PRIMERS EPISODIS PSICÒTICS, CÀNNABIS, FACTORS D'ESTRÈS, GÈNERE I ÈTNIA

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Sara Arranz García

TESI DOCTORAL 2020

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TESI DOCTORAL

Dirigida per

Vanessa Sánchez Gistau

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UNIVERSITAT ROVIRA i VIRGILI

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FAIG CONSTAR que aquest treball, titulat "primers episodis psicòtics, cànnabis, factors d'estrès, gènere i ètnia", que presenta Sara Arranz García per a l'obtenció del títol de Doctor, ha estat realitzat sota la meva direcció al Departament de Medicina I cirurgia d'aquesta universitat.

Reus, a 11 de gener del 2020

La Directora de la tesi doctoral

Vanessa Sanchez Gistau

A tots els amics/gues que m'heu ajudat en aquest projecte,
Que he iniciat ja gran, al voltant dels 40 anys, però amb
moltes més ganes que quan era jove.

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d'un primer episodi psicòtic.

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per marxar lluny tan jove
I seguir sent el meu principal suport.

PRÒLEG

Aquesta Tesi inclou 4 articles científics:

ARTICLE 1

Títol: ***The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis*****.**

Autors: Sara Arranz, Nuria Monferrer, M.José Algora, Angel Cabezas, Montse Sole, Elisabeth Vilella, Javier Labad, Vanessa Sanchez Gistau.

Revista: Schizophrenia Research

Any: 2018

Volum: 201

Pàgines: 352-359

DOI: 10.1016/j.schres.2018.04.040.

ARTICLE 2

Títol: Hypothalamic-pituitary-adrenal axis function and exposure to stress factors and cannabis use in recent-onset psychosis

Autors: Javier Lavad, Laura Ortega, Itziar Montalvo, Sara Arranz, Maria Jose Algora, Lourdes Martorell, Elisabeth Vilella, Vanessa Sanchez Gistau.

Revista: The world journal of biological psychiatry

Volum: 27

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ARTICLE 3

Títol: ***Comparison between a morocco and a native-born population, in a sample of first episode psychosis.***

Autors: Sara Arranz, Julia Camacho, Claudia Andrés, Inés Niubó, Vanessa Sanchez Gistau.

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ARTICLE 4

Títol: The impact of sex and cannabis on clinical features in first–admitted patients with psychosis

Autors: Sara Arranz, Anna Mané, Dani Bergé, Clara Monserrat, Angel Cabezas, Elisabet Vilella , and Vanessa Sanchez-Gistau

Estat: En revisió, European Neuropsychophramacology sept 2019

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ABREVIATURES

CAR	*Cortisol awakeing response , resposta del cortisol al despertar*
CDSS	*Calgary Depression Scale for Schizophrenia , escala per depressió en esquizofrènia*
CTQ-SF	*Childhood Trauma Questionnaire–Short Form , escala de trauma infantil*
DSM-5	*Manual de diagnòstic i estadístic dels trastorns mentals (cinquena edició)*
DUP	*Durada de la psicosi sense tractar*
EIP	*Equip de psicosi incipient*
EMAR	*Estats mentals d'alt risc*
FAST	*Functioning Assessment Short Test , test de funcionament curt*
GWAS	*Genome Wide Association Study; Estudi d'associació de tot el genoma*
HHA	*Eix hipotàlem-hipofisiàri-adrenal*
LAI	*Long acting injection, injectable de llarga durada*
OR	*Odds ratio*
PAE-TPI	*Programa d'Atenció Específica al Trastorn Psicòtic Incipient*
PANSS	*Positive and Negative Syndrome Scale ,escala de simptomatologia en esquizofrènia*
PEP	*Primer episodi psicòtic*
ROP	*Recent onset psychoses, psicosis d'inici recent*
UA	*Unitat d'aguts*

RESUM DE LA TESI DOCTORAL

L'esquizofrènia és una malaltia complexa que s'origina per una alteració del neurodesenvolupament causada per la interacció de factors genètics i ambientals al llarg de les diferents etapes de la vida . El primer episodi psicòtic (PEP) succeeix en èpoques primerenques, entre la adolescència i l'adultesa jove i la probabilitat de patir un episodi psicòtic per tant, té a veure amb la interacció de la vulnerabilitat genètica individual i els diferents factors ambientals.

L'estrès és un dels principals factors ambientals implicats en la etiologia de la psicosi dins el model diàtesis–estrès i per tant te especial rellevància la seva relació amb mesures de l'eix hipotàlem-hipòfisi-adrenal (HHA).

En el nostre estudi hem volgut també centrar-nos en un dels principals riscos ambientals evitables, que és el consum del cànnabis i veure la seva interacció amb factors estressants com son el trauma a la infància i els esdeveniments vitals estressants en pacients amb psicosi d'inici control comparats amb grup control. Posteriorment em valorat l'efecte d'aquests factors ambientals sobre mesures biològiques de l'eix HHA.

Per continuar hem explorat l'efecte del cànnabis i del gènere en les variables clíniques de pacients ingressats per un Primer Episodi Psicòtic (PEP), així com les diferencies en raons de consum de cànnabis entre homes i dones. Finalment hem explorat si existien diferències en prevalença de consum de cànnabis, esdeveniments estressants i també en les variables clíniques principals entre PEPs immigrants d'origen marroquí i PEPs població autòctona.

En conjunt aquests tesi posa en evidencia que existeix un efecte acumulatiu i un efecte dosi-resposta dels factors de risc ambientals estudiats en el risc de psicosi , essent el trauma a la infància el factor de risc més important. Alhora , el consum de cànnabis es va associar amb una alteració en les mesures de l'eix HHA però sense diferencies entre pacients i controls. Vàrem trobar diferencies de gènere en les raons de consum de

cànnabis i una interacció de gènere i cànnabis en el funcionament. Finalment , no vàrem trobar diferencies en la prevalença de esdeveniments estressants entre PEPs d'origen marroquí i PEPs de població autòctona i una menor tendència a consumir cànnabis en aquesta població i un pitjor funcionament.

1. INTRODUCCIÓ

1.1.Etiologia de l'esquizofrènia, genètica i factors de risc.

L'esquizofrènia és una síndrome complexa de manifestacions psicopatològiques, cognitives i conductuals que afecta aproximadament al 1% de la població (Owen et al., 2016). El primer episodi psicòtic es defineix com la "*primera manifestació de la malaltia complint els criteris diagnòstics i el criteri temporal*" (APA, 2018). Aquest primer episodi psicòtic *succeeix* en èpoques primerenques, entre la adolescència i l'adultesa jove. Aproximadament el 3% de la població general pateix un episodi psicòtic al llarg de la seva vida (Perälä et al., 2007).

En els darrers 50 anys ha quedat demostrada la importància de la genètica en la etiologia del trastorn. Sent l'heretabilitat, que és la proporció de la variància de la malaltia que queda explicada per factors genètics, entorn al 80 % (Sullivan et al., 2003). Els avenços en genètica molecular en els darrers 10 anys han demostrat que l'esquizofrènia es una malaltia poligènica amb elevada pleiotropia (Ripke et al., 2014).

En quant als factors ambientals, en un inici lligats a l'aparició de la teoria del neurodesenvolupament, van cobrar importància aquells que afectaven al desenvolupament primerenc. És a dir durant les etapes pre i perinatals . Més endavant però, amb els avenços en l'estudi dels factors ambientals, s'ha arribat a la conclusió de que no sol serien rellevants aquells que incideixen durant l'etapa intrauterina. Sinó que l'esquizofrènia seria el resultat d'un conjunt d'anomalies biològiques i ambientals que ocorren durant tot el procés, des de la fecundació fins que el cervell és adult. Per tant, la malaltia seria el resultat de la interacció de factors genètics i ambientals que apareixen en diferents moments de la vida (Craddock et al., 2009; O'Donovan et al., 2009; van Os et al., 2002). Alhora també està cobrant cada cop més importància el concepte d'epigenètica, que estudia com l'ambient i la història de l'individu influeixen sobre l'expressió dels gens i per tant com poden produir-se canvis en l'expressió gènica depenent de factors ambientals sense que hi hagi una alteració en la seqüència de nucleòtids (Morgan and Whitelaw, 2008).

1.1.1 Factors ambientals

Els factors ambientals inclouen factors biològics i psicosocials que ocorren en diferents moments de la vida: prenatals i perinatals, la infància, la adolescència i la adultesa jove i que s'han vist relacionats amb un increment de risc de patir esquizofrènia (Veure figura 1).

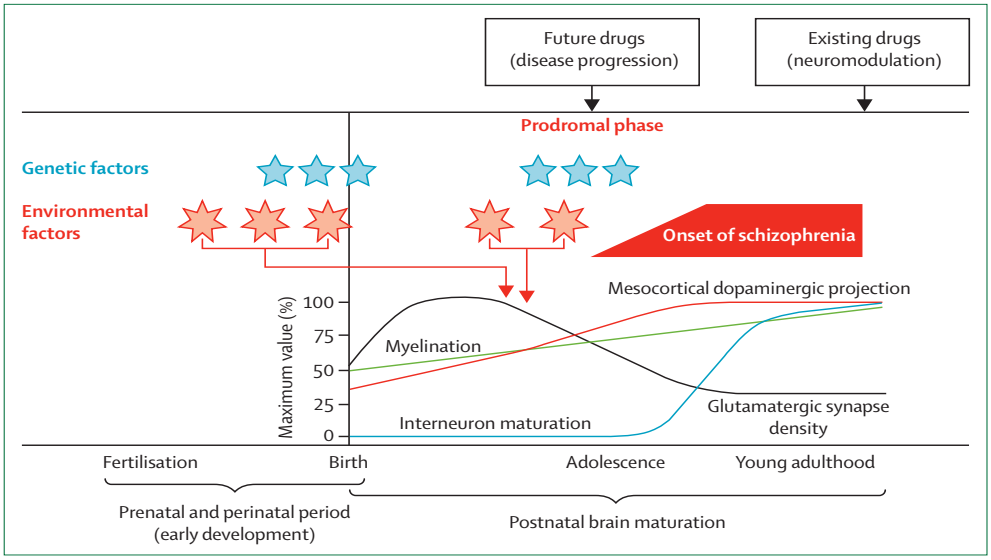
- *Factors prenatals i perinatals*: S'han relacionat diferents factors en aquest període, com les infeccions en el primer trimestre i l'augment del risc de desenvolupar esquizofrènia (Meyer et al., 2007). També incrementa el risc de la malaltia el fet d'haver nascut al final de l'hivern (Tandon et al., 2008). Però un dels factors ambientals més estudiats i replicats són les complicacions perinatals o obstètriques (Cannon et al., 2002).

- *Factors que intervenen en la infància*: El haver patit un trauma infantil (o maltractament infantil) ha estat demostrat en els últims anys com un important factor de risc en el desenvolupament de l'esquizofrènia (Janssen et al., 2004; Read et al., 2005; Varese et al., 2012).

La migració és també un factor important en aquesta època de la vida (Lim et al., 2011; Morgan and Hutchinson, 2009), i el haver nascut en un ambient urbà (Marcelis et al., 1999; Zammit et al., 2010).

- *Factors que intervenen en l'adolescència i adultesa jove*: El consum de cànnabis (Arseneault et al., 2002; Moore et al., 2007) seria el principal factor de risc estudiat en aquest període. L'estrès i les adversitats socials també es relacionen amb la generació de psicosis en aquesta fase del desenvolupament (Morgan et al, 2008).

Figura 1. Factors ambientals i genètics que actuen en diferents fases del creixement (adaptada de (Owen et al., 2016))



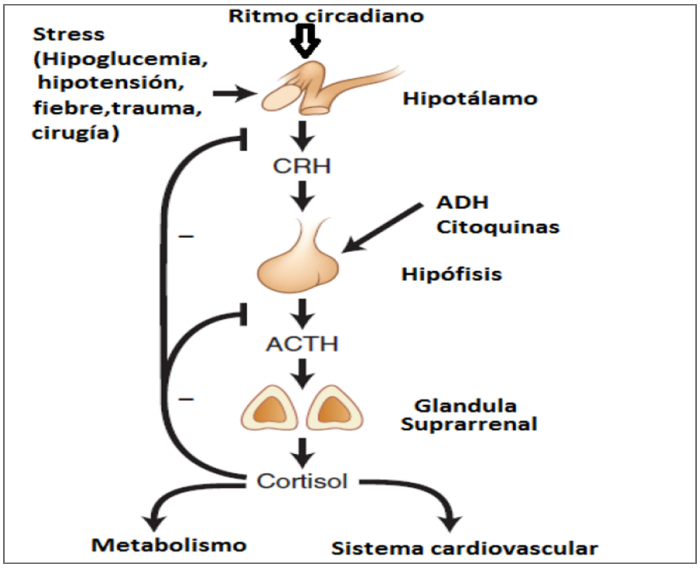
1.1.2 Estrès i Eix hipotàlem-hipofisiari-adrenal (HHA) en el primers episodis psicòtics.

L'estrès és una reacció fisiològica de l'organisme en la que intervenen diferents processos biològics i que ens permet sobreviure a una situació d'amenaça. El model neural clàssic de estrès-diàtesis de l'esquizofrènia suggereix que l'estrès social activa l'eix hipotàlem-hipofisiari-adrenal (HHA), induint l'alliberació de cortisol i augmentant la transmissió de dopamina que contribuiria a l'inici de la psicosis en individus vulnerables (Walker and Diforio, 1997). El model neural d'estrès-diàtesis es va proposar inicialment l'any 1977 i es va renovar l'any 1997, sent un dels més utilitzats per la explicació del desenvolupament de la psicosi (Pruessner et al., 2017).

El cortisol és un esteroide que s'obté a través de l'eix hipotàlem-hipofisiari-adrenal i que es modula per l'estrès. Veient-se afectada la seva producció tant en estrès aguts com en estrès crònic (Veure figura 2). El **cortisol** es secretat per la zona reticular i emmagatzemat a la zona fascicular de l'escorça suprarenal, una de las dues parts de la glàndula suprarrenal. Aquesta alliberació està controlada per l'hipotàlem, una part del cervell, en resposta a l'estrès o a un nivell baix de glucocorticoides en la sang.

La resposta del cortisol al despertar (CAR, son les seves sigles en anglès), definida com un increment de la alliberació del cortisol en resposta al procés de despertar-se, ha estat estudiada com a biomarcador potencial en la esquizofrènia (Mondelli et al., 2015).

Figura 2. Síntesi del cortisol (adaptada de la UNED, corteza suprarenal 2014)

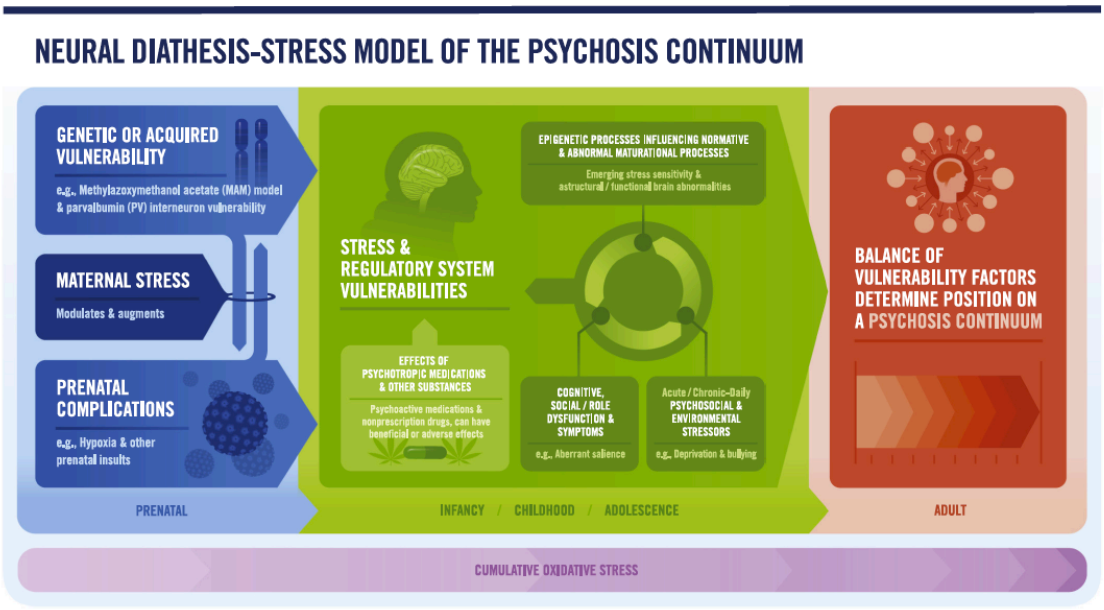


Estudis previs han descrit que els pacients amb un primer episodi psicòtic han patit més esdeveniments vitals estressants (Beards et al., 2013; Manzanares et al., 2014) mes estrès percebut (Pruessner et al., 2017) i més trauma o maltractament a la infància i per tant ha estat descrit que els factors estressants compleixen un rol important en l'inici de la malaltia (Mondelli et al., 2010; Phillips et al., 2007). Dins dels factors d'estres destaquem : el "trauma a la infantesa o maltractament infantil" i els "esdeveniments vitals estressants ".

Els “esdeveniments vitals” són situacions o circumstàncies que poden ser positius o negatius i que aporten un element d’amenaça a la persona que el pateix. Es descriuen com esdeveniments vitals recents aquells que han succeït en els últims 6-12 mesos (Beards et al., 2013; Brown and Birley, 1968).

El “trauma a la infància o maltractament” són les situacions negatives doloroses i angoixants que ocorren abans dels 16 anys (Bernstein et al., 2003; Mansueto and Faravelli, 2017; Plant et al., 2016).

Figura 3. Model del diàtesi-estrès (adaptada de (Mittal and Walker, 2019)



1.1.3 Cànnabis

1.1.3.1 El cànnabis com a factor de risc i raons de consum.

El cànnabis és la tercera droga en crear dependència en el món, després de l’alcohol i el tabac. En mostres de PEPs la prevalença de consum de cànnabis oscil·la entre un 40 al 50 % (Arranz et al., 2018; Barbeito et al., 2013; Núñez et al., 2016). Malgrat l’elevada prevalença de consum de cànnabis en PEPs, els motius de consum no han estat gaire estudiats, i cap estudi tampoc ha investigat les diferències de gènere en

els motius de consum de cànnabis. La majoria d'estudis que han investigat les raons del consum de cànnabis en primers episodis psicòtics troben que gran part d'aquests pacients consumeixen amb la finalitat de sentir els efectes propis de la intoxicació i per relaxar-se, millorar l'estat d'ànim i socialitzar-se (Archie et al., 2013; Kolliakou et al., 2012; Mané et al., 2015; Pencer and Addington, 2008).

Des de l'any 1987 diversos estudis de seguiment en població general han demostrat que existeix un risc de desenvolupar una psicosi en consumidors de cànnabis (Veure taula 1). Existeix un ampli consens científic actual en què en persones vulnerables, la interacció genètica-ambient determina un risc de psicosi per consum de cànnabis (Clausen et al., 2014; Marconi et al., 2016; Moore et al., 2007; Murray et al., 2017).

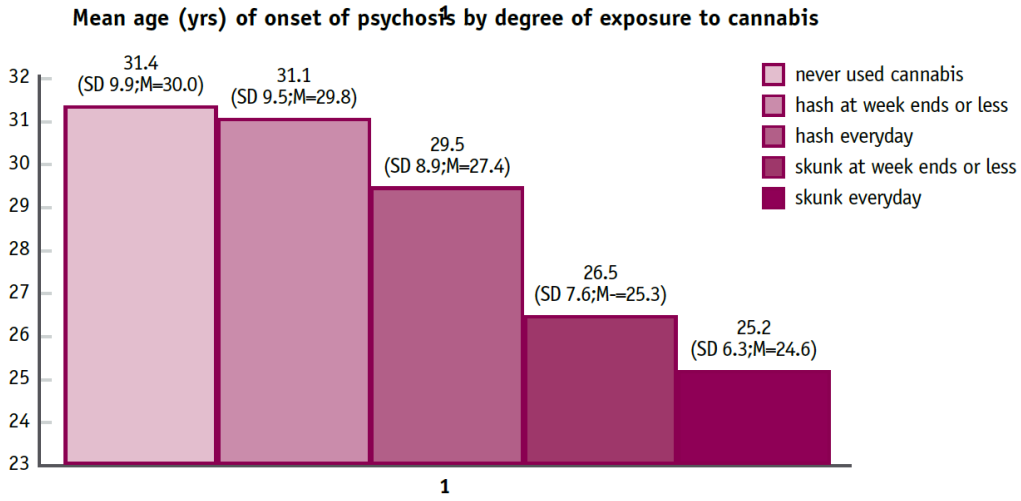
Taula1. Estudis de seguiment en població general sobre consum de cànnabis i risc de desenvolupament de psicosi (elaboració pròpia)

AUTORS	MOSTRA	SEGUIMENT	OR (interval de confiança del 95%)
Andreasson et al 1987	45570 reclutes suecs	15 anys	6.0 (4.0-8.9)
Zammit et al 2002	50087 reclutes suecs	27 anys	3.1 (1.7-5.5)
Arseneault et al 2002	1037 Nova zelanada (Dunedin) Cohort naixement	15 anys	3.1(0.7-13.3)
Van Os et al 2002	4104 Holanda NEMESIS	3 anys	2.8(1.2-6.5)
Fergusson et al 2003	1265 Nova Zelanda CHDS, Christchurch	3 anys	1.8 (1.2-2.6)
Henquet et al 2005	2437 Alemania EDSP	4 anys	1.7 (1.1-2.5)
Manrique-Garcia et al 2012	50.087 reclutes suecs	35 anys	3.7 (2.3-5.8)

1.1.3.2 Relació entre el consum de cànnabis i característiques clíniques de la psicosi.

S'ha demostrat que l'excés de consum en l'adolescència avança l'edat d'inici de la psicosi (Large et al., 2011). A més, a partir de l'estudi de Marta Di Forti i cols, es demostra que seria el cànnabis de major potencia el que estaria més relacionat amb una menor edat d'inici (Di Forti et al., 2014).

Figura 4. Gràfica que relaciona l'edat d'inici de la psicosi amb la quantitat de cànnabis i el tipus de consum (adaptat de(Di Forti et al., 2014))



D'altra banda, l'ús de cànnabis també s'ha associat a resistència al tractament antipsicòtic (Patel et al. 2016) i més recaigudes després d'un PEP (González-Pinto et al., 2008; Harrison et al., 2000) . No obstant això, hi ha menys consens sobre la influència del cànnabis en la gravetat dels símptomes positius i negatius (Linszen et al., 1994; van Dijk et al., 2012), la dosi efectiva antipsicòtics o la durada de l'hospitalització per aconseguir la remissió dels símptomes (Babatope et al., 2016; Patel et al., 2015).

1.1.3.3. Relació entre cànnabis i factors estressants

Atès que no tot tipus d'exposició donarà lloc irrevocablement a la psicosi, hi ha un interès creixent en l'estudi de la relació entre els diferents factors. Per tant, es probable que existeixi una associació entre els diferents factors ambientals, amb efectes de interacció, mediació, dosi-resposta i / o efectes acumulatius en diversos períodes de desenvolupament (Davis et al., 2016)

Alguns estudis han trobat que el cànnabis i el trauma infantil interaccionen per augmentar la probabilitat de psicosi (Houston et al., 2011, 2008; Murphy et al., 2013) però, altres tres estudis (Baudin et al., 2016; Kuepper et al., 2011; Sideli et al., 2015) no han reportat cap evidència d'interacció entre aquests factors. Altres han explorat el seu efecte acumulatiu o additiu (Harley et al., 2010; Konings et al., 2012; Morgan et al., 2014b; Padmanabhan et al., 2017a) suggerint que el trauma infantil i el consum de cànnabis en l'adolescència creen una vulnerabilitat que augmenta el risc de desenvolupar psicosi (Harley et al., 2010; Konings et al., 2012; Morgan et al., 2014a). La relació entre el trauma infantil i els esdeveniments vitals estressants amb la psicosi ha mostrat resultats contradictoris. Alguns autors han suggerit que les persones amb antecedents de trauma infantil són més sensibles als esdeveniments vitals estressants (Lardinois et al., 2011; Lataster et al., 2012), i altres han suggerit una contribució independent dels esdeveniments recents fins i tot en presència de trauma a la infància (Mansueto and Faravelli, 2017). No obstant això, hi ha una manca d'estudis controlats que investiguen la relació entre trauma infantil, esdeveniments estressants recents i l'ús de cànnabis amb psicosi des d'un punt de vista dosi-efecte .

Per altra banda pocs estudis han explorat l'associació entre consum de cànnabis, esdeveniments vitals estressants o trauma infantil i mesures de l'eix HHA en subjectes amb psicosi d'aparició recent. En un estudi que incloïa subjectes amb un PEP i un grup control sa mostrava que els PEPs tendien a mostrar taxes més altes de trauma a la infància , menor cortisol basal i millor supressió del cortisol amb dexametasona a dosis baixes (0,25 mg) (Phassouliotis et al., 2013), tot i que les mesures de cortisol no es van trobar associades a un trauma en la infància. En un altre estudi que també incloïa PEPs, els nivells diürns de cortisol es van correlacionar de forma negativa amb els esdeveniments vitals estressants i el CAR (Cortisol Awakeing Response) es va

correlacionar de forma positiva amb antecedents d'abús sexual (Mondelli et al., 2010). Però cap a estudiat la seva relació entre aquests factors i cànnabis amb mesures de l'eix HHA.

1.1.4. Migració

Un dels factors de risc ambientals per psicosi és el procés migratori, especialment durant la infància (Morgan et al., 2017; Veling et al., 2006), com es veu a la taula 2 el veure's afectat per un procés migratori en la infància es un dels principals factors de risc ambientals per desenvolupar una psicosi (Veure Taula 2). Així com era ben coneguda la relació dels processos migratoris amb les reaccions depressives, no ho era tant la seva relació amb l'inici més precoç de les psicosi i amb augmentar el risc de patir-la (Morgan et al., 2017; Zandi et al., 2011). En un estudi actual realitzat en 6 països diferents, entre ells Espanya, es va confirmar que els grups ètnics minoritaris, particularment en homes, presenten un major risc de desenvolupar un primer episodi psicòtic (Jongsma et al., 2018). No obstant, a partir dels estudis previs, sembla que no totes les poblacions migrats tenen el mateix risc, sinó que tindrien un especial risc, aquelles que pateixen una exclusió social en el país d'acollida o que han patit un gran estrès en el moment de la migració (Henssler et al., 2019; Janssen et al., 2003).

Taula 2. Odds Ratio d'altres factors de risc que també afecten a l'esquizofrènia (elaboració pròpia)

Factors de risc	ODDS RATIO OR	Estudis
Negre caribeny a Anglaterra	4'87	(Tortelli et al., 2015)
Maltractament infantil	2'87	(Varese et al., 2012)
Pes al néixer <2000 grams	2'46	(Cannon et al., 2002)
Urbanicitat	2.19	(Vassos et al., 2012)

1.1.4.1 Diferencies clíniques en PEP segons ètnia:

L' estudi de les diferencies ètniques en PEP han mostrat resultats molt diversos tant a Europa com a la resta del mon (Anderson et al., 2014; Lim et al., 2011; Morgan and Hutchinson, 2009). No hi ha descrites diferencies clíniques clares entre ètnies, però en molts estudis la variable ètnia s'ha definit com a "minoritària" barrejant en ella tot tipus d'orígens, el que ha portat a resultats inconsistents o contradictoris (Anderson et al., 2014; Mann et al., 2014). En quant al patró de consum de substancies, està descrit a la literatura que els pacients d'origen migratori consumeixen menys que els autòctons, tant sigui alcohol, cànnabis com altres drogues (Harris et al., 2019; Johnson et al., 2002; Qureshi et al., 2014).

Els programes d'atenció primerenca en psicosis atenen elevades ratios de població migrant (Collazos et al., 2005; Golay et al., 2019). Tot i així, en el nostre país, la investigació sobre aquest camp és encara molt limitada, existint pocs programes específics. Al Regne Unit, pioners a Europa en els programes d'atenció precoç, tenen programes com el ENRICH a Birmingham per l'atenció a la població migrant amb símptomes psicòtics (Singh et al., 2016).

La nostra mostra d'estudi de PEPs s'obté de Reus, tant de la unitat d'aguts i com de l'equip d'Intervenció precoç. De la població migrant empadronada a Reus, el principal col·lectiu és el marroquí, sent Reus la cinquena ciutat a Catalunya en número absolut de persones d'origen marroquí empadronats. El perfil demogràfic de la població empadronada a Reus consten 7.292 marroquins en total (3.660 homes i 3.632 dones) *(xifres oficials de Padró a 1 de Gener de 2018).* No hi ha cap estudi previ entre les diferències clíniques en PEPs entre població marroquí i autòctona.

1.1.5 Gènere

El rol del gènere en la psicosi ha estat un tema poc tractat fins els anys actuals, i és per això que no trobem tantes publicacions com en altres temes d'estudi (Køster et al., 2008). La menor edat d'inici en els homes , és la troballa més replicada en els estudis sobre diferències de gènere (Ochoa et al., 2012). Els estudis que analitzen la influencia del gènere en la simptomatologia descriuen resultats controvertits, ja que no tots troben diferencies (Gureje and Bamidele, 1998). Quan es descriuen diferencies en primers episodis, es descriu que les dones tenen més símptomes afectius (Chang et al., 2014; Cotton et al., 2009; Morgan et al., 2008) i els homes tenen més símptomes d'agressivitat (Drake et al., 2016; Thorup et al., 2014; Tseliou et al., 2017). En quan al tractament, encara hi ha menys evidència sobre les diferencies entre homes i dones. S'ha suggerit que les dones necessiten dosis antipsicòtiques més baixes, tenen nivells més alts de compliment terapèutic i tenen millor resposta al tractament que els homes, encara que aquestes troballes són inconsistents (Seeman, 2004; Smith, 2010; Usall et al., 2007). Com s'indica en una revisió recent de (Crawford and DeLisi, 2016) i les diferencies de gènere en la dosi d'antipsicòtic eficaç per a obtenir una resposta durant la fase aguda inicial han estat escassament investigades i han donat resultats conflictius. A més, pocs estudis han investigat la influència del gènere en les característiques clíniques i d'hospitalització quan els pacients es tracten per primera vegada per un PEP en una unitat d'aguts (Arranz et al., 2015; Shlomi Polachek et al., 2017).

1.1.5.1 Relació entre el gènere i cànnabis en les variables clíniques:

Els homes amb un primer episodi psicòtic consumeixen més cànnabis (Barrigón et al., 2015; Koskinen et al., 2010; Mazzoncini et al., 2010) i s'inicien abans que les dones en el consum (Haberstick et al., 2014; Kelley et al., 2016). Tot i que el gènere femení s'inicia més tard en el consum de cànnabis , així com en la resta de tòxics, s'ha descrit "l'efecte telescòpic", definit una ràpida evolució a la dependència i deteriorament físic. Tal i com ja s'havia descrit prèviament en dones amb alcohol i altres tòxics (Ehlers et al., 2010; Hernandez-Avila et al., 2004).

En vista del que s'ha anat descrivint al llarg de la introducció d'aquesta tesi, tant el gènere com el cànnabis poden influir en l'aparició clínica i la resposta del tractament en PEP; no obstant, hi ha una evidència molt limitada sobre els efectes de la relació entre el cànnabis i el gènere en aquestes variables (Setién-Suero et al., 2017). Tal i com s'indica en un estudi recent de Crocker i Tibbo, (2018), pocs estudis han específicament investigat l'efecte d'interacció del gènere i el cànnabis sobre les característiques clíniques de la psicosi. S'ha suggerit que les diferències de gènere relatives a l'edat d' l'inici, la psicopatologia i el pronòstic són menys evidents, o fins i tot desapareixen quan es controla per l'ús del cànnabis (Arranz et al., 2015; Di Forti et al., 2014; Helle et al., 2016; Lange et al., 2017; Patel et al., 2016). D'altra banda, actualment no hi ha cap estudi sobre l'impacte d'aquestes variables en els símptomes clínics, la resposta antipsicòtica i les variables relacionades amb l'hospitalització en els PEPs ingressats per primer cop en una unitat d'aguts.

2. OBJECTIUS I HIPÒTESI

HIPÒTESI GENERAL

El risc de desenvolupar una psicosi dependrà de la severitat de l'exposició al cànnabis i a l'estrès (trauma a la infància, esdeveniments vitals estressants i eix HHA). Existiran diferències de gènere i ètnia en el patró i en les raons de consum de cànnabis en primers episodis psicòtics.

OBJECTIUS

2.1. Objectiu 1

- Estudiar si el risc de psicosi depèn de la severitat de la exposició del maltractament infantil, dels esdeveniments vitals i del consum de cànnabis .
- Determinar si existeix una interacció o un efecte acumulatiu entre aquets tres factors en la aparició d'un primer episodi psicòtic.

2.1. Objectiu 2

- Explorar si el trauma infantil, els esdeveniments vitals estressants i el consum de cànnabis s'associen a mesures de l'eix hipotàlem-hipofisiari-adrenal (HHA).

2.1. Objectiu 3

- Estudiar si existeixen diferencies en la prevalença en consum de cànnabis i en els esdeveniments vitals estressants entre primers episodis d'origen marroquí i autòctons.
- Estudiar si existeixen diferències en les variables clíniques i de tractament entre primers episodis d'origen marroquí i autòctons.

2.1. Objectiu 4

- Estudiar si hi ha diferencies de gènere en el patró de consum de cànnabis i en les raons de consum de cànnabis en pacients ingressats per primer cop en una unitat d'aguts per un primer episodi psicòtic
- Estudiar si hi ha diferencies clíniques a l'ingrés i a l'alta en funció del gènere o del consum de cànnabis en pacients ingressats per primer cop en una unitat d'aguts per un primer episodi psicòtic

2.2.HIPÒTESIS

2.1.1. Hipòtesi 1

- El risc de psicosi dependrà de la severitat de l'exposició al cànnabis, trauma a la infància i esdeveniments vitals estressants
- Existirà un efecte acumulatiu i una interacció entre els diferents factors de risc

2.1.2. Hipòtesi 2

- Existirà una associació entre alteracions entre la secreció de cortisol i els factors estudiats: cànnabis, trauma a la infància i esdeveniments vitals estressants
- Aquesta associació serà major en pacients amb psicosi d'inici recent que en controls.

2.1.3. Hipòtesi 3

- Els pacients amb un primer episodi psicòtic d'origen marroquí tindran més esdeveniments vitals i consumiran més cànnabis que els pacients amb un primer episodi d'origen autòcton
- Els pacients amb un primer episodi psicòtic d'origen marroquí presentaran una simptomatologia més severa i requeriran major dosi d'antipsicòtics que els pacients amb un primer episodi d'origen autòcton

2.1.4. Hipòtesi 4

- Existiran diferències de gènere en el patró i en les raons de consum de cànnabis en primers episodis psicòtics
- Existiran efectes principals del gènere , cànnabis o efectes d'interacció entre gènere i cànnabis en les variables clíniques i de tractament

Hipòtesi	Estudi	Publicació
1	Estudi dels factors de risc d'estrès i cànnabis en psicosi d'inici recent a l'equip de psicosi incipient de Reus	**The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis.** Autors/es: Sara Arranz, Nuria Monferrer, M.José Algora, Angel Cabezas, Montse Sole, Elisabeth Vilella, Javier Labad, Vanessa Sanchez Gistau. Revista: Schizophrenia Research DOI: 10.1016/j.schres.2018.04.040
2	Estudi dels factors de risc d'estrès i cànnabis i la seva relació amb el cortisol i l'eix hipotàlem-hipofisiari-adrenal en psicosi d'inici recent a l'equip de psicosi incipient de Reus	**Hypothalamic-pituitary-adrenal axis function and exposure to stress factors and cannabis use in recent-onset psychosis** Autors/es: Javier Lavad, Laura Ortega, Itziar Montalvo, Sara Arranz, María José Algora, Lourdes Martorell, Elisabeth Vilella, Vanessa Sánchez Gistau. Revista: The world journal of biological psychiatry DOI: 10.1080/15622975.2019.1628301
3	Estudi dels factors de risc d'estrès i cànnabis en psicosi d'inici recent a l'equip de psicosi incipient de Reus	**Comparison between a morocco and a native-born population, in a sample of first episode psychosis.** Autors/es: Sara Arranz, Julia Camacho, Claudia Andrés, Inés Niubó, Vanessa Sánchez Gistau. Revista: Revista de psiquiatría y Salud mental DOI: 10.1016/j.rpsm.2019.03.004
4	Relació entre el consum de cànnabis i la tolerabilitat dels fàrmacs antipsicótics en pacients amb trastorns psicòtics incipients	**The impact of sex and cannabis on clinical features in first–admitted patients with psychosis** Autors/es: Sara Arranz, Anna Mané, Dani Bergé, Clara Monserrat, Angel Cabezas, Elisabet Vilella , and Vanessa Sanchez-Gistau Estat: En revisió a European psychopharmacology desde septembre 2019

3.1 POBLACIO OBJECTE D'ESTUDI

3.1.1 Estudis 1 i 2 :

Els participants dels 2 primers estudis es van reclutar a partir de l'equip d'intervenció precoç (EIP) de Reus de l'Hospital Universitari Institut Pere Mata (HUIPM). L'EIP forma part del Programa PAE-TPI (Programa d'Atenció Específica al Trastorn Psicòtic Incipient) des del 2009 i la seva àrea de referencia cobreix una zona urbana i rural de 194.255 habitants. El PAE-TPI està impulsat i finançat pel Sistema sanitari públic català per al diagnòstic i el tractament de subjectes de 14 a 35 anys que compleixen criteris d'Estat Mental en Risc (EMAR) o que pateixin un Primer Episodi de Psicosi (PEP). L'equip de l'EIP de Reus, es un equip comunitari i per tant d'atenció ambulatòria, que està format per dos psiquiatres, un psicòleg, una infermera o gestora de casos i un treballador social. Els membres de l'equip tenen experiència clínica i d'investigació i combinen la seva feina diària en tasques d'assistència clínica i investigació. Els subjectes EMAR son seguits durant un màxim de dos anys si no han fet transició a psicosi i els PEP durant el període crític (fins a cinc anys). Els usuaris inclosos en el PAE-TPI són tractats seguint les recomanacions de la International Early Psychoses Association (IEPA) *(https://iepa.org.au/services/first-episode-and-early-psychosis-assessment/)*

Els controls van ser reclutats a partir d'amics i coneguts dels pacients i no podien tenir antecedents personals de trastorn psiquiàtric ni familiars de primer o segon grau de psicosi.

3.1.1.1.Criteris d'inclusió i exclusió:

Taula 3. Criteris d'inclusió i exclusió dels estudis 1 i 2.

	Criteris d'inclusió	**Criteris exclusió**
Psicosi inici recent	Inici dels símptomes psicòtics en els darrers 6 mesos Edat entre 16 i 35 anys Capacitat per poder comprendre i parlar la llengua Sense historia de factors orgànics implicats en la etiologia de la psicosi	Embaràs Discapacitat intel·lectual Traumatisme cranioencefàlic greu Malaltia neurològica greu
Controls sans	Edat entre 16 i 35 anys Sense antecedents actuals o passats de trastorn psiquiàtric	

3.1.2. ESTUDIS 3 I 4:

Els pacients van ser obtinguts de les unitats d hospitalització d'aguts . Els pacients de l'estudi 3 a partir de la unitat d'aguts del HUIPM i l'estudi 4 a partir de pacients provinents de la unitat d'aguts del HUIPM i de la unitat d'aguts de l'Hospital Universitari Hospital del Mar, Barcelona.

La unitat d'aguts de I 'Institut Pere Mata és una unitat d'estança curta destinada a atendre a persones majors de 18 anys que presenten una situació de crisi que no es por solucionar de forma ambulatòria. Constava de 60 llits en el moment de fer l'estudi i els pacients provenien del servei propi d'urgències. L'Hospital del Mar disposa de diverses unitats d'hospitalització, però vam contar amb la unitat d'hospitalització d'aguts on ingressen els primers episodis. Vam seguir sempre el mateix protocol en els dos centres.

3.1.2.1 Criteris d'inclusió i exclusió:

Taula 4. Criteris d'inclusió i exclusió dels estudis 3 i 4.

	Criteris d'inclusió	**Criteris d'exclusió**
Primers episodis psicòtics	Pacients ingressats per primera vegada per un primer episodi psicòtic amb DUP < 12 mesos	Tractament antipsicòtic> 4 setmanes en el moment de l'ingrés
	Edat entre 18 i 35 anys	Embaràs
	Capacitat per poder comprendre i parlar la llengua	Discapacitat intel·lectual Malaltia neurològica greu
	Sense historia de factors orgànics implicats en la etiologia de la psicosi	Traumatisme cranioencefàlic greu

Figura 5. Interacció entre las mostres d'estudi.

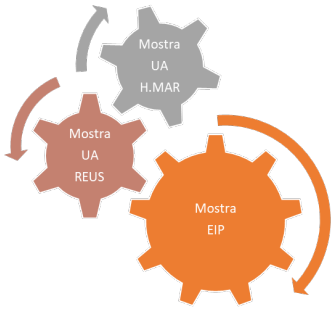


Figura 6. Mostres de l'equip de psicosi incipient

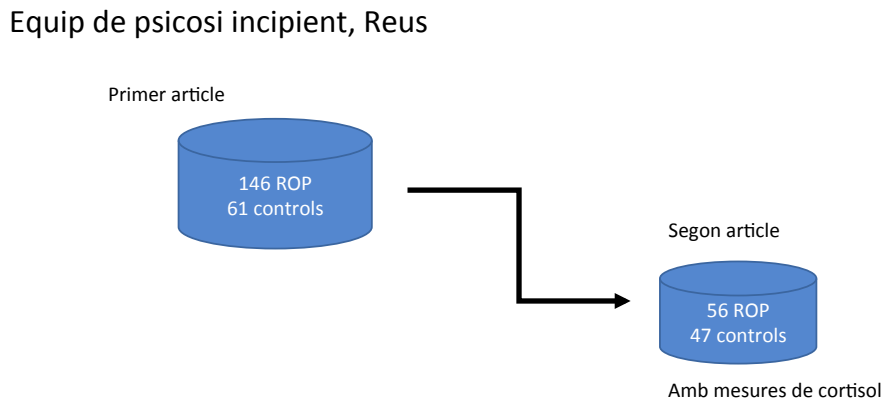
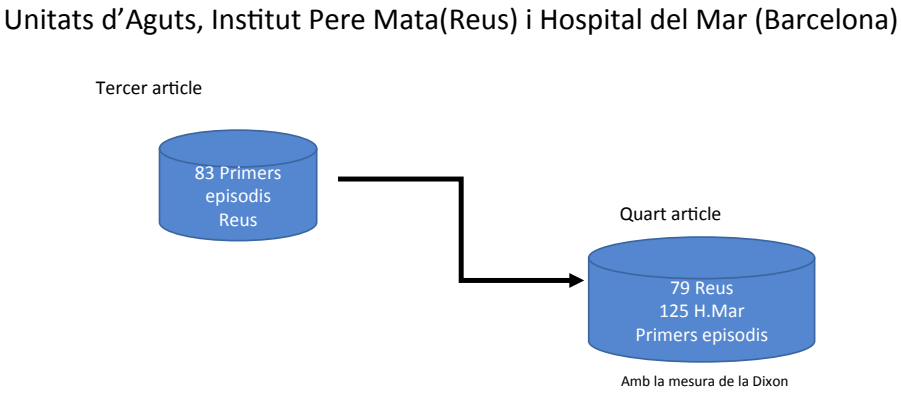


Figura 7. Mostres de les Unitats d'Aguts



3.2 AVALUACIONS

En el següent apartat es descriuran breument les avaluacions incloses en els estudis.

3.2.1. Variables sòcio-demogràfiques.

S'obtenen a partir de la entrevista clínica. La informació sobre l'origen migratori es va obtenir a partir del país de naixement i no es va considerar la segona generació (M. Adriaanse et al., 2015). Seguint estudis previs als Països Baixos i a Espanya, utilitzem la següent nomenclatura per diferenciar els dos grups: "població immigrant d'origen marroquí" i "població autòctona" (M Adriaanse et al., 2015; Veling et al., 2006)

3.2.2. variables clíniques

3.2.2.1 Diagnòstic:

Va ser confirmat fent servir la OPCRIT checklist v4.0 (Craddock et al., 1996) per generar diagnòstics DSM-IV.

3.2.2.2 Psicopatologia:

Les escales clíniques obtingudes van ser la Positive and Negative Syndrome Scale (PANSS), per avaluar simptomatologia positiva i negativa psicòtica (Kay et al., 1990), la Calgary Depression Scale for Schizophrenia (CDSS) per simptomatologia depressiva en esquizofrènia (Addington et al., 1993). La duració de la psicosi no tractada (DUP) definida com " temps des de inici dels símptomes psicòtics francs fins inici del primer tractament antipsicòtic " es va obtenir a través d'entrevista clínica

3.2.2.3 Funcionament :

Per el funcionament es va fer servir també la Functioning Assessment Short Test (FAST), en la seva versió espanyola (Rosa et al., 2007). La puntuació de la FAST és inversament proporcional al nivell de funcionament. També es fa servir la Global Assessment Functioning (GAF), per funcionament global amb una puntuació de 0 a 100, essent millor el funcionament a major puntuació.

3.2.2.4 Tractament farmacològic:

La informació sobre medicació es va obtenir a partir de les dades clíniques i seguint el model d'un estudi previ (Babatope et al., 2016) es van considerar les dosis a l'alta com les dosis efectives per aconseguir una resposta clínica. Les dosis d'antipsicòtic es van convertir en equivalents de clorpromazina (mg /dia)(Gardner et al., 2010), i les dosis de tractament injectable (LAI: Long Acting Inyectable) es van convertir fent servir el mètode de la dosi mínima efectiva (Rothe et al., 2018). Els efectes secundaris de les medicació antipsicòtica van ser avaluats mitjançant la UKU (Lingjaerde et al., 1987).

3.2.3. variables d'estrès

3.2.3.1 Variables psicomètriques d'estrès

- **Trauma infantil:** El trauma infantil es va avaluar amb la versió espanyola del 28 del Childhood Trauma Questionnaire−Short Form (CTQ-SF)(Hernandez et al., 2013).

El CTQ-SF és un instrument autoaplicat de 28 ítems per a l'avaluació retrospectiva del maltractament infantil. El CTQ-SF avalua cinc tipus de maltractament àmpliament acceptats: abús emocional, físic i sexual i negligència emocional i física. Cada ítem es puntua mitjançant respostes de tipus Likert que van des d'un punt "mai" fins a 5 punts "molt sovint" . A partir d'aquí es poden crear per crear subescales dimensionals i quatre punts de tall de gravetat en l'exposició per a cada subescala:

1- " de cap exposició a baixa exposició"
2- "de baixa exposició a moderada exposició"
3- "de moderada exposició a severa exposició"
4- " de severa exposició a exposició extrema".

La puntuació total del CTQ s'obté afegint les cinc puntuacions de subescales i oscil·la entre 25 i 75 punts.

- **Esdeveniments vitals estressants :**Els esdeveniments vitals estressants en els sis mesos anteriors van ser avaluats mitjançant l'escala de reajustament social de Holmes-Rahe (HR) (Holmes and Rahe, 1967), validada per a població de parla espanyola (Roca et al., 2013). Inicialment, la HR va ser desenvolupada per explorar les relacions entre reajustament social, estrès i susceptibilitat a la malaltia. Incorpora 43 esdeveniments vitals amb una puntuació d'estrès per a cada ítem, obtenint una puntuació final sumatòria de les puntuacions de tots els esdeveniments. Una puntuació de 150 punts o menys suggereix una baixa susceptibilitat a un problema de salut induït per l'estrès; De 150 a 300 punts suggereix susceptibilitat moderada, i més de 300 punts suggereix una alta susceptibilitat.

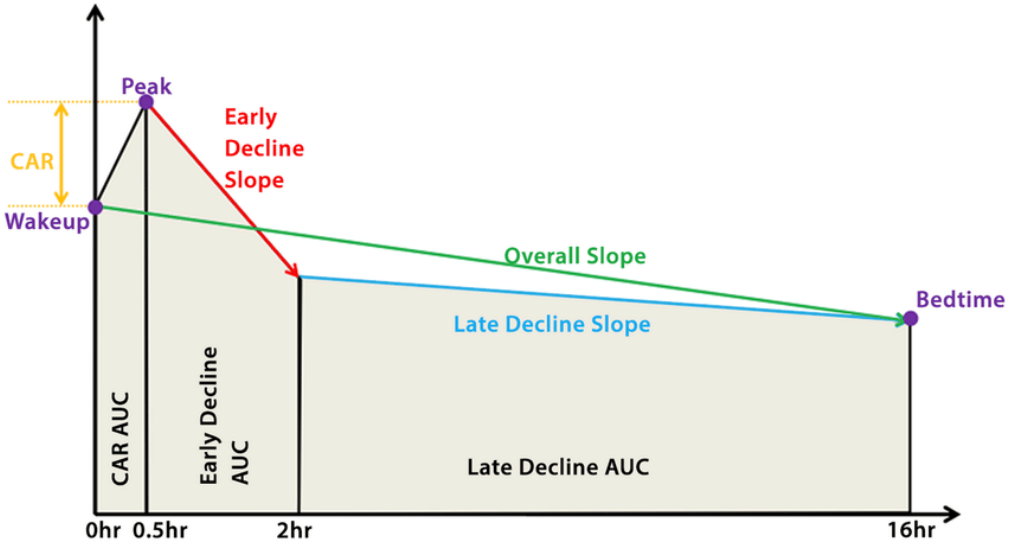
3.2.3.2. Mesures biològiques d'estrès

Les mesures de cortisol es van obtenir a partir de la saliva, fent servir els Salivette, al domicili. Les mostres havien de recollir-se al despertar-se (T1), 30 min després (T2), 60 min després (T3), a les 10:00 (T4) i ales 24;00h (T5). I posteriorment es va fer un test de supressió baix amb dexametasona que ja ha demostrat sensitivitat en saliva (Labad et al., 2016; Phassouliotis et al., 2013).

Amb aquestes mesures s'obtenen aquestes paràmetres dinàmics, veure la figura 8 com a guia.

- Cortisol al despertar (Cortisol awakening response (CAR)) càlcul del CAR amb l'àrea sota la corba respecte a l'increment
- Pendent circadiana de cortisol (Diurnal Cortisol Slope) pendent entre despertar i 23 hores
- Test de supressió amb Dexametasona (DSTR) després de 0.25 mg de dexametasona. DST ratio= cortisol a les 10h/cortisol a les 10h després de dexametasona

Figura 8. Pendent circadiana de cortisol



3.2.4. Variables relacionades amb el cànnabis.

3.2.4.1 Freqüència de consum

El consum de substàncies es va avaluar mitjançant entrevista clínica. A partir d'aquesta entrevista, es va determinar la freqüència de consum en els darrers 6 mesos mitjançant respostes tipus Likert: "diàriament" ,"diverses vegades a la setmana", "diverses vegades al mes", "menys de diverses vegades al mes", i en absolut.

La freqüència de consum es va classificar de la següent manera (Bugra et al., 2013):

1- "sense ús"
2- "ús esporàdic": definit com a menys d'una vegada al mes
3- "ús regular", definit com a més d'una vegada al mes.

Entre els usuaris amb un consum regular vàrem diferenciar dos nivells de severitat:

- "moderat", de més d'una vegada al mes a menys d'una vegada a la setmana
- "sever", de més d'una vegada a la setmana a l'ús diari.

3.2.4.2 Raons de consum de cànnabis :

Les raons pel consum de cànnabis es van avaluar mitjançant el Qüestionari de Dixon (Dixon et al., 1991). Aquest qüestionari consta de 17 ítems amb respostes dicotòmiques (sí / no) sobre diversos motius d'ús; En el 4 article d'aquesta tesi on s'inclouen les raons de consum no s'inclou l'ítem "efectes secundaris de la medicació", ja que la majoria dels pacients eren naïves al tractament AP.

Taula 5 . Llistat de raons de consum adaptat de (Dixon et al., 1991).

Raons de consum	SI	NO
Intoxicació/ "colocón"		
Disminuir la tristesa		
Relaxar-me		
Dormir millor		
Incrementar el plaer		
Incrementar la energia		
Pertànyer a un grup		
Incrementar les emocions		
Ser més parlador		
Ser més creatiu		
Per avorriment		
Satisfer la curiositat		
Millorar la concentració		
Organitzar els meus pensaments		
Treballar i /o estudiar		
Alleugerar els efectes secundaris de la medicació		
Disminuir al·lucinacions/suspicàcia		

3.4 ANALISI ESTADISTIC

Els anàlisis estadístics es van realitzar mitjançant el programa estadístic SPSS (SPSS Inc, Chicago, IL, USA), amb un nivell de significació (p) menor de 0,05. Donat que els anàlisis estadístics realitzats difereixen entre los 4 estudis, els detalls concrets s'especifiquen en l'apartat estadístic de cada publicació.

3.5. ASPECTES ETICS

Els estudis presentats en aquest treball van ser aprovats pels comitès d'ètica d'investigació dels respectius hospitals, i respecten els principis ètics de la Declaració de Hèlsinki del 2013. Tots els participants dels estudis van rebre la informació de les característiques del estudi i van signar el consentiment informat abans de la inclusió a l'estudi.

A continuació es mostren els principals resultats dels quatre articles

Els resultats més detallats s'exposen en els articles adjuntats en l'últim apartat d'aquest treball.

4.1. Resultats Article 1 :

- Els pacients amb psicosis d'inici recent (ROP) descrivien més trauma infantil, mes esdeveniments vitals estressants i més consum de cànnabis que els controls sans (veure taula 6)

Taula 6. Característiques sòcio-demogràfiques i clíniques de la mostra

	ROP N= 146	CONTROLS N=61	OR unadjusted	*p*
Socio-demographic variables				
Age, years (median IQR)	22 (18-26)	23(19-27)	0.97 (0.92-1.04)	.49
Sex (%)				
male	94 (64.4)	32(52.5)	1.63 (0.89-3.00)	.11
female	52 (35.6)	29 (47.5)	1.00	
Ethnicity (%)				
Caucasia	127(87.0)	57(91.9)	2.13 (0.69-6.55)	.18
minority	19 (13.0)	4(6.6)	1.00	
Family history psychotic disorder (%)				
yes	23 (15.8)	4 (6.6)	2.65(0.88-8.06)	.08
no	123 (84.2)	57 (93.4)	1.00	
Education years (median IQR)	10(9-12)	13(11-16)	**-0.71 (0.63-0.80)**	**.000**
Environmental risk factors				
Stressfull events				
HR total	169.61(110,.3)	116 (99.62)	**1.00(1.002-1.00)**	**.003**
Number of events *(median IQR)*	6 (3-8)	3(2-7)	**1.15(1.09-1.22)**	**.005**
HR re codified				
low risk	72 (49.3)	45 (73.8)	1.00	
moderate risk	54 (37.0)	11 (18.0)	**3.06 (1.45-6.48)**	**.003**
high risk	20 (13.7)	5 (8.2)	2.50 (0.87-7.13)	.08
Childhood trauma				
CTQ total score *(median IQR)*	37(33-47)	29(26-33)	**1.15(1.09-1.22)**	**.000**
Exposure to childhood trauma (%)				
Any or minimum	29(19.9)	38(62.3)	1.00	
Low to moderate	44(30.1)	17(27.9)	**3.39(1.61-7.10)**	**.001**
moderate to extreme	73(50.0)	6(9.8)	**15.94(6.08-41.74)**	**.000**
Cannabis use (%)				
Non users	76(61.8)	47(77.0)	1.00	
Regular users				
moderate	10(6.8)	6(9.8)	1.03(0.35-3.02)	.95
severe	60(41.1)	8(13.1)	**4.63(2.03-10.55)**	**.000**
Tobacco use (%)				
non user	49(33.6)	40(65.6)	1.00	
regular user	47(66.4)	21(34.4)	**3.77(2.00-7.08)**	**.000**

Abbreviations: ROP = recent onset psychosis; SD= standard deviation; IQR = interquartile range; PANSS = Positive and Negative Symptom Scale; HR = Holmes-Rahe Social Readjustment Scale; Life events = number of life events; CTQ= Childhood Trauma Questionnaire; OR = Odds ratio; results in bold signify P<0.05

[1] adjusted for socio-demographic and each environmental factor (as appropriate)

- Únicament els nivells més alts d'exposició a trauma infantil i a ús de cànnabis estan independentment associats amb el risc de psicosi (*veure taula 7).*
- El model predictiu mostra com augmenta la variància en el risc a psicosi quan s'inclouen jeràrquicament factors, sent l'exposició al trauma infantil el factor més contribuent (veure taula 7).

Taula 7. Model de regressió logística

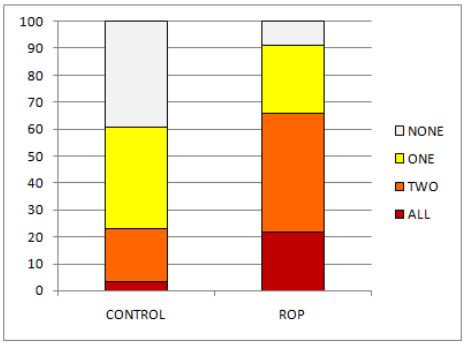
Predictor	-2log likelihood	R^2 Nagelkerke	$X^2_{(df)}$	B	SE	Exp(B) 95 CI	*p*
Step 1	**207.94**	**0.26**	**$43.06_{(5)}$**				**.000**
Block 1 Socio-demographic							
Age				.042	.042	1.04(0.96-1.13)	.32
Gender (male)				.360	.351	1.44(0.72-2.86)	.29
Years education				-.353	.069	0.70(0.61-0.80)	.000
Family history of psychosis				.874	.645	2.39(0.67-8.49)	.17
Ethnicity (white)				.347	.609	1.41(0.42-4.66)	.56
Step 2	**180.163**	**0.41**	**$27.782_{(7)}$**				**.000**
Block 1 Socio-demographic							
Age				.053	.045	1.05(0.96-1.15)	*.24*
Gender				.445	.390	1.56(0.72-3.35)	*.25*
Years education				-.289	.073	0.74(0.64-0.87)	*.000*
Family history of psychosis				.719	.684	1.77(0.47-6.60)	*.39*
Ethnicity				.749	.708	2.11(0.52-8.47)	*19*
Block 2 childhood trauma							
Childhood trauma							
low				1.12	.424	3.07(1.34-7.06)	*.008*
moderate-extreme				2.44	.522	11.55(4.15-32.14)	*.000*
Step 3	**173.524**	**0.44**	**$77.481_{(9)}$**				
Block 1 Socio demographic							
Age				.041	.046	1.04(0.95-1.14)	*.37*
Gender				.535	.405	1.70(0.77-3.78)	*.18*
Years education				-.277	.075	0.75(0.65-0.87)	*.000*
Family history psychosis				.719	.684	2.05(0.53-7.84)	*.29*
Ethnicity				.749	.708	2.11(0.52-8.47)	*19*
block 2 Childhood trauma (CTQ)							
- low				1.10	.439	3.03(1.28-7.17)	*.012*
- moderate -extreme				2.36	.543	10.61(3.66-30.75)	*.000*
Block 3 recent events (HR)							
- moderate				1.14	.463	3.14(1.26-7.79)	*.014*
- high				0.53	.639	1.70(0.48-5.95)	*.40*
Step 4	**164.239**	**0.49**	**$86.76_{(12)}$**				***.000***
Block 1 Socio-demographic							
Age				.038	.050	1.03(0.94-1.14)	*.43*
Gender				.283	.428	1.32(0.57-3.07)	*.50*
Years education				-.262	.078	0.76(0.66-0.89)	*.001*
Family history of psychosis				.746	.723	2.10(0.51-8.69)	*.30*
Ethnicity				.910	.715	2.48(0.61-10.09)	.20
Block 2 childhood trauma (CTQ)							
low				.814	.464	2.25(0.91-5.59)	*.07*
moderate-extreme				2.10	.560	8.18(2.73-24.52)	*.000*
Block 3 recent events (HR)							
moderate				.917	.483	2.50(0.97-6.45)	*.06*
high				.341	.661	1.40(0.38-5.14)	*.60*
Block 4 Misuse variables							
Cannabis regular use							
moderate				-.640	.721	0.52(0.12-2.16)	*.37*
severe				1.03	.503	2.82(1.05-7.55)	*.03*
Tobacco regular use				.700	.417	2.01(0.89-4.55)	*.09*

Note = Dependent variable: subjects' status (0=control; 1=psychotic patients).
Abbreviations:X^2= chi-square statistic; df= degrees of freedom; B= B coefficient; SE= standard error; Exp(B)= Exponentiation of the B coefficient; 95 CI= 95% confidence interval; p= significance level

- L'exposició a dos o tots els factors ambientals estudiats va augmentar significativament la probabilitat de psicosi, mentre que l'exposició a un únic factor no va augmentar el risc (Veure figura 9 I taula 8).

Figura 9. Acumulació de factors de risc en psicosis d'inici recent (ROP) versus controls.

Taula 8. Efecte del número de factors ambientals sobre el risc de psicosi.



0= "absència de factors ambientals",
1="presència d'un tipus de factor ambiental",
2- "presència de 2 tipus de factors ambientals" o
3- "presència de 3 tipus de factors ambientals", es a dir, exposat a trauma infantil, esdeveniments vitals estressants i cànnabis.

	OR unadjusted	*p*	(OR adjusted)[1]	*p*
Types of environmental factors				
-any	1		1	
-one	2.97(1.26-6.96)	.012	2.22(0.84-5.87)	.106
-two	9.84(3.94-24.5)	.000	7.51(2.6-21.12)	.000
-three	29.53(6.08-143.4)	.000	26.71(5.1-140.6)	.000

Dependent variable: subjects' status (0=control; 1=psychotic patients).
Abbreviations: OR.: Odds Ratio
[1] adjusted for age; gender, ethnic, and family history of psychosis.

4.2. Resultats Article 2

- No trobem diferencies significatives en les mesures de l'eix HHA comparant controls i psicosis d'inici recent (ROP) (Veure taula 9).

Taula 9. Resultats sòcio-demogràfics i clínics comparant ROP amb controls.

Table 1. Clinical and biological data by diagnostic group.

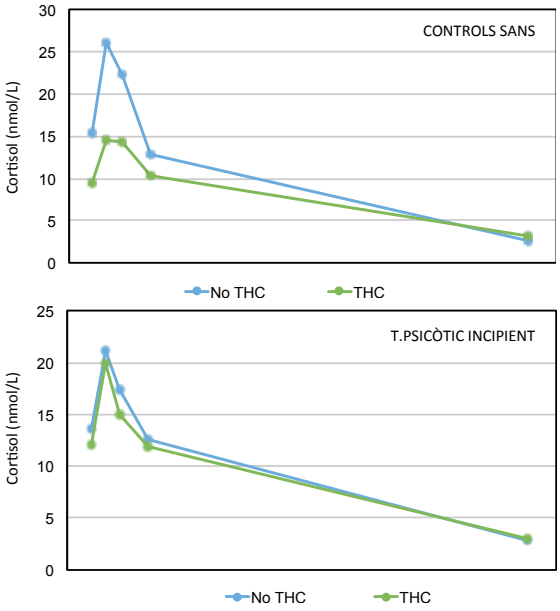
	Healthy controls ($N = 47$)	Recent-onset psychosis ($N = 56$)	p
Sociodemographic and clinical variables			
Age	23.8 (4.5)	24.8 (5.4)	0.357
Female gender, *n* (%)	22 (46.8%)	21 (37.5%)	0.340
Smoking, *n* (%)	9 (19.1%)	39 (69.6%)	**<0.001**
Cigarettes/day (all participants)	1.4 (4.0)	8.7 (9.1)	**<0.001**
BMI	22.5 (3.1)	24.5 (4.2)	**0.006**
Antidepressant treatment, *n* (%)	0 (0%)	6 (10.7%)	**0.030**
Antipsychotic treatment, *n* (%)	0 (0%)	46 (82.1%)	**<0.001**
Antipsychotic dose in chlorpromazine equivalents (mg/day)	0 (0)	384.6 (356.5)	**<0.001**
Environmental risk factors			
Childhood trauma			
CTQ-SF total score†	30.8 (5.9)	38.1 (10.7)	**<0.001**
History of childhood trauma, *n* (%)	4 (8.5%)	22 (39.3%)	**<0.001**
Recent life events			
HRSRS total score	110.6 (101.1)	166.9 (118.7)	**0.011**
Number of life events	3.9 (3.5)	5.8 (3.7)	**0.013**
Recent stressful life events (moderate to high risk), *n* (%)	14 (29.8%)	29 (51.8%)	**0.024**
Cannabis use, *n* (%)	8 (17.0%)	11 (19.6%)	0.733
HPA axis measures‡			
Cortisol at awakening (T1), nmol/l	14.4 (8.9)	13.1 (8.8)	0.503
Cortisol 30 min post-awakening (T2), nmol/l	24.1 (13.7)	21.0 (10.6)	0.522
Cortisol 60 min post-awakening (T3), nmol/l	21.1 (13.0)	16.9 (7.2)	0.419
Cortisol at 10:00 h (T4), nmol/l	12.5 (7.4)	12.4 (6.3)	0.701
Cortisol at 23:00 h (T5), nmol/l	2.7 (2.2)	2.8 (2.9)	0.936
Cortisol at 10:00 h after DXM (T6), nmol/l	9.2 (8.4)	9.0 (8.2)	0.695
CAR	41.7 (64.3)	44.4 (56.2)	0.817
Diurnal cortisol slope§	−0.81 (0.62)	−0.74 (0.62)	0.709
DSTRγ	3.1 (4.7)	6.7 (27.2)	0.448

Bold values represent statistical significance at $p < 0.05$.
BMI: body mass index; CTQ-SF: Childhood Trauma Questionnaire–Short Form; HRSRS: Holmes-Rahe Social Readjustment Scale; HPA: hypothalamic–pituitary–adrenal; CAR: cortisol awakening response; DSTR: dexamethasone suppression test ratio.
†CTQ-SF raw scores are shown. However, log transformed scores were used for comparing both groups with a *t*-test.
‡Untransformed cortisol levels are shown. However, transformed cortisol levels (Box-Cox transformation) were used for comparing both groups with a *t*-test.
§The diurnal cortisol slope was calculated using T1 and T5 samples (from awakening to 23:00 h). Raw slopes (calculated with untransformed cortisol values) are shown. However, for comparing both groups with a *t*-test, the slope calculated from transformed cortisol values was used (mean (SD) slope was −0.18 (0.11) for healthy controls and −0.17 (0.13) for recent-onset psychosis patients).
γDSTR, cortisol at 10:00 h (T4)/cortisol at 10:00 h after 0.25 mg dexamethasone (T6). Raw DSTRs are shown. However, for comparing both groups with a *t*-test, DSTRs were previously transformed (Box-Cox transformation).

- Els consumidors de cànnabis presenten una corba de cortisol diürna més aplanada que els que no consumeixen cànnabis sense diferències entre els controls i els pacients amb psicosi d'inici recent (Veure figura 10).

Figura 10. Corba de cortisol circadiana en pacients amb psicosi d'inici recent i controls sans.

El consum de cannabis s'associa a una pendent més aplanada a la secreció de cortisol, especialment en controls sans.



4.3. Resultats Article 3

En comparació al grup de PEP de població autòctona, el grup d'immigrants d'origen marroquí presenten:

- Una tendència a menys ús del cànnabis.
- Una prevalença més alta d'homes i menys anys d'educació .
- Una tendència a un major ús de LAI, però amb un menor perfil d'efectes secundaris.
- Un pitjor funcionament a l'ingrés i a l'alta.

No presenten diferencies en la prevalença d'esdeveniments vitals estressants ni en la severitat de la simptomatologia.

Taula 10. Comparació de la les característiques sòcio-demogràfiques de la població d'origen marroquí amb a població autòctona

	Inmigrantes de origen marroquí N= 24	Población autóctona N=59	t/χ^2/Z	*p*
Variables sociodemográficas				
Edad, años (m, DE)	26,83 (6,67)	24,47 (5,28)	−1,67	0,098
Sexo (%)				
Mujer	2 (8,3)	16 (27,1)	3,54	**0,050**
Hombre	22 (91,7)	43 (72,9)		
Años de educación (med, IQR)	10 (10-12)	12 (10-14)	−3,10	**0,002**
Variables clínicas al ingreso				
DUP (med, IQR)	105 (23-330)	60 (28-360)	0,80	0,421
FAST (m, DE)	48,63 (16,70)	40,39 (15,03)	8,23	**0,020**
N acontecimientos vitales (med, IQR)	0,5 (0-2)	1 (0-2)	−0,40	0,685
Puntuación total HR (m, DE)	43,63 (53,60)	49,61 (45,62)	0,49	0,650
PANSS-P (m, DE)	24,46 (7,57)	23,37 (7,09)	0,081	0,053
PANSS-N (m, DE)	14 (7,95)	14,15 (8,2)	0,052	0,938
PANSS-G (m, DE)	30,42 (12,70)	28,76 (10,53)	1,74	0,543
CDS (m, ES)	4,96 (6,39)	3,81 (5,88)	0,809	0,435
Consumo de tóxicos (N/%)				
Uso de tabaco				
Uso de cannabis				
Uso regular de cannabis (> 5 porros semanales)	20 (83,3)	43 (72,9)	1,01	0,430
Edad inicio cannabis (m, ES)	10 (41,7)	36 (61,0)	2,58	0,086
	9 (37,5)	32 (54,2)	1,91	0,167
	12,56 (6,64)	13,38 (5,13)	−0,485	0,630
Variables clínicas al alta				
PANSS-P (m, DE)	9,88 (5,43)	9,19 (3,59)	6,82	0,497
PANSS-N (m, DE)	11,00 (5,94)	14,26 (8,69)	−1,02	0,309
PANSS-GEN (m, DE)	19,92 (6,24)	19,61 (4,74)	0,243	0,809
CDS (m, DE)	3,33 (4,95)	2,29 (3,49)	1,08	0,297
GAF (m, DE)	59,96 (11,89)	66,08 (10,87)	−2,26	**0,026**
Días de ingreso (m, DE)	18,96 (8,28)	20,24 (9,85)	0,056	0,577
Variables de tratamiento				
Número AP (mediana,QR)	1 (1-2)	1 (1-2)	0,094	0,925*
Dosis total AP (mediana, IQR)	600 (400-900)	576 (384-675)	0,65	0,510*
Dosis AP oral (mediana, IQR)	600 (300-825)	400 (300-600)	0,88	0,370*
Dosis LAI (mediana, IQR)	384 (384-576)	392 (384-400)	−0,13	0,890*
Uso de LAI (%)	14 (58,3)	23 (39)	2,58	0,080
UKU (mediana, IQR)	0 (0-3)	2 (2-6)	−1,85	**0,022***

CDS: Escala Calgary de Depresión; DE: desviación estándar; Dosis AP oral: dosis total de antipsicóticos equivalente a clorpomazina; DUP: duración de la psicosis sin tratar; FAST: prueba breve de funcionamiento; GAF: Escala de funcionamiento global; HR: Holmes Rahe; IQR: rango intercuartil; LAI: *long acting injectable*; PANSS: Positive and Negative Syndrome Scale; UKU: escala de efectos secundarios de los antipsicóticos.
En negrita si el nivel de significación es <0,05.
* Variables no parámetricas.

- En l'anàlisi multivariant només un pitjor funcionament a l'alta , menys anys d'educació i una tendència a menor ús de cànnabis es van mantenir independentment associats al grup d'origen marroquí (Veure taula 11).

Taula 11. Regressió logística

	B	Wald	OR (IC)	p
Años de educación	−0,278	3,61	0,75 (0,56-1,01)	0,05
Sexo (mujer)	−1,36	1,87	0,25 (0,03-1,80)	0,17
Consumo de cannabis	−1,10	3,02	0,93 (0,88-0,99)	0,08
FAST	0,027	1,48	1,80 (0,51-6,30)	0,22
GAF	−0,068	5,19	0,93 (0,88-0,99)	0,02
UKU	−0,278	2,33	0,80 (0,60-1,06)	0,12
Tratamiento con LAI	0,590	0,86	1,80 (0,51-6,30)	0,35

Variable dependiente, ser inmigrante de origen marroquí.
FAST: prueba breve de funcionamiento; GAF: Escala de funcionamiento global; IC: intervalo de confianza; LAI: *long acting injectable*; OR: *odds ratio*; UKU: escala de efectos secundarios de los antipsicóticos.

4.4 Resultats Article 4 :

En comparació a les dones amb PEP , els homes amb un PEP presenten :

- Major prevalença d'us de cànnabis en homes (veure taula 12).
- La principal raó de consum de cànnabis en ambdós sexes es relaxar-se , però les dones ho reporten més freqüentment que els homes (Veure taula 12).

Taula 12. Raons de consum, seguint la escala de Dixon (Dixon et al., 1991) estratificat per gènere.

	TOTAL N= 204	MALE N= 131	FEMALE N = 73	Statistic (t,X^2,Z)	*p*
Age at onset of cannabis use(median, IQR)	16(15-17.5)	16 (14-17)	16 (15-18)	-1.019	.193*
Cannabis use at least weekly (yes)	54.9%	62.6%	41.4%	8.75	**.003**
Tobacco use (yes)	55.9%	57.3%	53.4%	.275	.598
Reasons for use					
To relax	80.0%	73.1%	100%	7.724	**.005**
To get high	35.6%	37.3%	30.4%	.354	.552
To increase pleasurable feelings	35.6%	35.8%	34.8%	.008	.928
To sleep better	63.3%	62.7%	65.2%	.047	.828
To reduce boredom	44.4%	43.3%	47.8%	.143	.705
To increase the intensity of emotions and feelings	20.0%	20.9%	17.4%	.131	.717
To be more creative	35.6%	38.8%	26.1%	1.209	.272
To satisfy curiosity	26.7%	25.4%	30.4%	.224	.636
To reduce feelings of sadness and depression	36.7%	38.8%	30.4%	.517	.472
To go along with the group	23.3%	22.4%	26.1%	.131	.717
To organize my thoughts	22.2%	26.9%	8.7%	3.27	.071
To work better	17.8%	19.4%	13.0%	.474	.491
To increase energy	14.4%	16.4%	8.7%	.826	.363
To concentrate better on some things	20.0%	22.4%	13.0%	.934	.334
To talk better to others	16.7%	16.4%	17.4%	.012	.914
To decrease my hallucinations	6.7%	7.5%	4.3%	.267	.605

Abbreviations: IQR = interquartile range; results in bold signify P< 0.05; * = non-parametric test.

En l'anàlisi univariant *(veure taula 13):*

- Els homes presenten una tendència a menor edat d'inici , simptomatologia positiva més severa l'ingrés i a l'alta i requereixen de dosis més altes d'antipsicòtics per aconseguir la remissió.
- Els consumidors de cànnabis presenten menor edat d'inici, més simptomatologia depressiva a l'ingrés, pitjor funcionament a l'alta i una tendència a més dies d'hospitalització.

Taula 13. característiques clíniques de la mostra estratificades per gènere i cànnabis

	TOTAL SAMPLE N= 204	MALE N= 131	FEMALE N = 73	(t/z)	p	*CAN – N=92*	*CAN+ N=112*	(t/z)	p
Age of FEP onset (m, SD)	23.5(4.8)	23.1(4.57)	24.3(5.2)	-1.82	.07	24.46(5.32)	22.74(4.23)	2.52	**.01**
Variables at admission									
DUP (*median, IQR)*	30(15-180)	47 (15-182)	30(12.5-120)	[a]-1.00	.31	45(13-183)	30(15-120)	[a]0.94	.34
PANSS (m, sd)									
Positive	25.97(6.3)	26.81 (6.22)	24.50(6.20)	2.52	**.01**	25.19(6.16)	26.62(6.36)	-1.60	.11
Negative	15.61(7.42)	15.23 (6.64)	16.29(8.63)	-0.90	.36	16.08(7.87)	15.23(7.05)	0.80	.42
General	39.15(13.56)	38.63 (13.24)	40.07(14.17)	-0.71	.47	40.27(13.26)	38.23(13.80)	1.05	.29
Total	80.73(21.34)	80.66 (20.11)	80.86(23.5)	-0.06	.95	81.53(21.29)	80.08(21.46)	0.47	.63
CDS (*median, IQR)*	2(0-6)	2(0-6)	3(0-7.75)	[a] -1.09	.27	2(0-5)	3(0-8)	[a] -2.24	**.02**
Variables at discharge									
PANSS: (m, sd)									
Positive	11.11 (4.95)	11.83 (5.19)	9.84 (4.22)	2.96	**.003**	10.64(4.95)	11.50(4,93)	-1.23	.21
Negative	13.44 (5.94)	13.57(5.94)	13.19 (5.97)	0.43	.66	13.26(6.17)	13.58(5.76)	-0.38	.70
General	25.75(8,47)	25.77(8,65)	25.73 (8.18)	0,03	.97	25.89(8.68)	25.64(8.33)	-0.10	.83
Total	50.24(16.60)	51,1(17.17)	48.75(15.55)	0,95	.34	49.79(16.88)	50.62(16.43)	-0.35	.72
GAF (m, sd)	60.60(13.33)	59.98(13.35)	61.71(13.31)	-.87	.38	62.78(13.42)	58.8(13.04)	2.12	.03
Hospitalization length *(days) (median, IQR)*	20(13-27)	19(10-26)	20.33(12-25)	[a] -0.52	.60	18(12,5-25)	22(14-28)	[a] -1.69	.09
Treatment variables:									
AP dose CPZE (mg/day) *(median, IQR)*	565(342-700)	613 (384-800)	473(300-600)	[a] -3.14	**.002**	500(384-684)	583(384-750)	[a] -0.87	.38
Number AP *(median, IQR)*	1.5(1-1)	1.20(1-1)	1.06(1-1)	[a] -2.26	**.024**	1 (1-1)	1(1-1)	[a] -0.74	.45

Abbreviations: DUP = Duration of untreated psychosis; CAN- : Cannabis non- user; CAN+ : Cannabis user ;CDS= Calgary Depression Scale; PANSS=Positive and Negative Syndrome Scale; GAF= Global Assessment of Functioning AP=Antipsychotic; CPZE=Chlorpromazine equivalent dose; IQR = Interquartile range. Results in bold signify P< 0.05; [a] Z= Mann-Whitney U test.

A partir de l'anàlisi multivariant

a) A l'ingrés

- *No trobem cap efecte principal del cànnabis, gènere ni interacció en la simptomatologia depressiva , simptomatologia positiva ni edat d'inici.*

b) A l'alta (veure taula 14) :

- Existeix un efecte principal del gènere de forma que els homes requereixen major dosi d'antipsicòtics que les dones i hi ha una tendència a major simptomatologia positiva.

- No trobem cap efecte principal del cànnabis en les variables a l'alta.
- Trobem una interacció entre el gènere i el cànnabis en el funcionament , el que indica que els homes que consumeixen tenen un funcionament més baix més baix mentre que en les dones el resultat seria a la inversa. Es a dir, les dones que consumeixen cànnabis tenen un funcionament millor que les que no consumeixen *(veure figura 11).*

Taula 14. Resultats de Mancova de les variables a l'alta.

Discharge characteristics	sex effect				Sex x cannabis effect			
	df	Mean square	F	EF	df	Mean square	F	EF
Hospitalization length (days)	1	0.28	0.40		1	0.12	1.81	
PANSS positive	1	0.29	13.13***	.06	1	0.01	0.86	
GAF	1	295.59	1.84		1	1255.4	7.81**	.04
Total CPZE AP	1	0.58	9.67**	.05	1	0.06	1.01	

Abbreviations: PANSS=Positive and Negative Syndrome Scale; GAF= Global Assessment of Functioning AP=Antipsychotic; CPZE=Chlorpromazine equivalent dose; df = Degrees of freedom; EF =effect size: partial eta squared.
**p< 0.05; ** p<.0.01; *** p<0.001*
Adjusted for: tobacco use, centre of recruitment and age at first episode

Figura 11. Interacció entre el GAF el gènere i el cànnabis

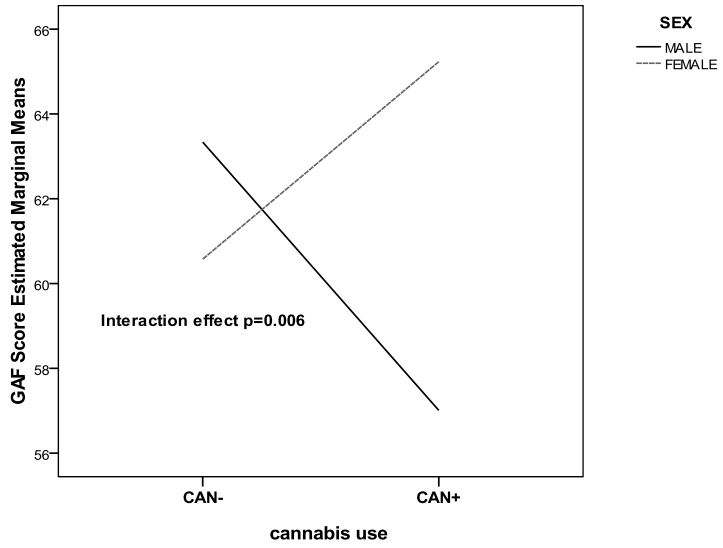


Figure 1: gender x cannabis effect on Global Assessment Functioning at discharge
[a] adjusted for: age at fisrt episode smoking tobacco (yes/no) and center of recruitment
CAN+: cannabis users; CAN- : cannabis non-users

En aquesta tesi ens vàrem plantejar per una banda determinar la implicació de diversos factors ambientals en la aparició de la psicosi i per altra banda, com diversos factors ambientals influïen en les variables clíniques en pacients amb psicosi d'inici recent. Tal i com àmpliament s'ha explicat en la introducció, cal destacar que hi ha pocs estudis en primers episodis psicòtics i psicosi d'inici recent que s'hagin focalitzat en l'estudi específic d'associacions de diversos factors ambientals i en l'estudi de diferències entre poblacions especifiques com son els subjectes d'ètnia minoritària i les diferencies de gènere. El cànnabis i els factors estressants son per tant el fil conductor d'aquesta tesi

Relació entre factors estressants I consum de cànnabis:

En quant al primer estudi, les principals troballes van ser que només els nivells més alts d'exposició al trauma infantil i cànnabis estaven associats de forma independent amb la psicosi. A més el model predictiu mostrava augments en la variància en el risc de patir psicosi quan els diversos factors s'incloïen jeràrquicament, sent la l'exposició a trauma a la infantesa el factor amb més contribució. Finalment, vàrem trobar que l'exposició a dos o tots els factors ambientals estudiats (cànnabis, trauma a la infància i esdeveniments estressants recents) augmentava significativament el risc de psicosi, mentre que l'exposició a un sol factor no va augmentar el risc.

En concordança amb altres estudis, vàrem trobar una prevalença més elevada de trauma infantil (Varese et al., 2012), un excés d'esdeveniments vitals recents (Beards et al., 2013) i un major percentatge d'ús de cànnabis (Moore et al., 2007) en el grup de psicosi recent comparat amb el grup control. En quant a l'associació entre els 3 factors ambientals, només els nivells més alts d'exposició al trauma infantil i el cànnabis es va associar significativament a la psicosi, fins i tot després del controlar per l'ús del tabac. A més, la nostra troballa que només l'alta exposició al cànnabis s'associa significativament amb la psicosi està en concordança amb estudis recents (Di Forti et al., 2014; Schoeler et al., 2016).

El model logístic jeràrquic ens va permetre testar la interacció i/o l'efecte acumulatiu dels diferents factors mediambientals. Contràriament a altres autors (Houston et al., 2011; Murphy et al., 2013), no hem pogut trobar una interacció entre els diferents factors mediambientals. Els nostres resultats, però, estan d'acord amb estudis més recents que també han fracassat en trobar una interacció entre el trauma infantil i el cànnabis quan es considerava el nivell

d'exposició (Baudin et al., 2016; Sideli et al., 2015). Per contra, trobem un efecte acumulatiu de factors ambientals sobre el risc de psicosi. Quan es va afegir un trauma infantil a factors sociodemogràfics, hi va haver un augment de la variància del 15% i augments addicionals del 4% i 5% quan els esdeveniments recents i cànnabis van ser inclosos consecutivament. Per tant, el trauma infantil sembla ser el major contribuent ambiental al risc de psicosi en la nostra mostra. Aquesta troballa és altament concordant amb estudis recents en individus d'ultra-risc per a la psicosi, en el qual el factor mediambiental més fort associat amb la transició psicosi era el trauma a la infància (Kraan et al., 2015; Mayo et al., 2017).

Un major nombre de tipus de factors ambientals va augmentar la probabilitat de psicosi, amb l'excepció d'estar exposat a un sol tipus de factor de risc ambiental (Husted et al., 2012; Shevlin et al., 2007; Stepniak et al., 2014). Els nostres resultats van ser similars als de Shevlin et al. (2007), que va trobar que experimentar dos o més traumes augmentava la probabilitat de desenvolupar psicosi. En aquesta línia, Husted et al. (2012) va proposar un índex de risc ambiental (entre 1 a 8) per psicosi, de forma que augmentava quan l'índex era superior a 3. Més recentment, Padmanabhan et al., 2017 va crear una mesura d'exposició additiva als factors de risc ambientals que es correlacionen amb la conversió de psicosi en la seva d'alt risc genètic

Totes aquestes troballes estan d'acord amb aquells que suggereixen que l'exposició continuada a factors d'estrès seqüencials pot augmentar el risc de desenvolupar psicosi (Fraguas et al., 2017; Padmanabhan et al., 2017b; van Os and Linscott, 2012). L'efecte acumulatiu dels factors està d'acord amb la teoria del múltiple-hit (Davis et al., 2016), que suggereix que l'esquizofrènia es desenvolupa després de diversos factors que apareixen en diverses ocasions durant el neurodesenvolupament. Més concretament, l'efecte acumulatiu dels factors sobre la psicosi pot ser degut a una major sensibilitat a l'estrès. D'una banda, s'ha postulat que l'exposició variable als primers factors estressants pot actuar com el "primer hit" i aquesta acumulació d'estressors pot augmentar la vulnerabilitat de l'eix HHA a els factors mediambientals futurs, incloent-hi ús regular de cànnabis (Davis et al., 2016; Fusar-Poli et al., 2013).

Tenint en compte l'escàs coneixement sobre la relació entre cànnabis i eix HHA ens vàrem plantejar el segon estudi d'aquesta tesi incloent una submostra de pacients del primer estudi que tenien recollides mesures de l'HHA. En aquest segon estudi vàrem trobar que l'exposició a cànnabis s'associa amb una pendent de cortisol diürna més aplanada de forma independent al ús de tabac , ja que totes les anàlisis van ser controlades per l'ús de tabac. En canvi no vàrem trobar cap efecte dels esdeveniments estressants recents ni del trauma a la infantesa en les mesures de l'eix HHA.

Fins ara , no existia cap estudi en psicosi d'inici recent que hagués investigat aquesta relació . Si hi havia un estudi previ en pacients amb alt risc de psicosi on s'havia trobat nivells més alts de cortisol diürn en pacients que consumien cànnabis (Carol et al. 2017). El nostre estudi suggereix que una corba circadiana de cortisol més aplanada s'associa a l'ús de cànnabis, però aquest efecte no va ser específic dels pacients amb psicosi d'inici recent, ja que aquest efecte era independent del grup diagnòstic (ROP o HC) .

Hi ha escassa evidencia sobre la relació entre el sistema de resposta a l'estrès i el sistema endocannabinoid en psicosi. La presència de receptors de cannabinoides CB1 dins els circuits corticolimbics que regulen l'eix HPA, en combinació amb les propietats reductores de l'estrès reportat pels usuaris del cànnabis, suggereix un paper del sistema endocannabinoid en la regulació de l'estrès (Mizrahi, 2016). L'ús del cànnabis i la interacció amb els amics i la família pot resultar en un estat de benestar que pot ser mediada pels efectes ansiolítics de l'increment d'activació de receptors cannabinoids i d'oxicitocina conjuntament amb l'elevació de dopamina del sistema de recompensa (Volkow et al., 2017).Per tant , la associació entre factors d'estrès i ús de cànnabis en pacients de psicosi d'inici recent planteja la pregunta de si els pacients poden utilitzar el cànnabis com a "automedicació" per afrontar l'estrès.

Entre els pacients amb PEPs la millora de la ansietat i de la tensió, són els motius més freqüentment reportats per al consum de cànnabis (Kolliakou et al., 2015; Pencer and Addington, 2008). Cap estudi previ , però, havia investigat si existien diferencies de gènere en les raons de consum . En base a aquestes qüestions ens vàrem plantejar estudiar les raons de consum de cànnabis en pacients ingressats per un PEP, trobant que la raó més freqüentment reportada era "sentir-se relaxat", essent aquesta raó significativament més reportada per les dones que per els homes. Tenint en compte la major prevalença d'ansietat en dones amb FEP descrit per alguns autors (Szymanski et al., 1995), podríem hipotetitzar que les dones amb psicosi poden experimentar ansietat amb més freqüència i poden ser més propenses a l'ús del cànnabis per alleujar-lo. Malauradament, no hem realitzat mesures específiques d'ansietat en el nostre estudi.

Efecte del cànnabis i gènere en les variables clíniques

Continuant amb les diferencies de gènere i la seva relació amb el cànnabis, hi ha una escassetat d'estudis que hagin investigat l'efecte del cànnabis i el gènere en les característiques clíniques i de tractament en pacients amb un PEP ingressats per primer cop en una unitat d'aguts i cap d'aquests estudis ha investigat l'efecte d'aquesta interacció sobre aquestes variables clíniques.

En el nostre cas, vàrem trobar que els homes eren més freqüentment consumidors de cànnabis que les dones; tanmateix, no vam trobar diferències en l'edat a l'inici del consum de cànnabis. Això és coherent amb troballes recents que posen de relleu que les dones estan consumint cada vegada més cànnabis a edats més joves, reduint-se la bretxa entre sexes (Carliner et al., 2017; Sallaup et al., 2016).

No hem trobat cap efecte principal del gènere o del consum de cànnabis ni cap d'interacció de cànnabis i gènere en la severitat dels símptomes clínics a l'ingrés . En quant a l'alta, la troballa més rellevant es una interacció entre gènere i cànnabis en el funcionament , de manera que els homes que fumaven cànnabis tenien una puntuació menor de GAF que els no fumadors, mentre que el contrari passava en les dones . D'una banda, estudis previs en PEPs han trobat un millor funcionament en les dones (Cotton et al., 2009; Jeyagurunathan et al., 2017; Ochoa et al., 2012). D'altra banda, hi ha resultats contradictoris respecte funcionament i ús de cànnabis en PEPs amb alguns estudis que indiquen puntuacions més baixes de GAF (Seddon et al., 2016) en consumidors de cànnabis i d'altres majors puntuacions (DeRosse et al., 2010) . Alhora també, s'ha suggerit un impacte més greu del consum de cànnabis en el curs de l'esquizofrènia en dones (Gearon and Bellack, 2000) ja que es descriuen reduccions més baixes de l'ús de cànnabis en les dones després de la fase aguda (Lange et al., 2014). Aquesta discrepància amb els nostres resultats es podria deure a la naturalesa del "curt termini" del nostre estudi. Els estudis de seguiment dissenyats per estudiar el paper del gènere i el cànnabis en els resultats funcionals a curt i llarg termini poden ajudar a aclarir aquest problema.

En concordança amb investigacions anteriors vam trobar que eren més freqüentment tractats amb dosis més elevades d'antipsicotics; tot i que s'ha de tenir en compte que hi ha escassa evidència sobre la dosi necessària d'antipsicòtics en funció del gènere ja que els assajos clínics amb antipsicòtics no solen tenir en compte aquesta la perspectiva (Crawford and DeLisi, 2016; Lange et al., 2017; Shlomi Polachek et al., 2017). Finalment, ni el cànnabis ni la interacció entre el gènere i el cànnabis van tenir cap efecte sobre la dosi d'antipsicòtics. Els pocs estudis que s'han centrat en l'efecte del cànnabis en la dosi d'antipsicòtics han reportat resultats conflictius i cap d'ells ha tingut en compte l'efecte del gènere (Babatope et al., 2016; Makkos et al., 2011; Patel et al., 2016).

Diferencies en consum de cànnabis , factors estressants i diferencies clíniques segons ètnia

Fins ara, aquest és el primer estudi que ha estudiat les diferencies ètniques en PEPs al nostre país. La distribució d'ètnies en la nostra regió és semblant a la representada per estudis en Països baixos, on la principal ètnia immigrant és la marroquí (Veling et al., 2006)

En contra a la nostres hipòtesis, vàrem trobar que el grup de PEPs immigrants d'origen marroquí tendien a consumir menys cànnabis comparat amb població autòctona i no hi havia diferencies significatives en quant al numero d'esdeveniments estressants recents. Altres estudis en altres poblacions minoritàries també han trobat una menor prevalença de consum de cànnabis en població immigrant (Harris et al., 2019; Qureshi et al., 2014). Per tant, podem concloure que aquest concepte està clarament estigmatitzat en la nostra societat que considera erròniament a la població d'origen marroquí com a major consumidora de cànnabis. Les nostres troballes respecte als esdeveniments estressants discrepen amb estudis anteriors en altres poblacions immigrants que si troben un major nombre d'esdeveniments vitals estressants (Morgan et al., 2010; Stilo et al., 2017) .Una possible explicació , es que en el nostre estudi ens vàrem focalitzar en els esdeveniments estressants recents dins dels 6 mesos previs al PEP i no en els esdeveniments vitals on estaria inclòs el procés migratori.

Respecte a les variables clíniques, no vàrem trobar diferències pel que fa a la intensitat de la simptomatologia ni en la DUP, però si un funcionament pitjor en el grup d'origen marroquí i una tendència a un major ús de LAIs, però amb un perfil menor d'efectes secundaris. Pel que fa al funcionament , tal i com hem comentat abans, el gènere femení sol ser un predictor de bon pronòstic (Ochoa et al., 2012) i en la mostra d'origen marroquí sol el 8,3% són dones. Malgrat això, al controlar pel gènere en el model multivariant, es manté el GAF més baix com una variable significativa en població d'origen marroquí. En relació al tractament amb AP, s'havia descrit en un estudi previ al nostre país una menor exposició a antipsicòtics en les dones marroquins (Cruz et al., 2012), però la baixa prevalença de dones en la nostra mostra no va permetre estudiar diferencies de gènere en la dosi total d'antipsicòtics. La major tendència a l'ús de LAIs en població immigrant, coincideix amb un estudi realitzat al Regne Unit (Das-Munshi et al., 2018). En ocasions, més enllà d'una opció voluntària, els LAIs poden considerar-se com un tractament imposat i ja s'ha descrit en altres estudis que el pertànyer a una ètnia minoritària augmentaria el risc de tenir un tractament comunitari obligatori (Kisely and Xiao, 2018; Mann et al., 2014), el que també podria estar en línia amb l'estigmatització per part del prescriptor en quant al compliment terapèutic de les ètnies minoritàries. En quan al perfil d'efectes adversos mesurats per la UKU, no hi ha evidencia prèvia en població marroquina. Una possible explicació, entre altres , seria altre cop la baixa prevalença de dones , ja que en estudis previs sobre efectes adversos es descriuen aquests en major mesura en les dones (Iversen et al., 2018).

LIMITACIONS:

a) Limitacions generals:

- La grandària de la mostra ens ha pogut limitar la detecció algunes associacions i grans efectes. Així com , algunes associacions observades tenen intervals de confiança amplis. Al tractar-se d'estudis amb un enfoc novedós i amb cap o escassa evidencia prèvia els resultats s'han d'interpretar amb cautela i en algun cas com preliminars i necessiten replicació
- La grandària de la mostra no ens ha permès poder fer subanàlisi per grups diagnòstics, considerant els PEPs com un mateix grup
- La naturalesa transversal dels estudis no ens permet inferir relacions causals
- Les mesures de trauma a la infantesa i d'esdeveniments estressants son mesures retrospectives avaluades amb instruments auto-informats , per tant un biaix de memòria no es pot descartar.
- La freqüència de consum de cànnabis es va avaluar mitjançant entrevista i no es van obtenir mesures quantitatives d'us de cànnabis ni es van poder obtenir els tipus de cànnabis utilitzats ni la proporció dels seus components CBD/THC. Les línies de recerca actuals subratllen la rellevància de considerar el patró d'ús de cànnabis en la interpretació de l'Associació de cànnabis amb psicosi. A més, hi ha un interès creixent per estudiar si la proporció de tetrahidrocannabinol (THC) i cannabidiol (CBD) va influir en aquesta associació (Marconi et al., 2016).

b) Limitacions especifiques:

- En l'estudi sobre associació de factors de risc no vàrem executar un anàlisis de mediació entre factors , però el disseny de dosi-resposta combinant 3 factors ambiental pot ser clarament un enfoc innovador
- En l'estudi de relació entre mesures de l'eix HPA i factors de risc s'ha de subratllar que la mostra encara era més reduïda. A més els pacients amb psicosi d'inici recent (ROP) estaven rebent tractament antipsicòtic, que pot normalitzar la hipersecreció de cortisol pacients psicòtics (Mondelli et al., 2010) pel què vàrem ajustant totes les anàlisis per tractament. La CAR es va calcular considerant les mostres salivals d'un sol dia. No vàrem recollir la CAR més de dos dies consecutius perquè la administració de dexametasona es va realitzar a les 23:00 h, cosa que podria afectar als resultats de la CAR del segon dia.

- En els estudis realitzats amb mostres de PEPs ingressats en unitat aguts, s'ha de tenir en compte que no es poden generalitzar els resultats a tots els PES, ja que solen ser els que tenen més gravetat clínica. Tampoc vàrem poder analitzar els resultats per tipus de símptomes recollits per PANSS o CDS pel què no es pot descartar que hi hagi algun símptoma més freqüent en funció del gènere o del grup ètnic.
- La manca de mediadors culturals en la unitat d'aguts a l'hora de realitzar les entrevistes pot donar lloc a dificultats en la comprensió dels símptomes per barrera idiomàtica i cultural.

FORTALESES:

Malgrat aquestes limitacions, el nostre enfocament en pacients psicòtics en fase primerenca de la malaltia minimitza l'impacte de la càrrega d'una malaltia crònica i tractament antipsicòtic a llarg termini. A més hem intentat superar les limitacions metodològiques d'estudis previs avaluant diversos nivells d'exposició als factors mediambientals i controlant per diversos confusors com l'ús del tabac. La majoria d'estudis relacionats amb factors d'estrès ambiental i cànnabis en psicosi així com sobre ètnia, s'han dut a terme al nord d'Europa i Anglaterra El nostre estudi, per tant, proporciona informació sobre l'efecte dels factors d'estrès i mesures de l'eix hipotàlem hipofisiari, l'ús de cànnabis i la seva interacció amb gènere en psicosi en un país del sud d'Europa. Donada la manca d'estudis previs , les nostres troballes poden facilitar el disseny de futurs estudis.

CONCLUSIONS

A continuació detallem les conclusions en relació als objectius plantejats en els estudis inclosos en aquesta tesi:

Article 1 : "*The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis*"

Article 2: "*Hypothalamic-pituitary-adrenal axis function and exposure to stress factors and cannabis use in recent-onset psychosis"*

1. Els subjectes amb una psicosi d'inici recent presenten una major prevalença de trauma infantil, un excés d'esdeveniments estressants recents i un major percentatge d'ús de cànnabis que el grup de control sans.
2. Hem trobat evidència d'un efecte dosi–resposta en la relació dels factors ambientals estudiats amb psicosi, ja que només els nivells més alts d'exposició a trauma a la infància i a cànnabis es va associar significativament a la aparició de psicosi
3. Hem trobat evidència d'un efecte acumulatiu en la relació dels factors ambientals estudiats amb psicosi.
    - El model predictiu mostrava augments en la variància en el risc de patir psicosi quan els diversos factors s'incloïen jeràrquicament, sent la l'exposició a trauma a la infantesa el factor amb més contribució.
    - l'exposició a dos o tots els factors ambientals estudiats (cànnabis, trauma a la infància i esdeveniments estressants recents) augmentava significativament el risc de psicosi, mentre que l'exposició a un sol factor no va augmentar el risc.
4. S'ha trobat un efecte de l'ús del cànnabis en els patrons de secreció de cortisol tant en els controls sans com en pacients amb psicosi d'inici recent , amb una pendent més aplanada de la secreció diürna de cortisol en les persones consumidores de cànnabis.

Article 3: "*Comparison between a morocco and a native-born population, in a sample of first episode psychosis" :*

1. Els PEPs d'origen marroquí presenten una menor freqüència de consum de cànnabis que els PEPs d'origen autòcton
2. No existeixen diferencies segons origen en els esdeveniments vitals estressants recents ni en la severitat de les variables clíniques

3. Els PEPs d'origen marroquí son més freqüent ment tractats amb LAIs i presenten menys efectes adversos que els PEPs d'origen autòcton

Article 4: "*The impact of sex and cannabis on clinical features in first–admitted patients with psychosis"*

1. Existeixen diferencies de gènere en la freqüència d'us de cànnabis i en les raons de consum de cànnabis essent la raó " per sentir-se relaxat " més freqüentment reportada per dones.
2. Existeixen diferencies de gènere en algunes característiques clíniques i de tractament dels pacients amb PEP de manera que els homes presenten més símptomes positius i son freqüentment tractats amb dosi més altes d'antipsicòtics que les dones .
3. No existeix evidència d'un efecte principal del cànnabis en la severitat de la simptomatologia ni en la dosi del tractament , ni tampoc interacció cànnabis x gènere en aquestes variables.
4. S'ha trobat un efecte d'interacció en el funcionament a l'alta entre cànnabis i gènere , de forma que els homes que consumeixen cànnabis tenen un pitjor funcionament mentre que en les dones aquest efecte és el contrari.

IMPLICACIONS CLINIQUES I DIRECCIONS FUTURES:

L'ús regular de cànnabis i els factors estressants sobretot el trauma a la infància són molt freqüents en la població amb psicosi i tenen efectes acumulatius i de dosi-resposta en la aparició de la psicosi. Per tant els nostres resultats recolzen una correcta avaluació i un adequat abordatge d'aquests factors des de la infantesa i durant la adolescència tant des de la intervenció com des del camp de la prevenció. En concret, el cànnabis és un dels factors de risc per psicosi més potencialment evitables, pel què tant la prevenció en el seu consum com la intervenció en la reducció o cessació del consum serien estratègies que s'haurien de tenir en compte tant a nivell de prevenció universal com de prevenció primària, secundària i terciària. A més tal i com s'ha comentat en les limitacions, en posteriors estudis que incloguin l'ús de cànnabis, s'hauria de tenir en compte el tipus de cànnabis consumit i la proporció de CBD/THC per tal de poder precisar quin és el risc concret segons el tipus de consum; sobretot tenint en compte la controvèrsia actual sobre els possibles efectes beneficiosos per la salut del CBD. Posteriors estudis amb mostres més grans i amb un disseny prospectiu combinant els tipus de factors ambientals i la seva resposta biològica i també factors genètics serien necessaris per poder seguir avançant en l'estudi de les associacions per risc de psicosi

Per altra banda els nostres resultats també posen de manifest que hi ha una manca d'evidència en quant a la clínica i a l'abordatge de poblacions especifiques en psicosi d'inici recent , el que dona com a resultat, que des de la perspectiva clínica els pacients són tractats de forma subjectiva. En la majoria d'assajos clínics amb antipsicòtics no s'ha considerat el gènere, sobretot tenint en compte la menor proporció de dones en psicosi i encara queda molt per saber sobre la dosi necessària per aconseguir resposta clínica i el perfil de efectes adversos específic més lligat al gènere. El mateix passa amb el grup de consumidors de drogues que habitualment son exclosos dels estudis i tampoc se sap gaire de les diferencies en el tractament segons ètnia o població migrant . En quan a població migrant destaquem que cada cop vivim en una societat més multicultural en la que la migració es un fet, amb taxes sol de població d'origen marroquí en Reus del 30%. Per tant una major formació dels clínics en competències culturals i la incorporació de mediadors culturals en els equips de psicosi incipient ajudarien a una millor comprensió dels símptomes reportats per aquest pacients i per tant una millor intervenció terapèutica.

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The relationship between the level of exposure to stress factors and cannabis in recent onset psychosis

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ABSTRACT

Background: There is a lack of studies investigating the dose-response effect of childhood trauma, recent events and cannabis use on recent psychosis. This study aims to determine the relationship between the level of exposure to stress factors and cannabis use with psychosis and to determine the combination effect among these factors in predicting a psychotic disorder.
Methods: 146 recent onset psychotic (ROP) patients and 61 healthy controls were included. Childhood trauma was evaluated using the childhood trauma questionnaire (CTQ) and recent events using the Holmes-Rahe social readjustment scale. The pattern of cannabis use was assessed by a detailed interview. A hierarchical multiple regression was run in order to determine both the cumulative and independent contribution of each factor in predicting a psychotic disorder.
Results: The highest levels of exposure to childhood trauma and cannabis were associated with psychosis while neither low nor high recent event exposure was associated. The combined effect of risk factors yielded a significant association with psychosis ($\times^2 = 86.76, p < .001$) explaining the 49% of its variation. ROP were more likely to be exposed to one, two or three environmental factors than HC. Exposed to two or all factors were 7.5-fold and 26.7-fold more likely to have a diagnosis of psychosis, respectively.
Conclusions: Our study provides evidence for a cumulative and a dose-response effect of environmental factors on recent psychosis. Considering that cannabis use and stress are highly prevalent in the population with psychosis, investigations of their relationships are needed to implement targeted prevention and treatment strategies.

1. Introduction

The aetiology of schizophrenia is multi-factorial, consisting of interactions between genetic vulnerability (Craddock et al., 2009; O'Donovan et al., 2009) and environmental risk factors (van Os et al., 2002a, 2002b). Some of the environmental factors that have been implicated in the origin of the psychotic illness are prenatal complications (Buka and Fan, 1999), childhood trauma (Janssen et al., 2004; Read et al., 2005; Varese et al., 2012), life events and recent adversity (Beards et al., 2013; Phillips et al., 2007), cannabis use (Arseneault et al., 2002; Moore et al., 2007; van Os et al., 2002a, 2002b) and urbanicity (Marcelis et al., 1999; Zammit et al., 2010).

With regard to stress factors, previous studies have demonstrated that exposure to stress has an important role in the Gene-environment model of schizophrenia (Mondelli et al., 2010; Phillips et al., 2007; van Os and Linscott, 2012). According to the vulnerability-stress model, patients with psychosis show a higher sensitivity to stress, reporting more childhood trauma (Matheson et al., 2013; Read et al., 2005), more recent events (Beards et al., 2013; Butjosa et al., 2016; Manzanares et al., 2014) and higher perceived stress (Mondelli et al., 2010; Pruessner et al., 2017). Childhood trauma is defined as "*events that occur before the age of 16*" (Bernstein et al., 2003; Mansueto and Faravelli, 2017; Plant et al., 2016), life events are defined as "*situations or occurrences that bring about a positive or negative change in personal circumstances and involve an element of threat*"(Beards et al., 2013); and recent events are defined as "*life events that occur generally within 6–12 months before the onset of a disorder*" (Brown and Birley, 1968). While there is accumulated evidence that childhood trauma might be

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an independent risk factor for psychosis (Barrigón et al., 2015; Lataster et al., 2012; Morgan et al., 2014c; Read et al., 2005; Varese et al., 2012), the role of recent events as an independent risk factor has been less consistent (Kraan et al., 2015).

Cannabis is the third most common drug of dependence in the world, after tobacco and alcohol. There is now strong evidence that cannabis use is a risk factor for the development of psychosis (Clausen et al., 2014; Gage et al., 2015; Marconi et al., 2016; Moore et al., 2007; Murray et al., 2016). Notably, two recent meta-analyses (Marconi et al., 2016; Schoeler et al., 2016a) have found a relationship between the pattern of use of cannabis and the risk of schizophrenia, suggesting a dose-response relationship between cannabis and psychosis with an increased risk at higher levels of exposure.

Given that not all kinds of exposure will irrevocably give rise to psychosis, there is increasing interest in the study of the relationship between these factors. It is likely that environmental factors may be associated with interactions, mediation, dose-response and/or cumulative effects at various periods of development (Davis et al., 2016). Some studies found that cannabis and childhood trauma interact to increase the likelihood of psychosis (Houston et al., 2008, 2011; Murphy et al., 2013); however, three other studies (Baudin et al., 2016; Kuepper et al., 2011; Sideli et al., 2018) reported no evidence of an interaction between these factors. Others have explored their cumulative or additive effect (Harley et al., 2010; Konings et al., 2012; Morgan et al., 2014c; Padmanabhan et al., 2017) suggesting that childhood trauma and cannabis use in adolescence creates a vulnerability that increases the risk of developing psychosis (Harley et al., 2010; Konings et al., 2012; Morgan et al., 2014c). The relationship between childhood trauma and recent events with regard to psychosis has however yielded conflicting results. Some authors have suggested that people with a history of childhood trauma are more sensitive to recent events (Lardinois et al., 2011; Lataster et al., 2012), and others have suggested an independent contribution of recent events even in the presence of childhood trauma (Mansueto and Faravelli, 2017).

However, there is a lack of controlled studies investigating the relationship between childhood trauma, recent events and cannabis use with psychosis from a dose–response perspective. The aims of this article are therefore to determine whether the risk of psychosis depends on the severity of exposure to childhood trauma, recent life events and cannabis use and to determine whether there is an interaction and/or a cumulative effect among these three factors in predicting a recent onset psychotic disorder (ROP).

2. Methods

2.1. Participants

Subjects aged 18 to 35 years close to the onset of their first episode of psychosis (FEP) are referred to the Early Psychosis Program (EIP) in Reus (HPU, Institut Pere Mata, Reus, Spain) and followed-up for 3 years. Subjects are systematically assessed at programme entry and at 12, 24 and 36 months.

The data analysed in this paper is derived only from the participants who provided full information at programme entry regarding the exposures of interest, including the assessments of childhood trauma, recent events and cannabis. Sample consisted in 146 recent onset psychotic patients (ROP), defined as onset of full psychotic symptoms within the last 6 months, and a control group of 61 healthy controls (HC) who were screened to rule out past or current history of psychiatric disorder. Recruitment of HC included patients' friends (90%) and university students (10%). Additional inclusion criteria were as follows: ability to speak Spanish well enough to complete the assessment; and no significant history of organic factors implicated in the aetiology of psychotic symptoms. Exclusion criteria were as follows: pregnancy; mental retardation; severe head injury or neurological disease; and active substance dependence (other than tobacco or cannabis). Ethical approval was obtained by the local Ethics Committee. After a complete description of the study was given to the subjects, written informed consent was obtained.

2.2. Measures

2.2.1. Demographic and clinical assessment

Demographic and clinical information was collected via direct interview by two psychiatrists during the first two baseline visits. Diagnosis of psychosis was confirmed using the psychiatric interview OPCRIT checklist v.4.0., which generates DSM-IV diagnoses for psychotic disorders (available at http://sgdp.iop.kcl.ac.uk/opcrit/).

2.2.2. Environmental factors

2.2.2.1. Childhood trauma. The presence of childhood trauma was assessed with the Spanish version Childhood Trauma Questionnaire —Short Form (CTQ-SF) (Hernandez et al., 2013). The CTQ-SF is a 28-item self-report instrument for the retrospective assessment of childhood maltreatment. The CTQ-SF assesses five widely accepted types of maltreatment: emotional, physical and sexual abuse and emotional and physical neglect. Each item is scored using Likert-type responses that range from 1 point "*never true*" to 5 points "*very often true*" to create dimensional subscales and four severity cut-off points for each subscale (1-"*none to low*", 2-"*low to moderate*", 3-"*moderate to severe*" *and* 4-"*severe to extreme*"). Total CTQ score is obtained by adding all 5 subscales scores and ranges between 25 and 75 points.

2.2.2.2. Recent events. Life events during the previous six months were assessed by the Holmes-Rahe social readjustment scale (HR) (Holmes and Rahe, 1967), which has been validated for Spanish-speaking populations (Roca et al., 2013). The HR was initially developed to explore the relationships among social readjustment, stress and susceptibility to illness. It incorporates 43 life events and returns a "stress score" for each item, obtaining a final score by adding the scores of all recent life events. A score of 150 points or less suggests low susceptibility to stress-induced health breakdown; 150 to 300 points suggests moderate susceptibility, and >300 points suggests high susceptibility.

2.2.2.3. Cannabis exposure. Cannabis and tobacco use was assessed by a detailed interview designed by EIP team. On the basis of this interview, we determined the previous 6-month frequency of cannabis use. Frequency of cannabis use was scored using Likert-type responses: daily, several times a week, several times a month, less than several times a month, and not at all (Bugra et al., 2013). For the purpose of this study, the pattern of cannabis and tobacco use was classified as follows: 1- "*no use*", 2-"*sporadic use*", defined as less than once a month, and 3-"*regular use*", defined as more than once per month. Among regular users, we differentiated two levels of severity: "*moderate*", more than once a month to less than once a week, and "*severe*", more than once per week to daily use.

2.2.3. Statistical analysis

The SPSS version 23.0 software (SPSS Inc., Chicago, Illinois, USA) was used to carry out the statistical analyses. Differences between the ROP and HC groups were first subjected to univariate logistic analysis. Unadjusted odds ratios (OR) and confidence intervals (CI) were calculated.

A hierarchical multiple regression model was run in order to determine the independent contribution of each factor in predicting the ROP status and to explore the change in the variance of dependent variable after consecutively entering the following independent variables. In the first block, we entered socio-demographical variables that have been identified as risk factors in previous studies, including male gender, age, years of education, minority ethnic status and family history of a psychotic disorder (Fusar-Poli et al., 2017). In the second block, we added "*the presence of at least one type of childhood trauma*" and in

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the third block "*the presence of recent events*". Cannabis exposure controlled for tobacco exposure was added in the last block.

Finally, we ran a multivariate logistic regression analysis, including diagnosis status as the dependent variable and the number of environmental factors as independent variables, in order to determine the cumulative effect of the number of environmental factors on the prediction of recent psychotic disorder. The independent variable was categorized as follows: 0="*absence of environmental factors*",1-"*presence of 1 type of environmental factor*",2-"*presence of 2 types of environmental factors*" or 3-"*presence of 3 types of environmental factors*", which means being exposed to childhood trauma, recent events and cannabis. A simple contrast was used, specifying the absence of environmental risk factors as the reference category. The results were controlled for socio-demographic variables. The significance level was set at $p < .05$, and adjusted OR and CI were also calculated.

3. Results

3.1. Socio-demographic characteristics

The characteristics of the sample are displayed in Table 1. The ROP and HC groups were not different with respect to age, gender, ethnic or family history of psychotic disorders, but the HC group had more years of education.

3.2. Environmental factor exposure

3.2.1. Childhood trauma

Compared to HC, the ROP group was more likely to report higher total scores of CTQ (Table 1). As we can see in Table 2, all types of childhood abuse and neglect were more frequent in the ROP group than in HC. The most frequently reported was emotional neglect, followed by emotional abuse. Any kind of exposure increased the likelihood of psychosis, with physical neglect giving the highest increase (*OR = 6.98, 95% CI = 2.39–20.36*; *p = 0.03*), followed by emotional neglect (*OR = 4.81, 95%CI = 2.36–9.79*, $p < .01$).

Cut-off subscale scores were re-built into a single variable named "*exposure to childhood trauma*", which means being exposed to at least one kind of childhood trauma (0 = any or minimum exposure; 1 = low to moderate and 2 = moderate to extreme childhood trauma exposure) (Table 1). Nearly 80% of the ROP group and 37.7% of HC reported some kind of childhood trauma. Compared to non-exposed, both low-to-moderate and moderate-to-extreme exposures were significantly associated with psychosis (Table 1).

3.3. Recent events

With respect to recent events, the ROP group scored higher in HR total score and reported a higher number of recent events. Compared with subjects with low vulnerability to stress, subjects scoring moderate but not high on the Holmes-Rahe scale were more likely to be psychotic patients (Table 1).

3.3.1. Cannabis exposure

Only 6 subjects in the entire sample reported sporadic cannabis use ("*smoking cannabis less than once a month*"); therefore, they were classified as non-users for the purposes of analysis. Nearly 50% of the ROP group and 23% of HC regularly smoked cannabis. Among ROP regular smokers 85.7% were severe cannabis smokers and 68.3% of them were daily smokers. As it is shown in Table 1, a severe cannabis smoking pattern was associated with psychosis, while moderate use was not.

Table 1
Socio-demographical and clinical characteristics of the sample.

	ROP N = 146	Controls N = 61	OR unadjusted	*p*
Socio-demographic variables				
Age, years (median IQR)	22 (18–26)	23(19–27)	0.97 (0.92–1.04)	.49
Sex (%)				
Male	94 (64.4)	32(52.5)	1.63 (0.89–3.00)	.11
Female	52 (35.6)	29 (47.5)	1.00	
Ethnicity (%)				
White Spanish	127(87.0)	57(91.9)	2.13 (0.69–6.55)	.18
Minority	19 (13.0)	4(6.6)	1.00	
Family history psychotic disorder(%)				
Yes	23 (15.8)	4 (6.6)	2.65(0.88–8.06)	.08
No	123 (84.2)	57 (93.4)	1.00	
Education years (median IQR)	10(9–12)	13(11–16)	−0.71 (0.63–0.80)	.000
Environmental risk factors				
Recent events				
HR total	169.61(110,0.3)	116 (99.62)	1.00(1.002–1.00)	.003
Number of events (median IQR)	6 (3–8)	3(2–7)	1.15(1.09–1.22)	.005
HR recodified				
Low risk	72 (49.3)	45 (73.8)	1.00	
Moderate risk	54 (37.0)	11 (18.0)	3.06 (1.45–6.48)	.003
High risk	20 (13.7)	5 (8.2)	2.50 (0.87–7.13)	.08
Childhood trauma				
CTQ total score (median IQR)	37(33–47)	29(26–33)	1.15(1.09–1.22)	0.000
Exposure to childhood trauma (%)				
Any or minimum	29(19.9)	38(62.3)	1.00	
Low to moderate	44(30.1)	17(27.9)	3.39(1.61–7.10)	.001
Moderate to extreme	73(50.0)	6(9.8)	15.94(6.08–41.74)	.000
Cannabis use (%)				
Non users	76(61.8)	47(77.0)	1.00	
Regular users				
Moderate	10(6.8)	6(9.8)	1.03(0.35–3.02)	.95
Severe	60(41.1)	8(13.1)	4.63(2.03–10.55)	.000
Tobacco use (%)				
Non user	49(33.6)	40(65.6)	1.00	
Regular user	47(66.4)	21(34.4)	3.77(2.00–7.08)	.000

Abbreviations: ROP = recent onset psychosis; SD = standard deviation; IQR = interquartile range; PANSS = Positive and Negative Symptom Scale; HR = Holmes-Rahe Social Readjustment Scale; Recent events = number of life events; CTQ = Childhood Trauma Questionnaire; OR = Odds ratio;

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Table 2
CTQ subscales of childhood trauma.

CTQ subscales	ROP N = 146 N (%)	Controls N = 61 N (%)	OR unadjusted[a]	P
Emotional abuse			3.69 (1.84–7.38)	0.000
-Any or minimum	73 (50.0)	48 (78.7)		
-Low-to-moderate	40 (27.4)	11 (18.0)		
-Moderate-to severe	14 (9.6)	0		
-Severe-to-extreme	19 (13.0)	2 (3.3)		
Emotional neglect			4.81 (2.36–9.79)	0.000
-Any or minimum	67 (45.9)	49 (80.3)		
-Low-to-moderate	45 (30.8)	9 (14.8)		
-Moderate-to severe	22 (15.1)	2 (2.3)		
-Severe-to-extreme	12 (8.2)	1 (1.6)		
Physical abuse			4.58 (1.33–15.7)	0.015
-Any or minimum	118 (80.0)	58 (95.1)		
-Low-to-moderate	13 (8.9)	1 (1.6)		
-Moderate-to severe	9 (6.2)	1 (1.6)		
-Severe-to-extreme	6 (4.1)	1 (1.6))		
Physical neglect			6.98 (2.39–20.36)	0.000
-Any or minimum	98 (67.1)	57 (93.4)		
-Low-to-moderate	30 (20.5)	3 (4.9)		
-Moderate-to severe	10 (6.8)	1 (1.5)		
-Severe-to-extreme	8 (5.5)	0		
Sexual abuse			3.02 (1.11–8.18)	0.03
-Any or minimum	115 (78.8)	56 (91.8)		
-Low-to-moderate	12 (8.2)	4 (6.6)		
-Moderate-to severe	13 (8.9)	1 (1.6)		
-Severe-to-extreme	6 (4.1)	0		

Abbreviations: ROP = recent onset psychosis; CTQ = Childhood Trauma Questionnaire; OR = Odds ratio.

[a] Reference category "any or minimum exposure" compared to "low-to-moderate; moderate-to severe; severe-to-extreme" recoded into a single category.

3.3.2. Hierarchical regression analysis

All interactions were primarily tested but none of them was found to be significant. As can be seen in Table 3 (last block). Moderate-to-extreme childhood trauma exposure and severe cannabis use continued to be associated with psychosis, while recent event exposure did not.

As a result of the hierarchical process, there was an increase in the determination coefficient when adding each consecutive block of variables. The combination of socio-demographic, stressful factors and cannabis exposure yielded a significant effect ($x^2 = 86.76$, $p < .001$) explaining the 49% of the variation of psychosis.

3.3.3. Cumulative effect of environmental factors

As it is shown in Fig. 1, nearly 90% of the ROP group reported being exposed to at least one type of environmental factor. A quarter of the ROP group reported being exposed to one type, 43.8% to two types and 21.9% reported being exposed to all factors. As we can see in Table 4, the ROP group was more likely to be exposed to one, two or three environmental factors than HC. After controlling for socio-demographic variables, exposure to one factor was no longer associated with psychosis. However, compared to the non-exposed group, those exposed to two or all factors were nearly 7.5-fold and 26.7-fold more likely to have a diagnosis of psychosis, respectively.

4. Discussion

The present study aimed to examine the association between various levels of exposure to three environmental factors and psychosis in a sample composed of ROP patients and HC. Our main findings are as follows: only the highest levels of exposure to childhood trauma and cannabis use are independently associated with psychosis. The predictive model shows increasing changes in the variance of psychosis when factors are hierarchically included, being childhood trauma exposure the most contributing factor. Finally, we have found that exposure to two or all the environmental factors studied significantly increased the likelihood of psychosis, while exposure to only one factor did not increase the risk.

4.1. Association of environmental factors and psychosis

In agreement with other studies, we found a higher prevalence of childhood trauma (Varese et al., 2012), an excess of recent events (Beards et al., 2013) and an increased percentage of cannabis use (Large et al., 2011) in the ROP group. We found that nearly half of the ROP group reported at least one kind of moderate-to-extreme childhood trauma. The prevalence of childhood trauma we reported accords with that of a study conducted in Spain by Barrigón et al. (2015), who reported 43% of childhood trauma in a sample of patients with a first psychotic episode. Among the various types of childhood trauma, exposure to physical abuse or neglect were most associated with psychosis, which is highly consistent with published data (Smeets et al., 2015; Varese et al., 2012). Fifty per cent of the ROP group reported at least moderate exposure to recent events, similar to the 55% prevalence reported by Mansueto and Faravelli (2017), assessed with different instruments. Focusing on the pattern of cannabis use, we found that nearly 50% were regular smokers, similar to the rates described in other first episode studies (Barbeito et al., 2013; Barrigón et al., 2015; Núñez et al., 2016).

The impact of childhood trauma, recent events and cannabis use on the likelihood of psychosis varied depending on the severity of exposure. Importantly, on multivariate analysis, only the highest level of exposure to childhood trauma and cannabis was significantly associated with psychosis, even after controlling for tobacco use. Our results, therefore, overcome the previous limitations regarding the use of tobacco as a potential confounder of the relationship between cannabis use and psychosis (Gurillo et al., 2015; Hickling et al., 2017). In addition, our finding that only the severe regular use of cannabis is significantly associated with psychosis agrees with recent studies (Di Forti et al., 2015; Schoeler et al., 2016b). Current lines of research highlight the relevance of considering the pattern of cannabis use when interpreting the association of cannabis with psychosis. Moreover, there is increasing interest in studying whether the proportion of tetrahydrocannabinol (THC) and cannabidiol (CBD) influenced this association (Marconi et al., 2016). Unfortunately, we were not able to measure the various components of cannabis used by our participants.

With regard to recent events, our results agree with those reported recently by Mansueto and Faravelli (2017), who found that recent events were associated with psychosis in the presence of childhood trauma. These authors did not consider the severity of cannabis use in the analysis, however we found that when cannabis exposure was added to the model, recent events were no longer associated with psychosis. As noted in the introduction, the relationship between psychosis and recent events is a subject of debate. Some studies observed no excess of recent events in psychotic patients or observed fewer recent events in psychotic patients compared with controls. These differences may derive from different definitions, different time periods considered, or different assessment tools (Beards et al., 2013). In addition, the findings of higher rates of recent events in ROP are consistent with the theoretical model of the socio-development perspective, considering that the higher report of recent events might be a reverse causation of psychosis (Morgan et al., 2010, 2014a, 2014b; Stilo et al., 2017).

4.2. Interaction and cumulative effect of environmental factors on psychosis

The hierarchical logistic model allowed us to test the interaction and/or cumulative effect of the various environmental factors. Contrary to other authors (Houston et al., 2011; Murphy et al., 2013), we failed to find an interaction among the different environmental factors. Our results, however, agree with more recent studies that also failed to find

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Table 3
Hierarchical logistic regression model.

Predictor	-2log likelihood	R^2 Nagelkerke	$\times^2$ (df)	B	SE	Exp(B) 95 CI	p
Step 1	207.94	0.26	$43.06_{(5)}$				.000
Block 1 socio-demographic							
Age				0.042	0.042	1.04(0.96–1.13)	.32
Gender (male)				0.360	0.351	1.44(0.72–2.86)	.29
Years education				−0.353	0.069	0.70(0.61–0.80)	.000
Family history of psychosis				0.874	0.645	2.39(0.67–8.49)	.17
Ethnicity (minority)				0.347	0.609	1.41(0.42–4.66)	.56
Step 2	180.163	0.41	$27.782_{(7)}$				.000
Block 1 socio-demographic							
Age				0.053	0.045	1.05(0.96–1.15)	*.24*
Gender				0.445	0.390	1.56(0.72–3.35)	*.25*
Years education				−0.289	0.073	0.74(0.64–0.87)	*.000*
Family history of psychosis				0.719	0.684	1.77(0.47–6.60)	*.39*
Ethnicity (minority)				0.749	0.708	2.11(0.52–8.47)	*19*
Block 2 childhood trauma							
Childhood trauma							
Low				1.12	0.424	3.07(1.34–7.06)	*.008*
Moderate-extreme				2.44	0.522	11.55(4.15–32.14)	*.000*
Step 3	173.524	0.44	$77.481_{(9)}$				
Block 1 sociodemographic							
Age				0.041	0.046	1.04(0.95–1.14)	*.37*
Gender				0.535	0.405	1.70(0.77–3.78)	*.18*
Years education				−0.277	0.075	0.75(0.65–0.87)	*.000*
Family history psychosis				0.719	0.684	2.05(0.53–7.84)	*.29*
Ethnicity (minority)				0.749	0.708	2.11(0.52–8.47)	*19*
Block 2 childhood trauma (CTQ)							
Low				1.10	0.439	3.03(1.28–7.17)	*.012*
Moderate -extreme				2.36	0.543	10.61(3.66–30.75)	*.000*
Block 3 recent events (HR)							
Moderate				1.14	0.463	3.14(1.26–7.79)	*.014*
High				0.53	0.639	1.70(0.48–5.95)	*.40*
Step 4	164.239	0.49	$86.76_{(12)}$				*.000*
Block 1 socio-demographic							
Age				0.038	0.050	1.03(0.94–1.14)	*.43*
Gender				0.283	0.428	1.32(0.57–3.07)	*.50*
Years education				−0.262	0.078	0.76(0.66–0.89)	*.001*
Family history of psychosis				0.746	0.723	2.10(0.51–8.69)	*.30*
Ethnicity (minority)				0.910	0.715	2.48(0.61–10.09)	.20
Block 2 childhood trauma (CTQ)							
Low				0.814	0.464	2.25(0.91–5.59)	*.07*
Moderate-extreme				2.10	0.560	8.18(2.73–24.52)	*.000*
Block 3 recent events (HR)							
Moderate				0.917	0.483	2.50(0.97–6.45)	*.06*
High				0.341	0.661	1.40(0.38–5.14)	*.60*
Block 4 misuse variables							
Cannabis regular use							
Moderate				0.640	0.721	0.52(0.12–2.16)	*.37*
Severe				1.03	0.503	2.82(1.05–7.55)	*.03*
Tobacco regular use				0.700	0.417	2.01(0.89–4.55)	*.09*

Note = Dependent variable: subjects' status (0 = control; 1 = psychotic patients).
Abbreviations: $\times^2$ = chi-square statistic; df = degrees of freedom; B =B coefficient; SE = standard error; Exp(B) = Exponentiation of the B coefficient; 95 CI = 95% confidence interval; p = significance level.
Italic values indicate significance at $p < 0.05$.

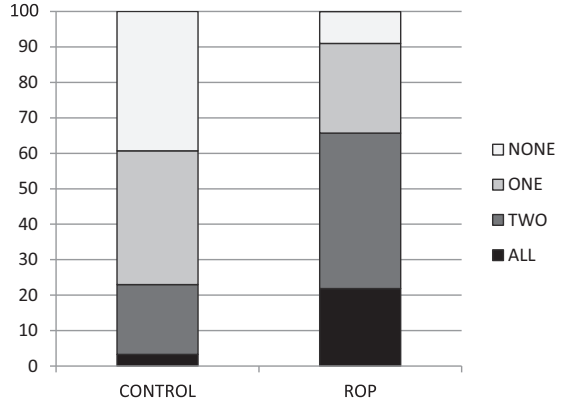

Fig. 1. Prevalence of ROP and HC exposed to different number of environmental risk factors.

an interaction between childhood trauma and cannabis when the level of exposure was considered (Baudin et al., 2016; Sideli et al., 2018). By contrast, we found a cumulative effect of environmental factors on psychosis risk. When childhood trauma was added to socio-demographical

Table 4
Effect of number of environmental factors on psychosis risk.

Types of environmental factors	OR unadjusted	p	OR unadjusted[a]	p
-Any	1		1	
-One	2.97(1.26–6.96)	.012	2.22(0.84–5.87)	.106
-Two	9.84(3.94–24.5)	.000	7.51(2.6–21.12)	.000
-Three	29.53(6.08–143.4)	.000	26.71(5.1–140.6)	.000

Dependent variable: subjects' status (0 = control; 1 = psychotic patients).
Abbreviations: OR: Odds Ratio.
[a] Adjusted for age; gender, years of education, ethnicity, and family history of psychosis.

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factors, there was an increased variance of 15% and additional increases of 4% and 5% when recent events and cannabis were consecutively included.

Childhood trauma therefore seems to be the strongest environmental contributor to psychosis in our sample. This finding is highly consistent with recent studies in individuals at ultra-high-risk for psychosis, in which the strongest environmental factor associated with psychosis transition was childhood trauma (Kraan et al., 2015; Mayo et al., 2017). Moreover concerning the link between childhood trauma and substance use, Khoury et al., 2010, confirmed a strong relationship between childhood trauma, posttraumatic disorder (PTSD) and substance use disorder. Additionally, PTSD has also been shown to predict cannabis use (Cornelius et al., 2010). In the present study, however, we were not able to explore the presence of present or past PSTD.

Larger numbers of various types of exposure increased the likelihood of psychosis, with the exception of being exposed to a one single type of environmental risk factor (Husted et al., 2012; Shevlin et al., 2007; Stepniak et al., 2014). Our results were similar to those of Shevlin et al. (2007), who found that experiencing two or more traumas increases the likelihood of developing psychosis. In this line, Husted et al. (2012) proposed an environmental risk index (between 1 and 8) including cannabis use (only as a dichotomic variable) and early adversity; the risk of psychosis increased when the index was >3. Stepniak et al. (2014) designed an extensive evaluation of environmental factors combined with genetic risk and found that patients with up to one environmental risk factor experienced prodromal psychosis 8 years later than did those with four or more environmental insults. More recently, Padmanabhan et al., 2017 created a measure of additive exposure to enviromental risk factors which correlated to psychosis convertion in their sample of genetic risk subjects.

All these findings together agree with those suggesting that continued exposure to sequential stressors may increase the risk of developing psychosis (Fraguas et al., 2017; Padmanabhan et al., 2017; van Os et al., 2010). The cumulative effect of factors accords with the multiple hit theory (Davis et al., 2016), suggesting that schizophrenia develops after multiple factors appear at various times during neurodevelopment. More specifically, the cumulative effect of factors on psychosis may be due to a higher sensitivity to stress. Previous studies reported that stress is an important risk factor for developing psychosis (Mondelli et al., 2010; Phillips et al., 2007). Although schizophrenia is usually considered a neurodevelopmental disorder, the involvement of the hypothalamic-pituitary-adrenal (HPA) axis in primary biological responses to stress has implicated this system in the development of psychosis (Pruessner et al., 2017; Walker and Diforio, 1997). Little is known about the relationship between cannabis and the HPA axis. On the one hand, it has been postulated that variable exposure to early stressors may act as the "first hit", according to the theory of Davis, and this accumulation of stressors may increase the vulnerability of the HPA axis to future environmental factors, including regular cannabis use (Davis et al., 2016; Fusar-Poli et al., 2013). On the other hand, it is also plausible that continued exposure to cannabis may amplify the response of the HPA axis to common stressors. In this respect, two studies found higher levels of cortisol in psychotic patients with chronic cannabis use (D'Souza et al., 2004; King et al., 2011). Moreover, a recent study conducted with patients at ultra-high risk of psychosis observed higher cortisol levels in the cannabis users group (Carol et al., 2017).

4.3. Limitations and strengths

This study, however, has certain methodological limitations that need to be considered when interpreting the results. First, the relatively modest sample size may be underpowered to detect some associations and large effects. Some of the observed associations have wide confidence intervals and require replication in larger samples. Second, the cross-sectional nature of the study did not allow us to infer causal relationships between the risk factors and psychosis. We neither have been able to run a mediation analysis, however our dose-response design combining 3 environmental factors might be an innovative approach for further studies. Third, childhood trauma and recent events were retrospectively assessed with a self-report instrument; thus, recall bias cannot be ruled out. In addition, our instrument could not differentiate between dependent and independent recent events and we did not assess the lifetime prevalence of PTSD. Finally, we did not report the types of cannabis used. Future investigations should focus on changes in the pattern of use and the type of cannabis used. Additionally, dimensional rather than a diagnostic perspective might be a better approach to the differential phenomenology of psychosis.

Despite these limitations, our focus on psychotic patients at early stage of the illness minimizes the impact of the burden of a chronic disease and long-term antipsychotic treatment. Moreover, we tried to overcome methodological flaws of previous studies by assessing various levels of exposure to environmental factors and by controlling for various confounders as tobacco use.

Given the lack of controlled studies on early psychosis combining various types of environmental factors and various levels of exposure, our findings may facilitate the design of future studies. In addition, the majority of studies involving environmental stress factors and cannabis in psychosis have been conducted in Northern Europe. Our study, therefore, provides information about the effect of stress factors and cannabis use on psychosis in a South European country.

4.4. Conclusions

In conclusion, our study provides evidence for a cumulative and a dose –response effect of environmental factors in the development of early psychosis. Considering that cannabis regular use and childhood trauma are highly prevalent in the population with psychosis, investigations of the factors influencing worse outcomes and early onset are needed in order to advance the search of new treatment options. We believe clinicians should regularly assess the dose-response of well-defined environmental factors. Cannabis is one of the most potentially avoidable risk factors for psychosis. Studying its effects and its relationship with other factors will help us to better understand the underlying mechanisms of psychosis.

Conflict of interest

The authors report no financial or other relationship relevant to the subject of this article.

Contributions

The contributions of each author to the paper are the following:

Drs. Arranz and Sanchez-Gistau designed the current study. Drs Arranz, Monferrer, Cabezas, Sole, Labad and Algora contributed to the acquisition of the data. Drs Arranz managed the literature searches. Drs Arranz, Vilella and Sanchez-Gistau undertook the statistical analysis. Dr. Arranz wrote the first draft of the article and all other authors provided their contributions to the first draft. All authors have approved the final manuscript.

Role of the founding source

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BRIEF REPORT

Hypothalamic-pituitary-adrenal axis function and exposure to stress factors and cannabis use in recent-onset psychosis

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ABSTRACT

Objectives: Previous studies suggest that childhood trauma, stressful life events, and cannabis use are associated with psychosis. We aimed to explore whether these environmental factors have an effect on hypothalamic–pituitary–adrenal (HPA) axis indices in recent-onset psychosis.

Methods: We studied 56 recent-onset psychosis outpatients and 47 healthy controls. Childhood trauma was assessed with the Childhood Trauma Questionnaire. Stressful life events were assessed with the Holmes-Rahe Social Readjustment Scale. Cannabis use was assessed by semi-structured interviews. Several HPA axis measures were analysed in saliva: cortisol awakening response (CAR), diurnal cortisol slope, and dexamethasone suppression test ratio (DSTR) after 0.25 mg of dexamethasone. Multiple linear regression analyses were conducted to explore the contribution of environmental factors to each HPA axis measure while adjusting for covariates (diagnosis, age, gender, smoking, body mass index and treatments).

Results: There were no significant differences in HPA axis measures between diagnostic groups. Cannabis use was associated with a more flattened diurnal cortisol slope (standardized $\beta = 0.21$, $p = 0.038$), independent of recent-onset psychosis diagnosis. No associations were found between environmental factors and other HPA axis measures (CAR, DSTR).

Conclusions: Our study provides evidence for the effect of cannabis exposure in cortisol secretion patterns in both healthy controls and recent-onset psychosis patients.

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Stress; cannabis; childhood trauma; cortisol; psychosis

1. Introduction

The diathesis-stress model has dominated theories about the pathophysiology of psychosis, suggesting a link between psychosocial stressors, glucocorticoid secretion and dopamine synthesis (Pruessner et al. 2017), although neuroinflammation/immune and endocannabinoid signalling are also thought to contribute to the pathogenesis of psychotic disorders (Mizrahi 2016; Tomas-Roig et al. 2018). The magnitude of the hypothalamic–pituitary–adrenal (HPA) axis response during adolescence may be influenced by the environment, including the history of childhood trauma, stressful life events and cannabis use, tipping the HPA axis into a state of hyperactivity and/or dysregulation characterised by increased plasma cortisol levels, decreased glucocorticoid receptor expression, a blunted cortisol awakening response (CAR) and a dampened cortisol response to stress (Pruessner et al. 2017). These changes may play a role in the development of subthreshold psychotic symptoms and increase the risk for developing a psychotic disorder.

Few studies have explored the association between cannabis use, stressful life events, or childhood trauma and HPA axis indices in people at ultra-high-risk (UHR) for developing psychosis or with recent-onset psychosis. Previous studies have reported increased morning cortisol levels in UHR individuals who are cannabis users when compared with those in non-users and healthy controls (Carol et al. 2017). Other studies have reported a correlation between hassles (but not stressful life events) and plasma cortisol levels in UHR individuals (Thompson et al. 2007). In a study that included first-episode psychosis and healthy controls, first-episode psychosis patients showed higher rates of childhood trauma, lower basal cortisol and enhanced cortisol suppression to low-dose (0.25 mg) dexamethasone (Phassouliotis et al. 2013), although the cortisol measures were not associated with childhood trauma.

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In another study that also included first-episode psychosis patients, diurnal cortisol levels were negatively correlated with stressful life events, and the CAR was positively correlated with a history of sexual abuse (Mondelli et al. 2010).

In a recent study by our group exploring the cumulative effect of exposure to childhood trauma, recent stressful life events and cannabis use on the risk of psychosis, the highest levels of exposure to childhood trauma and cannabis were associated with recent-onset psychosis (Arranz et al. 2018). In the current study, we aimed to explore whether childhood trauma, stressful life events and/or cannabis use are associated with HPA axis indices. Although these stress-related variables are known risk factors for psychosis, less studies have explored the interplay between them and the HPA axis in a sample of patients with recent-onset psychosis.

2. Materials and methods

2.1. Participants

Fifty-six outpatients with recent-onset psychosis (psychotic disorder with a duration of illness <3 years, 64% were FEP) from the Early Intervention Service of the Hospital Universitari Institut Pere Mata (Reus, Spain) were studied. We included a control group of 47 healthy individuals matched by sex and age who were recruited from the community using advertisements. All healthy individuals were screened to rule out past or current history of psychiatric disorder. This sample overlaps with that used in a previous study (Labad et al. 2016) that explored different hypotheses.

Ethical approval was obtained from the local ethics committee. All participants were informed about the study procedure, and written informed consent was obtained. All procedures are in accordance with the Declaration of Helsinki and with the following rules on personal data protection: Spanish Organic Law 15/1999 from 13 December 1999 and the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016.

2.2. Clinical assessment

All patients were administered the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (Wing et al. 1990) by an experienced psychiatrist (JL, IM or MS). This instrument is a semi-structured clinical interview used by trained clinicians to assess and diagnose psychiatric disorders among adults. A DSM-IV diagnosis of psychotic disorder was obtained by means of the OPCRIT checklist version 4.0 (available at http://sgdp.iop.kcl.ac.uk/opcrit/).

The 28-item Childhood Trauma Questionnaire – Short Form (CTQ-SF) (Hernandez et al. 2013) was used to retrospectively assess the presence of childhood trauma. This self-report instrument measures five dimensions of childhood trauma. Exposure to childhood trauma was determined when at least one CTQ-SF subscale was rated on or above the moderate cut-off score (emotional abuse $\geq$ 13; physical abuse $\geq$ 10; sexual abuse $\geq$ 8; emotional neglect $\geq$ 15; and physical neglect $\geq$ 10).

The Holmes-Rahe Social Readjustment Scale (HRSRS) (Holmes and Rahe 1967) was used for exploring the presence of stressful life events during the previous 6 months, and was heteroadministered by a clinical psychologist (AC). This scale was originally developed to assess the presence of 43 stressful life events that were assigned a stress score ('life change unit') depending on how traumatic it was felt to be by a large sample of participants. A global score is obtained by adding the scores of all recent stressful life events. A score of 150 points or higher suggests moderate to high susceptibility to stress-induced illness. Exposure to stressful life events was defined as an HRSRS score $\geq$ 150 points. This scale has been previously used to explore the relationship between life events and subclinical psychotic symptoms in the general population (Rössler et al. 2007) or with the risk of developing a psychotic disorder in UHR individuals (Labad et al. 2015).

Cannabis and tobacco use were assessed by a semistructured interview that was administered by a mental health nurse (LO or MJA). For the purpose of this study, cannabis use was defined as at least weekly use.

Current antidepressant and antipsychotic treatment was recorded. Each antipsychotic dose was converted to chlorpromazine equivalents in mg/day taking into account recommendations of an international consensus of antipsychotic dosing (Gardner et al. 2010).

2.3. HPA axis measures

Saliva was collected from all participants using Salivette tubes (Sarstedt, Nümbrecht, Germany). The day of the clinical assessment all participants were given six Salivette tubes to collect saliva samples at home during another day. Six collection times were considered: at awakening (T1), 30 min post-awakening (T2), 60 min post-awakening (T3), 10:00 h (T4) and 23:00 h (T5). Participants were instructed to take

0.25 mg dexamethasone at 23:00 h, just after T5 sample collection. The following day at 10:00 h, another salivary sample was obtained to assess post-dexamethasone cortisol levels (T6). The methodological decision to use a very low dose (0.25 mg) of dexamethasone has been previously explained in previous studies from our group (Labad et al. 2016, 2018). This dose has been also used by other research groups to assess the feedback sensitivity of the HPA axis in first-episode psychosis patients (Phassouliotis et al. 2013).

Saliva samples were processed at the IISPV Biobank and frozen at −20 °C until cortisol determination, as described elsewhere (Labad et al. 2016, 2018). A high-sensitivity enzyme-linked immunosorbent assay (IBL, Hamburg, Germany) was used for measuring salivary cortisol concentrations. The intra- and inter-assay coefficients of variation were under 8%. The sensitivity of the assay was 0.08 nmol/l.

Three dynamic measures of HPA axis function were considered in our study: the CAR, the diurnal cortisol slope and the dexamethasone suppression test. The CAR was calculated using the area under the curve with respect to an increase in T1–T3 samples by means of the trapezoid formula (Pruessner et al. 2003). The CAR is a physiological response to awakening that consists of a rise in cortisol levels following morning awakening. The diurnal cortisol slope was calculated as the slope between T1 (awakening) and T5 (23:00 h) samples. This measure indicates the rate of decline in cortisol levels across the day, from morning to evening, and it reflects the diurnal cortisol rhythm. A negative diurnal slope is generally considered indicative of healthy HPA axis function, and a more flattened slope is suggestive of potential HPA axis dysfunction. The cortisol suppression ratio in the dexamethasone suppression test ratio (DSTR) was calculated by dividing T4 and T6 samples. The DSTR provides information about the negative feedback system of the HPA axis. In this regard, a lack of suppression after dexamethasone administration is considered a measure of glucocorticoid resistance.

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM, Armonk, NY, USA). Cortisol values were transformed to approximate a normal distribution, as explained elsewhere (Labad et al. 2016, 2018). CTQ-SF scores were log(ln) transformed to normalise data in parametric and multivariate analyses. Comparison of categorical data between diagnostic groups was performed with Chi-square tests. *t*-Tests were used to compare continuous data between diagnostic groups. ANCOVA was used to compare HPA axis measures (CAR, diurnal cortisol slope and DSTR) between tobacco and cannabis use (defined as a categorical variable of three categories: (1) non-users, (2) tobacco users and (3) tobacco and cannabis users) and diagnostic groups. Statistical significance was defined as $p < 0.05$ (two-tailed).

To explore the association between environmental factors and HPA axis measures, we conducted hierarchical multiple linear regression analyses. HPA axis measures were considered the dependent variables (three equations were tested: CAR, diurnal cortisol slope and DSTR). Environmental factors, which were dichotomised using cut-off points mentioned in Section 2.2, were considered independent variables, along with other covariates (diagnosis, age, gender, smoking, BMI and treatments (antidepressants and antipsychotics)). Interactions between environmental factors and diagnosis were tested, and only significant interactions were included in the final model.

3. Results

The clinical characteristics and HPA axis measures of the sample are described in Table 1. Recent-onset psychosis patients reported more childhood trauma and stressful life events than healthy controls. There were no significant differences in HPA axis measures between recent-onset psychosis and healthy control groups. Cannabis users, who also used tobacco, showed a more flattened diurnal cortisol slope than non-users (Table S1). When exploring differences in stress factors (childhood trauma or stressful life events) between people with or without cannabis use, more accumulated environmental stress factors were reported by recent-onset psychosis patients (but not healthy controls) who were cannabis users (Table 2).

In multiple linear regression analyses (Table 3), cannabis use (but not stressful life events or childhood trauma) was associated with a more flattened diurnal cortisol slope (standardized $\beta = 0.21$, $p = 0.038$). No associations were found between stress factors or cannabis use and other HPA axis measures (CAR or DSTR). No interactions were found between these factors and recent-onset psychosis diagnosis.

4. Discussion

Our study suggests that exposure to cannabis use but not stressful life events or childhood trauma is

Table 1. Clinical and biological data by diagnostic group.

	Healthy controls ($N = 47$)	Recent-onset psychosis ($N = 56$)	p
Sociodemographic and clinical variables			
Age	23.8 (4.5)	24.8 (5.4)	0.357
Female gender, *n* (%)	22 (46.8%)	21 (37.5%)	0.340
Smoking, *n* (%)	9 (19.1%)	39 (69.6%)	**<0.001**
Cigarettes/day (all participants)	1.4 (4.0)	8.7 (9.1)	**<0.001**
BMI	22.5 (3.1)	24.5 (4.2)	**0.006**
Antidepressant treatment, *n* (%)	0 (0%)	6 (10.7%)	**0.030**
Antipsychotic treatment, *n* (%)	0 (0%)	46 (82.1%)	**<0.001**
Antipsychotic dose in chlorpromazine equivalents (mg/day)	0 (0)	384.6 (356.5)	**<0.001**
Environmental risk factors			
Childhood trauma			
CTQ-SF total score†	30.8 (5.9)	38.1 (10.7)	**<0.001**
History of childhood trauma, *n* (%)	4 (8.5%)	22 (39.3%)	**<0.001**
Recent life events			
HRSRS total score	110.6 (101.1)	166.9 (118.7)	**0.011**
Number of life events	3.9 (3.5)	5.8 (3.7)	**0.013**
Recent stressful life events (moderate to high risk), *n* (%)	14 (29.8%)	29 (51.8%)	**0.024**
Cannabis use, *n* (%)	8 (17.0%)	11 (19.6%)	0.733
HPA axis measures‡			
Cortisol at awakening (T1), nmol/l	14.4 (8.9)	13.1 (8.8)	0.503
Cortisol 30 min post-awakening (T2), nmol/l	24.1 (13.7)	21.0 (10.6)	0.522
Cortisol 60 min post-awakening (T3), nmol/l	21.1 (13.0)	16.9 (7.2)	0.419
Cortisol at 10:00 h (T4), nmol/l	12.5 (7.4)	12.4 (6.3)	0.701
Cortisol at 23:00 h (T5), nmol/l	2.7 (2.2)	2.8 (2.9)	0.936
Cortisol at 10:00 h after DXM (T6), nmol/l	9.2 (8.4)	9.0 (8.2)	0.695
CAR	41.7 (64.3)	44.4 (56.2)	0.817
Diurnal cortisol slope§	−0.81 (0.62)	−0.74 (0.62)	0.709
DSTRγ	3.1 (4.7)	6.7 (27.2)	0.448

Bold values represent statistical significance at $p < 0.05$.
BMI: body mass index; CTQ-SF: Childhood Trauma Questionnaire–Short Form; HRSRS: Holmes-Rahe Social Readjustment Scale; HPA: hypothalamic–pituitary–adrenal; CAR: cortisol awakening response; DSTR: dexamethasone suppression test ratio.
†CTQ-SF raw scores are shown. However, log transformed scores were used for comparing both groups with a *t*-test.
‡Untransformed cortisol levels are shown. However, transformed cortisol levels (Box-Cox transformation) were used for comparing both groups with a *t*-test.
§The diurnal cortisol slope was calculated using T1 and T5 samples (from awakening to 23:00 h). Raw slopes (calculated with untransformed cortisol values) are shown. However, for comparing both groups with a *t*-test, the slope calculated from transformed cortisol values was used (mean (SD) slope was −0.18 (0.11) for healthy controls and −0.17 (0.13) for recent-onset psychosis patients).
γDSTR, cortisol at 10:00 h (T4)/cortisol at 10:00 h after 0.25 mg dexamethasone (T6). Raw DSTRs are shown. However, for comparing both groups with a *t*-test, DSTRs were previously transformed (Box-Cox transformation).

Table 2. Presence of stress factors by diagnostic group and cannabis exposure.

	Healthy controls			Recent-onset psychosis		
	No cannabis use $N = 39$	Cannabis use $N = 9$	p (linear trend)	No cannabis use $N = 45$	Cannabis use $N = 11$	p (linear trend)
No other environmental stress factors	26 (66.7%)	5 (62.5%)	0.863	16 (35.6%)	0 (%)	**0.027**
Childhood trauma only	1 (2.6%)	1 (12.5%)		9 (20.0%)	2 (18.2%)	
Stressful life events only	10 (25.8%)	2 (25.0%)		12 (26.7%)	6 (54.5%)	
Combined childhood trauma and stressful life events	2 (5.1%)	0 (0%)		8 (17.8%)	11 (19.6%)	

Bold values represent statistical significance at $p < 0.05$.

associated with a more flattened diurnal cortisol slope. This pattern was independent of clinical diagnosis. All multiple linear regression analyses were adjusted for smoking, which suggests that the cannabis effect on the diurnal cortisol slope is independent of tobacco use. We failed to find an association between stressful life events or childhood trauma and HPA axis measures.

Other studies in recent-onset psychosis patients have reported a negative correlation between stressful life events and cortisol levels during the day (Mondelli et al. 2010), as well as a lack of association between childhood trauma and DSTR (Phassouliotis et al. 2013). Other studies that included UHR individuals have found that plasma cortisol is correlated with the experience of daily hassles but not with the experience of stressful life events (Thompson et al. 2007). Other authors have also suggested that minor daily stressors are more distressful for patients with schizophrenia than major life events (Norman and Malla 1991). Minor daily hassles, which could have a greater impact on HPA axis functioning when compared with major life events, were not assessed in our study.

Table 3. Results of the multiple linear regression analyses of the association between exposure to environmental factors and hypothalamic–pituitary–adrenal axis measures.

	CAR			Diurnal cortisol slope			DSTR		
	R^2 (p)	β	p	R^2 (p)	β	p	R^2 (p)	β	p
Step 1 (clinical variables)	0.120 (0.098)			0.160 (0.023)			0.112 (0.146)		
Age		−0.06	0.538		−0.17	0.083		−0.01	0.902
Female gender		−0.16	0.116		−0.12	0.252		0.04	0.727
Smoking (cig/day)		0.09	0.441		0.07	0.561		0.03	0.821
BMI		0.19	0.068		0.04	0.716		0.23	**0.033**
Antidepressant treatment		−0.16	0.132		−0.19	0.060		−0.14	0.177
Antipsychotic treatment (mg/day)		0.03	0.800		0.20	0.129		0.18	0.201
Recent-onset psychosis diagnosis		−0.06	0.618		−0.07	0.595		−0.07	0.599
Step 2 (+ childhood trauma)	0.126 (0.124)			0.173 (0.024)			0.113 (0.206)		
Age		−0.06	0.551		−0.17	0.091		−0.01	0.891
Female gender		−0.17	0.108		−0.12	0.222		0.04	0.719
Smoking (cig/day)		0.09	0.457		0.06	0.593		0.03	0.805
BMI		0.21	0.050		0.07	0.509		0.22	**0.049**
Antidepressant treatment		−0.15	0.169		−0.18	0.090		−0.15	0.167
Antipsychotic treatment (mg/day)		0.04	0.750		0.21	0.113		0.17	0.228
Recent-onset psychosis diagnosis		−0.11	0.444		−0.13	0.346		−0.05	0.745
History of childhood trauma†		0.09	0.430		0.13	0.238		−0.04	0.700
Step 3 (+ stressful life events)	0.130 (0.164)			0.182 (0.029)			0.115 (0.272)		
Age		−0.06	0.554		−0.17	0.087		−0.02	0.882
Female gender		−0.17	0.112		−0.12	0.234		0.04	0.711
Smoking (cig/day)		0.09	0.469		0.06	0.606		0.03	0.808
BMI		0.22	**0.048**		0.07	0.489		0.22	0.050
Antidepressant treatment		−0.15	0.157		−0.19	0.076		−0.15	0.160
Antipsychotic treatment (mg/day)		0.05	0.728		0.22	0.096		0.17	0.228
Recent-onset psychosis diagnosis		−0.12	0.394		−0.16	0.263		−0.06	0.699
History of childhood trauma†		0.09	0.438		0.12	0.252		−0.05	0.688
Recent stressful life events‡		0.06	0.553		0.10	0.304		0.05	0.667
Step 4 (+ cannabis use)	0.141 (0.166)			0.222 (0.011)			0.118 (0.338)		
Age		−0.04	0.684		−0.21	**0.038**		−0.01	0.949
Female gender		−0.18	0.082		−0.08	0.400		0.03	0.768
Smoking (cig/day)		0.09	0.444		0.06	0.621		0.03	0.800
BMI		0.21	0.061		0.09	0.395		0.22	0.057
Antidepressant treatment		−0.15	0.155		−0.19	0.070		−0.15	0.161
Antipsychotic treatment (mg/day)		0.06	0.640		0.20	0.117		0.18	0.210
Recent-onset psychosis diagnosis		−0.13	0.359		−0.14	0.314		−0.06	0.673
History of childhood trauma†		0.09	0.394		0.11	0.322		−0.04	0.719
Recent stressful life events‡		0.08	0.456		0.08	0.412		0.05	0.623
Current cannabis use		−0.11	0.274		0.21	**0.038**		−0.05	0.621

Standardized β coefficients are shown.
Bold values represent statistical significance at $p < 0.05$.
CAR: cortisol awakening response; DSTR: dexamethasone suppression test ratio; BMI: body mass index.
†History of childhood trauma determined when at least one subscale of the Childhood Trauma Questionnaire–Short Form was rated on or above the moderate cut-off score (emotional abuse ≥13; physical abuse ≥10; sexual abuse ≥8; emotional neglect ≥15; and physical neglect ≥10).
‡Recent SLEs were defined as a Holmes-Rahe Social Readjustment score for the previous 6 months of 150 points or higher.

In contrast, we found that cannabis use contributed to a more flattened diurnal cortisol slope. There are no previous studies exploring the relationship between cannabis use and the HPA axis in recent-onset psychosis patients, although increased morning cortisol levels in UHR individuals with cannabis use have been described (Carol et al. 2017). In patients with schizophrenia, cannabis exposure has been associated with a more flattened CAR (Monteleone et al. 2014). Our study suggests that a more flattened diurnal cortisol slope is associated with cannabis use, although in contrast to the study by Monteleone et al. (2014), this effect was not specific of recent-onset psychosis patients. In our study, we also found that cannabis use was associated with a higher level of exposure to other environmental factors (stressful life events and childhood trauma) in recent-onset psychosis patients, which could contribute to the more flattened diurnal cortisol slope in people who are cannabis users. Evidence regarding the link between abnormalities in the stress-response system and the endocannabinoid system in humans is limited, especially in the context of psychosis, although it has been suggested that a dysfunctional endocannabinoid system may play a role in the risk for cannabis abuse (Appiah-Kusi et al. 2016). Previous studies

(Ranganathan et al. 2009) have also demonstrated that the exogenous administration of delta-9-tetrahydrocannabinol increases plasma cortisol levels in both healthy controls and frequent users. In that study, placebo administration did not interfere with the normal diurnal rhythm of cortisol, whereas the normal diurnal cortisol decline was reduced with the administration of delta-9-tetrahydrocannabinol. These results are in accordance with our study, as cannabis users in our sample had a more flattened cortisol diurnal slope. In the study by Ranganathan et al. (2009), although delta-9-tetrahydrocannabinol induced cortisol release in both groups, frequent users had blunted increases in cortisol release compared with healthy controls. The authors discussed potential explanations, including innate differences in response to delta-9-tetrahydrocannabinol between both groups (healthy controls versus frequent users) or the development of tolerance in the hypothalamus following chronic exposure to cannabinoid agonists (Ranganathan et al. 2009).

In a previous study by our group, childhood trauma was also associated with the diagnosis of a psychotic disorder (Arranz et al. 2018). Our current study suggests that, in terms of HPA axis functioning, a history of childhood trauma is not associated with differences in cortisol secretion profiles. This finding is in accordance with previous studies that did not find an association between childhood trauma and DSTR in first-episode psychosis patients (Phassouliotis et al. 2013). Moreover, a recent meta-analysis of studies including self-report measures of childhood trauma has reported no overall effect of childhood trauma on the CAR, or the diurnal slope (Bernard et al. 2017). Diagnostic groups in our sample differed in terms of childhood trauma, stressful life events and cannabis use, and all recent-onset psychosis patients who smoked cannabis reported at least another stress factor (either recent stressful life events or a history of childhood trauma). The distribution of these variables in our sample limits the possibility of exploring the role of cannabis on HPA axis indices on recent-onset psychosis patients without childhood trauma or stressful life events. However, our study is an observational study conducted in a naturalistic setting, which reflects normal clinical practice.

The presence of CB1 cannabinoid receptors within the corticolimbic circuits regulating the HPA axis, in combination with the stress-reducing properties reported by cannabis users, suggests a role for the endocannabinoid system in stress regulation (Mizrahi 2016). Cannabis use and the interaction with friends and family can result in a state of well-being that could be mediated by the interactive anxiolytic effects of increased cannabinoid and oxytocin receptor activation, together with the rewarding effects of elevated dopamine (Volkow et al. 2017). The significant association between stress factors and cannabis use in recent-onset psychosis patients raises the question of whether patients could use cannabis as a 'self-treatment' strategy to cope with stress. Moreover, the endocannabinoid system has been suggested to be involved in the pathogenesis of psychosis (Mizrahi 2016; Tomas-Roig et al. 2018). In this regard, previous studies by Mizrahi's group have demonstrated a sensitised dopaminergic response to stress in UHR and patients with schizophrenia (Mizrahi et al. 2012), as well as a more prominent response in immigrants (Egerton et al. 2017). Interestingly, this same group has also demonstrated altered dopamine stress reactivity in UHR subjects who concurrently use cannabis, as compared with UHR subjects who are not cannabis users (Mizrahi et al. 2014).

Our study has some limitations that need to be acknowledged. The cross-sectional design prevents inference of causal relationships between environmental factors and HPA axis measures. CT was retrospectively assessed with a self-report instrument; thus, a recall bias may exist. Most recent-onset psychosis patients were receiving antipsychotic treatment, which can normalise the cortisol hypersecretion of psychotic patients (Mondelli et al. 2010). We aimed to solve this limitation by adjusting all analyses by treatment. The CAR was calculated considering salivary samples for only one day. We did not collect CAR samples over two consecutive days because we administered dexamethasone at 23:00 h, which could affect the results of the CAR on the second day. As the prevalence of cannabis use in our sample was relatively low (17% for healthy controls and 19% for recent-onset psychosis), we did not assess potential differences between light and heavy cannabis users. Further studies with larger sample sizes are needed to test whether there are differences in HPA axis indices taking into account the severity of cannabis use.

In conclusion, our study provides evidence for the effect of cannabis use in cortisol secretion patterns in both healthy controls and recent-onset psychosis patients, with a more flattened diurnal cortisol slope in people who smoke cannabis.

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Statement of interest

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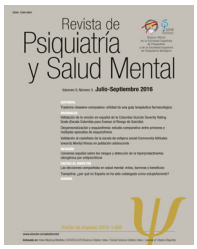

ORIGINAL

Diferencias en la presentación clínica de primeros episodios psicóticos entre población de origen marroquí y población autóctona

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PALABRAS CLAVE
Etnia;
Primeros episodios;
Antipsicóticos;
Migración;
Cannabis

Resumen

Introducción: Las diferencias étnicas han sido estudiadas tanto en esquizofrenia como en los primeros episodios psicóticos (PEP).??En estudios realizados en los Países Bajos se ha descrito que en los varones de origen marroquí es más frecuente un episodio psicótico y presentar mayor severidad en la sintomatología. Sin embargo, no existen estudios en España en PEP en población marroquí comparada con autóctona.

Objetivos: Explorar las diferencias clínicas entre la población inmigrante de origen marroquí y la población autóctona, en una muestra de PEP recogida en una unidad de hospitalización de agudos.

Material y métodos: Se evaluó la sintomatología y el funcionamiento al ingreso y al alta, así como el consumo de cannabis y la dosis de tratamiento antipsicótico y el perfil de efectos adversos en una muestra de 83 pacientes con PEP. Se compararon los pacientes de origen marroquí con los de la población autóctona mediante análisis univariantes y la independencia de las asociaciones fue evaluada mediante análisis de regresión logística.

Resultados: El 28,9% de la muestra era de origen marroquí. No se encontraron diferencias en cuanto a la sintomatología al ingreso y al alta. Comparados con los autóctonos, los de origen marroquí eran mayoritariamente hombres, tenían menos años de educación, presentaban peor funcionamiento, menor uso de cannabis, mejor perfil de efectos secundarios y una tendencia al mayor uso de LAI.

Tras el análisis multivariante, solo un peor funcionamiento (OR 0,93; IC 95%: 0,88-0,99; p = 0,02) y menos años de educación (OR 0,75; IC 95%: 0,56-1,01; p = 0,05) permanecieron significativamente asociados a ser de origen marroquí.

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Conclusiones: Existen diferencias sociodemográficas y clínicas entre personas con PEP de origen marroquí y población autóctona. Nuestros resultados señalan que debería contemplarse la trascendencia de la competencia cultural en la evaluación y tratamiento de los PEP.

KEYWORDS
Ethnicity;
First episode psychosis;
Antipsychotics;
Migration;
Cannabis

Comparison between a morocco and a native-born population, in a sample of first episode psychosis

Abstract
Introduction: Ethnic differences have been studied previously in schizophrenia and first episodes of psychosis (FEP). Previous studies in Netherlands have reported a higher incidence of psychosis in male Moroccan immigrants and more clinical severity. However there is lack of studies in Spain with morocco population and FEP.
Objectives: This study aims to determine the clinical differences in a sample of FEP between Morocco and Spanish population, recruited in a hospitalisation unit.
Material and methods: Descriptive and cross-sectional study of 83 inpatients (FEP). Functionality and symptomatology were evaluated at entry and discharge, the pattern of use of cannabis was evaluated at entry, the dose of antipsychotic and the pattern of side-effects at discharge. Comparisons between native-born population and Morocco population was made with univariate analysis and logistic regression was made for evaluating the independence of the associations.
Results: The 28.9% of the sample was Morocco group. No significance differences were found in clinical characteristics between groups at entry or at discharge. Compared with native-born, the Morocco group were more male, with less years of education, worse functionality, reported less use of cannabis, a better pattern of side effects and a tendency of more prescription of LAis.

After the multivariate analysis, just remains a lower functionality (OR 0.93; IC 95%: 0.88-0.99, *P*=0.02) and lower years of education (OR 0.75; IC 95%: 0.56-1.01, *P*=0.05), remain significative with being related with Morocco origin.
Conclusions: Our study provides evidence for ethnic differences in Morocco population with FEP. Patients with Morocco ethnicity have more probability of being males, less years of educations. Have lower functionality and a better profile of side effects.

Introducción

Alrededor del 3% de la población general sufre un episodio psicótico a lo largo de su vida[1]. El primer episodio de psicosis (PEP) suele ocurrir entre los 15 y los 30 años, con diferencias clínicas relevantes en función de la etnia[2-4]. La evolución clínica después de un PEP es que puede convertirse en una enfermedad crónica y hasta el 80% presentar una recaída durante los 5 años siguientes[5].

El estudio de las diferencias culturales o étnicas y el posible desarrollo de enfermedad psiquiátrica ha sido foco de interés desde hace años. En un primer estudio sobre migración y esquizofrenia se encontró un mayor riesgo para este trastorno psicótico entre inmigrantes[6]. En el Reino Unido varios autores han descrito un mayor riesgo de desarrollar una psicosis si el origen es negro caribeño. También en los Países Bajos se ha observado mayor riesgo en los inmigrantes de origen marroquí[7,8]. Durante la última década, el estudio de las diferencias étnicas en los casos de PEP ha mostrado características diferenciales tanto en Europa como en el resto del mundo[2,4,9,10]. Sin embargo, se han descrito algunas inconsistencias, lo que indica una disminución de estos porcentajes de riesgo al haber mejorado los instrumentos de detección y los entrenamientos para la evaluación en diferencias culturales[11-13].

Por otra parte, los factores sociales han sido evaluados como claves en el inicio de la psicosis y Morgan et al.[14] describieron la teoría del sociodesarrollo, considerando el origen de la psicosis como una acumulación de acontecimientos vitales estresantes[14-16].

Las indicaciones de protocolos y guías respecto a dosis y criterios de tratamiento farmacológico son las mismas en todas las poblaciones, sin tener en cuenta las diferencias étnicas. Sin embargo, los estudios previos indican que pertenecer a una etnia minoritaria aumenta la prescripción de inyectables de larga duración (LAI) y disminuye la prescripción de clozapina[17]. En cuanto al patrón de consumo de sustancias, se ha descrito en varias ocasiones que los pacientes nativos suelen tener tasas más elevadas de consumo[18,19].

No obstante, en muchos estudios la variable etnia se ha señalado como «minoritaria», mezclando en ella todo tipo de orígenes y considerando en cada estudio una proporción diferente de etnias. La escasez de estudios epidemiológicos actualizados y bien diseñados en los países de origen

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complica un análisis correcto del antes y el después de la migración, lo que probablemente ha llevado a resultados inconsistentes o contradictorios[9,20]. Parecería más lógico realizar los estudios en cada país concreto y con cada origen inmigrante por separado, para apoyar mejor en programas de detección y ayuda[11], de forma similar al Programa ENRICH de Birminghman[21].

En relación con la población marroquí, en Europa se han realizado estudios que determinan las diferencias culturales. Concretamente, en Holanda existe cierta evidencia sobre las diferencias clínicas en PEP en población marroquí: los hallazgos más frecuentes son el aumento del riesgo de desarrollar una psicosis, sobre todo en varones, y la mayor severidad en la sintomatología[22,23].

Una serie de estudios han analizado las diferencias culturales en España en salud mental[19,24-26], pero en nuestro país no hay estudios que determinen las diferencias entre población marroquí y española en cuanto a PEP.

Objetivo

Explorar las diferencias de presentación clínica y tratamiento farmacológico entre población marroquí y población autóctona en una muestra de personas tras un PEP que ingresaron en una Unidad de Agudos.

Método

Sujetos: 83 pacientes incluidos consecutivamente tras ser ingresados en la Unidad de Agudos del Hospital Universitario Pere Mata de Reus durante el año 2017.

Criterios de inclusión: edad entre 18 y 35 años, afectados de sintomatología psicótica con conocimiento suficiente del idioma para resolver los cuestionarios. Criterios de exclusión: presentar una enfermedad médica o neurológica que justificara la psicosis, o un trastorno por uso de sustancias (diferente de tabaco o cannabis).

El estudio fue aprobado por el Comité Ético de Investigación con medicamentos del Instituto de Investigación Sanitaria Pere Virgili. Todos los participantes firmaron el consentimiento informado, después de la descripción del estudio.

Instrumentos: Se realizó diagnóstico psiquiátrico mediante OPCRIT checklist v.4.0 (disponible en http://sgdp.iop.kcl.ac.uk/opcrit/).

La clasificación de la etnia se hizo preguntando al paciente por el país de origen, siguiendo el modelo de estudios previos, pero sin tener en cuenta segundas generaciones[27]. Conforme a estudios previos realizados en Holanda y en España, utilizamos la siguiente nomenclatura para diferenciar los 2 grupos: «población inmigrante de origen marroquí» y «población autóctona»[19,28].

Al ingreso y al alta, los síntomas psicóticos se evaluaron usando la *Positive and Negative Syndrome Scale* (PANSS) validada al español[29] y los síntomas depresivos mediante la Escala de Calgary para Depresión (CDS) en esquizofrenia en su versión en español[30]. El funcionamiento al ingreso se evaluó utilizando la prueba breve de evaluación del funcionamiento (FAST) —en su versión española[31]— y al alta mediante la *Global Assessment Functioning Scale* (GAF). La puntuación de la FAST es inversamente proporcional al nivel de funcionamiento.

La DUP, tiempo de psicosis sin tratar, se obtuvo de la historia clínica de los pacientes. La información sobre la medicación se obtuvo del informe de alta y se usaron las dosis al alta, como en un estudio previo[32]. La dosis de antipsicótico se convirtió a equivalentes de clorpromazina (en mg/día)[33] y las dosis de antipsicóticos inyectables fueron convertidas usando el método de la dosis mínima efectiva[34]. Evaluamos la presencia de efectos secundarios mediante la UKU[35].

Los acontecimientos vitales estresantes durante los últimos 6 meses se evaluaron mediante la *Holmes-Rahe Social Readjustment Scale* (HR)[36], que está validada para el español[37]. La HR es una escala que en un inicio se desarrolló para explorar la relación entre el ajuste social, el estrés y la susceptibilidad de desarrollar una enfermedad e incorpora 43 acontecimientos vitales. De esta escala se obtuvo la variable número de acontecimientos vitales.

El consumo de sustancias se evaluó mediante una analítica de orina en el momento del ingreso. Para evaluar la frecuencia del consumo de cannabis se preguntó al respecto en una detallada entrevista sobre los últimos 6 meses. Se definió uso de cannabis como «el consumo de ocasional hasta 5 porros semanales» y el uso regular de cannabis como «más de 5 porros semanales», ya que está descrita la importancia del consumo elevado en el inicio de la psicosis[38,39].

Análisis estadístico

Inicialmente se compararon las características de los 2 grupos mediante t de Student o U de Mann-Whitney para las variables continuas y mediante χ^2 con corrección de Yates o test de Fisher para las categóricas. Posteriormente se realizó un análisis de regresión logística binaria para testar la magnitud de las asociaciones encontradas en el análisis univariante. Se incluyó, por tanto, como variable dependiente el grupo (0 = origen autóctono, 1 = origen marroquí) y como variables independientes todas aquellas con un nivel de significación $p < 0,10$ en el análisis univariante. Se testaron las interacciones de las variables incluidas con el sexo y uso de cannabis, incluyendo aquellas que fueran significativas. Para evitar problemas de intercorrelación se realizaron análisis de correlación entre las variables continuas, considerándose alto un coeficiente de correlación >0,70. La significación se fijó en $p < 0,05$ y se calcularon las *odds ratio* (OR) e intervalos de confianza (IC) para determinar la contribución de cada variable.

Resultados

EL 28,9% de la muestra era inmigrante de origen marroquí. En la tabla 1 presentamos la comparación entre los pacientes que son inmigrantes de origen marroquí y los de población autóctona. En la población de origen marroquí había una menor proporción de sexo femenino ($\chi^2 = 3,54$; $p = 0,05$) y menos años de educación ($Z = -3,10$; $p = 0,002$). Encontramos un menor uso de cannabis (41,7% frente al 61% de la población autóctona), que no llega a ser significativo, pero sí aparece una tendencia ($\chi^2 = 2,58$; $p = 0,86$). No se describen diferencias respecto a la severidad de las variables

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Tabla 1 Comparación de las características sociodemográficas y clínicas de los pacientes de origen marroquí con población autóctona

	Inmigrantes de origen marroquí N= 24	Población autóctona N=59	t/χ^2/Z	*p*
Variables sociodemográficas				
Edad, años (m, DE)	26,83 (6,67)	24,47 (5,28)	−1,67	0,098
Sexo (%)				
Mujer	2 (8,3)	16 (27,1)	3,54	**0,050**
Hombre	22 (91,7)	43 (72,9)		
Años de educación (med, IQR)	10 (10-12)	12 (10-14)	−3,10	**0,002**
Variables clínicas al ingreso				
DUP (med, IQR)	105 (23-330)	60 (28-360)	0,80	0,421
FAST (m, DE)	48,63 (16,70)	40,39 (15,03)	8,23	**0,020**
N acontecimientos vitales (med, IQR)	0,5 (0-2)	1 (0-2)	−0,40	0,685
Puntuación total HR (m, DE)	43,63 (53,60)	49,61 (45,62)	0,49	0,650
PANSS-P (m, DE)	24,46 (7,57)	23,37 (7,09)	0,081	0,053
PANSS-N (m, DE)	14 (7,95)	14,15 (8,2)	0,052	0,938
PANSS-G (m, DE)	30,42 (12,70)	28,76 (10,53)	1,74	0,543
CDS (m, ES)	4,96 (6,39)	3,81 (5,88)	0,809	0,435
Consumo de tóxicos (N/%)				
Uso de tabaco				
Uso de cannabis				
Uso regular de cannabis (> 5 porros semanales)	20 (83,3)	43 (72,9)	1,01	0,430
Edad inicio cannabis (m, ES)	10 (41,7)	36 (61,0)	2,58	0,086
	9 (37,5)	32 (54,2)	1,91	0,167
	12,56 (6,64)	13,38 (5,13)	−0,485	0,630
Variables clínicas al alta				
PANSS-P (m, DE)	9,88 (5,43)	9,19 (3,59)	6,82	0,497
PANSS-N (m, DE)	11,00 (5,94)	14,26 (8,69)	−1,02	0,309
PANSS-GEN (m, DE)	19,92 (6,24)	19,61 (4,74)	0,243	0,809
CDS (m, DE)	3,33 (4,95)	2,29 (3,49)	1,08	0,297
GAF (m, DE)	59,96 (11,89)	66,08 (10,87)	−2,26	**0,026**
Días de ingreso (m, DE)	18,96 (8,28)	20,24 (9,85)	0,056	0,577
Variables de tratamiento				
Número AP (mediana,QR)	1 (1-2)	1 (1-2)	0,094	0,925*
Dosis total AP (mediana, IQR)	600 (400-900)	576 (384-675)	0,65	0,510*
Dosis AP oral (mediana, IQR)	600 (300-825)	400 (300-600)	0,88	0,370*
Dosis LAI (mediana, IQR)	384 (384-576)	392 (384-400)	−0,13	0,890*
Uso de LAI (%)	14 (58,3)	23 (39)	2,58	0,080
UKU (mediana, IQR)	0 (0-3)	2 (2-6)	−1,85	**0,022***

CDS: Escala Calgary de Depresión; DE: desviación estándar; Dosis AP oral: dosis total de antipsicóticos equivalente a clorpomazina; DUP: duración de la psicosis sin tratar; FAST: prueba breve de funcionamiento; GAF: Escala de funcionamiento global; HR: Holmes Rahe; IQR: rango intercuartil; LAI: *long acting injectable*; PANSS: Positive and Negative Syndrome Scale; UKU: escala de efectos secundarios de los antipsicóticos.
En negrita si el nivel de significación es <0,05.
* Variables no parámetricas.

clínicas. En cuanto a la funcionalidad, los de origen marroquí presentaban mayores puntuaciones en la FAST al ingreso (t = 8,23; p = 0,02) y menor GAF al alta (t = −2,26; p = 0,02). No encontramos diferencias en cuanto a la dosis total de tratamiento, sin embargo, había una tendencia en la prescripción de LAI en los marroquíes (χ^2 = 2,58; p = 0,80) y menores puntuaciones en la UKU (Z = −1,85; p = 0,02).

En la tabla 2 se muestran los resultados tras el análisis multivariante. Como variables independientes se incluyeron el sexo, consumo de cannabis, tratamiento con LAI, años de educación, FAST, UKU y GAF. No encontramos correlaciones >0,70 entre las variables continuas, por lo que se incluyeron todas en el análisis. Se testaron interacciones entre las distintas variables, sin encontrar ninguna interacción estadísticamente significativa. Por último, los resultados que se mantuvieron significativamente asociados a ser de origen marroquí fueron: menos años de educación (OR 0,75; IC 95%: 0,56-1,01; p = 0,05), menor GAF (OR 0,93; IC 95%: 0,88-0,99; p = 0,02) y una tendencia respecto al menor consumo de cannabis (OR 0,93; IC 95: 0,88-0,99; p = 0,08).

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Tabla 2 Modelo de regresión logística

	B	Wald	OR (IC)	p
Años de educación	−0,278	3,61	0,75 (0,56-1,01)	0,05
Sexo (mujer)	−1,36	1,87	0,25 (0,03-1,80)	0,17
Consumo de cannabis	−1,10	3,02	0,93 (0,88-0,99)	0,08
FAST	0,027	1,48	1,80 (0,51-6,30)	0,22
GAF	−0,068	5,19	0,93 (0,88-0,99)	0,02
UKU	−0,278	2,33	0,80 (0,60-1,06)	0,12
Tratamiento con LAI	0,590	0,86	1,80 (0,51-6,30)	0,35

Variable dependiente, ser inmigrante de origen marroquí.
FAST: prueba breve de funcionamiento; GAF: Escala de funcionamiento global; IC: intervalo de confianza; LAI: *long acting injectable*; OR: *odds ratio*; UKU: escala de efectos secundarios de los antipsicóticos.

Discusión

Los principales hallazgos de nuestro estudio son una mayor prevalencia de hombres y menos años de educación en el grupo de inmigrantes de origen marroquí comparado con la población autóctona. No hay diferencias en cuanto a la intensidad de la sintomatología, pero sí un funcionamiento peor en el grupo de origen marroquí y una tendencia a un menor uso de cannabis en esta población. A su vez, encontramos una tendencia a un mayor uso de LAI, pero con un perfil menor de efectos secundarios en población marroquí. Hasta ahora, este es el primer estudio que se centra en las diferencias étnicas en pacientes con PEP en nuestro país.

La distribución de etnias en nuestra región es parecida a la representada por estudios en Países Bajos, donde la principal etnia inmigrante es la marroquí[23,40]. Las diferencias de género que se describen en etnia marroquí (8,3% mujeres; $p < 0,05$) también se han descrito en estudios previos, que señalan que el riesgo de padecer un episodio psicótico es mayor en varones[41].

Hemos encontrado menos años de educación en la población marroquí, cifra que debe tomarse con cautela, ya que los sistemas de estudios cambian en cada país, como describe un reciente trabajo realizado en Noruega sobre población inmigrante y probabilidad de ingreso en el hospital general[42].

Respecto de las diferencias clínicas, no encontramos diferencias ni en la DUP ni en la sintomatología psicótica ni depresiva entre los 2 grupos. En contraste, había sido descrita anteriormente una DUP más larga en pacientes inmigrantes de diversos orígenes[20,22], si bien se señaló la necesidad de abordar más estudios para replicar estos resultados.

La prevalencia de uso de cannabis de la muestra es elevada (53%), pero similar a la encontrada en estudios con muestras de PEP[43,44]. Sin embargo, en coincidencia con estudios previos, encontramos una menor prevalencia de consumo de cannabis en población inmigrante. Este concepto está claramente estigmatizado por nuestra sociedad, que considera erróneamente a la población marroquí como principal consumidora[19,28].

En el número de acontecimientos vitales, no encontramos diferencias significativas, lo que discrepa de estudios previos[3]. Una posible explicación a nuestro hallazgo sería que la HR evalúa únicamente los acontecimientos vitales de los últimos 6 meses. El proceso migratorio y la pertenencia a una cultura diferente dificultan aún más la comparación entre grupos, lo que ejercería un estrés que favorecería el inicio de la psicosis o de otra psicopatología[13].

En cuanto al funcionamiento del paciente, encontramos un peor funcionamiento en la población marroquí, tanto previo al ingreso como al alta. El género femenino ya ha sido descrito como un predictor de buen funcionamiento tanto premórbido como en la evolución del trastorno[45], aunque nuestra muestra marroquí carecía de mujeres. Sin embargo, en el modelo de regresión logística controlando por género, se mantiene el GAF más bajo como una variable significativa en población de origen marroquí.

No se encuentran diferencias en las dosis totales de antipsicóticos, pero sí una tendencia a una mayor prescripción de LAI en población marroquí. En relación con las dosis totales de antipsicóticos, en nuestro país en un estudio previo[25] se describía una exposición menor en población inmigrante, especialmente en las mujeres marroquíes. Nuestros resultados coinciden con los últimos estudios que han comparado dosis de antipsicóticos en poblaciones inmigrantes[46,47]. En el estudio de Connoly y Taylor[46], realizado en el Reino Unido, se diferencia entre pacientes de raza negra y de raza blanca. Mientras que en el de Hassan et al.[47], diferencian entre europeos de raza blanca y no europeos. La variación de la agrupación de orígenes es extensa, si bien se precisa una mayor investigación en dosis farmacológicas[13]. En cuanto al uso de LAI, se muestra una tendencia a una mayor utilización en etnia marroquí, coincidiendo con Das-Munshi et al.[17] en un estudio realizado en el Reino Unido en el que describen una mayor prescripción de inyectables en pacientes de etnia minoritaria. En ocasiones, los LAI pueden considerarse como un tratamiento impuesto, en el que de forma periódica se

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administra el tratamiento, sin tener tan en cuenta la voluntad del paciente. Ya se ha descrito en otros estudios previos que el pertenecer a una etnia minoritaria aumenta el riesgo de tener un tratamiento comunitario obligatorio[9,48].

Por otra parte, el perfil de efectos secundarios medido con la UKU es peor en población española. No se han descrito evidencias sobre efectos secundarios en población marroquí, pero en un reciente trabajo sobre efectos adversos se describe un perfil de efectos secundarios más elevado en mujeres, y en nuestra muestra apenas disponemos de mujeres[49].

Limitaciones y puntos fuertes del estudio

Como principal limitación encontramos la dificultad de que se trate de un diseño transversal que no permite establecer causalidad. Además, el relativo pequeño tamaño muestral, con pocas mujeres, no permite hacer subgrupos, por lo que son precisos estudios con muestras mayores para confirmar estas diferencias. Por otra parte, la muestra está recogida en una unidad de hospitalización, por tanto, sin contar con los pacientes que nunca han ingresado y entre los que, probablemente, se visitan más mujeres. Tampoco se pudo recoger el nivel socioeconómico de los grupos ni valorar esta diferencia.

Respecto a la PANSS, no hemos podido realizar un subanálisis de los ítems, ya que el tamaño pequeño de la muestra limitaba este aspecto, por lo que no hemos podido diferenciar si algún síntoma pudiera ser más prevalente en algún grupo[50]. Otra limitación de nuestro estudio es la falta de mediadores culturales en las entrevistas con población marroquí, para disminuir la barrera idiomática y mejorar la recogida clínica.

A pesar del pequeño tamaño muestral, el estudio se realizó de forma sistemática y los pacientes están perfectamente fenotipados con los instrumentos adecuados. Además, a diferencia de otros trabajos anteriores con un enfoque multiétnico, hemos empleado únicamente la población inmigrante de origen marroquí para compararla con la población autóctona.

Conclusiones

Casi un 30% de nuestra muestra era de origen marroquí, con diferencias sociodemográficas y de funcionamiento entre la población marroquí y población española.

En la actualidad en España, donde hay una evolución hacia una sociedad cada vez más multicultural, debería contemplarse la trascendencia de la competencia cultural para realizar intervenciones que nos ayuden a paliar las dificultades que encontramos ante las diferencias culturales o étnicas. Y teniendo en cuenta nuestros resultados, deberían diseñarse medidas sociales de ayuda a la inmigración en los programas de intervención precoz en psicosis tempranas, como ya se hace en el Reino Unido.

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Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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Highlights

1. Cannabis use is more frequent in males than in females
2. Females are more likely to smoke cannabis to “feel relaxed” compared with males
3. Males present more severe positive psychotic symptoms and require higher doses of antipsychotics during hospitalization
4. There was an interaction effect of cannabis and sex on functioning score at discharge

ABSTRACT:

There is a scarcity of studies investigating the effect of sex on the clinical and treatment characteristics of first-admitted patients with first-episode psychosis (FEP). The reasons for using cannabis and the effect of cannabis on clinical features have not received enough attention either. We aim therefore, to investigate sex differences in the reasons for cannabis use and to determine the effects of sex, cannabis use and their interaction on clinical variables at admission and at discharge from the inpatient unit.

204 first-admitted FEPs in two inpatient units in Spain were included. The reasons for using cannabis were determined using the Dixon questionnaire. Clinical variables were compared between sexes and between cannabis users and non-users.

Cannabis use was more frequent in males, but females were more likely to smoke cannabis to "feel relaxed". There was a main effect of sex on positive psychotic symptoms and antipsychotics dose and an interaction effect of cannabis and sex on global functioning at discharge . Our findings show sex differences in the reasons for cannabis use and in some clinical and treatment characteristics among FEP patients. More studies focusing on gender perspectives are needed to develop more individualized treatments.

KEYWORDS: CANNABIS; FIRST EPISODE PSYCHOSIS; GENDER DIFFERENCES; SEX DIFFERENCES;

1. INTRODUCTION

The role of sex in the field of psychosis research has not received enough attention and as a consequence, there is a scarcity of studies on this subject compared with other topics in the field of psychosis(Køster et al., 2008). The few available studies point to sex differences in clinical features prior to the onset of the illness, at the onset of first-episode psychosis (FEP) and during the illness course (Cotton et al., 2009; Filatova et al., 2017; Häfner et al., 2013; Ochoa et al., 2012; Usall et al., 2003). An earlier age of psychosis onset in males is one of the most replicated findings, with male usually developing illness at the ages of between 18 and 25 years, compared with between 25 and 35 years of age among females (Ochoa et al., 2012). Positive symptoms, negative symptoms and violent behaviour have been described as prevalent at clinical onset in males (Drake et al., 2016; Thorup et al., 2014; Tseliou et al., 2017), while depressive symptoms are more frequent in females (Chang et al., 2014; Cotton et al., 2009; Morgan et al., 2008). Furthermore, better pre-morbid and long-term social functioning have been more frequently reported in females (Chaves and Seeman, 2006; Cotton et al., 2009; Ochoa et al., 2012).

There is less evidence regarding sex differences in treatment-related characteristics. It has been suggested that females require lower antipsychotic doses, have higher levels of compliance and have better treatment responses than males, although such reports are inconsistent (Seeman, 2004; Smith, 2010; Usall et al., 2007). As indicated in a recent review by (Crawford and DeLisi, 2016), sex differences in the effective antipsychotic dose to response during the initial acute phase have been scarcely investigated and have yielded conflicting results. In addition, few studies have investigated the influence of sex on clinical and hospitalization characteristics when patients are first treated for a FEP in an inpatient unit (Arranz et al., 2015; Shlomi Polachek et al., 2017)

With regard to cannabis, males with FEP use more cannabis (Barrigón et al., 2015; Koskinen et al., 2010; Mazzoncini et al., 2010) and start smoking cannabis earlier than females

(Haberstick et al., 2014; Kelley et al., 2016). Despite the elevated use of cannabis in FEP patients, their reasons for smoking cannabis have received little attention (Archie et al., 2013; Kolliakou et al., 2015; Mané et al., 2015; Pencer and Addington, 2008) and, to our knowledge, there is a lack of studies assessing sex differences in reasons for cannabis use. Moreover, cannabis use is associated with an earlier age of psychosis onset (Large et al. 2011, Di Forti et al. 2014), treatment resistance (Patel et al. 2016) and poorer functioning (González-Pinto et al., 2008; Harrison et al., 2008). However, there is less consensus regarding the influence of cannabis on the severity of positive and negative symptoms at illness onset (Linszen et al., 1994; van Dijk et al., 2012; Zisook et al., 1992), the effective antipsychotics dose to response (Babatope et al., 2016; Makkos et al., 2011) or the duration of hospitalization (Patel et al., 2016) needed to achieve symptom remission.

As described above, both sex and cannabis may influence the clinical onset, treatment response and illness course of FEP, but there is very limited evidence regarding the effects of the relationship between cannabis and sex and these outcomes (Setién-Suero et al., 2017). As indicated in a recent review by Crocker and Tibbo, (2018), few studies have specifically aimed to investigate the interaction effect of sex and cannabis on the clinical characteristics of psychosis. It has been suggested that sex differences regarding age at onset, psychopathology and prognosis are less evident or even disappear when cannabis use is controlled (Arranz et al., 2015; Di Forti et al., 2014; Helle et al., 2016; Lange et al., 2014; Patel et al., 2016). Moreover, there is currently no study on the impact of these variables on clinical symptoms, antipsychotic response and hospitalization-related variables in FEP patients at their first admission to an inpatient unit.

In view of the limited and inconclusive previous findings, we aim to investigate sex differences in cannabis use and reasons for cannabis use in patients experiencing FEP. In addition, we aim to determine the impact of gender, cannabis use and its interaction on

clinical variables at admission and at discharge in first-admitted FEP patients in two inpatient units.

2. METHODS

2.1 Participants

The patients included in the study met the following inclusion criteria: age between 18 and 35 years and admitted to an inpatient unit for the first time for FEP with psychotic symptoms of less than 12 months' duration. The exclusion criteria were as follows: Intellectual disability (including both an IQ below 70 and impaired functioning), history of head trauma with loss of consciousness, organic disease implicated in the aetiology of psychotic symptoms, treatment with antipsychotics for more than 4 weeks and inability to speak Spanish well enough to complete the assessment. Ethical approval was obtained by the Ethics Committee of each participating hospital.

The sample consisted of 204 patients recruited from two different inpatient psychiatric units in Catalonia, Spain:

- One hundred twenty-five FEP patients were consecutively admitted to the inpatient unit of University Hospital del Mar (Barcelona, Spain). This sample partially overlaps with the sample of a previous study that explored different hypotheses(Mané et al., 2015).
- Seventy-nine FEP patients were consecutively admitted to the inpatient unit of the University Hospital Institut Pere Mata (Reus, Spain).

2.2. Measures

2.2.1 Demographic and clinical assessment

All admitted patients were systematically clinically assessed at entry and at discharge by specialized psychiatrists as part of the First Episode Programmes at each site, which followed the same clinical and research protocol. Demographic and clinical information was collected

via direct interviews. Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1990). Depressive symptoms were assessed using the Calgary Depression Scale for Schizophrenia (CDS) (Addington et al., 1990). Global functioning was assessed using the Global Assessment Functioning Scale (GAF). The duration of untreated psychosis (DUP) was defined as the time from the first continuous psychotic symptom to the time the patient was admitted to the hospital.

2.2.2 Gender identification

We used biological sex criteria to divide the patient groups in male/female. (http://genderedinnovations.stanford.edu/methods/sex.html)

2.2.3 Treatment

The antipsychotics dose at discharge was obtained from medical records. The doses of antipsychotic (AP) medications were converted into chlorpromazine equivalents (in mg/day) for comparison purposes (Gardner et al., 2010). As in previous studies (Babatope et al., 2016), we assumed that the dose at discharge was the dose required for clinical response according to the treating psychiatrist.

2.2.4 Cannabis exposure

The cannabis and tobacco use was assessed by a detailed interview, during which we specifically inquired about the previous 6-month frequency of cannabis use and the age at onset of cannabis use. The frequency of cannabis use was scored using Likert-type responses: daily, several times a week, several times a month, less than several times a month, and not at all (Bugra et al., 2013). For the purpose of this study, cannabis users (CAN+) were those who smoked cannabis *"several times a* week" or "daily" during the target period. The group of (CAN-) included were those who smoked "several times a month", "less than several times a month" and "not at all". All patients were abstinent during the course of the hospitalization. The Age at onset of cannabis use was defined *as "the first cannabis exposure"(Arseneault* et

al*., 2002)*. The CAN+ patients were asked to complete the Dixon self-reported questionnaire to identify the reasons for cannabis use (Dixon et al., 1991). This questionnaire consists of 15 items with dichotomous (yes/no) responses to queries regarding various reasons for use; however, we rejected the item "side-effects of medication" as most of the patients were naïve to medication.

2.3 Statistical analysis

First, differences in cannabis-related variables between males and females were compared using the chi-square test or Fisher's exact test for categorical variables and Student's t test or the Mann-Whitney U test for quantitative data.

Second, clinical variables at admission and at discharge were compared between sexes and between cannabis users and non-users. The interaction effect of sex and cannabis use on clinical variables at admission and discharge was analysed in two sets of two-way multivariate analyses of covariance (MANCOVAs). Sex, cannabis use and their interaction term (sex x cannabis) were included as factors, and the model was controlled for age at first episode, centre of recruitment, and tobacco use. In the first analysis, clinical variables at admission with a p value < 0.10 in the univariate analysis were considered independent variables. In the second analysis, the independent variables were the clinical variables at discharge that had a p value< 0.10 in the univariate analysis. Normality was tested, and skewed variables were log transformed for the multivariate analysis. All analyses were conducted using IBM SPSS Statistics for Windows (version 20).

3. RESULTS

3.1. Pattern of substance use and reasons for cannabis use.

The cannabis use-related features of the total sample and stratified by sex are shown in table 1. Nearly 65% of the sample comprised males, and the mean age was 24 years, with no difference between sexes. Approximately 55% of the participants were cannabis users (CAN+),

with a median age of 16 years at first cannabis use. Males smoked cannabis more frequently than females *(X^2= 8,75; p= 0.03)*, but there were no differences in the age at first use. Among the CAN+ group, 96 patients (85.7%) completed the Dixon questionnaire, and *"feeling relaxed"* followed by *"sleeping better"* were the most frequent reasons for use reported by both sexes; however, "*feeling relaxed*" was significantly more frequently reported by females than by males (*X^2= 7.724; p= 0.005).*

3.2. Clinical characteristics at admission and discharge.

Table 2 shows the univariate clinical differences between groups stratified by sex and by cannabis use. Males presented more positive symptoms at hospital admission and at discharge and required a higher number and dose of APs than females. Compared with the CAN- group, the CAN+ group had FEP at an earlier age, had more depressive symptoms at entry, presented a higher level of dysfunction at discharge and tend to be hospitalized for more days.

3.3 Results of the multivariate analysis

3.3.1 Effect of cannabis and gender on clinical characteristics at admission.

The first MANCOVA analysis did not reveal a significant main effect of sex (F = 1.81, p =0.13, Wilks' Λ = .95) or cannabis use (F = 0.77, p = 0.54, Wilks' Λ = .98) or an interaction effect between these two factors (F = 0.74, p = 0.52, Wilks' Λ = .74) on the combined clinical variables, with a p value < 0.10 at admission (PANSS positive, CDS and age at first episode)**.**

3.3.2 Effect of cannabis and gender on clinical characteristics at discharge.

The second MANCOVA analysis showed a significant main effect of sex (F =6.06, p =0.001, Wilks' Λ = .910) and an interaction effect between cannabis use and sex (F = 2.66, p = 0.05, Wilks' Λ = .959), but no main effect of cannabis use (F = 0.36, p = 0.78, Wilks' Λ = .994), on the combined clinical variables with p value < 0.10 at discharge (hospitalization length, PANSS positive, CPZE and GAF). The MANCOVA between-groups analysis of variables at discharge showed an effect of sex on PANSS positive (*F=13.13;* p <0.001*, partial eta squared =.06)* and APs dose (*F=9.47;* p = *0.02, partial eta squared =.05) (table 3)*. In addition, there was a

significant interaction effect (cannabis x sex) on GAF score (*F=7.81;* p = *0.006, partial eta squared =.04)* (*see figure 1*): CAN^+ males had lower GAF scores than CAN- males, whereas CAN+ females had a higher GAF than CAN- females.

4. DISCUSSION

Our main findings are as follows: First, cannabis use was more frequent in males than in females, but females were more likely to smoke cannabis to "feel relaxed" compared with males. Second, males presented more severe positive psychotic symptoms and required higher doses of antipsychotics to achieve remission. Contrary to what we expected, cannabis had no effect on the clinical variables at admission or at discharge. Finally, we found an interaction effect of cannabis and sex on the GAF score at discharge, indicating that males who used cannabis presented a lower GAF than males who did not, while in females, the opposite result was observed.

There is a scarcity of studies investigating the effect of cannabis and sex on clinical and treatment characteristics in first-admitted patients with psychosis, and none of those studies investigated interaction effects. Given the lack of comparable studies, the results discussed below must be considered preliminary in nature and require replication.

As previously reported (Arranz et al., 2015; Barbeito et al., 2013; Crosas et al., 2018; Helle et al., 2016; Patel et al., 2016), we found that males use more cannabis than females; however, we did not find differences in the age at onset of cannabis use. This is consistent with recent findings highlighting that females are increasingly smoking cannabis at younger ages, narrowing the gap between the sexes(Carliner et al., 2017; Sallaup et al., 2016). With regard to reasons for using cannabis, both sexes reported "feeling relaxed" as the most common reason, but females reported it more frequently than male did. Different authors have investigated the reasons for cannabis use in schizophrenia patients (Addington and Duchak, 1997; Dixon et al., 1991; Goswami et al., 2004; Green et al., 2004; Kolliakou et al., 2012; Pettersen et al., 2013; Saddichha et al., 2010; Schnell et al., 2017) and FEP patients (Kolliakou et al., 2015, Archie et

al. 2013 Pencer and Addington, 2008)), but this is the first study to explore sex differences in the reasons for using cannabis in FEP. Most of the previous studies have indicated that patients may use cannabis to relieve symptoms that in part could be associated with the disease, including negative states, relaxation, and socialization(Gómez Pérez et al., n.d.) . Among FEP patients, enhancement properties and help coping with unpleasant affect, such as nervousness and tension, are the most often reported reasons for cannabis use (Kolliakou et al., 2015; Pencer and Addington, 2008). Thus, our findings are largely in agreement with previous research. We found that all the CAN+ females reported using cannabis *"to feel relaxed". G*iven the higher prevalence of anxiety in females with FEP described by some authors (Szymanski et al., 1995), we could hypothesize that females with psychosis may experience anxiety more frequently and may be more prone to use cannabis to relieve it. Unfortunately, we did not perform any specific measures of anxiety in our study.

We did not find a significant main effect of sex, cannabis use or a sex x cannabis interaction effect on the severity of clinical symptoms at admission or on hospitalization length. There is no agreement regarding the association of cannabis use with hospitalization length (Manrique-Garcia et al., 2014; Patel et al., 2016; Schoeler et al., 2016), and there is a lack of data regarding sex differences in first-admitted psychosis patients. In the multivariate analysis, only sex influenced the severity of positive symptoms at discharge which converged with previous FEP studies that described more severe psychotic symptoms in males than in females. In contrast to other studies (Chang et al., 2014; Cotton et al., 2009; Morgan et al., 2008), we did not find more depressive symptoms in females or more negative symptoms in men. Previous studies, however, were conducted in subjects after the acute phase (Drake et al., 2016; Thorup et al., 2014) or during established schizophrenia (Riecher-Rössler and Häfner, 2000), which makes their results difficult to compare with those of the present study.

We found that males who smoked cannabis had a lower GAF score than non-smokers, while the opposite was found for females. On the one hand, research studies that examined

sex differences in global functioning among patients with FEP have found better performance in females (Cotton et al., 2009; Jeyagurunathan et al., 2017; Ochoa et al., 2012). On the other hand, mixed findings have been reported regarding functioning and the use of cannabis, with some studies reporting lower GAF scores (Seddon et al., 2016) and others reporting increased GAF scores in FEP CAN+ (DeRosse et al., 2010). There is no evidence, however, from previous studies of first-hospitalized FEP patients that specifically studied the interaction effects of sex and cannabis on functionality. Alternatively, a more severe negative impact of cannabis use on the course of schizophrenia in female patients has been suggested (Gearon and Bellack, 2000), as lower reductions in cannabis use are described in females after the acute phase (Lange et al. 2104). This discrepancy with our results could be due to the short-term nature of our study. Follow-up research studies designed to study the role of sex and cannabis in short- and long-term functional outcomes may help to clarify this issue.

In agreement with some previous research, we found that males were more likely to be treated with higher doses of AP. However, whether there are sex differences in the effective AP dose to achieve psychotic remission remains to be determined (Crawford and DeLisi, 2016; Køster et al., 2008; Thorup et al., 2014) It has been highlighted that sex differences in the dosing of antipsychotic medications have not received adequate attention in the past (Crawford and DeLisi, 2016). Current treatment guidelines do not consider sex in the evaluation of antipsychotic treatment, and antipsychotic clinical trials do not usually consider the sex perspective (Crawford and DeLisi, 2016; Lange et al., 2017; Shlomi Polachek et al., 2017).

Finally, neither cannabis nor the interaction between sex and cannabis had an effect on the dose of APs. The few studies that have focused on the effect of cannabis on the dose of antipsychotics have reported conflicting results, and none of them have considered the effect of sex .Two studies have found lower doses of antipsychotics in cannabis users (Babatope et

al., 2016; Makkos et al., 2011), while a more recent study showed that cannabis users were treated with a greater number of antipsychotics(Patel et al., 2016).

4.1 Limitations and strengths

This study has certain methodological limitations that need to be considered. To increase the sample size, two centres in different regions in Catalonia participated in the study. Although both centres followed the same research protocol, we tried to minimize this potential bias by controlling for the centre in all the analyses.

Second, although the cannabis assessment was rather exhaustive, neither the type of cannabis that patients had used nor an objective quantitative measurement was performed. Third, the cross-sectional assessment did not allow us to infer causality, and our results cannot be generalized to FEP patients who did not require hospitalization. Finally, the small effect size of the associations found must be considered when interpreting the results.

Despite these limitations, this is the first study assessing the effects of both cannabis and sex on clinical and treatment characteristics in a relatively large sample of FEP patients admitted to an inpatient unit for their first treatment. The effect of sex and its interaction with cannabis have been understudied, and the present study's focus on psychotic patients at the very early stage of the illness can minimize the confounding effect of chronicity and its associated factors.

4.2 Conclusions

In conclusion, our findings indicate sex differences in the reasons for cannabis use and in some clinical and treatment characteristics of FEP patients. The study also suggests that FEP males who use cannabis have lower functionality. This study highlights that a sex perspective on the study of cannabis use, clinical characteristics and particularly the doses and type of antipsychotics used are urgently needed to develop more individualized, tailored treatments for FEP patients.

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The authors report no financial or other relationship relevant to the subject of this article

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Table 1.Comparison of reasons for cannabis use between sexes

	TOTAL N= 204	MALE N= 131	FEMALE N = 73	Statistic (t,X^2,Z)	*p*
Age at onset of cannabis use(median, IQR)	16(15-17.5)	16 (14-17)	16 (15-18)	-1.019	.193*
Cannabis use at least weekly (yes)	54.9%	62.6%	41.4%	8.75	**.003**
Tobacco use (yes)	55.9%	57.3%	53.4%	.275	.598
Reasons for use					
To relax	80.0%	73.1%	100%	7.724	**.005**
To get high	35.6%	37.3%	30.4%	.354	.552
To increase pleasurable feelings	35.6%	35.8%	34.8%	.008	.928
To sleep better	63.3%	62.7%	65.2%	.047	.828
To reduce boredom	44.4%	43.3%	47.8%	.143	.705
To increase the intensity of emotions and feelings	20.0%	20.9%	17.4%	.131	.717
To be more creative	35.6%	38.8%	26.1%	1.209	.272
To satisfy curiosity	26.7%	25.4%	30.4%	.224	.636
To reduce feelings of sadness and depression	36.7%	38.8%	30.4%	.517	.472
To go along with the group	23.3%	22.4%	26.1%	.131	.717
To organize my thoughts	22.2%	26.9%	8.7%	3.27	.071
To work better	17.8%	19.4%	13.0%	.474	.491
To increase energy	14.4%	16.4%	8.7%	.826	.363
To concentrate better on some things	20.0%	22.4%	13.0%	.934	.334
To talk better to others	16.7%	16.4%	17.4%	.012	.914
To decrease my hallucinations	6.7%	7.5%	4.3%	.267	.605

Abbreviations: IQR = interquartile range;results in bold signify P< 0.05; * = non-parametric test.

Table 2. Comparison of clinical characteristics stratified by sex and cannabis use.

	TOTAL SAMPLE N= 204	**MALE N= 131**	**FEMALE N = 73**	**(t/z)**	***p***	***CAN – N=92***	***CAN+ N=112***	**(t/z)**	**p**
Age of FEP onset (m, SD)	23.5(4.8)	23.1(4.57)	24.3(5.2)	-1.82	.07	24.46(5.32)	22.74(4.23)	2.52	**.01**
Variables at admission									
DUP (*median, IQR)*	30(15-180)	47 (15-182)	30(12.5-120)	[a]-1.00	.31	45(13-183)	30(15-120)	[a]0.94	.34
PANSS (m, sd)									
Positive	25.97(6.3)	26.81 (6.22)	24.50(6.20)	2.52	**.01**	25.19(6.16)	26.62(6.36)	-1.60	.11
Negative	15.61(7.42)	15.23 (6.64)	16.29(8.63)	-0.90	.36	16.08(7.87)	15.23(7.05)	0.80	.42
General	39.15(13.56)	38.63 (13.24)	40.07(14.17)	-0.71	.47	40.27(13.26)	38.23(13.80)	1.05	.29
Total	80.73(21.34)	80.66 (20.11)	80.86(23.5)	-0.06	.95	81.53(21.29)	80.08(21.46)	0.47	.63
CDS (*median, IQR)*	2(0-6)	2(0-6)	3(0-7.75)	[a] -1.09	.27	2(0-5)	3(0-8)	[a] -2.24	**.02**
Variables at discharge									
PANSS: (m, sd)									
Positive	11.11 (4.95)	11.83 (5.19)	9.84 (4.22)	2.96	**.003**	10.64(4.95)	11.50(4,93)	-1.23	.21
Negative	13.44 (5.94)	13.57(5.94)	13.19 (5.97)	0.43	.66	13.26(6.17)	13.58(5.76)	-0.38	.70
General	25.75(8,47)	25.77(8,65)	25.73 (8.18)	0,03	.97	25.89(8.68)	25.64(8.33)	-0.10	.83
Total	50.24(16.60)	51,1(17.17)	48.75(15.55)	0,95	.34	49.79(16.88)	50.62(16.43)	-0.35	.72
GAF (m, sd)	60.60(13.33)	59.98(13.35)	61.71(13.31)	-.87	.38	62.78(13.42)	58.8(13.04)	2.12	.03
Hospitalization length *(days) (median, IQR*)	20(13-27)	19(10-26)	20.33(12-25)	[a] -0.52	.60	18(12,5-25)	22(14-28)	[a] -1.69	.09
Treatment variables:									
AP dose CPZE (mg/day) *(median, IQR)*	565(342-700)	613 (384-800)	473(300-600)	[a] -3.14	.**002**	500(384-684)	583(384-750)	[a] -0.87	.38
Number AP *(median, IQR)*	1.5(1-1)	1.20(1-1)	1.06(1-1)	[a] -2.26	**.024**	1 (1-1)	1(1-1)	[a] -0.74	.45

Abbreviations: DUP = Duration of untreated psychosis; CAN^- : Cannabis non- user; CAN^+ : Cannabis user ;CDS= Calgary Depression Scale; PANSS=Positive and Negative Syndrome Scale; GAF= Global Assessment of Functioning AP=Antipsychotic; CPZE=Chlorpromazine equivalent dose; IQR = Interquartile range. Results in bold signify P< 0.05; [a] Z= Mann-Whitney U test.

Table 3. MANCOVAs of the between- groups' scores on clinical variables at discharge.

Discharge characteristics	sex effect				Sex x cannabis effect			
	df	Mean square	F	EF	df	Mean square	F	EF
Hospitalization length (days)	1	0.28	0.40		1	0.12	1.81	
PANSS positive	1	0.29	13.13***	.06	1	0.01	0.86	
GAF	1	295.59	1.84		1	1255.4	7.81**	.04
Total CPZE AP	1	0.58	9.67**	.05	1	0.06	1.01	

Abbreviations: PANSS=Positive and Negative Syndrome Scale; GAF= Global Assessment of Functioning AP=Antipsychotic; CPZE=Chlorpromazine equivalent dose; df = Degrees of freedom; EF =effect size: partial eta squared.

**p< 0.05; ** p<.0.01; *** p<0.001*

Adjusted for: tobacco use, centre of recruitment and age at first episode

fig1

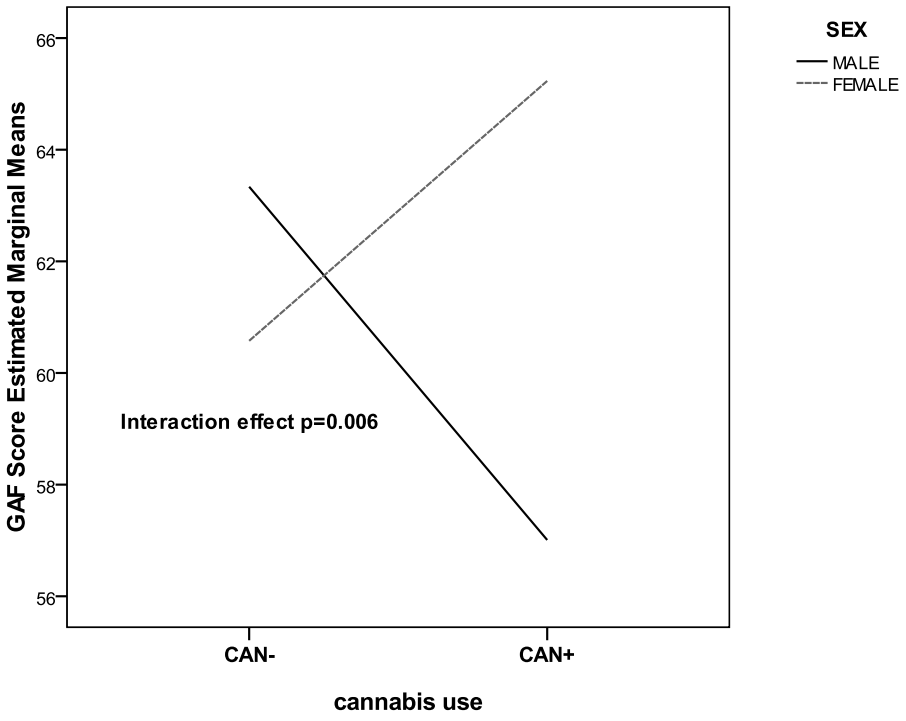

Figure 1: gender x cannabis effect on Global Assessment Functioning at discharge

[a] adjusted for: age at fisrt episode smoking tobacco (yes/no) and center of recruitment

CAN+: cannabis users; CAN- : cannabis non-users