused on SLEs related to the onset of FEP.

Within this context this doctoral thesis was aimed at the study of SLEs and FEP. In order to do this, a review of the literature was made demonstrating the lack of exhaustive analysis of SLEs in the FEP population. The review showed that there were more instruments to evaluate SLEs in depression and anxiety than in the FEP population. Furthermore, few instruments evaluate SLEs along life. This is very important since this thesis took into account the effect of the accumulation of these stressors during life and not only during the year prior to the evaluation as well as the period or stage at which the SLEs occur. Therefore, valid, reliable and context-adapted instruments are needed for the evaluation of SLEs in patients with FEP and healthy populations.

6.1. What do we know about the role of SLEs in FEP?

The literature review performed (Study 1) highlighted the importance of evaluating SLEs and analysing their presence, in addition to the type of circumstance involved, the emotional impact, and the individual's experience. This is consistent with the literature available (Beards et al., 2013).

Study 1 shows that the role SLEs play in the development/exacerbation of symptoms or the mechanisms which influence SLEs is not clear. At present, the relationship between SLEs and the onset of FEP (Jones et al., 1993) has been studied in two types of investigation addressing: i) a significant increase in independent SLEs at 3-weeks (Al Khani et al., 1986; Lukoff et al., 1984), 3 months (Raune et al., 2009; van Os et al., 1994), and 6 months prior to the onset of FEP (Rusaka & Rancāns, 2014); and ii) an increase in the number of SLEs before the onset of FEP (Canton & Fraccon, 1985).

In many circumstances it can be questioned whether the occurrence of SLEs can be separated or if together they affect the susceptibility to stress of the vulnerable person (van Os et al., 1994). However, several relevant factors may be critical to the outcome of such an interaction; e.g., the coping capacity (Nuechterlein & Dawson, 1984). This factor is essential for determining the impact of SLEs, since an individual with a broad spectrum of coping responses (Horan & Blanchard, 2003) may control SLEs that exceed the ability of other individuals with a lesser range of coping responses. With respect to vulnerability, individuals who develop FEP show psychobiological hypersensitivity towards socioenvironmental stressors. In addition, there are deficits in protective factors, such as interpersonal skills, coping/resilience, and social/family support (Lukoff et al., 1984; Pruessner et al., 2011). Figure 6 shows the different approaches used in the management of SLEs in patients with FEP and healthy controls, and how the variables of coping and resilience intervene.

It is therefore necessary to take into account the importance of certain psychosocial factors (e.g., SLEs) that may cause a significant change in the subject's life and, consequently, require an adaptation response (Cornes, 1994). The central nucleus of these events is the adaptation to the environment and, consequently, the production of dynamic changes in the individual.

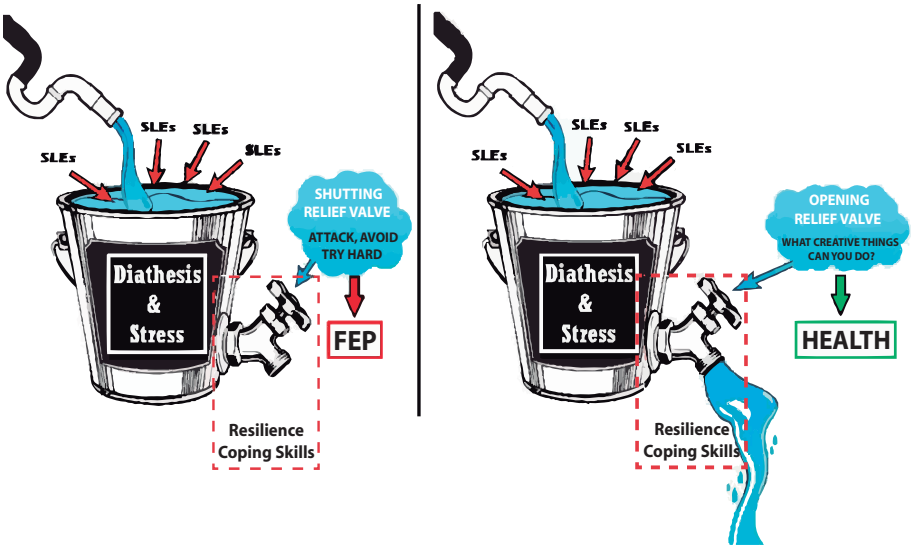

Figure 6. Management of stressful life events.

In summary, Study 1 provides a better understanding of the framework of SLEs and FEP, in which nuclear issues (the stress-vulnerability model, the features of SLEs, adolescence, coping/resilience, and ethnic differences) are analysed. This information could be used to improve our knowledge about premorbid development in psychosis and may help to develop theories about the aetiology and heterogeneity of this population, as well as serve as a basis for early detection strategies.

It is also important to understand the cultural and ethnic background to reflect on and discuss the need to prioritize future interventions related to early care in patients with SLEs. Finally, Study 1 provides new pathways of future research, in relation to the characteristics of SLEs, their accumulation along life, the increase of SLEs in patients with FEP, the type of SLEs (e.g. work, academic) and an individual's coping and resilience abilities as tools in emotional management.

6.2. How are sociodemographic and clinical variables related to SLEs in FEP patients?

We have also made an in depth study of the incidence of SLEs and the influence of sociodemographic and clinical variables (age at onset of FEP, psychotic symptoms and family history) on the appearance of FEP (Study 2). This study has shown that adolescence is a period of change and detailed analyses of SLEs are significant since they have a clear relationship with this vulnerable age group.

Our study indicates that there is a high incidence of SLEs in the FEP population. First, significant differences according to gender were only found for the legal affairs category in adolescent males (Bruyn, Dekovic, & Meijnen, 2003; Jiménez et al., 2008): men are more individualistic/ instrumental, and women depend on their assessment over relational/ interdependence aspects with their environment.

Second, the effect of specific SLEs on the age at onset of FEP indicates an overall increase in the frequency of SLEs during early and middle adolescence, and in the family environment and among the peer group (Graber, 2004; Musitu, Buelga, Lila, & Cava, 2004). Third, in the relationship between family history and SLEs and the onset of FEP, there is a greater influence of maternal family history of attachment, interpretation and coping skills when a SLE occurs. Four, in the relationship between psychotic symptomatology and SLEs and the development of FEP, SLEs could be prodromal events which, together with other events, may contribute to the emergence of psychotic symptomatology.

The research conducted in Study 2 provides more knowledge about clinical variables which can help to understand how SLEs affect the evaluation of the mediating factors of psychosis.

In summary, Study 2 provides a better understanding of the assessment of premorbid functioning and allows direct observation of the early stages of schizophrenia. In addition the results obtained will improve strategies for dealing with the accumulation of psychosocial stress and promote positive processes of adaptation.

6.3. Assessment of SLE in FEP patients

Most scales measure exposure to trauma in multiple areas of the lives of children and adolescents (Cristofaro et al., 2013). However, few studies have assessed the role of SLEs and less so in adult life events.

Thus, exposure to childhood and adult SLEs may combine in complex ways to lead some individuals along the pathway to a psychotic disorder (Bebbington et al., 2011; Lataster et al., 2012). In addition, the studies available on SLEs show the need to identify the most important SLEs and evaluate the different properties of SLEs in different types of samples (Abad et al., 2000; Lemos et al., 2002). In this thesis, in addition to an FEP sample a sample of healthy controls was included in order to assess the most influential SLEs. The subjective burden of stress was also included in each item of SLE since stress can affect their perception. This led to the development and validation of the QSLE that could be helpful to identify which SLEs should be evaluated before an FEP, and to assess SLEs as well as other specific variables along life such as age at the time of the SLE, and qualitatively, the level of stress or emotional impact (Study 3).

The analysis showed that the QSLE is an empirically supported and evidence-based instrument to investigate the prevalence and impact of SLEs in a Spanish population. The QSLE showed satisfactory psychometric characteristics and capacity to discriminate patients with FEP and healthy controls. The good indices of sensitivity and specificity (64.8% and 65%, respectively) support the decision validity of the instrument, which is always a requirement for a screening tool. In particular 18 items had high relevance in the detection of patients and controls. These specific items demonstrated that concrete areas of SLEs, many of which affect patients with FEP (e.g., reduced social networks and support), seem to pre-date the onset of a psychotic disorder (Gayer-Anderson & Morgan, 2013).

There is strong evidence that social support, in particular the support of an adult, can limit the negative consequences of abuse and other adversities in childhood (Morgan & Gayer-Anderson, 2016).

In summary, the development and validation study of the QSLE showed that this questionnaire is a very promising measure for future prevention studies in FEP patients. Evaluation of the presence and levels of stress of certain life events could help us to understand the impact of these events on the risk of developing psychosis and determine which SLEs are most relevant in early and adult intervention. Our instrument is designed to provide continuous scores (thereby enhancing variability and facilitating statistical analyses) of SLEs across social, familial, and environmental contexts over a lifetime. The consequences of childhood/adolescent/adult life events are comprehensive, and the QSLE may be useful for a number of research questions, and to also potentially learn how to improve recovery outcomes in FEP populations.

Apart from the theoretical applicability of this thesis -with more evidence on the relevance of the SLEs and the associated clinical variables- we must emphasize on their clinical applicability. Specifically, the new tool QSLE, developed and validated in this thesis, is to be implemented as part of may be part of a protocol in an early prevention program, following the clinical staging model. From a therapeutic point of view -considering psychotic phenomena as a point of continuum-, it is useful for achieving a strategy based on the risk of continuity and it is crucial for identifying targets for future interventions. So, this protocol would be previous at the beginning of a FEP with an area of applicability to non-clinical subjects (both healthy subjects and high-risk population).

The idea is that early detection along with a convenient intervention will improve the prognosis of the individuals, delaying the appearance of the problem and may even avoid its appearance. QSLE will be part of this early prevention, and it will be implemented in the social field (e.g. social services), education (e.g. school and high school) and diverse clinical settings (e.g. primary care).

For example, if subjects score in the QSLE and they are also distressed, they have a decline in social functioning and they have transient or attenuated psychotic symptoms or other experiences or behaviour suggestive of possible psychosis or a first-degree relative with psychosis or schizophrenia, refer them for assessment without delay to a specialist mental health service or for an early intervention in psychosis service because they may be at increased risk of developing psychosis.

In summary, the thesis wants to achieve the following highlights: i) early detection and intervention in emerging psychosis, ii) reducing treatment delay at the FEP (duration untreated psychosis), and iii) providing a new screening instrument suitable in both clinical and research settings, the QSLE, that could also be used to measure SLEs in other studies; and consequently, for other diseases.

7. Limitations

There are some limitations that should be considered in the development of this doctoral thesis. From a general point of view, one of the limitations that should be mentioned is the retrospective accounts of events prior to the FEP, with the SLEs collected being related to the year before the onset FEP. This may make it difficult to distinguish between SLEs and residual prodromal symptoms and recall biases. However, this is the way in which SLE instruments commonly evaluate this concept. Another limitation is that we did not consider environmental aspects such as different cultural, socioeconomic, family, and ethnic circumstances that may influence the perception of stress and the evaluation of SLEs. The last general limitation is the selection bias: subjects willing to participate in a demanding study protocol may be different from those included other psychiatric studies that are less demanding, or subjects who refuse to participate in research.

There are also some limitations concerning the specific objectives of this doctoral thesis. In Study 2, the sample consisted predominantly of adolescents and young people, the age groups in which FEP usually appears. This may influence the likelihood of observing academic SLEs and reduce the incidence of events in relation to being a parent and the work category. In addition, the analyses are based on cross-sectional data. In Study 3, there is a lack of detailed content information about SLEs. This procedure is designed to elicit in depth accounts of the events experienced to enable experienced investigators to rate the relevant characteristics of the events. Moreover, it is difficult to evaluate distal SLEs since there may be biases in the level of stress at that time.

8. Challenges and Future Directions

Some of the above limitations may provide recommendations for future work in SLEs. First, further research should include different cultural, socioeconomic, family, and ethnic aspects which may influence the perception of stress and the evaluation of certain life events. The context is very important, since there may be differences in the ways of interpreting stress and perception of SLEs. Second, a study similar to Study 2 should be carried out taking into account some interesting modifications: i) the sample size should be increased, ii) other types of mental disorders should also be analysed (e.g., depression or affective disorders), and iii) the QSLE should be used to obtain more in depth information related to the SLEs such as the number of SLEs, levels of stress and the age at which the event occurred. Third, longitudinal studies should be conducted to determine differences in the perception of events and their variability. Fourth, the role of resilience and coping skills in the adaptation of SLEs should be taken into account. Resilience is characterised by the development of models of positive adaptation or competition in contexts of risk or adversity (Luthar, Cicchetti, & Becker, 2000; Monroy & Palacios, 2011; Rutter, 2007). Subjects with greater resilience to SLEs have lower emotional distress (Hjemdal, Aune, Reinfjell, Stiles, & Friborg, 2007; Smith, 2009). Along this line, resilient adolescents present greater protective factors (adaptability and positive family relationships) characterised by emotional cohesion, which, in situations of significant adversity, acts as a protector of behavioural and psychological adjustment (Oliva et al., 2008). These variables as important as keys that should be taken into account in the analysis of SLEs and psychosis.

Fifth, the importance of carrying out research in which the comparison groups consist of the siblings of schizophrenia patients should also be stressed in order to observe the parenting style of schizophrenia patients and compare it with that of families without mental illness. This will allow the determination of differences between biological vulnerability and stress.

This doctoral thesis has focused on the study of SLEs and psychosis. The objective of identifying SLEs across the stress-vulnerability model psychosis phenotype continuum may provide insights into the aetiology of this disorder and lead to the development of strategies for prevention and treatment. Furthermore, different studies have suggested that SLEs play an important role in the precipitation and relapse of psychiatric disorders; however, the relationship is not so simple. There are other vulnerabilities that may influence the precipitation of the disorder, such as differences in the social support system, skills, attitudes, beliefs and personality characteristics (Cohen & Hamrick, 2003; Fumero, Santamaría, & Navarrete, 2009; Pandurangi & Kapur, 1980). These factors may make some people relatively immune to disease-induced stress and others relatively susceptible, leading to the development of a FEP.

A large number of causative factors as well as the wide developmental time period and the presence of numerous moderating resilience factors seem to be consistent with the psychopathological space between healthy individual differences in schizotypal personality traits and severe psychotic psychopathology. In addition, it has been shown that there are dynamic developmental changes in the individual's position along this hypothetic continuum of risk and resilience to psychosis.

There is evidence that SLEs interact with FEP, and consequently, the determination of SLEs might be particularly useful to develop strategies to prevent the development of FEP. We provide further evidence that rather than being a correlate of frank psychosis, the variability of SLEs may play an important role in FEP populations and this is of great relevance to the practice of professionals dedicated to detecting, caring for, and treating people with this disease.

Epidemiological studies have shown an association among psychosocial factors at both macro (e.g., urbanicity, poverty, minority status) and micro (e.g. family environment, childhood adversity, SLEs) levels and schizotypal traits, and subclinical and clinical expression of psychotic phenomena (Bentall, Wickham, Shevlin, & Varese, 2012; Kwapil, Brown, Silvia, Myin-Germeys, & Barrantes-Vidal, 2012). The work presented in this thesis is framed within the stress-vulnerability model and the clinical staging model, which considers the phenotypic continuum reflecting a shared interactive set of diathesis, psychosocial and sociocultural factors.

Currently, few studies have evaluated SLEs in these sample types and there is a need to obtain more in depth information on the influence of SLEs in these populations in which genetics and stress play a relevant role.

Along this line, it is important to note that the author of this thesis has broadened her knowledge on FEP populations within the research domain at the Department of Psychiatry & Neuropsychology of Maastricht University (Maastricht, Netherlands) and at the Center for Contextual Psychiatry of KU Leuven (Leuven, Belgium) under the supervision of Prof. Dr. Inez Myin Germeys and Dr. Ulrich Reininghaus.

These stays were financied by the Fondo de Investigación Sanitaria del Instituto Carlos III, Ministerio de Investigación e Innovación (Spain) and 'Programa d'ajuts per a accions especials de recerca' (Faculty of Psychology, Universitat de Barcelona, Spain). These stays abroad have allowed the doctoral candidate to become familiarised with the latest research projects in FEP populations, the Dutch longitudinal observational study called the 'Genetic Risk and Outcome of Psychosis Project' (GROUP; Korver, Quee, Boos, Simons, & de Haan, 2012) in Europe. The GROUP study is on vulnerability and resilience factors for the development of a psychotic disorder and the variation in the course of the disorder.

Our group is currently studying the relationship of SLEs with the course of schizotypy symptoms over time in siblings of patients with FEP and healthy controls. This future paper is entitled 'The effects of stressful life events on schizotypal symptoms and subclinical psychotic experiences in siblings and healthy controls'. This original article analyses: i) the association between SLEs and schizotypal symptoms and subclinical psychotic experiences in siblings and healthy controls, ii) the association between the quality of the SLEs (independent vs. dependent; positive vs. negative; pleasant vs. unpleasant) and subclinical psychotic experiences in siblings and healthy controls, and iii) the association between appreciation, emotional impact, and type of SLEs (measured in wave/phase 2) and subclinical psychotic experiences (measured in wave/phase 3) in siblings and healthy controls over time.

This study will help to design developmental models of psychosis vulnerability and may have allow the identification of key targets for prophylactic intervention among individuals exposed to SLEs.

9. Conclusions

The studies presented in this thesis provide new insights of the different dimensions of the role of SLEs in FEP patients. Overall, the main conclusions of the present thesis are:

1) Within the context of the stress-vulnerability model, evaluation of the characteristics and the types of SLEs, adolescence, coping skills/resilience, and ethnic differences, provides a better understanding of SLEs in FEP.

2) There is a higher incidence of SLEs in FEP patients, and a relationship between SLEs and sociodemographic and clinical variables in FEP patients:

2.1) There are significant differences according to gender only in relation to legal affairs in adolescent males.

2.2) FEP patients with a maternal/paternal family history of mental disorders have more SLEs: there is an association between paternal family history and social activities and between maternal family history and academic and love and marriage problems.

2.3) Patients who develop FEP at an early age more frequently present SLEs related to academic and social activities. In contrast, those with late onset FEP more frequently present SLEs related to work and children.

2.4) Subjects with more negative psychotic symptoms have fewer SLEs associated with children and finances.

2.5) An elevation of depressive symptomatology is related to academic SLEs.

3) The QSLE is a reliable and valid instrument in FEP patients:

3.1) The QSLE is an empirically supported and evidence-based instrument to investigate the prevalence and impact of SLEs in a Spanish population.

3.2) The QSLE showed satisfactory psychometric characteristics and the capacity to discriminate patients with FEP and healthy controls.

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11. Annexes

Annex 1

Study 1:

Butjosa, A., Gómez-Benito, J., & Ochoa, S. (2014). Acontecimientos vitales estresantes y primer episodio psicótico. *Psiquiatría Biológica, 21*(2), 43–58. http://doi.org/10.1016/j.psiq.2014.05.001

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Revisión

Acontecimientos vitales estresantes y primer episodio psicótico

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RESUMEN

El presente trabajo compila y discute la información publicada sobre los acontecimientos vitales estresantes y su influencia en la aparición de un primer episodio psicótico. El objetivo es actualizar y promover la investigación sobre dichos eventos en el marco del modelo de vulnerabilidad al estrés. Se seleccionaron estudios punteros en referencia a la temática clave de los acontecimientos vitales estresantes, como son adolescencia, afrontamiento, resiliencia y diferencias étnicas. Se realizó una búsqueda bibliográfica en las bases de datos PsycINFO, MEDLINE y PSICODOC entre los años 1980 y 2013 de los siguientes términos: acontecimientos vitales estresantes, adolescencia, afrontamiento, resiliencia, esquizofrenia, estrés, primer episodio psicótico y vulnerabilidad. Se encontraron un total de 289 estudios, de los cuales se seleccionaron 59 para su revisión. La valoración integrada de los sucesos vitales estresantes, junto con otras variables individuales y contextuales, conforman un acercamiento para la detección precoz como instrumento de prevención. Los resultados evidencian la necesidad de un abordaje múltiple e integral, ya que son varios los factores que están implicados en toda la red que conforma un primer episodio psicótico.

Stressful life events and first-episode psychosis

Keywords:
Stressful life events
Adolescence
Coping
Stress
First-episode psychosis
Resilience
Vulnerability

ABSTRACT

This paper reviews and discusses the published information on stressful life events and their influence on the onset of a first psychotic episode. The aim is to update and promote further investigation into these events in the context of a stress-vulnerability model. Milestone studies that referred to the key thematic stressful life events, such as adolescence, coping, resilience, and ethnic differences. A search was conducted using PsycINFO, MEDLINE and PSICODOC between 1980 and 2013 using the following terms: Stressful life events, adolescence, coping, resilience, schizophrenia, stress, first psychotic episode, and vulnerability. A total of 289 studies were found, of which 59 were selected for review. The integrated assessment of stressful life events, along with other individual and contextual variables, allow an approach for an early detection and a prevention tool. The results suggest the need for a multiple and integrated approach, since there are several factors that are involved in the whole network which forms a first psychotic episode.

Introducción

Existe interés en comprender de qué manera interacciona el individuo con el ambiente, con el fin de describir y explicar el comportamiento relacionado con las diferencias individuales. La percepción y valoración de nuestros propios recursos, el estilo

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de afrontamiento y la resiliencia nos hacen reaccionar de manera singular ante los acontecimientos que nos rodean. Aunque la literatura propone que los acontecimientos vitales estresantes (AVE) juegan un papel importante en la precipitación y recaída de los trastornos psiquiátricos, la relación no es tan sencilla. Existen otros factores de vulnerabilidad que aportan un valor en la precipitación, como son diferencias en el sistema de apoyo social, habilidades, actitudes, creencias y características de personalidad (Fumero et al[1]., 2009; Cohen y Hamrick[2], 2003; Pandurangi y Kapur[3], 1980). Estos factores producen que algunas personas sean relativamente inmunes a la tensión inducida por la enfermedad, y otros, relativamente susceptibles, como por ejemplo, en el desarrollo de un primer episodio psicótico (PEP).

La definición de PEP presenta dificultades, ya que no existe un grupo homogéneo de pacientes en cuanto a presentación clínica, inicio y contexto. Asimismo, adolescencia y adultez temprana son etapas con grandes cambios a nivel familiar, social y biológico. Así, se enfatiza la naturaleza cambiante de este período evolutivo, donde los propios procesos madurativos del desarrollo pueden estar jugando un papel importante. Durante este período las personas enfermas no suelen solicitar ayuda, o si lo hacen, con frecuencia no son correctamente diagnosticadas. También el retraso en la identificación y en la instauración del tratamiento adecuado facilita la progresión de formas más deteriorantes y crónicas de la enfermedad (Norman y Malla[4], 2001). En consecuencia, existe la necesidad de poner en marcha estrategias que garanticen la identificación de la psicosis y el tratamiento en la fase más temprana, además de controlar precozmente el sufrimiento que la enfermedad produce al paciente y las figuras clave de su entorno.

Existe un modelo basado en la investigación y manipulación de marcadores de vulnerabilidad, denominado *modelo conceptual de vulnerabilidad-estrés* (Zubin y Spring[5], 1977). Dicho modelo será útil para enmarcar el presente estudio, ya que postula la presencia de una vulnerabilidad específica (diátesis) para la esquizofrenia, que se define como rasgo dimensional, duradero y relativamente permanente, que puede ser precipitada por distintos factores ambientales (estrés). Desde el punto de vista evolutivo, el estrés psicológico, si los estímulos estresantes se mantienen, bien sea por la estabilidad de un marco social, bien por la recurrencia de eventos psicológicos estresantes, la respuesta de estrés no tiene utilidad física; en consecuencia, se producen efectos indeseables para el organismo. De modo que hay una compleja interrelación entre biología y emociones, diferentes formas de personalidad, sentimientos y pensamientos que se reflejan e influyen en el individuo.

En síntesis, el objetivo principal de esta investigación se centra en cuál es el papel que desarrollan los AVE en el inicio del PEP. Actualmente, investigar la presencia de acontecimientos vitales en relación con el inicio de la psicosis es novedoso, ya que existen pocos estudios que analicen dichos constructos.

Los objetivos de la revisión bibliográfica son los siguientes:

1. Analizar artículos que relacionen vulnerabilidad y estrés asociado al PEP.
2. Recopilar artículos que relacionen sucesos vitales estresantes con PEP.
3. Determinar de qué manera afectan el tipo de afrontamiento y resiliencia, los sucesos vitales estresantes y el desarrollo del PEP.
4. Explicar la afectación de los sucesos vitales estresantes en la adolescencia y PEP.
5. Evaluar el efecto cultural en relación con los AVE y PEP.

Método

Se incluyeron artículos del año 1980 al 2013 con la finalidad de explorar estudios que nos puedan aportar información sobre la influencia de los AVE en el inicio del PEP. La búsqueda bibliográfica se realizó en las bases de datos MEDLINE, PsycINFO y PSICODOC. El rastreo se realizó de forma sistemática, exhaustiva y estructurada, teniendo en cuenta no solo los repertorios documentales estándares, sino también posibles fuentes de material no indizado de forma estandarizada, ni contenida en bases de datos bibliográficas. Los criterios de inclusión fueron los relacionados con las siguientes temáticas: adolescencia, afrontamiento y resiliencia, esquizofrenia, vulnerabilidad al estrés y diferencias étnicas. La localización de los estudios fue conseguida mediante las bases de datos mencionadas, en las cuales se utilizaron las siguientes palabras clave: *acontecimientos vitales estresantes, adolescencia, afrontamiento, resiliencia, esquizofrenia, estrés, primer episodio psicótico* y *vulnerabilidad*. Se localizaron un total de 289 estudios, de los cuales se seleccionaron 59 para su revisión. La selección de los artículos se centró en los AVE y su relación en el desarrollo de PEP. Para discriminar los artículos de interés para el estudio, se realizó una lectura previa de los resúmenes que presentan las diferentes bases de datos analizadas. Una vez seleccionados los de utilidad, se inició una lectura más extensa mediante los artículos originales. Se descartaron aquellos que no tenían relación con la temática evaluada.

Inicialmente, se realizó una exploración mediante la base de datos bibliográfica MEDLINE, en la cual se emplearon operadores booleanos para realizar una búsqueda más concreta. Se utilizaron como descriptores y operadores lógicos los siguientes: [*psychotic episode AND life events*], donde aparecieron 66 artículos, de los cuales 11 se incluyeron. Además, se utilizó el tesauro de MEDLINE para el vocablo *psychotic episode* para realizar un control terminológico más estricto apareciendo el término *first-episode psychosis*. Debido al uso de los siguientes operadores lógicos: [*first-episode psychosis AND life events*] [*adolescence AND coping*] [*vulnerability AND schizophrenia*] se localizaron 15 artículos, de los cuales 5 fueron analizados.

En referencia a la base de datos de PsycINFO, se exploraron los siguientes descriptores: [*life events AND psychotic episode*], con un resultado de 64 artículos, de los cuales 10 se utilizaron en la investigación. Con el uso del tesauro en la instrucción *life events*, resultó *life experiences*. También se aplicó el uso del tesauro a *psychiotic episode*, donde surgió *acute psychosis*. Se realizó una búsqueda de los operadores lógicos siguientes: [*life experiences AND acute psychosis*], en los que se hallaron 38 resultados, de los cuales se incluyeron 10. Además, en la búsqueda se añadieron: [*stress AND first episode psychosis AND vulnerability*], con 16 resultados, de los cuales se emplearon 3. Y también los siguientes descriptores: [*stressful life events and acute psychosis*], con 13 resultados, de los que se incluyó un estudio.

Por lo que se refiere a la base de datos de PSICODOC, se halló el siguiente operador lógico: [*esquizofrenia AND estrés*]. Además, se concretó el tipo de documento, aceptándose solamente artículos. En esta búsqueda aparecieron 67 resultados, de los cuales 11 eran analizables. También se concretó la búsqueda en [*sucesos vitales AND esquizofrenia*], donde aparecieron 3 artículos, de los cuales se analizó uno. Además de las bases de datos mencionadas, se rastrearon otras fuentes. Concretamente, en revistas que publican artículos sobre dicha especialidad (*Psicothema*, *Developmental Psychology*, *Pscychological Bulletin*, etc.). En estas se encontraron 7 artículos relacionados con la temática de estudio y analizables (ver diagrama de flujo de la información de la revisión bibliográfica, Figura 1).

Se excluyeron artículos relacionados con psicosis y rehabilitación, otros trastornos mentales que no fueran PEP ni esquizofrenia (por ejemplo, el trastorno por estrés postraumático), psicosis no tratada, recaída y tratamiento (psicológico y farmacológico), además de los factores de riesgo en relación con el ámbito de las drogodependencias.

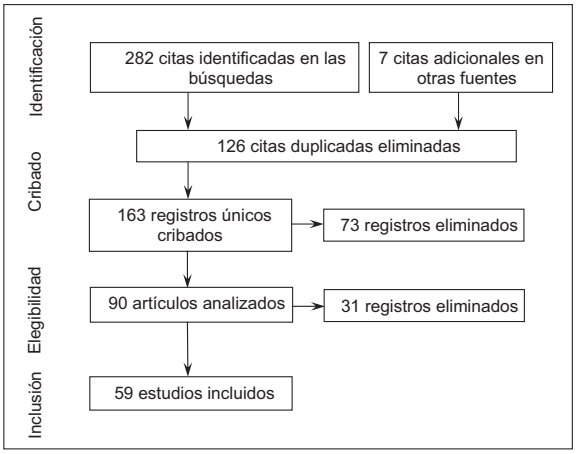

Figura 1. Diagrama de flujo de la información de la revisión bibliográfica.

Una vez obtenidos estos datos, se estructuraron para ser utilizados como fuente de información detallada. Primeramente, los artículos analizados se asignaron a las siguientes secciones temáticas (los artículos de las secciones temáticas están expuestos por orden de aparición en el texto): 1) modelo de vulnerabilidad al estrés; 2) AVE y PEP; 3) adolescencia: etapa de cambio; 4) afrontamiento, resiliencia y sucesos vitales estresantes, y 5) diferencias étnicas, AVE y PEP. Además, se dividió cada uno de los artículos en los siguientes criterios: a) autor y año; b) objetivos; c) método, y d) resultados y conclusiones.

Resultados

Modelo de vulnerabilidad al estrés

En esta sección se incluyeron un total de 14 artículos (ver tabla 1, estudios sección modelo de vulnerabilidad al estrés). El modelo de vulnerabilidad al estrés ha proporcionado un marco de referencia para tratar de entender la compleja interacción entre medio ambiente, estrés y sensibilidad latente en la expresión de la enfermedad psicótica. En consecuencia, un individuo con una alta predisposición y AVE está en alto riesgo de desarrollar síntomas de la enfermedad. Además, se considera vulnerabilidad como la evolución epigenética a través de las transacciones individuales y el medio ambiente durante toda la vida (aunque con importantes impactos desde la concepción hasta la adolescencia). En estas etapas vitales aparecen factores de protección y factores patógenos, tales como apoyo social o eventos vitales estresantes que pueden llegar a ser importantes (Brody[6], 1981).

Históricamente, la idea de que los AVE podían provocar un episodio psicótico proviene de regímenes de rehabilitación estrictos en hospitales psiquiátricos, donde estos estimulaban la reaparición de alucinaciones e ideas delirantes en individuos aparentemente estables (Nuechterlein y Dawson[7], 1984). Además, estudios previos sobre el estrés se han centrado en el impacto de los sucesos vitales como precursores de la aparición de la enfermedad y su exacerbación (Ventura et al.[8], 1989).

El modelo de vulnerabilidad al estrés asume que la probabilidad de desarrollar una enfermedad está en función de la magnitud de la vulnerabilidad biológica y la influencia de la tensión que el individuo tiene que afrontar. Un estudio destacable dentro del modelo es el de Van Os et al.[9] (1994). Se compararon pacientes con episodios provocados por sucesos vitales estresantes con aquellos cuyas recaídas no fueron precedidas por ese tipo de sucesos. En un seguimiento de 3 años, los primeros pacientes recibieron menos medicación antipsicótica y pasaron más tiempo en remisión. Este hecho sería consistente con el modelo de vulnerabilidad al estrés: pacientes con menos vulnerabilidad intrínseca (necesitan menos medicación y muestran una mejor remisión de los síntomas) requieren de acontecimientos estresantes para desencadenar una recaída.

La base teórica para la investigación prodrómica se encuentra en el modelo de vulnerabilidad al estrés de la esquizofrenia (Zubin y Spring[5], 1977), donde la vulnerabilidad y el PEP son vistos como un estado-rasgo, mientras los síntomas psicóticos se consideran que son provocados por los AVE o una situación de estrés prolongado. Precisamente, Rodríguez et al.[10] (1992) apuntaron que con estrés crónico aparece una incidencia significativamente más elevada de sujetos con diagnóstico psicótico y traumatismo agudo. Sin embargo, estos síntomas también pueden resolverse espontáneamente sin conducir a la psicosis (Yung y McGorry[11], 1996). Los sucesos vitales podrían tratarse como acontecimientos prodrómicos, que junto con otros, coadyuvarán a la aparición de sintomatología psicótica posterior. En cierto modo, es probable que la diversidad de influencias ambientales asociadas con la esquizofrenia pueda vincularse con un número igual de diferentes mecanismos subyacentes. Myin-Germeys et al.[12] (2005) proponen que la sensibilización en relación con el estrés ambiental puede interpretarse según la hipótesis de la sensibilización dopamínica de los síntomas psicóticos. Existe una hiperresponsividad de las neuronas dopamínicas a estímulos ambientales. Collip et al.[13] (2008) proponen que en la interacción de los factores epigenéticos, las exposiciones ambientales pueden inducir a alteraciones psicológicas y/o fisiológicas y, por lo tanto, a la sensibilización. En consecuencia, se facilita la instauración y la persistencia de síntomas psicóticos. Por otro lado, Mason et al.[14] (2004) investigaron si antecedentes familiares, complicaciones obstétricas, funcionamiento premórbido social, personalidad premórbida, AVE más recientes y síntomas actuales serían capaces de mejorar las predicciones de psicosis en un grupo de jóvenes identificados de alto riesgo. El estudio concluyó que la mitad de la muestra desarrolló un trastorno psicótico. Además, el predictor más fiable era el grado de presencia de características de personalidad esquizotípica. Ahora bien, la influencia de los AVE no tuvo una presencia significativa en el desarrollo de la psicosis. Otros estudios hacen hincapié en la existencia de déficits de procesamiento de la información, anomalías en la reactividad autonómica,

Tabla 1
Estudios sección modelo de vulnerabilidad al estrés

Autor y año	Objetivos	Método	Resultados y conclusiones
Brody[6] (1981)	Revisar estudios sobre la vulnerabilidad y el desarrollo de la esquizofrenia	Revisión	Se considera la vulnerabilidad como la evolución epigenética a través de las transacciones individuales y el medio ambiente durante toda la vida (aunque con importantes impactos desde la concepción hasta la adolescencia). En estas etapas vitales aparecen factores de protección y factores patógenos, tales como el apoyo social o los eventos vitales estresantes que pueden llegar a ser importantes. Además, el nivel socioeconómico parece tener una influencia importante de la infancia a la edad adulta
Nuechterlein y Dawson[7] (1984)	Crear un modelo teórico	Se presenta un modelo de PEP, basado en la evidencia de que ciertas características de los individuos pueden servir como factores de vulnerabilidad	Los factores ambientales estresantes pueden precipitar períodos psicóticos en individuos vulnerables. Algunos déficits de procesamiento de la información, anomalías en la reactividad autonómica, la competencia social y las limitaciones de afrontamiento son observados como factores de vulnerabilidad potenciales. Los factores de estrés en forma de acontecimientos vitales y el nivel de estrés social son factores que interactúan como características de vulnerabilidad, que conducen a episodios psicóticos. Aparece una distinción entre los indicadores de vulnerabilidad estable, por un lado, y los indicadores de desarrollo del episodio psicótico, por otro
Ventura et al.[8] (1989)	Incidencia de los AVE en la recaída o exacerbación psicótica	Estudio prospectivo, longitudinal, de 11 pacientes ambulatorios con esquizofrenia que cumplían criterios de recaída psicótica o exacerbación psicótica significativa durante un período de un año con medicación de mantenimiento, y 19 pacientes sin recaída durante este período de seguimiento. Se entrevistaron de manera mensual para evaluar los AVE	Los pacientes que recaen tienen un número significativamente mayor de AVE independientes
Van Os et al.[9] (1994)	Influencia de los AVE en el desarrollo de un PEP	La muestra está formada por 59 pacientes con PEP del Estudio Camberwell Collaborative Psychosis. Se revisó la experiencia de AVE previos al PEP. Fueron seguidos durante 42 meses	Del total, 30 pacientes (51%) habían experimentado un AVE en los 3 meses inmediatamente previos a la aparición del episodio. Sin embargo, 29 pacientes no habían experimentado ningún AVE
Rodríguez et al.[10] (1992)	Incidencia de los primeros eventos traumáticos de la vida, el estrés crónico durante el año anterior, y los AVE en los 6 meses anteriores a la primera hospitalización psiquiátrica	La muestra era de 25 pacientes de diferentes diagnósticos psicóticos y 24 pacientes ingresados para el tratamiento de traumatismo agudo. El cuestionario de evaluación era la Escala Paykel	Los pacientes con trastornos de estrés crónico fueron significativamente más frecuentes en ambos grupos de pacientes
Yung y McGorry[11] (1996)	Revisar la literatura sobre los pródromos e identificación de marcadores biológicos, en el proceso de conversión al PEP. Además, describe los síntomas, signos, patrones y duraciones de los pródromos de las psicosis que derivan en una esquizofrenia y psicosis afectivas	Revisión	Existe confusión sobre la naturaleza de las funciones prodrómicas y las preocupaciones con respecto a la fiabilidad de su medición. En este artículo se propone un modelo alternativo para conceptualizar los cambios prodrómicos (el modelo híbrido/interactivo). Se destaca la necesidad de una evaluación más sistemática de la fase prodrómica del PEP
Myin-Germeys et al.[12] (2005)	Investigar el impacto de la tensión de la vida diaria en la intensidad de la psicosis	Los pacientes con psicosis en remisión (n = 42), los parientes de primer grado (n = 47) y los sujetos control (n = 49) fueron estudiados a través de la evaluación del contexto actual y la psicopatología de la vida cotidiana. Se evaluó: a) el estrés subjetivo relacionado con los AVE, y b) la intensidad de las experiencias psicóticas en la vida cotidiana	Existe un aumento significativo en la intensidad de la psicosis asociada con un aumento en la actividad subjetiva y el estrés relacionado con el suceso vital en los pacientes. La sensibilización del comportamiento ante el estrés ambiental puede ser un marcador de vulnerabilidad para la esquizofrenia, lo que refleja la hiperresponsividad dopaminérgica en respuesta a los estímulos ambientales

Tabla 1 (*continuación*)

Autor y año	Objetivos	Método	Resultados y conclusiones
Collip et al.[13] (2008)	Revisar la importancia de diferentes factores ambientales en el desarrollo de enfermedades psicóticas	Revisión	Es probable que la diversidad de las influencias ambientales asociadas con la esquizofrenia pueda vincularse con muchos mecanismos subyacentes diferentes. Se dispone de indicios de que, en interacción con factores (epi)genéticos, las exposiciones ambientales pueden inducir alteraciones psicológicas o fisiológicas que pueden localizarse en una vía común final de sesgos cognitivos y/o una neurotransmisión alterada de la dopamina. Esta se relaciona con la sensibilización, lo que facilita la instauración y la persistencia de síntomas psicóticos. En las poblaciones expuestas a factores de riesgo ambientales asociados con estrés o fármacos agonistas de la dopamina, el fenotipo de conducta de sensibilización puede examinarse por cuantificación: a) del aumento de la tasa de persistencia (indicando una sensibilización duradera) de las expresiones evolutivas de experiencias psicóticas subclínicas normalmente transitorias, y b) del posterior aumento de la tasa de transición a trastornos psicóticos clínicos
Mason et al.[14] (2004)	Estudiar si las medidas de los antecedentes familiares, las complicaciones obstétricas, el funcionamiento social premórbido, la personalidad premórbida, los acontecimientos vitales y los síntomas psicóticos actuales podrían mejorar las predicciones de la psicosis en un grupo de jóvenes identificados en situación de riesgo	La muestra del estudio está formada por 74 sujetos seguidos al menos un año después de la evaluación inicial. La mitad de la muestra pasó a desarrollar un trastorno psicótico	El predictor más fiable era el grado de presencia de características de la personalidad esquizotípica. Sin embargo, los elementos individuales de la evaluación de creencias raras/pensamiento mágico, marcado deterioro en el desempeño de funciones, embotamiento afectivo o inapropiado, anhedonia/asociabilidad y alucinaciones auditivas también fueron altamente predictivos de la transición, dando una buena sensibilidad (84%) y especificidad (86%). Estos predictores están relacionados con un mal funcionamiento premórbido en el periodo anterior a la transición al trastorno psicótico.
Myin-Germeys et al.[15] (2001)	Investigar la interacción entre la vulnerabilidad personal y los factores de estrés ambientales, además de estudiar la reactividad emocional del estrés de la vida diaria, como un marcador de vulnerabilidad para la enfermedad psicótica	Los pacientes con enfermedad psicótica (n = 42), sus familiares de primer grado (n = 47) y los sujetos control (n = 49) fueron estudiados con el método de muestreo Experience Sampling Method (una técnica estructurada para evaluar los pensamientos, el contexto actual y el estado de ánimo en la vida cotidiana). Se evaluó: a) el estrés subjetivo de los acontecimientos diarios y las perturbaciones más pequeñas de la vida cotidiana, y b) la reactividad emocional (cambios tanto en el afecto negativo como en el positivo)	Un incremento en el estrés subjetivo se asoció con un aumento en el afecto negativo y una disminución en el afecto positivo en todos los grupos. Sin embargo, estos difieren cuantitativamente en su patrón de reacciones al estrés. Los pacientes con enfermedad psicótica reaccionan con emociones más intensas a las apreciaciones subjetivas de estrés en la vida cotidiana que los sujetos control. La disminución en el afecto positivo en los familiares fue similar a la de los pacientes. Los niveles más altos de riesgo familiar de psicosis se asociaron con niveles más altos de reactividad emocional a la tensión de la vida diaria. Alteraciones sutiles en la forma en que las personas interactúan con su entorno pueden constituir parte de la vulnerabilidad a la enfermedad psicótica.
Brenner et al.[16] (1987)	Estudio de las dimensiones de la esquizofrenia y los esfuerzos de autoprotección en pacientes con esquizofrenia, neuróticos y controles sanos	La muestra está compuesta por 60 pacientes con esquizofrenia, 30 pacientes neuróticos y 30 controles sanos. El instrumento de medida para la evaluación fue a través del Frankfurt Complaint Questionnaire	Los pacientes con esquizofrenia tenían ambas disfunciones (trastornos de la información y la experiencia subjetiva) con resultados significativos. Los pacientes con esquizofrenia experimentaban trastornos básicos de tensión mucho más emocional y angustia existencial

Tabla 1 (*continuación*)

Autor y año	Objetivos	Método	Resultados y conclusiones
Horan et al.[17] (2005)	Evaluar qué características de la personalidad están implicadas en la etiología y la expresión fenotípica de la esquizofrenia	La estabilidad de las 5 características de la personalidad derivadas del MMPI-168 fueron examinadas en pacientes con esquizofrenia de aparición reciente (n = 59) y en los controles sanos (n = 39). Entre los pacientes, también se examinaron asociaciones entre características de personalidad y los síntomas clínicos y la exposición a eventos vitales estresantes	Los pacientes tuvieron mayores niveles de neuroticismo, cinismo e ideación psicótica que los controles; además, la tendencia psicopática era de nivel más bajo, y también la negación de las quejas somáticas. Las diferencias individuales estables en la personalidad son detectables durante el curso temprano de la esquizofrenia y pueden ayudar a explicar la heterogeneidad de los síntomas clínicos y los resultados funcionales. Los sujetos con PEP informan de menos AVE que los sujetos control antes de la exacerbación de la enfermedad. Sin embargo, dichos eventos son percibidos como menos controlables y manejables
Norman y Malla[18] (1993)	Investigar la relación entre los factores de estrés de eventos vitales y la esquizofrenia; se revisa críticamente	Revisión crítica	De acuerdo con la opinión de que los pacientes que padecen esquizofrenia son vulnerables al estrés, existe evidencia de una relación entre los factores de estrés y la variación en la gravedad de los síntomas. No obstante, existe una correlación débil con relación a que los pacientes con esquizofrenia han tenido niveles más altos de factores estresantes que la población general o que los pacientes que sufren de otros trastornos psiquiátricos
Goldstein M. Psychosocial issues. Schizophr Bull. 1987;13(1):157–71.	Revisar la evidencia de las relaciones familiares estresantes como potenciadoras de la vulnerabilidad en la esquizofrenia	Revisión de la evidencia	Los factores de estrés, en particular los procedentes de la dinámica familiar, se examinan en relación con el curso de la esquizofrenia. Los datos de emoción expresada se han replicado más a menudo que no, las actitudes de alta emoción expresada. Las actitudes de emoción expresada no se relacionan tanto con la gravedad del trastorno de un familiar, pero sí pueden correlacionar con la cantidad de tiempo entre la aparición inicial de la enfermedad y primera hospitalización.

AVE: acontecimientos vitales estresantes; PEP: primer episodio psicótico.

competencia social y limitaciones de afrontamiento, que son observados como factores de vulnerabilidad potenciales en el desarrollo del PEP (Nuechterlein y Dawson[7], 1984).

También existe evidencia de que los acontecimientos estresantes acumulativos aumentan la reactividad emocional en pacientes con esquizofrenia, aumentando su vulnerabilidad (Myin-Germeys et al.[15], 2001; Myin-Germeys et al.[12], 2005; Brenner et al.[16], 1987). En consecuencia, existe un incremento de sensibilidad en el grado de percepción de los estímulos sensoriales y sociales. En esta línea, Horan et al.[17] (2005) concluyeron que sujetos con un PEP informaban de menos sucesos vitales estresantes que sujetos control antes de la exacerbación de la enfermedad. Sin embargo, dichos eventos son percibidos como menos controlables y manejables.

En síntesis, destaca una investigación de Norman y Malla[18] (1993) donde se revisaron 3 tipos de estudios. El primero, comparaba sujetos con esquizofrenia con otros pacientes psiquiátricos. El 56% de los estudios analizados mostraron mayores niveles de estímulos estresantes en otros pacientes psiquiátricos. En la segunda tipología de estudios, se compararon pacientes con esquizofrenia y sujetos de la población general. El 36% de las investigaciones analizadas presentaron mayores niveles de situaciones estresantes en sujetos con esquizofrenia. Por último, el tercer tipo de estudios relacionaba el momento de ocurrencia de los sucesos vitales estresantes y el empeoramiento de los síntomas. Se revisaron estudios que relacionaban el nivel de estrés con el de síntomas en sujetos con esquizofrenia. El 77% de los estudios resultaron ser estadísticamente significativos con mayores niveles de sucesos vitales estresantes que estaban asociados al inicio del empeoramiento de los síntomas. En definitiva, existe la tendencia de que los pacientes con esquizofrenia tienen niveles más elevados de factores estresantes que la población general o pacientes que sufren otros trastornos psiquiátricos.

Acontecimientos vitales en psicosis

En esta sección se incluyeron un total de 18 artículos (ver la tabla 2, estudios sección acontecimientos vitales en psicosis). Las personas con diagnóstico de esquizofrenia, al igual que el resto de la población, señalan un aumento en el estado de ánimo y los síntomas de ansiedad en respuesta a los AVE. Sin embargo, difieren de la población general en que están predispuestos a experimentar síntomas psicóticos, y también pueden sufrir exacerbaciones de los síntomas de estrés (Horan y Blanchard[19], 2003; Scholten et al.[20], 2006). Además, en las psicosis relacionadas con el estrés aparece una evolución más rápida y completa de la enfermedad (Pedrós et al.[21], 2005).

El concepto de acontecimiento vital es complejo. Implica que no solo las enfermedades psiquiátricas son iniciadas por interacciones entre entorno e individuo, sino que los sucesos vitales modifican dicha interacción. Cornes[22] (1994) define los AVE como sucesos que directa o indirectamente afectan de forma subjetiva y/u objetiva a un individuo y que amenazan con romper sus actividades cotidianas normales y sus recursos de afrontamiento. En general, se acepta la idea de que los AVE pueden desempeñar un papel etiológico en los trastornos afectivos (Lukoff et al.[23], 1984; Day et al.[24], 1987). No obstante, en la psicosis la influencia de los acontecimientos

Tabla 2
Estudios sección acontecimientos vitales estresantes y primer episodio psicótico

Autor y año	Objetivos	Método	Resultados y conclusiones
Horan y Blanchard[19] (2003)	Examinar la asociación entre los rasgos afectivos, el estilo de afrontamiento, el funcionamiento neurocognitivo y las respuestas emocionales subjetivas ante interacciones sociales estresantes en personas con esquizofrenia	La autovaloración del estado de ánimo se evaluó en pacientes ambulatorios con esquizofrenia varones (n = 36) y controles pareados no psiquiátricos (n = 15) durante una prueba de role playing que comprende situaciones sociales simuladas que requieren habilidades asertivas	Los resultados proporcionan apoyo para la validez de la prueba de role playing social como paradigma para examinar el estrés psicosocial en la esquizofrenia. Plantean que el rasgo de afectividad negativa y mala adaptación de afrontamiento se relacionan con las diferencias individuales en las respuestas emocionales al estrés psicosocial en la esquizofrenia. Durante la prueba de role playing, los pacientes con esquizofrenia y los controles reportaron elevaciones similares en el estado de ánimo negativo y disminución en el estado de ánimo positivo, en comparación con el estado de ánimo de referencia durante las escenas
Scholten et al.[20] (2006)	Examinar la sensibilidad al estrés del sistema de inhibición conductual, y el sistema de activación conductual en la esquizofrenia y su relación con la psicopatología y la fisiología	La muestra está compuesta por 42 pacientes con esquizofrenia (26 hombres y 16 mujeres) y 37 controles sanos (17 hombres y 20 mujeres). Fueron evaluados con el uso de inhibición de la conducta y escalas de activación de la conducta. Además, se evaluaba el aumento de la frecuencia cardíaca media y la disminución de la variabilidad del ritmo cardíaco	En el sistema de inhibición conductual, los pacientes mostraron una mayor sensibilidad a la amenaza que los sujetos control. Los pacientes con esquizofrenia (mujeres y hombres) son más sensibles a la amenaza que los controles sanos. Este hecho puede reflejar una característica relacionada con el rasgo, y no se refleja en las medidas psicofisiológicas relacionadas con el estado
Pedrós et al.[21] (2005)	Analizar las características clínicas, sociodemográficas, así como los factores predisponentes y desencadenantes de un grupo de pacientes con psicosis agudas	Se estudian pacientes ingresados diagnosticados de trastorno psicótico breve, trastorno psicótico no especificado, trastorno psicótico inducido por sustancias y trastorno esquizofreniforme. La muestra estaba comprendida por 58 pacientes ingresados. Se utilizó como instrumento la Entrevista Estructurada para la Valoración de Episodios Psicóticos Agudos. Además, se recogió información sociodemográfica, clínica, así como de factores predisponentes, desencadenantes y de evolución del episodio psicótico agudo	El estrés parece ejercer un papel determinante en el trastorno psicótico breve y no especificado. La evolución es más rápida y completa en las psicosis relacionadas con el estrés
Cornes[22] (1994)	Efectuar una aproximación a la estructura y funciones del apoyo social. Establecer la relación y posibles mecanismos explicativos del apoyo social sobre la salud física y mental	Análisis de los modelos explicativos	El apoyo social disponible, accesible, percibido y adecuado constituye un recurso de significativa importancia para la protección y promoción de la salud física y mental
Lukoff et al.[23] (1984)	Revisar estudios sobre el PEP y la vulnerabilidad	Revisión	Estudios recientes han aislado factores socioambientales que parecen predecir la aparición de PEP en personas vulnerables. En particular, los AVE se han encontrado entre las 3 y las 4 semanas anteriores al episodio psicótico. Además, los AVE, como por ejemplo una gran movilidad geográfica, juegan un papel activo en la precipitación de la aparición de los episodios de enfermedad en muchos sujetos con esquizofrenia. También se ha encontrado que actitudes hostiles, críticas y de sobreprotección emocional en el entorno familiar hacia el paciente están relacionadas con las recaídas. Asimismo, irregularidades en el estilo de comunicación de los padres también predicen el posterior desarrollo de trastornos del espectro esquizofrénico entre adolescentes con factores predisponentes. Muchos pacientes con esquizofrenia tienen dificultades en habilidades de afrontamiento para actuar ante las pérdidas causadas por sucesos vitales o para resolver de manera eficaz situaciones familiares estresantes. Por lo tanto, pueden experimentar un nivel mayor y más prolongado de estrés debido a la inadecuación de las habilidades sociales, de resolución de problemas y de las redes sociales de apoyo

Tabla 2 (*continuación*)

Autor y año	Objetivos	Método	Resultados y conclusiones
Day et al.[24] (1987)	Informar sobre los resultados de una investigación transnacional sobre los AVE y la esquizofrenia	La muestra es de 386 pacientes con un episodio psicótico seleccionados de 9 centros de investigación de campo ubicados en los países desarrollados y en desarrollo (Aarhus, en Dinamarca, Agra, en India, Cali, en Colombia, Chandigarh, en India, Honolulu, en EE. UU., Ibadán, en Nigeria, Nagasaki, en Japón, Praga, en República Checa, Rochester, en EE. UU.)	Los factores de estrés socioambientales pueden precipitar episodios psicóticos, y estos eventos tienden a agruparse en el plazo de 2 a 3 semanas inmediatamente anteriores al inicio de la enfermedad
Al Khani et al.[25] (1986)	Investigar si existe una asociación entre el PEP y los AVE	La muestra está compuesta por 48 sujetos con PEP de entre 14 y 44 años, de la población de la región Najd (Arabia Saudita), y 62 sujetos control. Se recogieron las historias de sucesos vitales 6 meses antes de la aparición o la recaída comparados con 62 controles. Se utiliza una versión en árabe de la Present State Examination, complementado por el programa informático de clasificación CATEGO	Existe una asociación positiva entre los sucesos y el inicio del episodio psicótico, solo para mujeres casadas, aunque hubo una tendencia paralela entre hombres y mujeres solteros que sufren un PEP. El impacto observado de acontecimientos vitales se limitaba a las 3 semanas antes de su inicio. Los resultados se discuten a la luz de la cultura saudí, que está cambiando rápidamente debido al desarrollo económico
Jones et al.[26] (1993)	Investigar el tiempo y los precursores del déficit social en la esquizofrenia y las psicosis afectivas	La muestra está formada por 195 sujetos con PEP y clase social baja (Estudio Camberwell Collaborative Psychosis)	Existe una disminución en el estatus social, después de la aparición de la psicosis. Estos resultados indican que hay factores sociales que pueden influir en la aparición de la psicosis
Raune et al.[27] (2009)	Probar la hipótesis de que los AVE, en particular los intrusivos, se agruparían antes de la primera aparición de la psicosis	La muestra está formada por 41 pacientes con un PEP. Se entrevistaron sobre los AVE y las dificultades en la planificación para evaluar los sucesos un año antes de la aparición de la enfermedad	Los sucesos eran muy frecuentes en el año anterior al inicio de la psicosis. Los AVE eran más comunes en los 3 meses antes de la aparición en comparación con los últimos 9 meses. Los pacientes con PEP tenían significativamente más probabilidades de presentar un evento intrusivo en los 3 meses antes de la aparición (OR = 17,1; 34 vs. 3%). Los sucesos vitales pueden ser factores que predisponen en muchos casos a un PEP. El efecto emerge varios meses antes de la aparición, sobre todo si los eventos son intrusivos
Rusaka y Rancans[28] (2013)	Explorar el primer episodio de TPAT, describiendo las características clínicas, analizando los cambios longitudinales de diagnóstico y asociados a las características sociodemográficas	Revisión retrospectiva de los pacientes hospitalizados por primera vez que cumplían criterios de la CIE-10 para TPAT atendidos en el Centro de Psiquiatría de Riga, Trastornos de adicción, en Letonia, durante un período de 3 años. Los pacientes fueron seguidos y evaluados con instrumentos estandarizados. La muestra fue de 294 pacientes	Los AVE en los 6 meses previos al PEP se encontraron en el 44% de los pacientes
Leff y Vaughan[29] (1980)	Estudiar cuál es la incidencia de los AVE 3 meses antes de la aparición de un PEP	Se registró la historia de AVE en los 3 meses antes de la aparición de la enfermedad. La muestra estaba compuesta por un grupo de pacientes con esquizofrenia y un grupo de sujetos con depresión neurótica. Se midió la EE de los familiares clave de los pacientes	No hubo diferencias entre los pacientes con esquizofrenia y los sujetos con depresión en la tasa de eventos en el período de 3 meses antes de la aparición. Sin embargo, los 2 grupos mostraron significativamente diferentes patrones de interacción entre los AVE y la EE de los familiares. Los pacientes con esquizofrenia que viven con familiares de alta EE tenían una baja tasa de sucesos vitales en comparación con los que viven con parientes con un bajo nivel de EE. En cambio, los sujetos con depresión que viven con familiares con altos niveles de crítica tuvieron una alta tasa de eventos en comparación con los que viven con familiares con bajo nivel de crítica
Cullberg[30] (2003)	Investigar la frecuencia y los tipos de AVE que preceden el PEP	Pacientes con PEP de 18-45 años. Es un estudio longitudinal de 2-3 años. No se utilizan instrumentos, sino la experiencia clínica del autor	Un AVE no puede ser considerado la «causa» del PEP, sino un factor de impulso más o menos importante. Esta es una interacción complicada entre los factores de vulnerabilidad biológicos y psicológicos

Tabla 2 (*continuación*)

Autor y año	Objetivos	Método	Resultados y conclusiones
Canton y Fraccon[31] (1985)	Comparar los AVE entre sujetos con un PEP y sujetos control	Administración de la entrevista (Paykel's Interview for Recent Life Events) de los últimos sucesos vitales. La muestra estaba formada por 54 pacientes con esquizofrenia (edad promedio de 30,3 años) emparejados por edad, sexo, estado civil y clase social, con 54 sujetos control. La entrevista se realizó sobre eventos que sucedieron en los 6 meses antes de ingresar por PEP. Los sujetos control fueron entrevistados en la fase de screening	Los sujetos con esquizofrenia indican más AVE que los controles en las áreas de trabajo, salud y relaciones sociales y familiares. Además, experimentaron más eventos de impacto negativo de moderado a severo. Estos resultados confirman la hipótesis de que los AVE pueden, en muchos pacientes, ser considerados factores de riesgo para el desarrollo de un PEP
Rabkin[32] (1980)	Evaluar los estudios publicados sobre la frecuencia y la naturaleza de los AVE en pacientes con esquizofrenia	Se identifican 3 diseños de estudios: el primero, la correlación entre pacientes con esquizofrenia y otros sujetos psiquiátricos; el segundo, pacientes con esquizofrenia y sujetos control (sin enfermedad psiquiátrica); el tercer estudio lo formaban pacientes que habían recaído y sujetos sin recaída	La evidencia indica una relación débil entre los AVE y el PEP. Sin embargo, aparecen patrones de estrés que influyen en el tiempo y la probabilidad de aparición de la enfermedad
Renwick et al.[33] (2009)	Analizar la relación entre la percepción individual de la tensión y la sintomatología en sujetos con un PEP en la presentación a los servicios comunitarios de salud mental	Se evaluaron 123 personas con medidas estandarizadas de síntomas, calidad de vida, estrés percibido, funcionamiento global y duración de la psicosis sin tratar. Se utilizó el cuestionario The Psychosis Screening Questionnaire	Los sujetos con más síntomas depresivos y con una reducción en el funcionamiento general eran más propensos a tener mayores niveles de estrés percibido. Las personas con menos síntomas positivos estaban experimentando mayores niveles de estrés subjetivo. Según el modelo de vulnerabilidad al estrés, el funcionamiento y los síntomas pueden influir en la evaluación individual del estrés
Bechdolf et al.[34] (2010)	Replicar el hallazgo de alta prevalencia de historia de trauma en pacientes con UHR con trastorno psicótico. Investigar si el trauma predice la conversión a psicosis en pacientes con UHR	Para evaluar la historia de trauma se administró el General Trauma Questionnaire. La muestra fue de 92 pacientes con UHR	El 70% de la muestra había experimentado un AVE. El 21,7% desarrolló un PEP durante el seguimiento (media de 615 días). Los pacientes que habían experimentado un trauma sexual (36%) eran significativamente más propensos a desarrollar un PEP (OR 2,96). Los pacientes UHR tienen una alta prevalencia de historia de trauma. El trauma sexual anterior puede ser un predictor de la aparición de trastorno psicótico en esta población
Pruessner et al.[35] (2011)	Comparar los niveles de estrés mediante autoinforme de la autoestima, apoyo social y afrontamiento activo	La muestra está compuesta por 32 pacientes con PEP, 30 individuos en psicosis UHR) y 30 controles sanos. La recogida de datos se realizó a través de autoinformes	Las personas en UHR tuvieron niveles significativamente más altos de estrés en comparación con los pacientes con PEP. Ambos grupos de pacientes mostraron una autoestima más baja en comparación con los controles, y el grupo UHR resultó tener menor apoyo social y afrontamiento activo que los controles. Estas diferencias entre los grupos no se podrían explicar por la edad y la dosis de la medicación antipsicótica en el grupo de PEP. En el grupo de UHR, mayores niveles de estrés y baja autoestima se asociaron con síntomas positivos y depresivos más graves. Los análisis de regresión múltiple mostraron que el estrés era el único predictor significativo para ambas medidas de los síntomas y que la relación no fue moderada por la autoestima
Casado y Vaz[36] (1998)	Demostrar la relación entre los AVE y la esquizofrenia en una muestra de pacientes	La muestra estaba compuesta por 129 pacientes, de los cuales 54 ingresaron de forma voluntaria y 75 lo hicieron de forma involuntaria. Fueron ingresados a lo largo de 24 meses en la Unidad de Agudos del Hospital Psiquiátrico de Mérida (Badajoz). Se les aplicó el cuestionario de cambios vitales de Paykel, Prusoff y Uhlenhut (1971)	Existe la presencia de determinados factores psicosociales, con cierto valor patógeno, que pueden provocar una modificación importante en la vida del sujeto con esquizofrenia y exige una respuesta de adaptación. Los cambios vitales más estresantes son aquellos relacionados con determinadas situaciones personales y familiares

AVE: acontecimientos vitales estresantes; EE: Emoción Expresada; PEP: primer episodio psicótico; TPAT: trastorno psicótico agudo y transitorio, F23, CIE-10; UHR: ultra-high risk.

vitales no está ampliamente estudiada. La investigación que examina la relación entre sucesos vitales y la aparición del PEP se puede dividir en 2 grupos principales. El primer grupo de estudios está formado por los que han localizado un aumento significativo en los acontecimientos vitales independientes. Dichos eventos son aquellos que no están influidos o causados por el comportamiento del propio individuo; por ejemplo, la muerte de un ser querido. Aparecen autores que estudian la etiología del PEP que demuestran que existe una incidencia mayor de AVE de diversa gravedad durante un intervalo de 3 semanas antes de la presentación del PEP (Lukoff et al.[23], 1984; Al Khani et al.[25], 1986; Day et al.[24], 1987). También, Jones et al.[26] (1993) apuntan que existe una relación significativa entre los acontecimientos vitales y el inicio del episodio psicótico. En la misma línea, Van Os et al.[9] (1994)

muestran que el 51% de los pacientes con PEP había experimentado un AVE en los 3 meses anteriores a la aparición del primer episodio. De modo similar, Raune et al.[27] (2009), con una muestra de 41 pacientes con PEP, hallaron que los sucesos estresantes fueron más comunes en los 3 meses antes de la aparición en comparación con los últimos 9 meses. Del mismo modo, Rusaka y Rancans[28] (2013) concluyen que el 44% de los pacientes con trastorno psicótico agudo sufrieron un AVE en los 6 meses previos al PEP. Si bien Leff y Vaughan[29] (1980) informan de la no existencia de relación entre sucesos vitales y la aparición de un PEP. Sin embargo, existe como factor independiente moderador que puede interferir, la emoción expresada. Esta implicación emocional familiar media y condiciona el afrontamiento del sujeto ante el AVE.

El segundo grupo de estudios lo constituyen los que han hallado un aumento en el número de los sucesos vitales antes de la aparición del PEP. Desde un punto de vista cuantitativo, la acumulación de elementos estresantes supone una mayor amenaza para el ajuste. Cullberg[30] (2003) concluyó que una situación estresante no puede ser considerada como causa de psicosis, sino como un factor de impulso. Canton y Fraccon[31] (1985) mostraron que sujetos con esquizofrenia tenían más AVE que sujetos control en las áreas de trabajo, salud y relaciones sociales/familiares. Asimismo, pacientes con esquizofrenia experimentaron más eventos de impacto negativo, moderados y severos. Sin embargo, la ocurrencia de los acontecimientos vitales no es independiente de la influencia de la conducta del individuo. Los sucesos vitales *no independientes*, como por ejemplo ser despedido de un trabajo, un divorcio o un examen, pueden reflejar el período prodrómico de la enfermedad o un proceso psicótico en curso. Zubin y Spring[5] (1977) identificaron los procesos por los cuales sujetos con esquizofrenia a menudo tienen un exceso de acontecimientos vitales denominado *tendencia vital a patrones de estrés*. Esta predisposición aumenta el nivel de estrés e influye en el tiempo y en la probabilidad de aparición de la enfermedad (Rabkin[32], 1980). En relación con la percepción individual de la tensión y sintomatología en pacientes con PEP, Renwick et al.[33] (2009) indicaron que sujetos con más síntomas depresivos mostraban mayores niveles de estrés percibido.

Los acontecimientos vitales extraordinarios y/o traumáticos forman parte del continuum en la psicosis. Bechdolf et al.[34] (2010) apuntaron que sujetos con alto riesgo *(ultra high risk)* de padecer psicosis tienen una alta predicción de historia de trauma. Por lo tanto, experiencias traumáticas conducen a una mayor sensibilidad al estrés y ello puede contribuir al desarrollo de un PEP bajo circunstancias estresantes (Pruessner et al.[35], 2011). Los cambios vitales que se consideran más estresantes son los relacionados con situaciones familiares o personales, como en el área académica, laboral, vida amorosa y matrimonio, residencia, asuntos legales y actividades sociales (Casado y Vaz[36], 1998).

Adolescencia: etapa de cambio

En esta sección se incluyeron un total de 7 artículos (ver tabla 3, estudios sección adolescencia: etapa de cambio). La adolescencia es una etapa vital caracterizada por profundas transiciones. La aparición de numerosos e intensos cambios ha llevado a considerarla como una etapa especialmente vulnerable a la experimentación de estrés psicosocial. Estudios realizados en población normativa apuntan que en la adolescencia se produce un aumento considerable en la frecuencia de AVE (Ge et al.[37], 1994).

Los resultados disponibles hasta el momento reflejan que los AVE más importantes en esta etapa tienden a ser eventos no normativos, es decir, sucesos que son menos frecuentes. Según la revisión de la literatura realizada por Jiménez et al.[38] (2008) de los sucesos no normativos, destacan la muerte de un progenitor, el divorcio de los progenitores, el ingreso en prisión de algún miembro de la familia, el embarazo propio o de la pareja y el desempleo parental. Entre los sucesos de carácter normativo, es decir, que se suelen experimentar con frecuencia durante la adolescencia (preocupaciones, dificultades y tensiones cotidianas), predominan los que provienen del ámbito familiar y del grupo de iguales. En referencia al contexto de desarrollo, es importante destacar el ámbito escolar. Lemos[39] (1989) apunta que futuros sujetos del espectro psicótico habían presentado conductas perturbadoras en el colegio. En definitiva, adolescentes que posteriormente desarrollarán un problema psicológico de tipo psicótico suelen exhibir una serie de cambios emocionales, comportamentales, del pensamiento y del lenguaje, así como de personalidad y relaciones sociales, antes del inicio del problema (Keshavan et al.[40], 2005; Yung et al.[41], 2006).

En lo que refiere al ajuste premórbido de los sujetos con PEP, solo si se conoce el grado de madurez relacional, cognitiva y comportamental del individuo antes del inicio del episodio, tiene una implicación directa en aspectos que preceden y pertenecen al trastorno como el curso, la respuesta al tratamiento y los síntomas actuales (Johnstone et al.[42], 1990). En esta línea, existe un potencial pronóstico del ajuste premórbido en todas las psicosis y existen conductas observables en el medio escolar y social años antes del inicio del PEP, es decir, aparece un déficit relacional en la vulnerabilidad del propio sujeto (Stranghellini[43], 2000).

Afrontamiento, resiliencia y sucesos vitales estresantes

En esta sección se incluyeron un total de 8 artículos (ver la tabla 4, estudios sección afrontamiento, resiliencia y sucesos vitales estresantes). Cualquier acontecimiento puede llegar a ser un factor estresante en algún momento, en función, no solo del tipo de circunstancia de que se trate, sino también de cómo la persona responda o afronte dicha circunstancia (Cornes[22], 1994). El estrés se basa en la evaluación de la perturbación por parte del individuo. Sin esta evaluación, el estrés psicológico no existiría, independientemente del grado de peligro real para el organismo (Lazarus[44], 1993). Inicialmente, lo estresante depende de las cualidades del ambiente y de la evaluación de los propios recursos para abordar la situación. Durante el curso del episodio estresante, la persona juzga continuamente el grado en que sus esfuerzos de afrontamiento son exitosos. En dicha evaluación aparece la consideración de ser o no un suceso vital estresante. Además, dichos acontecimientos y el nivel de estrés social se consideran factores que interactúan como características de vulnerabilidad en el desarrollo de un episodio psicótico (Nuechterlein y Dawson[7], 1984).

Las estrategias de afrontamiento y habilidades cambian con el curso de la enfermedad. Las personas pueden modificar la evaluación de los acontecimientos con el fin de comprender y atribuir significado a ellos mismos (Phillips et al.[45], 2007), es decir, ser sujetos resilientes. La resiliencia es un proceso en el que el individuo está expuesto a un elevado nivel de estrés y sus esfuerzos para afrontarlo terminan por una adaptación positiva, a pesar de sufrir agresiones a lo largo del proceso de desarrollo (Monroy y Palacios[46], 2011).

La relación que existe entre la evaluación y afrontamiento de los AVE y las diferencias de género es un tema polémico. En general, los datos disponibles no permiten confirmar la existencia de diferencias entre hombres y mujeres en la acumulación de elementos estresantes. Los estudios más recientes indican que ambos experimentan un número similar de dificultades en sus vidas (Jiménez et al.[38], 2008; Oliva et al.[47], 2008). No obstante, los resultados relativos al impacto emocional causado por estos eventos son menos concluyentes. Algunos estudios no han hallado diferencias significativas en cómo hombres y mujeres perciben los sucesos estresantes (Kim et al.[48], 2003; Oliva et al.[47], 2008). Sin embargo, otros autores han confirmado tales diferencias, indicando que las mujeres suelen sentirse más afectadas emocionalmente por la presencia

Tabla 3
Estudios sección adolescencia: etapa de cambio

Autor y año	Objetivos	Método	Resultados y conclusiones
Ge et al.[37] (1994)	Estudiar la afectación de los AVE, sintomatología depresiva y divorcio	Estudio longitudinal de sujetos con sintomatología depresiva entre 550 hombres y mujeres que crecen en familias divorciadas y no divorciadas en el medio oeste rural (EE. UU.)	Se demuestra que, en primer lugar, los síntomas depresivos cambian de acuerdo con un patrón curvilíneo, especialmente para las mujeres. De modo que aumentan a principios de la media adolescencia y posteriormente disminuyen de la adolescencia tardía a la edad adulta. En segundo lugar, las mujeres experimentaron un mayor número de síntomas depresivos en la adolescencia y la edad adulta temprana. En tercer lugar, los varones que experimentaron el divorcio de los padres a los 15 años, manifestaron un aumento agudo de los síntomas depresivos en comparación con los de las familias en las que no hay divorcio. En cuarto lugar, los AVE en niños después del divorcio de los padres son mediados por los síntomas depresivos. En quinto y último lugar, los AVE, en particular los relacionados con la relación y la pérdida de personas, varían con el tiempo y se asociaron significativamente con las diferentes trayectorias de los síntomas depresivos. Además, con población adolescente normativa se produce un aumento considerable en la frecuencia de AVE
Jiménez et al.[38] (2008)	Analizar cuantitativa y cualitativamente el estrés psicosocial experimentado por una amplia muestra de adolescentes, y explorar posibles diferencias en esta dimensión entre chicos y chicas	La muestra consistió en 623 chicos y chicas de entre 11 y 17 años de edad. Se aplicó el Inventario de Acontecimientos Vitales Estresantes	Los resultados obtenidos mostraron la relevancia de determinados AVE durante la adolescencia, particularmente los relacionados con el ámbito escolar y familiar. En segundo lugar, se observó la existencia de un patrón compartido en el modo en que chicos y chicas experimentan estrés psicosocial durante la adolescencia. Asimismo, aparecen diferencias significativas entre unos y otras en cuanto al tipo de situaciones más frecuentes y el impacto emocional con que se viven
Lemos[39] (1989)	Analizar la relación entre los rasgos de personalidad y la aparición de esquizofrenia	Revisión	Se describen los puntos de vista categoriales y dimensionales sobre la naturaleza de este trastorno. Se analizan los criterios diagnósticos de la personalidad esquizotípica, matizando que en la noción de esta entidad diagnóstica han confluido 2 corrientes diferentes. La primera es la conocida como familiar, que acentúa los rasgos distintivos que se han observado en familiares de sujetos con enfermedad psicótica. La segunda constituye un enfoque clínico centrado en pacientes que, sin manifestar un diagnóstico típico de esquizofrenia, presentan de manera atenuada algunas características que forman parte de los síntomas fundamentales de la esquizofrenia. Finalmente, se revisan las investigaciones longitudinales realizadas sobre cohortes de alto riesgo y se derivan algunas conclusiones en torno al conocimiento que actualmente se tiene sobre la relación personalidad-esquizofrenia. La impresión clínica, sin embargo, parece indicar que las características premórbidas de la personalidad o precursores etiológicos de la esquizofrenia estarían relacionadas con los rasgos negativos observados en la investigación familiar
Keshavan et al.[40] (2005)	Estudiar una visión general de teorías y las limitaciones de los estudios sobre familiares de jóvenes con UHR. Se ofrece un resumen de los datos de los estudios en curso de familiares jóvenes en situación de riesgo para la esquizofrenia en Pittsburgh	Revisión	Estos datos pueden ayudarnos a predecir la posible aparición de la esquizofrenia, y su espectro en esta psicopatología

Tabla 3 (*continuación*)

Autor y año	Objetivos	Método	Resultados y conclusiones
Yung et al.[41] (2006)	Determinar la validez predictiva de los criterios para la identificación de los sujetos en situación de riesgo para la aparición de un episodio psicótico	La muestra está compuesta por 292 sujetos de 15-24 años que fueron remitidos, pero no necesariamente tratados, a un servicio psiquiátrico. El estado de UHR se determinó al inicio del estudio y el estado de psicosis se evaluó a los 6 meses de seguimiento. El funcionamiento psicosocial también se evaluó como un posible factor de predicción de la psicosis. En la muestra de 292 sujetos, 119 (40,7%) cumplieron criterios de UHR. De estos sujetos UHR, 12 se convirtieron en sujetos psicóticos a los 6 meses, y 107 no lo hicieron	Los individuos UHR fueron significativamente más propensos a convertirse en sujetos psicóticos
Johnstone et al.[42] (1990)	Analizar los pacientes con PEP en términos de ocupación y en número de días de hospitalización desde el PEP, en relación con los servicios sociales, el comportamiento, el estado mental y las medidas neurológicas en el ingreso inicial	El resultado se evaluó a los 2 años de que los pacientes fueran elegidos para el estudio de PEP en términos de ocupación (n = 237) y en términos de número de días de hospitalización desde el momento del primer ingreso (n = 252)	Aparecieron signos de inactividad, disminución de las presentaciones sociales y más signos neurológicos leves. Si existen manifestaciones tempranas, solo en la medida en que se logra y se conoce el grado de madurez relacional, cognitiva y comportamental que ha alcanzado un individuo antes del inicio del PEP, puede relacionarse y tiene una implicación directa en aquellos aspectos que preceden el trastorno con aquellos pertenecientes a este, como son el curso, la respuesta al tratamiento y los síntomas actuales
Stranghellini[43] (2000)	Describir el estado actual y las posibles investigaciones futuras sobre las dimensiones de vulnerabilidad y los trastornos del sentido común	Análisis cualitativo y cuantitativo para la evaluación de la interacción entre las dimensiones de vulnerabilidad y los trastornos del sentido común	Existen 3 dimensiones de la vulnerabilidad en la esquizofrenia, que son las siguientes: la sensorial, la conceptual y la actitudinal. Los trastornos sensoriales son aberraciones de la percepción. Los trastornos de la conceptualización son trastornos en la atribución de significados e intenciones. Y por último, los trastornos actitudinales consisten en excentricidades en la estructura de la persona de valores y creencias, que se caracterizan por la desconfianza hacia el conocimiento convencional y la sintonía

AVE: acontecimientos vitales estresantes; PEP: primer episodio psicótico; UHR: ultra-high risk.

de circunstancias de estrés que los hombres. Las mujeres tienen más probabilidades de experimentar problemas de internalización, depresión y ansiedad que los hombres en la etapa adolescente, independientemente del país y de la cultura (Abad et al.[49], 2000; Lemos et al.[50], 2002). En la misma línea, Pedrós y Tenías[51] (2006) confirman que el factor estudiado relacionado con el desarrollo de un PEP en las mujeres es el estrés, mientras que en los hombres es el consumo de drogas.

Diferencias étnicas y primer episodio psicótico

En esta sección se incluyeron un total de 12 artículos (ver tabla 5, estudios sección diferencias étnicas y primer episodio psicótico). Las diferencias étnicas tienen impacto en los AVE y el PEP. Morgan et al.[52] (2009) investigaron la prevalencia y los correlatos sociales de la psicosis en una muestra de población general de británicos de raza negra y blanca. Los resultados mostraron que existe una mayor prevalencia de AVE –del 19%– en sujetos del Caribe negro y en sujetos de raza negra, pero no africanos. Uno de los motivos por el cual existía una alta prevalencia de sujetos del Caribe negro se explicó por los altos niveles de desventaja social. También Morgan y Fearon[53] (2007) apuntaron que poblaciones africanas del Caribe negro en el Reino Unido tienen más riesgo de padecer un PEP, en comparación con la población británica de raza blanca. Igualmente, Le Roux et al.[54] (2007) investigaron el papel de los rituales de iniciación de la cultura *xhosa* (tribu de Sudáfrica). Los resultados evidenciaron que el 10,7% de la muestra con diagnóstico de esquizofrenia manifestaba que los ritos de iniciación eran percibidos como sucesos vitales estresantes. Estos datos evidencian que las experiencias sociales adversas son relevantes etiológicamente en el desarrollo del PEP (Harland[55] et al., 2004; Cooper[56], 2005; Selten y Cantor-Graae[57], 2005). La alta incidencia de esquizofrenia en los grupos de inmigrantes y minorías étnicas es uno de los hallazgos más consistentes en epidemiología psiquiátrica (Cantor-Graae y Selten[58], 2005; Sharpley et al.[59], 2001).

Los descubrimientos más sólidos hasta el momento sobre las diferencias étnicas van en la línea de la separación temprana o por la pérdida de un progenitor. Como bien sabemos, las experiencias de separación pueden dar lugar a consecuencias significativas y duraderas en el establecimiento de vínculos seguros y estables. También, la separación de los padres o la pérdida de un progenitor se asocia con una gama de experiencias tempranas adversas, incluyendo conflictos familiares, problemas socioeconómicos, situaciones de abandono y abuso (Rutter[60], 2007). No obstante, Gureje y Adewunmi[61] (1988), en el contexto de la cultura nigeriana, encuentran que el inicio del PEP no fue precedido por un aumento de los AVE. El estudio estaba formado por un grupo de sujetos con PEP y otro grupo control. Se concluyó que los sujetos control habían experimentado más sucesos vitales el mes anterior a la entrevista. Estos sujetos eran varones control, donde el papel de la familia era notable.

Las revisiones recientes refutan la idea de que la incidencia de la esquizofrenia es uniforme en todo el mundo y que, por consiguiente, esta enfermedad tendría que ser básicamente

Tabla 4
Estudios sección afrontamiento, resiliencia y sucesos vitales estresantes

Autor y año	Objetivos	Método	Resultados y conclusiones
Lazarus[44] (1993)	Investigar el afrontamiento como concepto clave para la teoría y la investigación sobre la adaptación y la salud	Artículo teórico	Se contrastan 2 enfoques: el afrontamiento como una característica de la personalidad y el afrontamiento como proceso adaptativo
Phillips et al.[45] (2007)	Estudiar las experiencias de estrés en adolescentes que han sido identificados como de alto riesgo	Artículo teórico	La investigación de las experiencias de estrés de los jóvenes que han sido identificados como en riesgo mayor de desarrollar un trastorno psicótico también daría lugar a una comprensión más completa de la relación entre la experiencia de estrés y la aparición del trastorno psicótico
Monroy y Palacios[46] (2011)	Revisar el concepto de resiliencia, aspectos biológicos, formas en las que se puede medir y posibles intervenciones	Revisión	Además de los aspectos biológicos, para el estudio de la resiliencia se tienen en cuenta otros factores que podrían contribuir a que el proceso resiliente se inicie o no, como los factores de riesgo y vulnerabilidad, y los factores protectores. Estos factores se estudian en 3 áreas: los propios de los niños, en el ambiente familiar y en la comunidad
Oliva et al.[47] (2008)	Analizar el impacto de la ocurrencia de AVE en el ajuste adolescente	La muestra fue de 101 adolescentes estudiados en 2 momentos temporales, cuando se encontraban en la adolescencia media (15-16 años) y 2 años después (17-18 años). Los participantes se evaluaron con instrumentos para analizar: los AVE, las relaciones familiares y el ajuste adolescente	Existe influencia significativa de los AVE sobre la satisfacción vital, los problemas emocionales y, sobre todo, los problemas exteriorizantes. Además, la utilización de un análisis centrado en el sujeto reveló que los adolescentes resilientes gozaban de relaciones familiares de mayor calidad que los adolescentes mal adaptados. Por lo tanto, las relaciones familiares positivas durante la adolescencia pueden ser consideradas como un factor de protección ante las consecuencias negativas de los AVE
Kim et al.[48] (2003)	Observar la influencia entre los AVE y la inadaptación adolescente utilizando datos de un estudio longitudinal de 6 años, prospectivo	Se evaluó una muestra de adolescentes (215 hombres y 236 mujeres) del medio oeste rural de EE. UU. Se evaluaron las experiencias vitales estresantes y los síntomas de internalización y externalización de sus comportamientos	Los AVE y la inadaptación correlacionaban en el tiempo. Por ejemplo, los AVE en un momento determinado predijeron conductas delictivas un año más tarde, lo que, a su vez, predijo significativamente los AVE un año más tarde. Los resultados proporcionan evidencia de la desventaja en la acumulación de AVE para los adolescentes. Además, estas situaciones están reforzadas por circunstancias problemáticas y dificultades en el ajuste del tiempo. No se han hallado diferencias significativas
Abad et al.[49] (2000)	Analizar la validez y fiabilidad del YSR a partir de la versión española de Lemos	La muestra es de 342 estudiantes de primero de BUP de Barcelona. Como prueba de contraste se ha empleado el CAQ	En el YSR, la consistencia interna es más homogénea y elevada para los síndromes de internalización y externalización que para los de banda estrecha. Aparecen covariaciones entre el síndrome de internalización y las escalas de depresión y desajuste psicológico del CAQ, si bien el peso explicativo preferente para dicha internalización viene dado por contenidos psicológicos diferentes para chicos y chicas. El síndrome de externalización, por el contrario, no muestra un patrón consistente de relación con el CAQ
Lemos et al.[50] (2002)	Analizar el cuestionario de psicopatología internalizante y externalizante	Se ha realizado un análisis de componentes principales y rotación varimax para cada sexo con los ítems del YSR que describen conductas problema, sobre una muestra de 2.833 estudiantes de 11 a 18 años	A partir de los 9 factores de primer orden derivados para cada sexo, se derivaron los siguientes 8 síndromes centrales, que resultaron ser algo diferentes a los obtenidos por Achenbach: Depresión, Agresividad verbal, Conducta delictiva, Problemas de pensamiento, Quejas somáticas, Problemas de relación social (aislamiento), Búsqueda de atención y Conducta fóbico-ansiosa. A partir de dichos síndromes se obtuvieron 2 factores de segundo orden que corresponden a psicopatología internalizante vs. externalizante (es decir, trastornos emocionales/trastornos de conducta), coincidentes con los obtenidos en otros análisis multivariados
Pedrós y Tenías[51] (2006)	Estudiar las diferencias de género en la sintomatología, los factores predisponentes y desencadenantes, así como la remisión clínica, en la psicosis aguda	Análisis por género de pacientes ingresados que al alta son diagnosticados de episodio psicótico agudo (trastorno psicótico breve, trastorno psicótico no especificado, trastorno esquizofreniforme y trastorno psicótico inducido por sustancias). La muestra está compuesta por 58 pacientes ingresados (39 hombres y 19 mujeres) entre 1996 y 2001 en la Unidad de Hospitalización Psiquiátrica del Hospital Lluis Alcanyís de Xàtiva (Valencia), diagnosticados de episodio psicótico agudo. Se utilizó como instrumento la Entrevista Estructurada para la Valoración de Episodios Psicóticos Agudos	El factor estudiado más relacionado en el desarrollo de la psicosis aguda en las mujeres es el estrés, mientras que en los hombres el consumo de drogas resulta más significativo

AVE: acontecimientos vitales estresantes; CAQ: Cuestionario de Análisis Clínico de Krug; YSR: Youth Self Report.

Tabla 5
Estudios sección diferencias éticas, acontecimientos vitales estresantes y primer episodio psicótico

Autor y año	Objetivos	Método	Resultados y conclusiones
Morgan et al.[52] (2009)	Investigar la prevalencia y los correlatos sociales de las experiencias psicóticas en una muestra de población general británica de raza blanca y negra	Los datos se obtuvieron de sujetos control, seleccionados como parte del estudio AESOP. Se escogieron 3 centros de estudio basado en población con PEP. La muestra estaba formada por 72 sujetos de raza negra del Caribe y 372 sujetos de raza negra africana. El instrumento utilizado fue The Psychosis Screening Questionnaire	La proporción de sujetos que informaron de una o más experiencias psicóticas fue del 19%. Estas fueron más frecuentes en sujetos de raza negra del Caribe (OR 2,08) y de raza negra africana (OR 4,59), en comparación con sujetos blancos británicos. Además, un determinado número de indicadores en la infancia y la desventaja social en los adultos se asociaron a experiencias psicóticas. Aparecen datos significativos en relación con los sujetos adultos, de raza negra y africanos, con desventaja social y la separación de los padres. Se halla una alta prevalencia de experiencias psicóticas en sujetos de raza del Caribe negro, y no de raza negra africana. La alta prevalencia en los sujetos del Caribe negro se explica por los altos niveles de desventaja social durante el curso de la vida
Morgan y Fearon[53] (2007)	Proporcionar una visión general de los resultados iniciales del estudio ESOP en el Reino Unido relativa a la etnia, los factores de riesgo social y la psicosis, y establecer las conclusiones de este estudio en el contexto de otras investigaciones	La muestra del estudio comprende: a) todos los pacientes con un PEP que realizaron la educación secundaria y terciaria en servicios dentro de las zonas del sureste de Londres, Nottingham y Bristol, Reino Unido, durante 3 años, y b) una muestra aleatoria de controles sanos de la comunidad	Los análisis de los datos relativos a los factores de riesgo sociales evidencian que varias formas de la primera infancia y la adversidad adulta y las características del vecindario, incluyendo la densidad étnica, pueden ser particularmente importante para contribuir a un mayor riesgo en estas poblaciones. Estos datos demuestran que las experiencias sociales adversas pueden ser etiológicamente relevantes en la esquizofrenia y otras psicosis
Le Roux et al.[54] (2007)	Analizar los AVE en la cultura *xhosa* (rituales de iniciación)	La muestra es de 75 sujetos hombres diagnosticados de esquizofrenia. Fueron entrevistados para examinar sus percepciones sobre el papel de la iniciación en la aparición y evolución de su enfermedad	Ocho pacientes (10,7%) perciben los rituales de iniciación como un evento estresante que había provocado la aparición de un episodio psicótico, y 6 (8%) sintieron que precipitó una recaída. Los rituales de iniciación pueden ser percibidos como un AVE que influye en la aparición y el curso de la esquizofrenia. Esto subraya la importancia de comprender el trasfondo cultural de los pacientes
Harland et al.[55] (2004)	Revisar el papel del entorno social (factores socioambientales) como predisponentes en el desarrollo de la esquizofrenia y otras psicosis	Revisión de modelos	Las tasas de esquizofrenia son más altas en grupos de emigrantes
Cooper[56] (2005)	Revisar la incidencia de la esquizofrenia en las clases sociales más bajas	Revisión	En el Reino Unido, las tasas de incidencia de 4 o superior se han estimado tanto para la clase social más baja en la población indígena y blanca, como para los grupos de inmigrantes negros. Estos datos proporcionan la evidencia más convincente del papel de los factores socioeconómicos en la etiología de la esquizofrenia
Selten y Cantor-Graae[57] (2005)	Analizar la afectación del estrés crónico y el desarrollo social en el aumento de factores de riesgo en la esquizofrenia	Revisión	Se propone la hipótesis de que la experiencia social crónica puede aumentar el riesgo al desarrollo de esquizofrenia. Este aumento de riesgo puede resultar de la sensibilización del sistema mesolímbico de la dopamina y/o el aumento de la actividad basal de este sistema
Cantor-Graae y Selten[58] (2005)	Analizar y revisar la migración como factor de riesgo para el desarrollo de la esquizofrenia	Revisión entre los años 1977 y 2003	El riesgo relativo de medias ponderadas para el desarrollo de la esquizofrenia entre los inmigrantes de primera generación (40 tamaños del efecto) fue de 2,7 (IC 95% 2,3-3,2). Un análisis independiente realizado por inmigrantes de segunda generación (7 tamaños del efecto) produjo un riesgo relativo de 4,5 (IC 95% 1,5-13,1). Un análisis realizado para los estudios en relación tanto de primera como de segunda generación de inmigrantes y estudios que no distinguen entre las generaciones (50 tamaños del efecto) produjo un riesgo relativo de 2,9 (IC 95% 2,5-3,4). Comparaciones de subgrupos rindieron significativamente mayores tamaños del efecto para los migrantes de países en desarrollo frente a los países desarrollados (riesgo relativo 3,3; IC 95% 2,8-3,9) y para los migrantes procedentes de zonas donde la mayoría de la población es de raza negra (riesgo relativo 4,8; IC 95% 3,7-6,2). Una historia personal o familiar de migración es un factor de riesgo importante para la esquizofrenia. El patrón de riesgo diferencial a través de subgrupos evidencia un papel de la adversidad psicosocial en la etiología de la esquizofrenia

Tabla 5 (*continuación*)

Autor y año	Objetivos	Método	Resultados y conclusiones
Sharpley et al.[59] (2001)	Evaluar las explicaciones biológicas, psicológicas y sociales en el desarrollo de trastornos psicóticos	Artículo teórico	La población afrocaribeña en Inglaterra está en mayor riesgo de padecer esquizofrenia y manía. Las tasas más altas se mantienen cuando se utilizan los criterios diagnósticos operativos. El exceso de los 2 trastornos psicóticos tiene un origen probable: los pacientes afrocaribeños con esquizofrenia muestran más síntomas afectivos y un curso más recurrente, con una mayor desorganización social, pero menos síntomas negativos crónicos, que los pacientes blancos. Es necesario plantear hipótesis más complejas, ya que la variación cultural tiene gran relevancia, y también por el grado de desventaja social relacionado
Rutter[60] (2007)	Revisar las interacciones biológicas y el ambiente	Articulo teórico	Los hallazgos empíricos informan de la interacción entre los factores genéticos y biológicos, junto con el medio ambiente
Gureje y Adewunmi[61] (1988)	Analizar las variables sociodemográficas y de AVE en sujetos con PEP	Es una muestra nigeriana de 42 pacientes con PEP y 42 sujetos control sanos. Se compararon las historias de vida de los eventos de un grupo de sujetos con PEP y otro de sujetos control. Seis meses antes de la aparición del PEP se evaluaron los 2 grupos mediante la entrevista diagnóstica Research Diagnostic Criteria y la Life Events Schedule	El inicio de la enfermedad no fue precedido por un aumento de los AVE. La única observación importante fue que los sujetos control habían experimentado más sucesos el mes antes de la entrevista. Estos sujetos eran varones control, donde el papel de la familia era relevante. Las observaciones se discuten en el contexto de la cultura nigeriana
Jablensky et al.[62] (1992)	Estudiar la esquizofrenia y trastornos relacionados en 10 países (Colombia, República Checa, Dinamarca, India, Irlanda, Japón, Nigeria, Unión Soviética, Reino Unido y EE. UU.)	La muestra estaba formada por 1.379 pacientes (15-54 años). La evaluación se realizó durante 2 años	Las manifestaciones conductuales tempranas de la enfermedad psicótica eran similares en todos los puntos geográficos. El tipo de inicio y ajuste (en país en desarrollo o país desarrollado) fueron los predictores más importantes del curso de los 2 años
El-Rufaie[63] (1986)	Estudiar los factores culturales que afectan al PEP precedido por AVE	Los pacientes representados son de 3 nacionalidades que trabajan bajo condiciones de estrés similares. Los pacientes de este estudio son de Abu Dhabi (Emiratos Árabes Unidos). Se utilizó el Standardized Clinical Review para evaluar a los sujetos	Se evidencia que los factores culturales juegan un papel en la etiología del PEP

AVE: acontecimientos vitales estresantes; IC: intervalo de confianza; OR: odds ratio; PEP: primer episodio psicótico.

un trastorno genético (Jablensky et al.[62], 1992). En síntesis, los factores culturales juegan un papel relevante en la etiología de un PEP (El-Rufaie[63], 1986).

Discusión y conclusiones

Como se ha evidenciado en la exploración bibliográfica realizada, es importante realizar aproximaciones a los AVE, analizando no solo la presencia o número de estos, sino el tipo de circunstancia de que se trate y el impacto emocional, además de la vivencia del individuo.

Ante los estudios revisados, no está demasiado claro cuál es la función que tienen los sucesos vitales estresantes en el desarrollo o exacerbación de los síntomas, ni a través de qué mecanismos influyen en ellos. Realmente, en muchas circunstancias se puede cuestionar si la ocurrencia de acontecimientos vitales se puede separar de la propensión al estrés de la persona vulnerable o simplemente van unidas de la mano. Sin embargo, existen factores importantes que pueden ser críticos para el resultado de dicha interacción. Por ejemplo, la capacidad de afrontamiento es esencial para determinar el impacto de los sucesos potencialmente estresantes: un individuo con un amplio repertorio de respuestas de afrontamiento puede dominar estímulos estresantes que superarían la capacidad de individuos con una serie de respuestas de afrontamiento menor.

Dentro del modelo de la vulnerabilidad al estrés, el individuo que desarrolla un episodio psicótico muestra una hipersensibilidad psicobiológica hacia los estresores socioambientales. Además, aparecen déficits en los factores protectores, como por ejemplo habilidades interpersonales, afrontamiento y resiliencia, y soporte social y familiar. Por una parte, el estado sintomático y social de individuos con vulnerabilidad biológica está determinado en cualquier momento temporal por la cantidad y el tipo de AVE. Y por otra parte, por la capacidad de resolución y afrontamiento de los problemas de dichos sujetos, en detrimento de la red de apoyo social que posean. En la presente revisión se pone de relieve la importancia de determinados factores psicosociales que pueden provocar una modificación importante en la vida del sujeto y, en consecuencia, exigen una respuesta de adaptación. También la epigenética está tomando un papel central en el desarrollo de la psicosis entre otras enfermedades psiquiátricas. El núcleo central es la adaptación al medio y, en consecuencia, la producción de cambios dinámicos en el individuo. Un ejemplo lo hallamos en el efecto de los sucesos vitales estresantes, considerados factores del entorno que provocan conflicto, reto y cambio en los sujetos. La habituación o ajuste a una determinada situación se refleja también en los estudios de poblaciones de inmigrantes, cuya mayor incidencia de PEP parece relacionarse con constantes dificultades sociales a las que se enfrentan.

En conclusión, el enfoque más prometedor parece ser la detección del alto riesgo de sujetos que experimentan síntomas similares a los psicóticos, el grupo prodrómico. Existen estudios en los cuales el conocimiento previo sobre el desarrollo premórbido en la psicosis puede ayudar a crear teorías sobre la etiología y la heterogeneidad de esta población, además de servir como base en iniciativas de detección precoz. Igualmente, es importante comprender el

trasfondo cultural y étnico para reflexionar y discutir sobre la necesidad de priorizar una atención precoz en el ámbito de los sucesos vitales estresantes como foco para futuras intervenciones.

Conflicto de intereses

Las autoras declaran no tener ningún conflicto de intereses.

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Annex 2

Study 2:

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Incidence of stressful life events and influence of sociodemographic and clinical variables on the onset of first-episode psychosis

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ABSTRACT

This study presents a quantitative analysis of the incidence of stressful life events (SLEs) and the variables gender, age at onset, family history and psychotic symptoms in patients with first-episode psychosis (FEP). A descriptive, cross-sectional methodology was used to interview 68 patients with FEP between 13 and 47 years of age. The Psychiatric Epidemiology Research Interview Life Events Scale collected one-year period prior to onset of FEP – used to analyse the subcategories *academic, work, love and marriage, children, residence, legal affairs, finances* and *social activities*-, Positive and Negative Syndrome Scale, and Clinical Global Impression-Schizophrenia scale were used to assess the relevance of certain SLEs during adolescence. Age at onset showed a significant negative correlation with the categories *academic* and *social activities*. By contrast, it showed a positive correlation with *work* and *children*. A significant relationship was found between paternal family history and *social activities* and between maternal family history and *academic* and *love and marriage*. Finally, an inverse relationship was observed between negative symptoms and the categories *children* and *finance*. Depressive symptoms were significantly correlated with the category *academic*. Our results show the importance of SLEs during adolescence and suggest that there is a clear need to develop preventive actions that promote effective strategies for dealing with the accumulation of psychosocial stress.

1. Introduction

Vulnerability-to-stress models link neurobiological vulnerability and SLEs to the onset and course of psychosis (Corcoran et al., 2003; Walker and Diforio, 1997; Zubin and Spring, 1977). Most studies focus on how SLEs affect psychotic symptomatology (Phillips et al., 2007). Increased sensitivity to stress plays an important role in the emergence of FEP. Aiello et al. (2012) showed that over-exposure to environmental stress contributes to the generation of prodromal symptoms and transition to FEP, in individuals at genetic risk of psychosis and, with sensitivity in the hypothalamic-pituitary-adrenal (HPA) axis. Similarly, psychosocial stress is considered a relevant factor in the worsening of psychotic symptoms (Myin-Germeys et al., 2005). Nevertheless, research of this type in the initial phases of psychosis is limited (Pruessner et al., 2011). Research suggests an association between SLEs and

Abbreviations: SLEs, stressful life events; FEP, first-episode psychosis

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psychosis (Phillips et al., 2007) but one that is too weak to allow consistent conclusions to be drawn (Beards et al., 2013). However, the claim that SLEs can raise risk is supported by the appearance of plausible mechanisms that indicate how exposure to external stress factors can affect individuals and increase the risk of psychosis. Studies of the relationship between life events and the appearance of FEP show a higher incidence of SLEs of varying severity (Jones et al., 1993; Canton and Fraccon, 1985) during a three-week period prior to onset (Lukoff et al., 1984; Al Khani et al., 1986; Day et al., 1987). Similarly, van Os et al. (1994) and Raune et al. (2009) concluded that SLEs were more frequent in the three months prior to the onset of FEP. Rusaka and Rancāns (2014) observed that 44% of acute psychotic disorder patients experienced a SLE during the six-month period before FEP.

The age at onset is an important feature associated with the course of psychotic disorders. For instance, earlier ages of onset of psychosis are associated with more psychopathology (Langeveld et al., 2012), greater cognitive impairment (Rajji et al., 2009), earlier conduct problems (Vinokur et al., 2014), premorbid personality changes (Skokou et al., 2012), and structural brain changes (Burke et al., 2008). Furthermore, adolescent-onset patients often exhibit unfavorable risk factors such as longer duration of untreated psychosis (DUP) (Ballageer et al., 2005), poorer premorbid adjustment (Larsen et al., 2004), and higher rates of substance abuse (Pencer et al., 2005). Age at onset is an important variable in schizophrenia expression. Although first psychotic episodes appear mainly between 15 and 30 years of age, approximately 4% of schizophrenia cases are diagnosed before the age of 15 and around 1% of all FEP before the age of 12 (McClellan, 2000; Werry and Taylor, 1994). SLEs may be the key and play an important role in the vulnerable period of adolescence and younger people have more SLEs. In this period of life, there are a lot of changes (e.g. changing of school or of training program, working for the first time or starting a relationship) and distinct roles (e.g. the need for more freedom) which represent new challenges. The transitional nature of this stage of life, the numerous, intense changes and the many roles that an adolescent is expected to play mark this as a vulnerable period (Tournier, 2013), although there are currently no published studies that associate age at onset of FEP with SLEs.

One of the main factors in the heterogeneity of psychotic disorders is gender. According to the literature, the illness appears on average 5 years earlier in men than in women (Häfner et al., 1993). The highest incidence in men is seen between the ages of 16 and 25, while in women, the illness manifests between 25 and 35 years old. Various authors have pointed to the role of estrogens, neurodevelopment factors and family risk factors as biological co-contributors to the gender differences observed in age at onset of schizophrenia (Salem and Kring, 1998). Relevant prognostic factors in FEP patients have been thoroughly analysed and several studies identify gender as a key factor (Segarra et al., 2012; Barajas et al., 2010; Cotton et al., 2009; Køster et al., 2008; Mattsson et al., 2007; Szymanski et al., 1995). Gender modifies the phenotypic expression of schizophrenia and has an effect on the prognostic and therapeutic implications of these differences (Segarra et al., 2012; Möller et al., 2010; Cotton et al., 2009; Usall et al., 2003, 2002; Angermeyer et al., 1990). There are few studies that examine familial psychiatric morbidity in FEP patients. Marneros and Pillmann (2004) showed a high incidence of family members with mental disorders for psychotic patients. If we analyse the family history of psychosis in particular, the average risk is higher for transition to a FEP (Yung et al., 2004), and subjects with a genetic disposition to psychosis show an increase in emotional reaction to stress (Aiello et al., 2012; Collip et al., 2011; Lataster et al., 2010; Myin-Germeys and van Os, 2007; Myin-Germeys et al., 2001). As such, the association between SLEs and psychosis may be influenced by genetic susceptibility resulting from a variation in the underlying DNA sequence or due to epigenetic variation in gene expression (Beards et al., 2013).

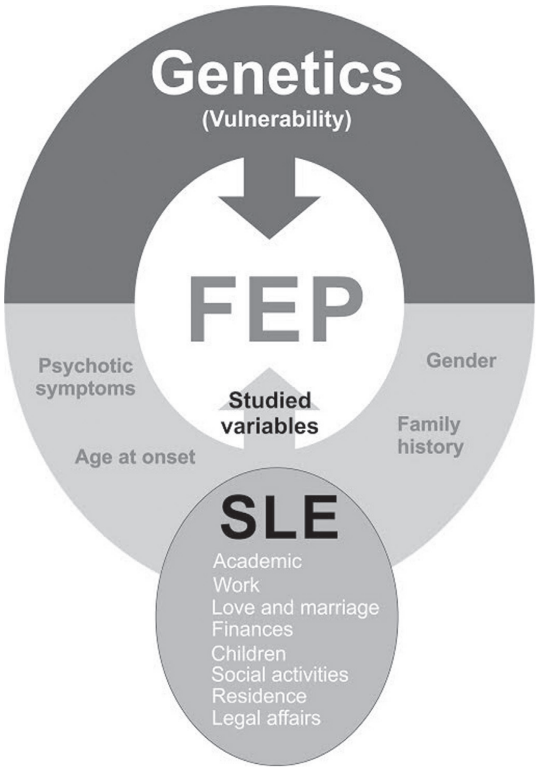

Fig. 1. FEP and the influence of distinct variables (gender differences, age at onset, family history and psychotic symptomatology) in relation to SLEs.

With regard to psychotic symptomatology and FEP, there is evidence of an estimated prevalence of persistent negative symptomatology post-FEP of around 15% (Hovington et al., 2012; Kirkpatrick et al., 2001), which fails to respond to antipsychotic medication (Pruessner et al., 2011; Szymanski et al., 1996). These symptoms are associated with poor quality of life and a worse prognosis (Mäkinen et al., 2008). Subjects with more depressive symptoms show higher levels of perceived stress (Barrantes-Vidal, 2014; Renwick et al., 2009).

To sum up, there are few studies that relate life events with clinical variables. Therefore, this overview leads to the need to study their relationship. In simple terms, there appears to be a relationship between SLEs and FEP. This study attempts to add to the empirical knowledge of SLEs in FEP patients by analysing the incidence of certain SLEs in the appearance of FEP and examining the influence of distinct variables (gender differences, age at onset, family history and psychotic symptomatology) on SLEs (see Fig. 1).

In addition, we will focus on the analysis of correlations between different types of SLEs and clinical variables. These associations indicate which are the categories -academic, work, love and marriage, children, residence, legal affairs, finances and social activities- that are either related or not to clinical variables in patients with FEP. The key is to examine fine-grained differences in the type of SLEs that precede the onset of FEP to determine whether SLEs may, indeed, be more strongly associated – or not – with the gender differences, age at onset, family history and

psychotic symptomatology. Currently, there are no studies that analyse the relationship between these variables.

2. Methods

A descriptive, cross-sectional study was carried out. Patients were selected through consecutive sampling as they accessed the public health network.

2.1. Participants

The sample was recruited as a part of the GENIPE study, a longitudinal study focusing on gender differences and clinical variables in the FEP patients.

FEP subjects who contacted any service at the Parc Sanitari Sant Joan de Déu or child-adolescent mental health centre in the Sant Joan de Déu Hospital and clinic network were included in the study from January 2006 to December 2011 in Barcelona and surrounding areas. The study sample consisted of 68 patients aged between 13 and 47 years who presented with FEP. The inclusion criteria were the same than GENIPE study: two or more psychotic symptoms of schizophrenia criteria A (DSM-V); age between 7 and 65 years; less than 6 months since the first contact with the medical service; and less than a year since development of symptoms. Patients diagnosed with intellectual disabilities (Premorbid IQ < 70) or traumatic brain injury were excluded from the study. The diagnosis was confirmed on the basis of the criteria for any psychotic disorder, as assessed by the Structured Clinical Interview for DSM-IV (SCID).

2.2. Instruments

The assessment was performed by two trained psychologists in the Parc Sanitari Sant Joan de Déu or child-adolescent mental health centre in the Sant Joan de Déu Hospital. The evaluators scored over 0.70 in the intraclass correlation coefficient of the instruments prior to the study.

Sociodemographic characteristics and clinical variables were collected through a questionnaire. The Family History-RDC interview (Andreasen et al., 1977) was used to record family data and to analyse the presence of mental health disorder in first-degree relatives (only parents) in all the sample. The variable included in the analysis was the sum of separately mental disorder family history for both parents (mother/father). Several cohort studies of high-risk (for serious mental disorder) reveal the importance of genetic susceptibility (Beards et al., 2013). For instance, the offspring of mothers with schizophrenia was found not only to have elevated risks for schizophrenia but also for a range of psychotic, affective, and personality disorders (Mortensen et al., 1999). In this way, we have thought in splitting the family history into maternal and paternal and their relationship with SLEs. To measure SLEs, the Psychiatric Epidemiology Research Interview (PERI-M) Life Events Scale was used (Dohrenwend et al., 1978; Vizcarro, 1984). The presence or absence of distinct SLEs (positive and negative) was assessed in the FEP sample. The internal consistency of the scale was good. Factorial analysis was held in which four areas were identified: functional discomfort, work-related stress, health problems and relationship problems, with Cronbach's alpha coefficients between 0.73 and 0.77. In addition, there is an adapted version for adolescent population (Casullo and Fernández Liporace, 2005). In the Spanish version, they were grouped into 8 categories: *academic, work, love and marriage, children, residence, legal affairs, finances* and *social activities*. Within the categories there is a total of 102 items, which are marked according to the presence or absence of each event. SLEs collected relate to the year before FEP. Information on clinical variables was obtained through the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Peralta Martín and Cuesta Zorita, 1994) of psychotic symptomatology, which consists of 30 items (symptoms) scored on a Likert-type scale ranging from 1 (absent) to 7 (extreme). Ratings were obtained for three subscales: positive symptoms, negative symptoms and general psychopathology. PANSS presented good interobserver and construct validity, internal consistency (Cronbach's alpha of 0.73 for the positive scale, 0.83 for negative and 0.87 for general psychopathology) and adequate test-retest reliability. The intraclass correlation coefficient is around 0.80 for the three subscales. In the sample of adolescents, we evaluated with KIDDIE-PANSS (Positive and Negative Syndrome Scale for Children and Adolescents (Fields et al., 1994), 6–16 years. Data on illness severity and psychotic symptomatology were assessed using the Clinical Global Impression-Schizophrenia (CGI-S) scale (Haro et al., 2003). CGI-S scale is a valid and reliable instrument. Given its simplicity, concision and clinical face validity, the scale is appropriate for use in observational studies and routine clinical practice. We have administered it in all the sample. CGI-S scale measures the severity of positive, negative, cognitive and depressive symptoms. A general illness severity score was also generated. We have employed two measures of psychotic symptomatology and severity to reinforce the results with solid instruments of reliability and validity.

2.3. Ethics committee

All participants were informed about the study aims and methodology and provided signed informed consent. The study was approved by the Sant Joan de Déu Research and Ethics Committee.

2.4. Statistical analyses

Statistical analyses of clinical and sociodemographic data were carried out using the SPSS (version 21). The normality assumption, tested using the non-parametric Kolmogorov-Smirnov test ($p < 0.05$), was not met. As a result, non-parametric tests were used for all study variables. SLEs were analysed against the different variables. Statistical significance was set at 0.05. Specifically, with respect to the frequencies in the PERI-M (Dohrenwend et al., 1978), only those SLEs which registered a 15% presence were described. For the statistical analysis, means were compared for independent samples through the non-parametric Mann-Whitney *U* test, which allowed PERI-M scores to be compared according to gender and family history of psychotic episodes. Effect sizes (ES, Cohen's *d*) were calculated for the PERI-M categories with respect to gender (male/female) and family history (father/mother). The Spearman correlation was used to examine the relationships between different variables. The values for three cases with paternal family history of FEP were lost as they could not be corroborated in the interview. We could not certify in any case the parental history of mental illness.

3. Results

Thirty-seven men (54.4%) and thirty-one women (45.6%) with a mean age of 20.8 years (SD = 7.03) were included in the study (see Table 1 for more details). The sample of 16% of immigrants is established in Spain. We have consulted data from the National Statistics Institute of Spain and the data indicates that there is equivalence with our values in Spanish population.

In what refers to the family history of mental illness, a total of 5 subjects presented a paternal history of psychosis and 3 subjects

Table 1
Sociodemographic characteristics of the sample.

Characteristic	Mean (SD; range) or N (%)
Age	20.8 (7.03; 13–47)
Gender	
Men	37 (54.4%)
Women	31 (45.6%)
Marital status	
Single	62 (91.2%)
Married/partner	4 (5.9%)
Separated/divorced	2 (2.9%)
Formal education	
Primary, incomplete	28 (41.2%)
Primary, completed	11 (16.2%)
Secondary, incomplete	17 (25%)
Secondary, completed	1 (1.5%)
University, incomplete	6 (8.8%)
University, completed	5 (7.4%)
Employment status (last month)	
Employed	14 (20.6%)
Unemployed	13 (19.1%)
Student	34 (50%)
Homemaker	1 (1.5%)
Supervised employment	1 (1.5%)
On leave	5 (7.4%)
Admission centre	
Clinic	19 (27.9%)
Hospital	48 (70.6%)
Place of birth	
Spain	57 (83.8%)
Outside Spain (foreigner)	11 (16.2%)

had a maternal history of psychosis. Overall, 9 subjects had a family history of psychosis (mother, father, or both). Specifically, other diagnoses were found in the paternal family history: 6 subjects with major depressive disorder, 5 subjects with alcohol dependence, 3 subjects with anxiety disorders, 2 subjects with bipolar disorder and 1 subject who committed suicide. On the other side, in the maternal family history, there were the following diagnoses: 16 subjects with major depressive disorder, 2 subjects with alcohol dependence, 2 subjects with anxiety disorders, 2 patients with adjustment disorders and 1 subject with bipolar disorder.

Table 2 shows the most significant items in the PERI-M categories, including those with higher than 15% presence. Fig. 2 shows the percentage presence of SLEs in the PERI-M categories; *academic* and *social activities* are particularly prevalent. Table 3

Table 2
Frequencies and percentages (%) of PERI-M items.

Category	Items	Frequencies (%)
Academic	Changed school or training program.	13 (19.4)
	Had problems at school or with training program.	43 (64.2)
	Failed school or training program.	32 (47.8)
	Did not graduate from school or training program.	24 (35.8)
Work	Started work for the first time.	23 (33.8)
	Had trouble with a boss.	17 (25)
	Took on a greatly increased work load.	13 (19.1)
Love and marriage	Engagement was broken.	12 (17.6)
	Started a relationship.	18 (26.5)
Social activities	Took a vacation.	22 (32.4)
	Made new friend.	19 (27.9)
	Broke up with a friend.	21 (30.9)

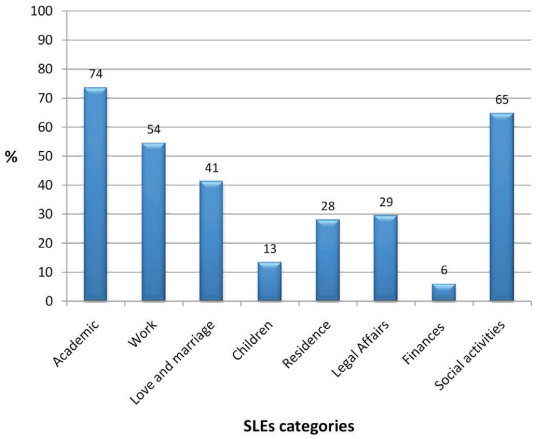

Fig. 2. Percentage presence of at least one SLE in the PERI-M Life Events Scale.

Table 3
Correlations between PERI-M categories.

	Acad.	Work	Love	Child.	Resid.	Leg.	Finan.
Work	0.02						
Love	−0.17	0.14					
Child.	−0.13	0.15	−0.01				
Resid.	0.30*	−0.19	−0.06	−0.04			
Leg.	0.11	0.30*	−0.00	−0.09	−0.05		
Finan.	−0.03	0.40**	0.13	0.08	0.25*	0.02	
Social	0.18	−0.07	−0.07	−0.34**	0.43**	0.02	0.08

Notes: Acad.: Academic; Love: Love and marriage; Child.: Children; Resid.: Residence; Leg.: Legal affairs; Finan.: Finances; Social: Social activities.

* $p < 0.05$.

** $p < 0.01$.

shows a summary of the correlations between the distinct SLE categories: *academic* correlated significantly with *residence* category ($p < 0.05$); a relationship can be observed between *work* and *finances* ($p < 0.01$) and *legal affairs* ($p < 0.05$); *children* shows a significant relationship with *social activities* ($p < 0.01$), and *residence* appears to be more closely linked to *social activities* ($p < 0.01$) and less significantly to *finances* ($p < 0.05$).

3.1. Comparative and relational analysis

3.1.1. SLEs and gender

Table 4 shows a significant predominance of men in the *legal affairs* category ($p = 0.01$), with a medium effect size. No significant differences were found in the other categories.

3.1.2. SLEs and first-degree relatives with history of mental disorders

The influence of the presence or absence of maternal or paternal family history on the distinct SLE categories is shown in Table 5. A total of 66.92% of participants had no family history of mental disorders. Paternal family history was associated with a significant increase in influence on the *social activities* category ($p = 0.03$), with a large effect size. Significant results were also obtained in the overall SLE total ($p = 0.02$), with a large effect size. Similarly, maternal family history of psychotic episodes was found to have a significant influence on the categories *academic* ($p = 0.02$) and *love and marriage* ($p = 0.03$), with a medium effect size.

Table 4
Comparative analysis of PERI-M categories and gender (men and women).

Category	Total sample Mean (SD)	Men (n=37) Mean (SD)	Women (n=31) Mean (SD)	*P*	ES
Acad.	1.89 (1.57)	1.84 (1.54)	1.97 (1.63)	0.67	−0.08
Work	1.49 (1.77)	1.57 (1.82)	1.39 (1.75)	0.66	0.10
Love	0.71 (1.01)	0.57 (0.93)	0.87 (1.09)	0.16	−0.29
Child.	0.15 (0.40)	0.14 (0.35)	0.16 (0.45)	0.95	−0.05
Resid.	0.29 (0.49)	0.24 (0.43)	0.35 (0.55)	0.43	−0.22
Leg.	0.49 (0.89)	0.70 (1.02)*	0.23 (0.63)*	0.01	0.54
Finan.	0.13 (0.62)	0.11 (0.52)	0.16 (0.73)	0.87	−0.08
Social	1.81 (1.88)	1.83 (1.86)	1.79 (1.93)	0.83	0.02
Total	6.93 (4.11)	7.03(4.14)	6.81 (4.15)	0.91	0.05

Notes: Acad., Academic; Love, Love and marriage; Child., Children; Resid., Residence; Leg., Legal affairs; Finan., Finances; Social, Social activities; Total, Total stressful life events; SD, standard deviation; ES, effect size Cohen's *d*.

* $p < 0.05$.

3.1.3. SLEs and age at onset of FEP

The PERI-M event categories were independently correlated with the variables age-at-onset. The correlations between PERI-M categories and age at onset of FEP are shown in Table 6 and Fig. 3. A significant relationship was observed with *academic* events ($p < 0.01$); the younger the subject, the greater the influence of the academic environment. A significant relationship was also found with *work* events ($p < 0.01$); the later the onset, the greater the effect of the *work* category. Similarly, age of onset was found to have a significant correlation with the categories *children* ($p < 0.01$) and *social activities* ($p < 0.05$).

3.1.4. SLEs and psychotic symptomatology (PANSS)

The PERI-M event categories were independently correlated with psychotic symptomatology. Table 6 shows significant relationships between the negative symptoms scale and the *children* ($p < 0.05$) and *finances* categories ($p < 0.05$). The general psychopathology scale was also found to have a significant correlation with the *children* category ($p < 0.05$). By contrast, no significant correlations with the different categories were observed for the positive symptoms scale.

3.1.5. SLEs and illness severity (CGI-S)

Significant correlations with negative symptomatology were identified for the *children* category ($p < 0.05$), and an inversely proportional correlation was identified with the *finances* category ($p < 0.05$). By contrast, positive symptomatology was not found to correlate with any of the SLE categories. Depressive symptomatology showed a significant correlation with the *academic* category ($p < 0.05$) and with the SLE overall total ($p < 0.05$). In the case of cognitive symptoms, no significant relationship was found with any of the SLE categories. Finally, the global CGI-S was found to correlate significantly with two categories: *children* ($p < 0.01$) and *residence* ($p < 0.05$).

4. Discussion

Our results indicate that there is a high incidence of SLEs in FEP subjects. In addition, distinct SLE categories may appear together. There appear to be no major differences in the presence of SLEs according to gender, but more SLEs were observed in individuals with a maternal or paternal family history of FEP, and age at onset and symptoms were also associated with the presence of SLEs.

Significant differences according to gender were only found for the *legal affairs* category, suggesting that a particular focus should be placed on the problems experienced by adolescent males (Jiménez et al., 2008; Bruyn et al., 2003; Martin and Velarde, 2001). Our results have shown that men were more likely to report exposure to legal events. For instance, some items of legal category are: she/he was attacked, she/he was stolen, she/he was involved in a legal process or she/he was arrested. These differences have been widely mentioned in the literature (De Bruyn et al., 2003). The gender differences were taken into account with aspects of social cognition associated with roles and functions established by the social environment and standards. This conditioning is evidenced by observing that women depend on their assessment over relational aspects and interdependence with their environment, while men are more individualistic and instrumental.

In assessing the effect of age at onset of FEP on specific SLEs, significant negative correlations were observed with the categories *academic* and *social activities* (Canton and Fraccon, 1985). In general terms, the data on the age at onset of FEP indicate an overall increase in the frequency of SLEs during early and middle adolescence (Goossens, 2006; Graber, 2004). According to Oliva et al. (2008), the most common SLEs in adolescents were change of class, breaking up with a boyfriend or girlfriend and death of a close family member, the first two of which coincide with our study. Other authors (Allen et al., 2001; Davidson et al., 1999), in common with our results, have identified a significant relationship between social factors and age at onset. Available results indicate that the most influential or the most severe SLEs during adolescence tend to be unusual events (Raune et al., 2009) such as the death of a parent, parental divorce, incarceration of a family member, pregnancy/partner becoming pregnant, and parental unemployment (Jiménez et al., 2008). Of the more common place

Table 5
Relational analysis between PERI-M categories and family history (FH).

Categories	FH Mental illness, father (N=65)				FH Mental illness, mother (N=68)			
	Absent (n=41) Mean (SD)	Present (n=24) Mean (SD)	*P*	ES	Absent (n=40) Mean (SD)	Present (n=28) Mean (SD)	*P*	ES
Acad.	1.70 (1.51)	2.29 (1.65)	0.14	−0.38	1.52 (1.43)*	2.44 (1.63)*	0.02	−0.61
Work	1.35 (1.70)	1.59 (1.99)	0.77	−0.13	1.56 (1.62)	1.38 (2.02)	0.32	0.10
Love	0.68 (1.01)	0.83 (1.05)	0.56	−0.15	0.92 (1.12)*	0.39 (0.74)*	0.03	0.54
Children	0.18 (0.45)	0.08 (0.28)	0.42	0.25	0.18 (0.39)	0.11 (0.42)	0.23	0.17
Resid.	0.22 (0.42)	0.46 (0.59)	0.08	−0.49	0.25 (0.44)	0.36 (0.56)	0.47	-0.22
Leg.	0.44 (0.92)	0.52 (0.85)	0.44	−0.09	0.38 (0.77)	0.67 (1.04)	0.35	−0.33
Finan.	0.10 (0.50)	0.21 (0.83)	0.58	−0.17	0.21 (0.80)	0.04 (0.19)	0.47	0.27
Social	1.33 (1.44)*	2.65 (2.31)*	0.03	−0.73	1.68 (1.92)	2 (1.84)	0.36	−0.17
Total	5.95 (3.64)*	8.85 (4.66)*	0.02	−0.72	6.78 (3.96)	7.16 (4.39)	0.82	−0.09

Notes: Acad., Academic; Love, Love and marriage; Child., Children; Resid., Residence; Leg., Legal affairs; Finan., Finances; Social, Social activities; Total, Total stressful life events; SD, standard deviation; ES, effect size Cohen's *d*.

* $p < 0.05$.

Table 6
PERI-M category correlations, age at onset and psychotic symptomatology assessed on the PANSS (Positive and Negative Syndrome Scale) and the CGI-S (Clinical Global Impression-Schizophrenia scale).

	Onset	PANSS-P	PANSS-N	PANSS-G	CGI-P	CGI-N	CGI-D	CGI-C	CGI-G
Acad.	−0.39**	0.09	0.20	0.22	0.09	0.17	0.27*	0.09	0.18
Work	0.45**	0.17	−0.20	−0.20	0.05	−0.10	−0.08	0.04	−0.15
Love	0.12	0.20	−0.09	0.09	0.21	−0.15	0.16	0.01	0.17
Child.	0.39**	0.01	−0.29*	−0.26*	−0.18	−0.30*	−0.16	−0.14	−0.39**
Resid.	−0.13	0.10	−0.02	0.16	0.18	−0.06	0.23	−0.07	0.27*
Leg.	−0.06	0.16	−0.06	−0.01	0.08	0.04	0.02	0.21	0.05
Finan.	0.23	0.03	−0.29*	−0.14	0.09	−0.26*	−0.01	−0.12	−0.02
Social	−0.25*	−0.10	0.05	−0.07	−0.05	0.07	0.22	−0.08	0.14
Total	−0.06	0.18	−0.12	−0.04	0.12	−0.07	0.26*	−0.01	0.15

Notes: Onset: Age at onset; PANSS-P: Positive symptoms scale; PANSS-N: Negative symptoms scale; PANSS-G: General pathology scale. CGI-P: Positive symptoms; CGI-N: Negative symptoms; CGI-D: Depressive symptoms; CGI-C: Cognitive symptoms; CGI-S: Global severity, Acad.: Academic; Love: Love and marriage; Child.: Children; Resid.: Residence; Leg.: Legal affairs; Finan.: Finances; Social: Social activities; Total: Total stressful life events.

* $p < 0.05$.
** $p < 0.01$.

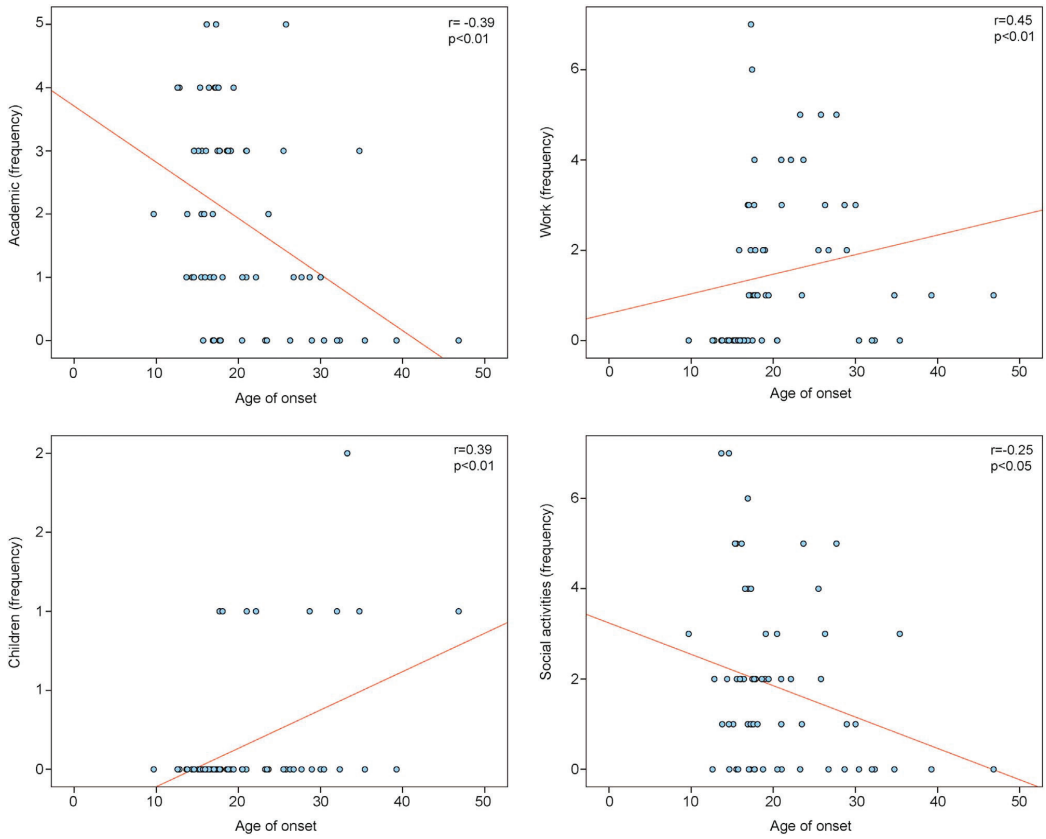

Fig. 3. Graphic of age at onset and frequency of stressful life events.

events (worries, difficulties and daily tensions), the most frequent are those that arise in the family environment and among the peer group, as was found in our study for change of educational centre and relationship problems with peers (Graber, 2004; Musitu et al., 2004). In short, academic and social changes appear before the onset of the FEP. Moreover, age at onset of FEP shows a significant positive correlation with the categories *work* and *children*: the later the onset of FEP, the greater the number and influence of SLEs, e.g., the birth of a child. Therefore, we can consider the existence of SLE patterns between age at onset and specific events.

Regarding the relationship between family history and SLEs in the onset of FEP, in agreement with other studies (Tsuang et al., 2014; Wancata et al., 2008; Gottesman and Erlenmeyer-Kimling, 2001), one third of our sample reported a family history of mental illness. In this study, a significant increase in the influence of SLEs on in the *social activities* category was associated with paternal

family history. If we focus on the maternal family history of psychotic episodes, significant relationships are observed with the categories *social activities* and *academic*. Goodman (1987) suggested that there is a greater influence of maternal family history on attachment, interpretation and coping skills when a SLE occurs.

With regard to the relationship between psychotic symptomatology and SLEs in the development of FEP, SLEs should be understood as prodromal events which, together with others, contribute to the emergence of subsequent psychotic symptomatology. These stressors also increase the intensity of psychotic symptoms (Myin-Germeys et al., 2005). Analysis of psychotic symptomatology indicates that more negative symptomatology is associated with fewer SLEs in the categories *children* and *finances*. There are more features of FEP observed in families with schizophrenia, especially those characteristics related to negative symptoms (Baron et al., 1985; Kendler, 1985). In follow-up studies, the degree of negative symptomatology is a prognostic indicator of poor social functioning, less valued work and worse quality of life (Fuller, 2002). There is a significant correlation between depressive symptomatology and the category *academic* and total SLEs.

The basis of depressive symptomatology would suggest poor development of the abilities and competences required to cope with and adapt to new situations, thereby causing greater emotional distress (Renwick et al., 2009). The severity of general psychotic symptomatology has a direct and inversely proportional relationship with the category *children*; it is therefore more difficult to maintain social interactions that lead to the establishment of a loving relationship and having children. By contrast, there is a positive correlation with the category *residence*; that is, higher scores for psychotic symptomatology are more strongly associated with, for instance, changes of residence (Lukoff et al., 1984).

Several methodological limitations should be considered. First, our study is based on retrospective accounts of events prior to a key episode, so the SLEs collected relate to the year before the FEP. It may therefore be difficult to distinguish between SLEs and residual prodromal symptoms. Second, the sample consists predominantly of adolescents and young people, the age groups in which FEP usually appears. This may influence the likelihood of observing academic SLEs and reduce the incidence of events in the *children*/*work* categories. Third, the subjective burden of stress factors is not considered. This can affect the perception of SLEs. Fourth, a sample of healthy controls should be included in order to assess the most influential SLE in both healthy controls and patients with FEP. Fifth, the analyses are based on cross-sectional data. Furthermore, some significant associations were found, but some caution should be taken in interpreting these results when taking multiple testing into account. Sixth, the sample size which is relatively small -especially taking into account the amount of variables that were studied. These limitations identify areas for improvement in future research, such as adding a sample of healthy controls, evaluating the subjective burden of SLE and considering causality analysis with confounding variables like gender and age. We would also stress the importance of carrying out research in which the comparison groups consist of the siblings of schizophrenia patients, so that the parenting style of schizophrenia patients can be observed and compared with that of families without mental illness.

It can be concluded from our study that as adolescence is a period of constant change and adaptation, detailed analyses of SLEs are vital, as they have a clear relationship with this vulnerable age group. There is a need for preventive actions that promote efficacious strategies for dealing with the accumulation of psychosocial stress and encourage positive processes of adaptation. Furthermore, studies of patients who present with FEP facilitate the assessment of premorbid functioning and its relationship with other clinical variables, which permits direct observation of the early stages of schizophrenia.

Contributors

Susana Ochoa, Judith Usall, Montserrat Dolz and Bernardo Sánchez designed the study and wrote the protocol. Anna Butjosa and Juana Gómez carried out the literature searches and analyses. Iris Baños, Ana Barajas, Janina Carlson, Elena Huerta-Ramos, Núria del Cacho and Anna Butjosa conducted patient assessments and follow-up. Anna Butjosa and Susana Ochoa performed the statistical analysis. All authors contributed to the draft of the manuscript and have approved the final version.

Declaration of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Annex 3

Study 3:

Butjosa, A., Gomez-Benito, J., Myin-Germeys, I., Barajas, A., Baños, I., Usall, J., Grau, N., Granell, L., Sola, A., Carlson, J., Dolz, M., Sánchez, B., Haro, J.M., GENIPE group and Ochoa, S. (2017). *Development and validation of the Questionnaire of Stressful Life Events (QSLE)*. Manuscript submitted for publication in Journal of Psychiatric Research.

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Abstract

Stressful life events (SLEs) are important indicators prior to the onset of first-episode psychosis (FEP). Although there are well-validated interviews and self-reports for assessing SLE on proximate events, unfortunately there are no instruments to assess SLE covering an entire lifetime. This study includes detailed specific items of childhood, adolescence, and adulthood focused on the presence of SLE, emotional impact (stressfulness), and the age at which the event occurred. Our research describes 2 studies designed to develop and validate a new scale to assess SLE: the Questionnaire of Stressful Life Events (QSLE). In Study 1, an over-inclusive item pool was generated based on review of group of experts at Parc Sanitari Sant Joan de Déu and content validity was examined by an Expert Survey. The whole scale represents the content domain. In Study 2, item-level analyses revealed good distributional properties, intra-rater reliability, and convergent and discriminant validity. In the sensitivity and specificity analysis, 18 items had high relevance in the discriminability between patients with FEP and healthy controls. We note that there was an AUC of 0.676, indicating a good predictor. Using 7 as a cutoff to predict an individual as a patient would yield a sensitivity of 64.8% and a specificity of 65%. Overall, the QSLE displayed satisfactory psychometric characteristics in a Spanish population. These results suggest that QSLE gives us the opportunity to investigate childhood, adolescent, and adult life events by measuring the stress and age at the moment on a continuous scale.

Keywords	Scale development; validity; first-episode psychosis; life events.
Taxonomy	Environmental Epidemiology, Schizophrenia
Manuscript region of origin	Europe

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27th February, 2017
Dr Florian Holsboer and Dr Alan Schatzberg
Journal of Psychiatric Research

Dear Dr Holsboer and Dr Schatzberg,

Please find attached the manuscript, "Development and validation of the Questionnaire of Stressful Life Events (QSLE)", which we submit for consideration for publication in *Journal of Psychiatric Research*. We hope that you consider it of interest to the readers of your journal.

This study provides information on detailed specific items of childhood, adolescence, and adulthood focused on the presence of stressful life events (SLEs), emotional impact (stressfulness), and the age at which the events have in patients with first-episode psychosis (FEP) and healthy controls. Our research describes 2 studies designed to develop and validate a new scale to assess SLEs: the Questionnaire of Stressful Life Events (QSLE). In Study 1, an over-inclusive item pool was generated based on review of group of experts at Parc Sanitari Sant Joan de Déu and content validity was examined by an Expert Survey. In Study 2, item-level analyses revealed good distributional properties, intra-rater reliability, and convergent and discriminant validity. The whole scale represents the content domain. In the sensitivity and specificity analysis, 18 items had high relevance in the discriminability between patients with FEP and healthy controls. Overall, the QSLE displayed satisfactory psychometric characteristics in Spanish population.

We believe our study results suggest that QSLE gives us the opportunity to investigate childhood, adolescent, and adult life events by measuring the stress and age at the moment on a continuous scale.

All study authors participated in the study design, assessment of patients, and drafting and review of the manuscript. There are no conflicts of interest. The project was funded by CIBERSAM.

Please do not hesitate to contact us if you require any further information.

We look forward to hearing from you.

Yours sincerely,

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Conflict of interest

None to declare.

Introduction

Research into the etiology of psychotic disorders has shown a complex interaction between genetic and environmental factors (Jablensky and Kalaydjieva, 2003; Cannon and Clarke, 2005; van Winkel et al., 2008; van Os, Kenis, and Rutten, 2010).There is a long history in terms of the connections between stressful life events (SLEs) and clinical disorders, as life events are an important predictor of the onset and course of various disorders across the life span, such as depression and psychosis (Brown, 2002; Howes et al., 2004; Beards et al., 2013; Spence et al., 2015). The claim that SLEs increase the risk of developing first-episode psychosis (FEP) is supported by the appearance of cognitive models of psychosis. These indicate how external exposure to stress factors can affect individuals. Consequently it is possible that exposure to intrusive events influences how individuals appraise their social worlds, perhaps leading to hostile perceptions of the external world.

Studies that explore the relationship between life events and FEP show a higher incidence of SLEs of varying severity (Canton and Fraccon, 1985; Jones et al., 1993) during a three-week (Lukoff, Snyder, Ventura, and Nuechterlein, 1984; Al Khani, Bebbington, Watson, and House, 1986; Day et al., 1987), three month (van Os et al., 1994; Raune, Kuipers, and Bebbington, 2009), and six-month period prior to the onset of FEP (Rusaka and Rancāns, 2014).

In addition to counting the number of SLEs, it is also important to consider the distress associated with a life event. A life event can become a stressor at certain points in life, depending not only on the type of situation but also on self-efficacy at that moment (Yu and Chung, 2004). Thus, the potential for an event to influence life will be related to different variables:the appreciation of the event, individual characteristics that determine vulnerability, coping strategies, and contextual cues. Therefore, it is important to add assessments of SLEs, analyzing not only the presence or number, but also the type of circumstance—domains of SLEs (education, work, partner, family, home, legal, finances, social, and health)—and emotional impact. Experiences of adversity, particularly during childhood and adolescence,

when thinking styles and beliefs about the self and the world crystallize, may have an impact on each of these and may contribute to the development of a worrying thinking style, negative beliefs about self, and reasoning biases (Freeman and Garety, 2014).

Most scales measure traumatic exposures in multiple areas of children's and adolescents' lives (Cristofaro et al., 2013). Fewer studies have assessed the role of adult life events in the onset of psychosis. There is some evidence that exposure to adult life events is associated with increased risk of psychotic disorder and subclinical psychotic experiences. Focusing clinical attention on adult experiences of adverse or traumatic events may result in greater benefit than focusing on childhood experiences alone. There seems to be a synergistic interplay between different risk factors, such as between childhood abuse and adult life events, as well as cannabis use (Morgan et al., 2014; Peters et al., 2016), suggesting that exposure to childhood and adult disadvantages may combine in complex ways to push some individuals along the pathway to psychotic disorder (Bebbington et al., 2011; Lataster et al., 2012). In the same line, exposure to adult experiences may be a more important predictor of mental health, physical health, quality of life, social functioning, and recovery than childhood experiences. Interestingly, emotional neglect in adulthood—not feeling loved and supported in one's family—was negatively associated with recovery, highlighting the underlying importance of current relationships in the process of recovery, above and beyond other adverse experiences (Stumbo et al., 2015). Decisions, experiences, and accomplishments during these years point individuals in many directions, making this period a powerful prism through which life trajectories reflect and re-direct. Noting the features of tools in the evaluation of SLEs, the role of adult life events, and the research reviewed, we saw the need to create a new instrument. The development and validation of the Questionnaire of Stressful Life Events (QSLE) takes into account the following features: (1) it adds a few closed-question probes after a positive response to a broad checklist category, as was done by Goodman et al. (1998), and (2) it builds detailed specific items, with the goal of reducing intra-category variability by permitting

identification of the event characteristics of interest and avoiding excessively broad categories. In this vein, we focused on the particulars of SLEs, for instance appraisal of stressfulness—emotional impact—by the respondent and age that the event occurred, as the QSLE covers the entire life cycle. In addition, the questionnaire needed to have practical considerations such as not requiring a trained interviewer and being less expensive. QSLE was developed as a self-report scale.

The development of the scale and the psychometric properties of the measurements obtained with it are presented over two studies (Figure 1, outlines select methodological steps taken in this project). In Study 1, we tackled the development and generation of the item pool, review of the items, and establishment of content validity. In Study 2, we provided different validity evidence of the scale's measures: psychometric evaluation, sensitivity, and specificity.

Study 1

Overview

Study 1 was designed to establish the content and generate the refined items. First, the questionnaire was developed by a group of experts at Parc Sanitari Sant Joan de Déu and Hospital Sant Joan de Déu. Afterwards, content validity was examined by an Expert Survey.

Development and generation of the item pool

To begin, several days of expert consensus meetings at Parc Sanitari Sant Joan de Déu proceeded with developing item pool generation. The experts worked on the creation and agreement of the items. The first step was comparing and contrasting types of checklist approaches for their ability to screen the events of interest and to measure their important characteristics in samples of respondents from relevant populations of interest (FEP). The focus was on the occurrence of such events over the lifetime. Once the information was identified, the next step was to develop structured, closed questions, the answers to which

would provide direct indicators of the nature and severity of the threat posed by the different types of events reported.

Following revision of the feasibility study, the QSLE included 66 items covering SLEs (1) Education (6 items covering problems and changes in the school), (2) Work (14 items covering problems with boss/colleagues, low salary, and changes of shift in workplace), (3) Partner (12 items covering starting to live together with a partner, sexual problems, instability, unfaithful, sexual problems), (4) Family (13 items covering child, family relationships), (5) Home (1 item covering change of residence/leaving home), (6) Legal (6 items covering judicial process, robbery, and physically assault), (7) Finances (2 items covering payment problems), (8) Social (7 items covering friend relationship, illness of close friend, pet death) and (9) Health (5 items covering serious illness, accidents). The domains were assessed based on review questionnaires about life events, such as the PERI Life Events Scale-Modified (Dohrenwend, et al., 1978), and reports of experiences and personal interviews of experts about life events in patients with FEP.

We opted for over-inclusiveness with respect to the number of items, recognizing that our systematic data analytic approach to scale development would result in a smaller psychometric instrument. All items were rated with absence/presence of the life event, the stress level (1=no stress, 10=maximum stress) and age when the event occurred. The time period covered by the interview was the entire lifetime.

Review of the items and establishment of content validity

In order to examine content validity an Expert Survey was adopted. The experts can determine if an instrument satisfies the extent to which a measurement reflects the specific intended domain of content. An electronic version was used to obtain expert opinion. This process included questions regarding the background of experts. In addition, we asked about the content of the items. Experts received written instructions to rate each item on a scale of 1 to

5 according to representativeness criteria (whether the item was representative of a life event). Finally, experts were asked to make comments/suggestions to modify the items.

It was considered that an item was modified if the average of representativeness score was <3, showing that the panel of experts did not consider that the item fitted life events adequately, in accordance with participants' suggestions (see Table 1). These analyses influenced the design of a final version of the QSLE. Note all tables showing the items of the initial questionnaire in two columns: the first column shows the original items (total of 66 items), and the second column indicates the number of new items obtained with the new analyses performed.

Relevance of content

A total of 9 experts in SLEs and FEP participated in the study. The expert panel was 88.9% female and 11.1% male. Of these, 66.7% were psychologists, 22.2% psychiatrists, and 11.1% medical statisticians. The panelists' countries were Denmark (22.2%), Italy (22.2%), The Netherlands (22.2%), Spain (22.2%), and Switzerland (11.1%). Regarding their degree of knowledge, 88.9% had knowledge about life events and FEP. Of these, regarding the degree of influence of the sources of argument in their degree of knowledge, 55.6% had theoretical analysis and study of research about life events and FEP.

The Expert Survey reviewed QSLE. Following their suggestions, a new questionnaire of 54 items was obtained. Some items were re-structured in the final version of the QSLE because the experts considered that the information was radically formulated. Other items that experts evaluated <3 —Item 5, 6, 16, 19, 25, 26, 40, 51, 53, 58, 59, 60, 64 and 65— were removed.

Furthermore, the appraisal was reformulated. We are now inquiring about distress rather than anxiety because the experts considered stress amore neutral descriptor of psychological burden. The final version of the questionnaire is shown in Appendix A. Each item is scored on

the occurrence of item—presence (yes)/absence (no)—the level of stress from 1 to 10 in which higher scores are indicative of high stress, and finally, age when the event occurred.

Referring to the categories of the QSLE, experts questioned the purpose of grouping items into categories. The reason was that some items could be associated with two or more categories. Our team accepted this idea and we decided not to associate items with categories.

Study 2

Overview

Study 2 was designed to provide evidence of the psychometric property evaluation of QSLE. Examination of the reliability and validity of this instrument was guided by the Standards for Educational and Psychological Testing jointly developed by the American Educational Research Association (AERA), American Psychological Association (APA), and the National Council on Measurement in Education (NCME) (2014). These were used as a conceptual framework in the validation process.

Method

Participants.Participants were 224 people with FEP (n=102) and healthy controls (n=122), ages 11-47 years (☒=20.02, SD=7.51). The target population was young and adult patients with FEP recruited from the Parc Sanitari Sant Joan de Déu or child-adolescent mental health centre in the Sant Joan de Déu Hospital and clinic network. An FEP was defined as fulfilling the criteria for two or more psychotic symptoms of schizophrenia criteria A (DSM-V): less than 6 months since the first contact with the medical service; and less than a year since development of symptoms. Exclusion criteria were: diagnosis of intellectual disability, traumatic brain injury, and dementia. The sample of healthy controls was recruited from Parc Sanitari Sant Joan de

Déu, School of Sant Josep and School Pedagogium COS in Sant Boi del Llobregat. Healthy controls were defined as people without psychotic episode and no history of first psychotic-episode in first-degree relatives (mother or father).

Procedure.Participants were informed about the research and, after voluntarily signing the consent form, asked to complete anonymous questionnaires. The study was approved by the Research Ethics Committee at Parc Sanitari Sant Joan de Déu.

Instruments.Four additional measures were included to characterize all samples and establish relationships with other variables: the Scale of Life Events (PERI-Modified; Dohrenwend et al., 1978); the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, and Opler, 1987); the Clinical Global Impression-Schizophrenia scale (ICG-ESQ; Haro et al., 2003); and the Global Assessment of Functioning Scale (GAF; Hall, 1995).

Data analysis.Data analyses included multiple procedures: a) Item-level descriptive statistics, including item-total correlations; b) items with temporal stability—Cohen's Kappa, Gamma; c) Correlational analyses to assess whether the QSLE significantly correlated with the PERI-Modified and other variables (PANSS, ICG-ESQ and GAF);and d) Sensitivity and specificity analyses: the discriminability of the binary items (presence/absence)—chi-square and odds ratios—and sensitivity, specificity, and AUC of the sum of all SLEs in the sample of FEP and healthy controls. All analyses were carried out using SPSS version 22 and Rversion 3.0.3 (2014).

Results

Demographic characteristics of the sample.Demographic information on the sample can be found in Table 2.

Test-retest reliability.The QSLE was administered twice with a time period of two weeks. Intra-rater reliability (see Table 3) was found to be good. The test-retest reliability separately for

presence/absence, age, and stress variables was assessed by the Cohen's Kappa in categorical variables and Gamma in scalar variables, and was good.

Internal consistency.This was good for the total score scale (Cronbach's alpha=.79). The item-total correlation was high, and no increase of the reliability of the scale if the item were deleted (range .771 to .796), showing that all items are relevant in the questionnaire.

Relationship with other variables.The QSLE total scores strongly converged with the Gold Standard, the PERI-Modified global score at r=.52 (p<.001). The QSLE total score did not correlate with positive, negative, and general symptoms (PANSS),negative, depressive, and cognitive severity (ICG), and functioning (GAF). Otherwise, the QSLE total scale correlated with positive symptom severity (r=.39; p<.05).

Sensitivity and specificity.49 items were included in the analyses as some items were eliminated because they were only applicable to women (e.g., pregnancy). The original sample was 122 healthy controls and 102 patients, but many of them had items missing, especially patients. Therefore, we eliminated all subjects who were missing more than 25% of the items, remaining 174 subjects (120 healthy controls and 54 patients). First, we analyzed the discriminability of 49 binary items (presence/absence)with the significance of the differences (chi-square) and odds ratios in both samples. The result of the discrimination analysis shows that there were18 items with good discriminability (p<.05) and higher odds of SLEs between the two samples (see Table 4). Second, in the sensitivity and specificity analysis of the questionnaire, missing values were imputed by the mean of non-missing values within groups. In this analysis we could observe that the instrument was able to discriminate between patients and healthy controls. We noted that there was an AUC of 0.676, indicating a good predictor (see Figure 2). Using 7 as a cutoff to predict an individual as a patient would yield a sensitivity of 64.8% and a specificity of 65%.

Discussion

The goal of this collaborative project was to develop and validate a questionnaire of SLEs that could be helpful to identify the SLEs that should be evaluated before an FEP. The main psychometric properties of the QSLE are presented in terms of reliability estimates and evidence of validity, both of which proved to be very satisfactory. QSLE is a very promising measure for future prevention studies in high risk psychosis patients. Evaluating presence and levels of stress of certain life events could help us to understand the impact on risk of psychosis. Thus we could learn which SLEs were the most relevant in early and adult intervention.

The results show that the QSLE is an empirically supported and evidence-based instrument to investigate the prevalence and impact of SLEs in a Spanish population. The QSLE shows satisfactory psychometric characteristics and capacity to discriminate patients with FEP and healthy controls. In this study, we used a consensus—item pool generation and Expert Survey—approach to select appropriate items and develop measures to prevent FEP, and then evaluate these measures in a real-world practice environment. Regarding evidence of content validity, it can be stated that the QSLE was based on logical and empirical analysis of the adequacy with which the whole scale represents the content domain. Item-level analyses revealed good distributional properties. In addition, intra-rater reliability was found to be good. The test-retest reliability was good for the categorical variables. In the same line, other studies argue that memories of adversities seem reasonably stable in patients with FEP (Fisher et al., 2011), and similarly biased for people with and without psychopathology (Fergusson et al., 2000). In terms of validity, results demonstrated that the QSLE total score showed clear convergent validity with PERI-Modified global score ($r=.52$; $p<.001$). QSLE was largely independent of other scales about symptoms, severity, and functioning. However, the QSLE total score correlated with positive symptom severity ($r=.39$; $p<.05$). This finding was unexpected and the simple explanation is that the QSLE is sensitive to positive symptoms.

Another possible explanation is that QSLE contains some items that, rather than being fundamentally important environmental incidents, could include manifestations of psychiatric disorder (e.g., the marital separation from mate, and being fired from work). Depending on the circumstances in which they occur, these examples could be indicators of problems in social functioning related to the presence of a psychiatric disorder. In addition, SLEs are associated with positive symptoms (e.g., delusions, hallucinations, paranoia) (Tessner, Mittal, and Walker, 2011; Bentall et al., 2012). The mesolimbic dopaminergic system is involved in the mediation/modulation of the effect of SLEs on the vulnerability to psychosis (Ira et al., 2014). Therefore it is not surprising that such events correlate highly with psychopathology (Brett, et al., 1990). To the extent that a checklist has categories that can include symptoms of psychological disorder related to such disorder, the measurement of SLEs as a putative antecedent risk factor will be confounded with the measurement of the psychiatric outcome (Dohrenwend, 2006).

In the sensitivity and specificity analysis, the scale set has a good discriminative power between patients and controls. But it should be noted that in particular 18 items have high relevance in the detection of patients and controls. Overall, these specific items mark concrete areas of SLEs, many affecting patients with FEP. For instance, reduced social networks and support appear to pre-date onset of psychotic disorder (Gayer-Anderson and Morgan, 2013; Butjosa et al., 2016). There is strong evidence that social support, in particular the support of an adult, can limit the negative consequences of abuse and other adversities in childhood (Morgan and Gayer-Anderson, 2016). This, then, is an important avenue for future research in SLEs. Investigating why some people are resilient in the face of often extensive adversities in childhood or SLEs during their lifetime is of direct relevance to understanding how we can intervene to minimize risk and maximize resilience (Butjosa, Gómez-Benito, and Ochoa, 2014; Morgan and Gayer-Anderson, 2016).

The good indices of sensitivity and specificity (64.8% and 65%, respectively) support the decision validity of the instrument, which is always a requirement for a screening tool such as the QSLE. Whenever a test is to be used for screening purposes the cut-off point chosen must imply greater sensitivity, as what is most important is to obtain as few false negatives as possible and to enable the most suitable intervention to be chosen. The results obtained here therefore demonstrate the usefulness of the scale.

Two conditions of the study make these findings especially promising. Firstly, the QSLE did not explore a recent or fixed period of time. Usually, studies focus on proximate events. In this study, we analysed SLEs during life retrospectively, assessing the presence (cumulative stressors), the age when the events occurred, and the emotional impact. Secondly, this research aimed at developing an accurate instrument for researching in natural contexts, prioritizing the diversity of the population.

These results suggest that QSLE gives us the opportunity to investigate childhood, adolescent, and adult life events by measuring the stress and age at the moment on a continuous scale. Instruments such as the QSLE might help to determine whether or not certain risks for developing a psychotic disorder are interactive or independent, such as the interaction between early cannabis use and childhood trauma (Houston et al., 2011). Our instrument is designed to provide continuous scores (thereby enhancing variability and facilitating statistical analyses) of SLEs across social, familial, and environmental contexts during a lifetime. The consequences of childhood/adolescent/adult life events are comprehensive, and the QSLE might be useful for a number of research questions, and potentially also to learn how we can improve recovery outcomes for high risk populations. It is important to consider appraisals as one of a variety of other relevant variables in life stress processes. Thus, with the QSLE it becomes possible to investigate how appraisals are related to objectively measured events and other important variables in life stress processes. The availability of such a classification system on the distribution of important events within it would make it possible to identify and follow

over time groups at high risk of exposure to severe environmental stressors. The questionnaire should be included in early prevention programs. Early detection of problems and timely intervention will improve the prognosis, delaying the appearance of the problem, and even prevent its onset. The QSLE can be applied in healthcare, education, and research. The proposed QSLE scale can be useful as an instrument to evaluate SLEs during the lifetime. With it, professionals from different disciplines can detect and evaluate which life events have been experienced, the accumulation of life events (how often they have experienced them), and level of stress and age when the event occurred. With this information, the professional can better judge the accumulation of life events and the predisposition to developing FEP. This information is useful for proposing a good preventive action plan for people that might develop FEP, and helping those that do to recover. Nowadays, the methods of choice that are likely to be used to take important next steps in research on SLEs as detection for various types of psychopathology over the life course is a matter of key importance. One important point in our research was focused on FEP and the general population sample.

In conclusion, the results regarding the psychometric properties of the QSLE confirm its suitability for measuring SLEs during the lifetime in the sample of FEP patients and healthy people.

Although a number of positive outcomes from this study of the QSLE validation have already been mentioned, certain limitations must also be acknowledged. The first is the lack of detailed information about the event. This procedure is designed to elicit accounts of the events experienced in sufficient detail so that trained investigators can rate the important characteristics of the events. Second, we think it is necessary to more closely examine the different cultural, socioeconomic, family, and ethnic aspects that influence the perception of stress and the value of certain life events. Third, the sampling method used in this study contributed to having a small variety in the sample, with only patients with FEP and controls. The results need to be corroborated with larger samples and other types of sample. Fourth, we

did not make a subjective assessment of SLEs as valence positive or negative. Fifth, there is a difficulty in the evaluation of the distal SLEs; there may be biases in stress level at the time.

All of this has great relevance for the practice of professionals dedicated to detecting, caring for, and treating people associated with this disease, whether healthy or people at risk of FEP.

In summary, whether or not a person develops a FEP depends on diverse conditions, such as previous life experiences, psycho-biological characteristics, the accumulation of stressors, and the subjective evaluation of the event and its consequences.

In the not too distant future, we will create the English version of the scale; this will be developed in order to facilitate cross-cultural comparisons and to provide a valid scale for measuring the SLEs in an English-speaking population.

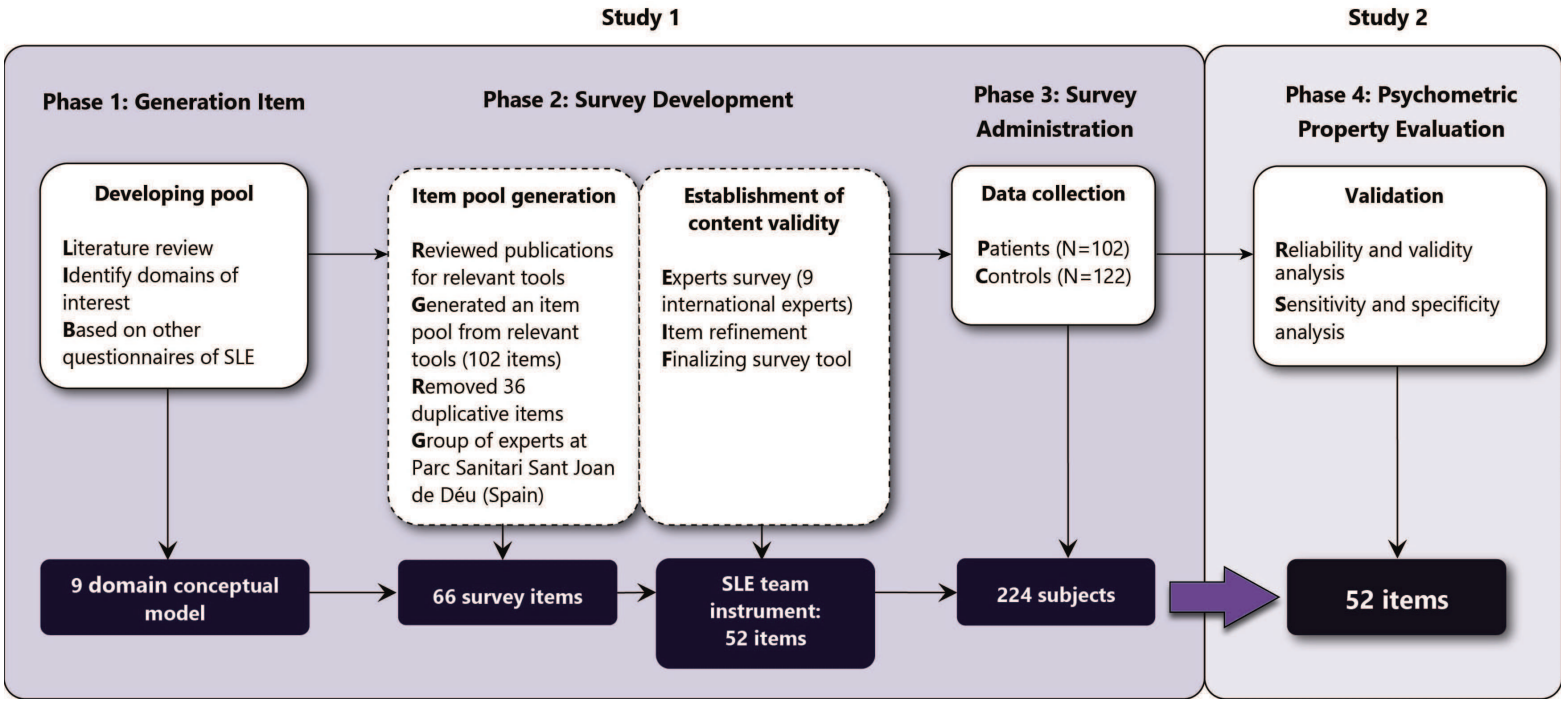

*Figure 1.*Flowchart of development and validation phases of the instrument Questionnaire of Stressful Life Events (QSLE).

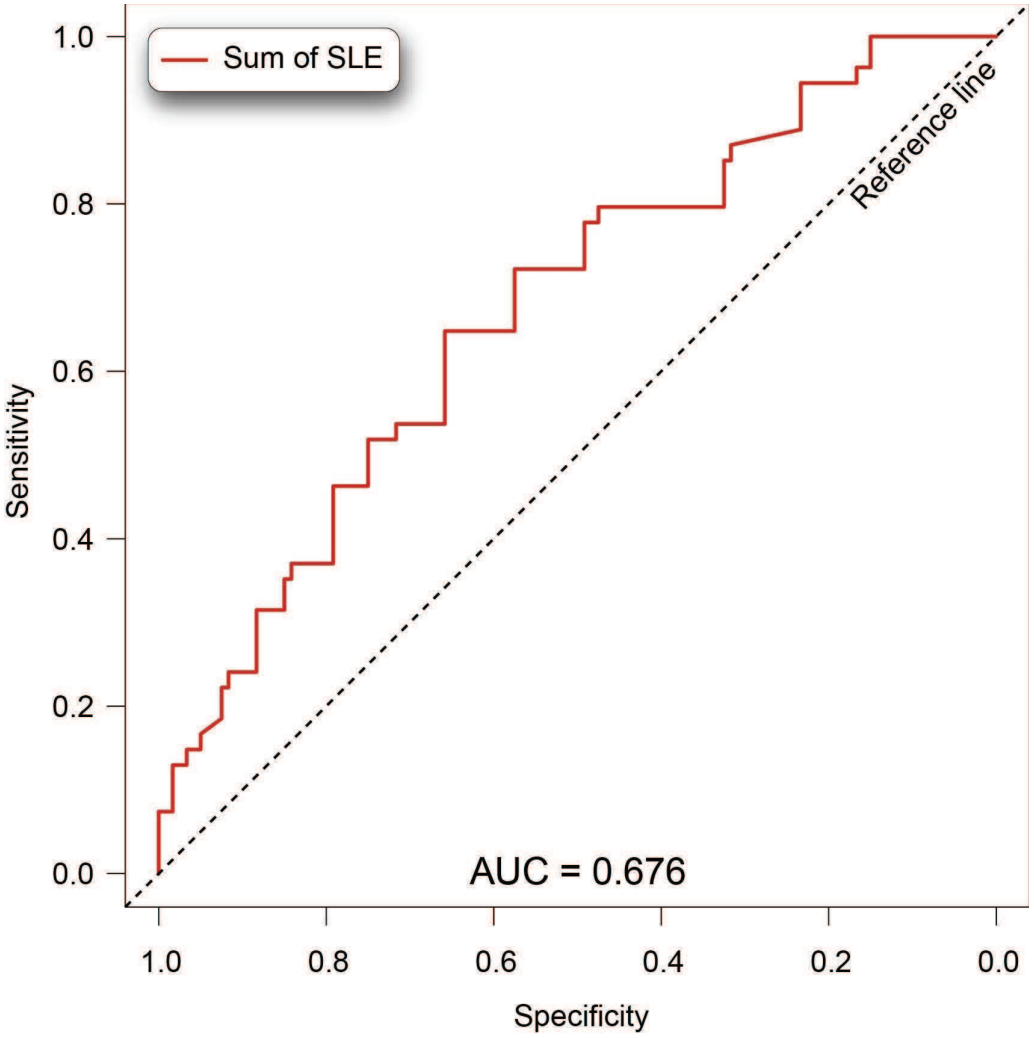

*Figure 2.*Cut-off of sum of stressful life events to predict an individual as a patient with first-episode psychosis.

Table 1

Score of representativeness of SLEs items by Experts Survey

Items[a]	New items[b]	Items	Average
Item 1	Item 1	Have you failed more than three subjects in an academic year?	2.89*
Item 2	Item 2	Have you suffered from bullying or conflict with peers that led to changing school or making an official complaint?	4.22
Item 3	Item 3	Have you been expelled from school for more than 15 days?	3.11
Item 4	Item 4	Have you changed school or moved to a higher level of education?	3.00
Item 5	-	Have you returned to studying after more than five years since you last studied?	2.33†
Item 6	-	Have you voluntarily given up studying?	2.89†
Item 7	Item 5	Have you started working?	3.67
Item 8	Item 6	Have you had or are you having severe problems with your boss?	3.67
Item 9	Item 7	Have you had or are you having severe problems with your colleagues that have led to official complaints, giving up work, serious fights and/or aggression?	3.67
Item 10	Item 8	Have you been sacked before the end of your contract?	3.33
Item 11	Item 9	Have you been promoted to a higher position involving more responsibility and/or a higher salary?	3.11
Item 12	Item 10	Have you been demoted to a lower position involving fewer responsibilities and/or a lower salary?	3.33
Item 13	Item 11	Have you changed job 3 or more times in a year?	3.33
Item 14	Item 12	Are there changes of shift at your workplace, for instance, mornings, evenings or nights?	3.11
Item 15	Item 13	Has your work schedule been extended by more than 10 hours per week?	3.11
Item 16	-	Has your work schedule been reduced by more than 10 hours per week?	2.67†
Item 17	Item 14	Have you been on sick leave for more than 3 months?	3.44
Item 18	Item 15	Have you started your own business as a self-employed worker?	3.11
Item 19	-	Have you retired due to age or taken early retirement?	2.89†
Item 20	Item16	Have you been unemployed for more than 6 months?	3.78
Item 21	Item17	Have you started living together with your partner?	3.78
Item 22	Item18	Have you started a romantic relationship?	3.78
Item 23	Item19	Have you and your partner gone through a break-up, separation or divorce?	3.89
Item 24	Item 20	Have you had problems with your partner that made you think about ending the relationship?	3.56
Item 25	-	Have you had instability with partners, starting more than 3 relationships in a year?	2.89†
Item 26	-	Have you ever experienced unrequited love?	2.78†
Item 27	Item 21	Have you had any sexual problems?	3.56
Item 28	Item 22	Have you been unfaithful?	3.22
Item 29	Item 23	If you have or had a partner, did he or she mistreat you psychologically and/or physically?	4.22
Item 30	Item24	If you have or had a partner, has he or she taken toxic substances (drugs)?	3.11
Item 31	Item25	If you have or had a partner, has he or she been seriously ill, affecting your daily life?	4.00

Item 32	Item26	Have any of your partners died?	4.00
Item 33	Item27	Have you become pregnant?	3.89
Item 34	Item28	Have you had or adopted a child?	3.56
Item 35	Item29	Have you had an abortion?	4.22
Item 36	Item 30	Are you sterile? (more than 8 months without being able to conceive)	3.00
Item 37	Item 31	Were you adopted? (degree of anxiety at the time of learning about it or at the time of adoption)	3.00
Item 38	Item 32	Have you been abandoned, suffered abuse or mistreatment?	3.56
Item 39	Item 33	Have your parents separated?	3.67
Item 40	-	Has a relative come to live with you?	2.67†
Item 41	Item 34	Has any of your family left home?	3.11
Item 42	Item 35	Has any first-degree relative (parents, children, etc.) had a serious illness that led to changes in your daily life?	3.89
Item 43	Item 36	Has any first-degree relative (parents, children, etc.) abused drugs or alcohol?	3.78
Item 44	Item 37	Has any first-degree relative died?	4.00
Item 45	Item 38	Has any other relative died?	3.44
Item 46	Item 39	Have you ever changed residence or left home?	3.67
Item 47	Item 40	Have you ever been robbed or physically assaulted?	4.11
Item 48	Item 41	Have you ever been sexually assaulted by a person who was not your partner or a member of the family?	3.67
Item 49	Item 42	Have you participated in a judicial process?	3.00
Item 50	Item 43	Are you or have you ever been an immigrant?	3.22
Item 51	-	Have you ever lost your driving license?	2.33†
Item 52	Item 44	Have you ever been to prison?	3.44
Item 53	-	Have you started to pay rent or a mortgage?	2.78†
Item 54	Item 45	Have you had any payment problems that have caused anxiety and/or sadness?	4.00
Item 55	Item 46	Have you ever broken up with your circle of friends?	3.78
Item 56	Item 47	Has a close friend suffered a serious illness that has led to a change in your daily life?	3.89
Item 57	Item 48	Has a friend died?	3.89
Item 58	-	Have you ever joined an ideological group?	2.67†
Item 59	-	Have you ever left an ideological group?	2.78†
Item 60	-	Have you ever done military or social service?	2.78†
Item 61	Item 49	Has a pet died?	3.78
Item 62	Item 50	Have you recently learned that you have a serious illness which has led to a change in your daily life?	4.00
Item 63	Item 51	Have you ever been or are you addicted to drugs?	2.89*
Item 64	-	Have you had your first period?	2.56†
Item 65	-	Have your periods stopped because you have started the menopause?	2.44†
Item 66	Item 52	Have you had an accident (industrial, traffic, domestic) that has led to disability?	3.89
	Total		**3.38**

Note. **[a]:** Original items;**[b]:** New items obtained with the new analyses performed;†: Item removed; *: Item modified.

Table 2

Demographic information (n=224)

	Patients (102)	Controls (122)	
	Mean (SD) or Percent		*P*-value
Age (years)	20.87 (7.04)	19.30 (7.84)	.120[a]
Sex			.06[b]
Female	39.2%	52.5%	
Male	60.8%	47.5%	
Formal education			<.001[c]*
Primary incomplete	19.2%	1.6%	
Primary complete	16.2%	0	
Secondary incomplete	37.4%	50.8%	
Secondary complete	11.1%	27%	
University incomplete	7.1%	9.8%	
University completed	8.1%	8.2%	
Other school programs	0	2.5%	
Employment situation (last month)			<.001[b]*
Employed	19.4%	13.9%	
Unemployed	16.1%	2.5%	
Student	52.7%	83.6%	
Homemaker	3.2%	0	
Supervised employment	1.1%	0	
Off work	7.5%	0	
Civil status			<.001[b]*
Single	87.9%	69.7%	
Married/partner	7.1%	28.7%	
Separated/divorced	5.1%	1.6%	

Note.[a]computed using two-tailed Student's *t*-test;[b]computed using Pearson chi-square test; [c]computed using Gamma; *statistically significant (p<.05).

Table 3

Intra-rater reliability (N = 105; 210 evaluations). Test-retest of categorical variable presence/absence and ordinal variables stress and age of SLEs

Items[a]	New items[b]	Presence/Absence		Stress		Age	
		Kappa (95%CI)	p-value	Gamma	p-value	Gamma	p-value
Item 1	**Item 1**	.89	<.001	.82	<.001	.83	<.001
Item 2	**Item 2**	.89	<.001	1	<.001	1	<.001
Item 3	**Item 3**	.89	<.001	-	-	-	-
Item 4	**Item 4**	.89	<.001	.89	<.001	.96	<.001
Item 7	**Item 5**	.93	<.001	.94	<.001	.87	<.001
Item 14	**Item 12**	.65	<.001	1	.014	-	-
Item 15	**Item 13**	1	<.001	-	-	-	-
Item 18	**Item 15**	.66	<.001	-	-	-	-
Item 20	**Item 16**	.66	<.001	-	-	-	-
Item 22	**Item 18**	.88	<.001	.93	<.001	.93	<.001
Item 23	**Item 19**	.93	<.001	.74	<.001	.95	<.001
Item 24	**Item 20**	.8	<.001	.84	<.001	.9	<.001
Item 27	**Item 21**	.79	<.001	-	-	-	-
Item 28	**Item 22**	.92	<.001	1	<.001	1	<.001
Item 30	**Item 24**	-	-	1	.014	1	-
Item 39	**Item 33**	.97	<.001	.97	<.001	1	<.001
Item 41	**Item 34**	.93	<.001	1	<.001	.67	.002
Item 42	**Item 35**	.82	<.001	.76	<.001	1	<.001
Item 44	**Item 37**	.94	<.001	.81	<.001	1	<.001
Item 45	**Item 38**	.9	<.001	.79	<.001	.89	<.001
Item 46	**Item 39**	.86	<.001	.8	<.001	.86	<.001
Item 47	**Item 40**	.91	<.001	.78	<.001	.98	<.001
Item 49	**Item 42**	.8	<.001	-	-	-	-
Item 50	**Item 43**	-	-	1	.014	1	.014
Item 55	**Item 46**	.86	<.001	.81	<.001	.94	<.001
Item 56	**Item 47**	.82	<.001	.84	<.001	.85	.001
Item 57	**Item 48**	-	-	.81	.002	.85	<.001
Item 61	**Item 49**	.84	<.001	.76	<.001	.74	<.001
Item 62	**Item 50**	-	-	1	<.001	1	-
Item 63	**Item 51**	.66	<.001	-	-	-	-
Item 66	**Item 52**	.79	<.001	-	-	-	-

Note.[a]**:** Original items;[b]**:** New items obtained with the new analyses performed.The following items do not appear in the table because there are no values (see the column New items): 6 to 11, 14, 17, 23, 25 to 32, 36, 41, 44 and 45.

Table 4

Detectabilityof items between patients and healthy controls

New items[a]	X^2	*P*-value	OR	95%CI
Item 1. Have you failed more than three subjects in an academic year?	25.41	<.001*	5.75	2.82-11.72
Item 2. Have you suffered from bullying or conflict with peers that led to changing school or making an official complaint?	10.7	.001*	3.53	1.61-7.73
Item 3. Have you been expelled from school for more than 15 days?	24.85	<.001*	34.29	4.32-271.72
Item 4. Have you changed school or moved to a higher level of education?	1.51	.220	.66	.34-1.28
Item 5. Have you started working?	7.58	.006*	2.52	1.29-4.91
Item 6. Have you had or are you having severe problems with your boss?	21.07	<.001*	16.71	3.59-77.80
Item 7. Have you had or are you having severe problems with your colleagues that have led to official complaints, giving up work, serious fights and/or aggression?	1.04	.307	2.29	.45-11.75
Item 8. Have you been sacked before the end of your contract?	9.58	.002*	5.80	1.70-19.78
Item 9. Have you been promoted to a higher position involving more responsibility and/or a higher salary?	.68	.409	1.65	.49-5.44
Item 10. Have you been demoted to a lower position involving fewer responsibilities and/or a lower salary?	1.81	.178	4.58	.41-51.59
Item 11. Have you changed job 3 or more times in a year?	10.19	.001*	14.87	1.74-126.85
Item 12. Are there changes of shift at your workplace, for instance, mornings, evenings or nights?	.79	.372	1.84	.47-7.14
Item 13. Has your work schedule been extended by more than 10 hours per week?	4.16	.041*	3.62	.98-13.42
Item 14. Have you been on sick leave for more than 3 months?	.77	.379	1.82	.47-7.08
Item 15. Have you started your own business as a self-employed worker?	.01	.931	1.11	.09-12.55
Item 16. Have you been unemployed for more than 6 months?	1.33	.249	1.84	.65-5.22
Item 17. Have you started living together with your partner?	3.04	.081	.28	.06-1.27
Item 18. Have you started a romantic relationship?	.29	.587	.83	.42-1.64
Item 19.Have you and your partner gone through a break-up, separation or divorce?	.91	.340	.70	.34-1.45
Item 20. Have you had problems with your partner that made you think about ending the relationship?	0	1	1	.46-2.17
Item 21. Have you had any sexual problems?	1.62	.203	2.79	.54-14.34
Item 22. Have you been unfaithful?	1.87	.171	2.15	.70-6.59
Item 23. If you have or had a partner, did he or she mistreat you psychologically and/or physically?	1.41	.234	2.24	.57-8.76
Item 24. If you have or had a partner, has he or she taken toxic substances (drugs)?	.29	.586	.64	.13-3.16
Item 25. If you have or had a partner, has he or she been seriously ill, affecting your daily life?	2.68	.101	-	-
Item 28. Have you had or adopted a child?	.27	.604	.57	.06-4.99
Item 29. Have you had an abortion?	2.36	.124	3.15	.68-14.57
Item 31. Were you adopted? (degree of anxiety at the time of learning about it or at the time of adoption)	.35	.551	2.28	.14-37.19
Item 32. Have you been abandoned, suffered abuse or mistreatment?	5.62	.018*	6.07	1.14-32.36
Item 33. Have your parents separated?	.69	.404	1.60	.52-4.89
Item 34. Has any of your family left home?	4.86	.027*	2.25	1.08-4.67
Item 35. Has any first-degree relative (parents, children, etc.) had a serious illness that led to changes in your daily life?	3.14	.076	2.02	.92-4.45

Item 36. Has any first-degree relative (parents, children, etc.) abused drugs or alcohol?	7.71	.006*	5.91	1.46-23.81
Item 37. Has any first-degree relative died?	.11	.745	1.22	.37-4.04
Item 38. Has any other relative died?	.12	.732	.83	.29-2.35
Item 39. Have you ever changed residence or left home?	.26	.613	.84	.44-1.62
Item 40. Have you ever been robbed or physically assaulted?	1.67	.197	1.59	.78-3.20
Item 41. Have you ever been sexually assaulted by a person who was not your partner or a member of the family?	9.35	.002*	-	-
Item 42. Have you participated in a judicial process?	5.74	.017*	3.21	1.19-8.66
Item 43. Are you or have you ever been an immigrant?	4.56	.033*	3.45	1.04-11.43
Item 44. Have you ever been to prison?	8.02	.005*	12.24	1.39-107.52
Item 45. Have you had any payment problems that have caused anxiety and/or sadness?	1.44	.230	2.34	.56-9.73
Item 46. Have you ever broken up with your circle of friends?	1.96	.161	1.59	.83-3.04
Item 47. Has a close friend suffered a serious illness that has led to a change in your daily life?	.001	.978	.98	.38-2.56
Item 48. Has a friend died?	.34	.558	.73	.25-2.12
Item 49. Has a pet died?	3.43	.064	.53	.27-1.04
Item 50. Have you recently learned that you have a serious illness which has led to a change in your daily life?	30.62	<.001*	9.71	3.95-23.87
Item 51. Have you ever been or are you addicted to drugs?	30.01	<.001*	42	5.35-329.55
Item 52. Have you had an accident (industrial, traffic, domestic) that has led to disability?	21.01	<.001*	10.41	3.23-33.51

Note.[a]**:** New items obtained with the new analyses performed;X^2: chi-square test; OR: odds ratio; 95%CI: 95% confidence interval.

*p<.05

Items 26, 27 and 30 do not appear because there was insufficient data to compare between patients and controls.

Title: Development and validation of the Questionnaire of Stressful Life Events (QSLE)

Abstract: Stressful life events (SLEs) are important indicators prior to the onset of first-episode psychosis (FEP). Although there are well-validated interviews and self-reports for assessing SLE on proximate events, unfortunately there are no instruments to assess SLE covering an entire lifetime. This study includes detailed specific items of childhood, adolescence, and adulthood focused on the presence of SLE, emotional impact (stressfulness), and the age at which the event occurred. Our research describes 2 studies designed to develop and validate a new scale to assess SLE: the Questionnaire of Stressful Life Events (QSLE). In Study 1, an over-inclusive item pool was generated based on review of group of experts at Parc Sanitari Sant Joan de Déu and content validity was examined by an Expert Survey. The whole scale represents the content domain. In Study 2, item-level analyses revealed good distributional properties, intra-rater reliability, and convergent and discriminant validity. In the sensitivity and specificity analysis, 18 items had high relevance in the discriminability between patients with FEP and healthy controls. We note that there was an AUC of 0.676, indicating a good predictor. Using 7 as a cutoff to predict an individual as a patient would yield a sensitivity of 64.8% and a specificity of 65%. Overall, the QSLE displayed satisfactory psychometric characteristics in a Spanish population. These results suggest that QSLE gives us the opportunity to investigate childhood, adolescent, and adult life events by measuring the stress and age at the moment on a continuous scale.

Keywords: Scale development, validity, first-episode psychosis, life events.

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Contributors

Susana Ochoa, Judith Usall, Luís Granell, Montserrat Dolz, and Bernardo Sánchez designed the study and wrote the protocol. Anna Butjosa and Juana Gómez managed the literature searches and analyses. Iris Baños, Ana Barajas, Janina Carlson, Norma Grau, Andrea Sola, and Anna Butjosa worked on the evaluations of the patients and follow-up. Anna Butjosa, Susana Ochoa, Juana Gómez, and Daniel Cuadras performed the statistical analysis. All authors contributed to the draft of the manuscript and have approved the final version.

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QSLE (Questionnaire of Stressful Life Events)

Instructions: This is a self-administered questionnaire about events that have happened during your life. In each of the items, you must indicate with a cross whether the event didn't happen (check "**no**") or did happen (check "**yes**").
Secondly, if the event did occur, you will have to indicate the **number of situations** and assess the **degree of stress** produced from **1** (low stress) to **10** (high stress) in each of these situations. You must also indicate your **age** (years) at the time the event occurred. If the event occurred more than 5 times, *select the 5 most important.*
Please do not leave items blank. Here is an example of how to complete the questionnaire.

Example:

Items	Did this event happen in your life?				Number of situations				
	No	Yes			1	2	3	4	5
		Once	More than once (nº)						
1. Have you failed more than three subjects in an academic year?		**X**		Stress (1-10)	**5**				
				Age	**15**				
2. Have you suffered from bullying or conflict with peers that led to changing school or making an official complaint?	**X**			Stress (1-10)					
				Age					
3. Have you been expelled from school for more than 15 days?			**X (2)**	Stress (1-10)	**8**	**7**			
				Age	**13**	**14**			

Items	Did this event happen in your life?				Number of situations				
	No	Yes			1	2	3	4	5
		Once	More than once (nº)						
1. Have you failed more than three subjects in an academic year?				Stress (1-10)					
				Age					
2. Have you suffered from bullying or conflict with peers that led to changing school or making an official complaint?				Stress (1-10)					
				Age					
3. Have you been expelled from school for more than 15 days?				Stress (1-10)					
				Age					
4. Have you changed school or moved to a higher level of education?				Stress (1-10)					
				Age					

Items	Did this event happen in your life?				Number of situations				
	No	Yes			1	2	3	4	5
		Once	More than once (nº)						
5. Have you started working?				Stress (1-10)					
				Age					
6. Have you had or are you having severe problems with your boss?				Stress (1-10)					
				Age					
7. Have you had or are you having severe problems with your colleagues that have led to official complaints, giving up work, serious fights and/or aggression?				Stress (1-10)					
				Age					
8. Have you been sacked before the end of your contract?				Stress (1-10)					
				Age					
9. Have you been promoted to a higher position involving more responsibility and/or a higher salary?				Stress (1-10)					
				Age					
10. Have you been demoted to a lower position involving fewer responsibilities and/or a lower salary?				Stress (1-10)					
				Age					
11. Have you changed job 3 or more times in a year?				Stress (1-10)					
				Age					
12. Are there changes of shift at your workplace, for instance, mornings, evenings or nights?				Stress (1-10)					
				Age					
13. Has your work schedule been extended by more than 10 hours per week?				Stress (1-10)					
				Age					
14. Have you been on sick leave for more than 3 months?				Stress (1-10)					
				Age					
15. Have you started your own business as a self-employed worker?				Stress (1-10)					
				Age					
16. Have you been unemployed for more than 6 months?				Stress (1-10)					
				Age					

Items	Did this event happen in your life?				Number of situations				
	No	Yes			1	2	3	4	5
		Once	More than once (nº)						
17. Have you started living together with your partner?				Stress (1-10)					
				Age					
18. Have you started a romantic relationship?				Stress (1-10)					
				Age					
19. Have you and your partner gone through a break-up, separation or divorce?				Stress (1-10)					
				Age					
20. Have you had problems with your partner that made you think about ending the relationship?				Stress (1-10)					
				Age					
21. Have you had any sexual problems?				Stress (1-10)					
				Age					
22. Have you been unfaithful?				Stress (1-10)					
				Age					
23. If you have or had a partner, did he or she mistreat you psychologically and/or physically?				Stress (1-10)					
				Age					
24. If you have or had a partner, has he or she taken toxic substances (drugs)?				Stress (1-10)					
				Age					
25. If you have or had a partner, has he or she been seriously ill, affecting your daily life?				Stress (1-10)					
				Age					
26. Have any of your partners died?				Stress (1-10)					
				Age					

Items	Did this event happen in your life?				Number of situations				
	No	Yes			1	2	3	4	5
		Once	More than once (nº)						
27. Have you become pregnant?				Stress (1-10)					
				Age					
28. Have you had or adopted a child?				Stress (1-10)					
				Age					
29. Have you had an abortion?				Stress (1-10)					
				Age					
30. Are you sterile? (more than 8 months without being able to conceive)				Stress (1-10)					
				Age					
31. Were you adopted? (degree of anxiety at the time of learning about it or at the time of adoption)				Stress (1-10)					
				Age					
32. Have you been abandoned, suffered abuse or mistreatment?				Stress (1-10)					
				Age					
33. Have your parents separated?				Stress (1-10)					
				Age					
34. Has any of your family left home?				Stress (1-10)					
				Age					
35. Has any first-degree relative (parents, children, etc.) had a serious illness that led to changes in your daily life?				Stress (1-10)					
				Age					
36. Has any first-degree relative (parents, children, etc.) abused drugs or alcohol?				Stress (1-10)					
				Age					
37. Has any first-degree relative died?				Stress (1-10)					
				Age					
38. Has any other relative died?				Stress (1-10)					
				Age					

Items	Did this event happen in your life?			Number of situations				
	No	Yes		1	2	3	4	5
		Once	More than once (nº)					
39. Have you ever changed residence or left home?				Stress (1-10)					
				Age					
40. Have you ever been robbed or physically assaulted?				Stress (1-10)					
				Age					
41. Have you ever been sexually assaulted by a person who was not your partner or a member of the family?				Stress (1-10)					
				Age					
42. Have you participated in a judicial process?				Stress (1-10)					
				Age					
43. Are you or have you ever been an immigrant?				Stress (1-10)					
				Age					
44. Have you ever been to prison?				Stress (1-10)					
				Age					
45. Have you had any payment problems that have caused anxiety and/or sadness?				Stress (1-10)					
				Age					

Items	Did this event happen in your life?				Number of situations				
	No	Yes			1	2	3	4	5
		Once	More than once (nº)						
46. Have you ever broken up with your circle of friends?				Stress (1-10)					
				Age					
47. Has a close friend suffered a serious illness that has led to a change in your daily life?				Stress (1-10)					
				Age					
48. Has a friend died?				Stress (1-10)					
				Age					
49. Has a pet died?				Stress (1-10)					
				Age					

Items	Did this event happen in your life?				Number of situations				
	No	Yes			1	2	3	4	5
		Once	More than once (nº)						
50. Have you recently learned that you have a serious illness which has led to a change in your daily life?				Stress (1-10)					
				Age					
51. Have you ever been or are you addicted to drugs?				Stress (1-10)					
				Age					
52. Have you had an accident (industrial, traffic, domestic) that has led to disability?				Stress (1-10)					
				Age					