UNIVERSITAT DE BARCELONA

Intervención precoz de precisión en primeros episodios psicóticos: uso de modelos estadísticos avanzados para predecir el diagnóstico, la evolución funcional y el riesgo suicida tras un primer episodio psicótico

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CERTIFICAN que han guiado y supervisado esta tesis doctoral titulada "INTERVENCIÓN PRECOZ DE PRECISIÓN EN PRIMEROS EPISODIOS PSICÓTICOS: Uso de modelos estadísticos avanzados para predecir el diagnóstico, la evolución funcional y el riesgo suicida tras un primer episodio psicótico", que se presenta para la obtención del título de Doctora por la candidata **Estela Salagre Muñoz**. Los supervisores por tanto confirman que esta tesis cumple con los requisitos establecidos por la Universidad de Barcelona y autorizan el depósito de la misma.

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LISTADO DE ABREVIATURAS

AIC: *Akaike Information Criteria* (Criterio de Información de Akaike)

aBIC: *adjusted Bayesian Information Criteria* (BIC ajustado al tamaño de la muestra)

BIC: *Bayesian Information Criteria* (Criterio de Información Bayesiano)

CI: Cociente Intelectual

COWAT: *Controlled Oral Word Association Test* (Test de Asociación Controlada de Palabras)

CPT-II: *Continuous Performance Test-II* (Test de Ejecución Continua de Conners-II)

CVLT: *California Verbal Learning Test* (Test de Aprendizaje Verbal de California)

DE: Desviación Estándar

DUP: *Duration of untreated psychosis* (Duración de la psicosis no tratada)

FAST: *Functional Assessment Short Test* (Prueba Breve de Evaluación del Funcionamiento)

FES: *Family Environment Scale* (Escala de Clima Social en la Familia)

GMM: *Growth Mixture Modeling*

IC: Intervalo de Confianza

K-SADS-PL: *Kiddie-Sads-Present and Lifetime Version*

LCA: *Latent Class Analysis (*Análisis de Clases Latentes)

LCGA: *Latent Class Growth Analysis (*Análisis de Crecimiento de Clases Latentes)

MADRS: *Montgomery-Åsberg Depression Rating Scale* (Escala de Depresión de Montgomery-Åsberg)

MSCEIT: *Mayer-Salovey-Caruso Emotional Intelligence Test* (Prueba de Inteligencia Emocional de Mayer – Salovey – Caruso)

PANSS: *Positive and Negative Syndrome Scale* (Escala de los Síndromes Positivo y Negativo)

PAS: *Premorbid Adjustment Scale* (Escala de Ajuste Premórbido)

PEP: Primer Episodio Psicótico

SCID: *Structured Clinical Interview for DSM-IV Axis I Disorders*

SOS: *Symptom Onset in Schizophrenia inventory* (Inventario de Aparición de Síntomas en Esquizofrenia)

TAVEC: Test de Aprendizaje Verbal España-Complutense

TMT: *Trail Making Test* (Test del trazo)

TQ: *Trauma Questionnaire*

WAIS-III: *Wechsler Adult Intelligence Scale* (Escala de Inteligencia para Adultos de Wechsler)

WCST: *Wisconsin Card Sorting Test* (Prueba de Clasificación de Tarjetas de Wisconsin)

WISC-IV: *Wechsler Intelligence Scale for Children* (Escala de Inteligencia de Wechsler para Niños)

YMRS: *Young Mania Rating Scale* (Escala de Young para la Evaluación de la Manía)

LISTADO DE ARTÍCULOS

Esta tesis se ha realizado como compendio de 5 artículos científicos. A continuación, se expone el listado de artículos científicos resultantes de la línea de investigación en psiquiatría de precisión e intervención precoz en la que ha trabajado la candidata. Se han marcado con un asterisco (*) los artículos incluidos en la presente tesis por centrarse en primeros episodios psicóticos o por formar parte del marco teórico de esta tesis. Para cada artículo incluido en este trabajo se proporciona el factor de impacto (FI) correspondiente al año de publicación o al año más cercano, el cuartil y el área de conocimiento. Así, la presente tesis consta de **2 revisiones que conforman el marco teórico de la tesis y 3 artículos originales que responden a los 3 objetivos de la tesis**. De esta forma se cumple el requisito establecido por la Universidad de Barcelona de aportar un mínimo de dos trabajos originales publicados en revistas indexadas.

El factor de impacto total de los artículos incluidos en este trabajo es de 29,7.

(**1***) Vieta E, **Salagre E**, Grande I, Carvalho AF, Fernandes BS, Berk M, et al. Early Intervention in Bipolar Disorder. American Journal of Psychiatry. 2018;175(5):411-426. doi: 10.1176/appi.ajp.2017.17090972. **FI 2018: 13,6 (Psychiatry; D1)**

(2*) Salagre E, Dodd S, Aedo A, Rosa A, Amoretti S, Pinzon J, et al. Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0. Frontiers in Psychiatry. 2018;9:641. doi: 10.3389/fpsyt.2018.00641. **FI 2018: 3,2 (Psychiatry; Q2)**

Tomioka Y, Jiménez E, **Salagre E**, Arias B, Mitjans M, Ruiz V, et al. Association between genetic variation in the myo-inositol monophosphatase 2 (IMPA2) gene and age at onset of bipolar disorder. Journal of Affective Disorders. 2018;232:229-236. doi: 10.1016/j.jad.2018.02.002.

Mas S, Boloc D, Rodríguez N, Mezquida G, Amoretti S, Cuesta MJ, et al. **PEPs Group (Estela Salagre).** Examining Gene–Environment Interactions Using Aggregate Scores in a First-Episode Psychosis Cohort. Schizophrenia Bulletin. 2020; 46:1019–1025. doi:10.1093/schbul/sbaa012.

Silva Ribeiro J, Pereira D, **Salagre E**, Coroa M, Santos Oliveira P, Santos V, et al. Risk Calculators in Bipolar Disorder: A Systematic Review. Brain Sciences. 2020;10(8):525. doi: 10.3390/brainsci10080525.

(3*) (Objetivo 1) **Salagre E**, Grande I, Vieta E, Mezquida G, Cuesta MJ, Moreno C, et al. Predictors of Bipolar Disorder Versus Schizophrenia Diagnosis in a Multicenter First Psychotic Episode Cohort: Baseline Characterization and a 12-Month Follow-Up Analysis. The Journal of clinical psychiatry. 2020;81(6):19m12996. doi: 10.4088/JCP.19m12996.
FI 2019: 4,2 (Psychiatry; Q1)

(4*) (Objetivo 2) **Salagre E**, Grande I, Solé B, Mezquida G, Cuesta MJ, Díaz-Caneja CM, et al. Exploring Risk and Resilient Profiles for Functional Impairment and Baseline Predictors in a 2-Year Follow-Up First-Episode Psychosis Cohort Using Latent Class Growth Analysis. J Clin Med. 2020;10(1):73. doi: 10.3390/jcm10010073.
FI 2019: 3,3 (Psychiatry; Q1)

(5*) (Objetivo 3) **Salagre E,** Grande I, Jiménez E, Mezquida G, Cuesta MJ, Llorente C, et al. Trajectories of suicidal ideation after first-episode psychosis: a growth mixture modeling approach. Acta Psychiatr Scand. 2021. doi: 10.1111/acps.13279. PMID: 33501646. **FI 2019: 5,4 (Psychiatry; Q1)**

RESUMEN

Los trastornos psicóticos representan una de las principales causas de discapacidad a nivel mundial, además de asociarse a un mayor riesgo de muerte prematura. Para mejorar el pronóstico de los pacientes con un primer episodio psicótico es primordial establecer una intervención precoz lo más adaptada posible a las características y necesidades de cada paciente. La intervención precoz engloba estrategias para establecer un diagnóstico certero de manera temprana, incrementando así las probabilidades de responder al tratamiento, y estrategias de prevención de complicaciones asociadas a la enfermedad, como el deterioro funcional o la ideación suicida. Hasta el momento, la mayoría de estudios que han examinado estrategias para un diagnóstico precoz en primeros episodios psicóticos se han centrado en investigar factores predictores del diagnóstico de esquizofrenia y se ha prestado menos atención a los factores asociados con el diagnóstico de psicosis afectiva, si bien este subgrupo de trastornos psicóticos requiere una aproximación terapéutica muy distinta. Por otro lado, la mayoría de trabajos que han examinado factores asociados con el deterioro funcional o la ideación suicida tras un primer episodio psicótico no han tenido en cuenta la variabilidad interindividual, algo necesario para poder hacer predicciones más precisas y adaptadas a cada individuo. Por este motivo, los objetivos del presente trabajo fueron definir mejor qué factores se asocian con un diagnóstico de psicosis afectiva tras un primer episodio psicótico y examinar la heterogeneidad en la evolución funcional y en el desarrollo de ideación suicida en sujetos con un primer episodio psicótico, para crear modelos predictivos más precisos. Para tener en cuenta la variabilidad interindividual, se utilizaron métodos estadísticos avanzados como es el análisis de clases latentes.

Nuestros resultados apuntan al funcionamiento psicosocial, la sintomatología negativa y el desempeño en funciones ejecutivas como factores clave para diferenciar entre psicosis afectivas y psicosis no afectivas. Además, identificamos distintas evoluciones o trayectorias de funcionamiento psicosocial e ideación suicida en pacientes con un primer episodio psicótico y confirmamos predictores de evolución funcional y de desarrollo de ideación suicida descritos anteriormente, si bien, de manera importante, observamos que no todos los predictores influyen igual en cada una de las trayectorias. Así, encontramos que un mejor nivel socioeconómico familiar, un mejor ajuste premórbido, menos síntomas negativos y una memoria y aprendizaje verbal más conservados podrían mediar

en la resiliencia funcional. La memoria y aprendizaje verbal sería útil para identificar a los pacientes con mayor probabilidad de presentar una recuperación funcional entre aquellos que presentan marcadas dificultades psicosociales en el debut psicótico. En cuanto a los predictores de ideación suicida, los pensamientos pesimistas, la incapacidad para sentir y un peor clima familiar percibido se asociaron con la presencia de ideación suicida aguda en el debut psicótico −que mejoró durante el seguimiento−, mientras que una edad más avanzada, una DUP más prolongada y las dificultades para dormir se relacionaron con un mayor riesgo de presentar ideación suicida subaguda tras el primer episodio psicótico.

En conclusión, los resultados del presente trabajo apuntan a que existen elementos presentes ya en el primer episodio psicótico que pueden servir para orientar un futuro diagnóstico de psicosis afectiva y para estratificar a los pacientes en subgrupos según su evolución más probable a nivel de funcionamiento psicosocial o de riesgo suicida. Esto apoya que una intervención precoz de precisión es posible en primeros episodios psicóticos, con implicaciones para el diagnóstico precoz de psicosis afectivas y la prevención del deterioro funcional y el suicidio en esta población.

RESUM

Els trastorns psicòtics representen una de les principals causes de discapacitat a nivell mundial, a més d'associar-se a un major risc de mort prematura. Per millorar el pronòstic dels pacients amb un primer episodi psicòtic és primordial establir una intervenció precoç el més adaptada possible a les característiques i necessitats de cada pacient. La intervenció precoç engloba estratègies per establir un diagnòstic precís de manera primerenca, incrementant així les probabilitats de respondre al tractament, i estratègies de prevenció de complicacions associades a la malaltia, com el deteriorament funcional o la ideació suïcida. Fins ara, la majoria d'estudis que han examinat estratègies per a un diagnòstic precoç en primers episodis psicòtics s'han centrat en investigar factors predictors del diagnòstic d'esquizofrènia. Els factors associats amb un futur diagnòstic de psicosi afectiva s'han estudiat menys, si bé aquest subgrup de trastorns psicòtics requereix una aproximació terapèutica molt diferent. D'altra banda, la majoria de treballs que han examinat factors associats amb el deteriorament funcional o la ideació suïcida després d'un primer episodi psicòtic no han considerat la variabilitat interindividual, quelcom necessari per arribar a fer prediccions més precises i adaptades a cada individu. Per aquest motiu, el present treball té com objectius definir millor quins factors s'associen amb un diagnòstic de psicosi afectiva després d'un primer episodi psicòtic i examinar l'heterogeneïtat en l'evolució funcional i en el desenvolupament d'ideació suïcida en individus amb un primer episodi psicòtic, per tal de crear models predictius més precisos. Per tal de tenir en compte la variabilitat interindividual, en aquest treball es van utilitzar mètodes estadístics avançats, com és l'anàlisi de classes latents.

Els nostres resultats apunten al funcionament psicosocial, la simptomatologia negativa i el nivell de preservació de les funcions executives com a factors clau per diferenciar entre psicosi afectives i psicosi no afectives. A més, en aquest treball vam identificar diferents evolucions o trajectòries de funcionament psicosocial i ideació suïcida en pacients amb un primer episodi psicòtic i vam confirmar predictors d'evolució funcional i de desenvolupament d'ideació suïcida descrits anteriorment, si bé, de manera important, vam observar que no tots els predictors influeixen igual en cadascuna de les trajectòries. Així, vam trobar que un millor nivell socioeconòmic familiar, un millor ajust premòrbid, menys símptomes negatius i una memòria i aprenentatge verbal més conservats podrien influir en la resiliència funcional. La memòria i aprenentatge verbal seria útil per identificar

aquells pacients amb major probabilitat de presentar una recuperació funcional entre aquells que presenten marcades dificultats psicosocials en el debut psicòtic. Pel que fa als predictors d'ideació suïcida, els pensaments pessimistes, la incapacitat per a sentir i un pitjor clima familiar percebut es van associar amb la presència d'ideació suïcida aguda en el debut psicòtic −que va millorar durant el seguiment−, mentre que una edat més avançada, un DUP més llarga i les dificultats per dormir es van relacionar amb un major risc de presentar ideació suïcida subaguda després del primer episodi psicòtic.

En conclusió, els resultats del present treball apunten a que hi ha elements presents ja en el primer episodi psicòtic que poden servir per orientar un futur diagnòstic de psicosi afectiva i per estratificar als pacients en subgrups segons la seva evolució més probable a nivell de funcionament psicosocial o de risc suïcida. Això dóna suport a la idea que una intervenció precoç de precisió és possible en primers episodis psicòtics, amb implicacions pel diagnòstic precoç de psicosi afectives i per la prevenció del deteriorament funcional i el suïcidi en aquesta població.

SUMMARY

Psychotic disorders represent one of the main causes of disability worldwide and they are associated with an increased risk of premature death. In order to improve the prognosis of patients with first-episode psychosis, it is essential to establish early interventions as adapted as possible to the patient's characteristics and needs. Early intervention includes strategies to establish an early and accurate diagnosis, thus increasing the chances of a favorable treatment response, and strategies to prevent complications associated with the disease, such as functional impairment or suicidal ideation. To date, most of the research examining strategies for an early diagnosis in first-episode psychosis has focused on investigating predictors of the diagnosis of schizophrenia, while less studies have addressed the question of which factors might be associated with the diagnosis of affective psychosis, despite this subgroup of psychotic disorders requires a very different therapeutic approach. On the other hand, most of the studies that have examined factors associated with functional impairment or suicidal ideation after the first psychotic episode have not taken into account interindividual variability, which is important to make more precise predictions adapted to each individual. For this reason, the objectives of this study were to better define which factors are associated with a diagnosis of affective psychosis after first-episode psychosis and to examine the heterogeneity in the evolution of psychosocial functioning and in the development of suicidal ideation in subjects with first-episode psychosis, in order to create more accurate predictive models. Latent class analysis, an advanced statistical method, was used to take into account interindividual variability.

Our results point to psychosocial functioning, negative symptoms and performance in executive functions as key factors to differentiate between affective and non-affective psychoses. In addition, we identified different evolutions or trajectories of psychosocial functioning and suicidal ideation in patients with first-episode psychosis. We also confirmed previously described predictors of functional evolution and development of suicidal ideation, although, importantly, we observed that the relevance of those predictors differs between trajectories. We found that a better family socioeconomic level, a better premorbid adjustment, fewer negative symptoms, and more preserved memory and verbal learning could mediate functional resilience. Memory and verbal learning could be useful to identify those patients with a greater probability of presenting

functional recovery among those who present marked psychosocial difficulties in the psychotic onset. Regarding the predictors of suicidal ideation, pessimistic thoughts, inability to feel and a worse perceived family climate were associated with the presence of acute suicidal ideation at illness onset −which improved during follow-up−, while an older age, a longer DUP and sleeping difficulties were associated with a higher risk of presenting subacute suicidal ideation after the first episode of psychosis.

In conclusion, the results of the present study suggest that there are elements already present in the first psychotic episode that may serve to guide a future diagnosis of affective psychosis and to stratify patients into subgroups according to their most probable evolution at the level of psychosocial or psychosocial functioning. suicidal risk. Thus, our results support that an early and precise intervention is possible in first-episode psychosis, with implications for the early diagnosis of affective psychosis and the prevention of functional deterioration and suicide in this population.

1. JUSTIFICACIÓN

Los trastornos psicóticos son una de las principales causas de discapacidad a nivel mundial, además de estar asociados a una importante morbimortalidad y a un considerable impacto en la salud pública dado su carácter crónico (1, 2). Por ello se requieren estrategias que permitan mejorar el pronóstico de estas enfermedades actuando desde etapas tempranas (3). La evidencia actual sugiere que tanto las psicosis afectivas como las psicosis no afectivas tienen una naturaleza progresiva (4). Esto implica que la enfermedad progresa desde estadios tempranos menos severos, que incluirían la etapa asintomática, la etapa prodrómica y el primer episodio psicótico (PEP), hasta estadios más graves y crónicos de la enfermedad. Esta naturaleza progresiva hace que tanto las psicosis afectivas como no afectivas sean candidatas ideales para las estrategias de intervención precoz (5).

Una de las áreas para la intervención precoz en PEPs es la distinción temprana entre psicosis afectivas y no afectivas. La importancia de esta distinción temprana radica en que estas dos condiciones precisan un enfoque terapéutico distinto. En el caso de las psicosis afectivas, un diagnóstico erróneo de psicosis no afectiva puede conducir a tratamientos prolongados con antipsicóticos de manera innecesaria, los cuales no están exentos de efectos secundarios y, en el caso particular del trastorno bipolar, podrían incluso inducir un episodio depresivo. En el caso del trastorno bipolar, además, un diagnóstico erróneo retrasaría el inicio de un tratamiento profiláctico adecuado con fármacos eutimizantes. Este retraso puede influir en el pronóstico de la enfermedad, ya que hay datos que sugieren que la respuesta al tratamiento eutimizante es generalmente mejor si se inicia en etapas tempranas de la enfermedad (6-8). Un diagnóstico erróneo también entraña un mayor riesgo de confundir sintomatología depresiva post-psicótica con sintomatología negativa, lo que de nuevo desembocaría en un tratamiento erróneo para el paciente (9). Por ello, a pesar del solapamiento clínico entre estos dos grandes grupos diagnósticos, es importante caracterizar bien a los pacientes con un primer episodio psicótico e identificar factores que puedan ser útiles para pronosticar un futuro diagnóstico de trastorno afectivo.

Otra área para la intervención precoz en PEPs es la prevención de complicaciones asociadas a la enfermedad. Entre las más destacadas se encuentran el deterioro en el funcionamiento psicosocial y el riesgo autolítico (3). La evidencia sugiere que lograr la recuperación funcional completa poco después del PEP es un predictor mejor de remisión

funcional completa a largo plazo que la remisión sintomática (10, 11). Además, se ha descrito que el período inmediatamente posterior al PEP es una etapa donde existe un alto riesgo de presentar ideación suicida e intentos suicidas (12). Por ello es importante intervenir de manera precoz para evitar el deterioro funcional y disminuir el riesgo suicida en pacientes con un debut psicótico. No obstante, hay que considerar que la evolución funcional y la evolución del riesgo autolítico puede ser muy heterogénea entre pacientes con un PEP, por lo que no todos ellos requerirán el mismo tipo de intervención (12, 13). De ahí la importancia de una psiquiatría de precisión (14, 15) que tenga en cuenta esta heterogeneidad. Un primer paso en la psiquiatría de precisión en PEPs podría ser estratificar a los pacientes con un PEP en función de su pronóstico más probable a nivel de estas características particulares, lo que posibilitaría una intervención precoz mucho más adaptada a las necesidades particulares del paciente. Esta estratificación, además, permitiría optimizar recursos.

Hasta el momento, sin embargo, esta heterogeneidad ha sido poco estudiada y la mayoría de estudios que han explorado factores predictores de funcionamiento psicosocial e ideación suicida tras un PEP no han tenido en cuenta la variabilidad interindividual (16, 17). Así, para alcanzar esta estratificación en primeros episodios psicóticos, primero se precisa definir mejor las posibles evoluciones o trayectorias que un individuo puede presentar tras un PEP para, a continuación, identificar factores predictores de pertenencia a cada una de las trayectorias. Si bien uno de los objetivos de la psiquiatría de precisión es incorporar el componente biológico a la psiquiatría (18), a falta de biomarcadores biológicos validados, las estrategias de intervención de precisión pueden empezar centrándose en modelos predictivos que incluyan factores sociodemográficos, clínicos y cognitivos para alcanzar esta estratificación, que posteriormente podrían incorporar el componente biológico.

La línea de investigación del presente trabajo se planteó con el objetivo de contribuir a avanzar hacia una intervención precoz de precisión mediante una mejor definición de las etapas tempranas de la psicosis afectivas y no afectivas. Por un lado, se intentaron identificar factores que facilitaran el diagnóstico diferencial entre estos dos grandes grupos diagnósticos. Por otro lado, se intentaron describir distintas trayectorias de funcionamiento psicosocial e ideación autolítica y los factores sociodemográficos, clínicos y cognitivos asociados a cada una de ellas.

Así, el primer estudio de este trabajo se enfocó en el problema relativo al diagnóstico diferencial entre psicosis afectivas y no afectivas, en concreto en la diferenciación entre esquizofrenia y trastorno bipolar. En este caso, quisimos identificar factores pronósticos de trastorno bipolar en pacientes con un primer episodio psicótico, un área mucho menos explorada que los factores predictores de trastorno bipolar en pacientes con depresión unipolar. Mediante un análisis de regresión logística, pudimos encontrar factores clínicos, cognitivos y de funcionamiento psicosocial asociados con el diagnóstico de trastorno bipolar vs. esquizofrenia. La principal ventaja de este estudio respecto a estudios anteriores es su carácter prospectivo, la amplia muestra de pacientes y la exhaustiva caracterización de los participantes, que nos permitió investigar un amplio abanico de potenciales predictores sociodemográficos, clínicos y cognitivos Hasta donde sabemos, este es el primer modelo predictivo de psicosis afectiva vs. no afectiva en primeros episodios psicóticos que tiene en cuenta variables sociodemográficas, clínicas y cognitivas. Además, el modelo predictivo final de este estudio incluye variables fácilmente medibles tanto en entornos hospitalarios como ambulatorios, lo que facilitaría su aplicabilidad en la práctica clínica habitual.

Los siguientes estudios se centraron en examinar la heterogeneidad en la evolución funcional y en el desarrollo de ideación suicida en sujetos con un PEP. Para ello, exploramos subgrupos de pacientes con trayectorias similares a nivel de estas dos características utilizando modelos de trayectorias de clase latentes. Los modelos de trayectorias de clase latentes (*Latent Class Analisys,* LCA) permiten establecer subgrupos dentro de una muestra general teniendo como criterio de agrupación la evolución de una determinada característica, de tal manera que el grado de similitud en la evolución de esa característica sea máximo dentro de estos subgrupos y mínimo entre los subgrupos. Estas técnicas han sido escasamente utilizadas en cohortes de PEPs, si bien estos modelos presentan una serie de ventajas sobre otros modelos con objetivos similares, como el análisis de Clústeres, donde también se persigue encontrar grupos o tipos de casos en función de los datos observados. Por ejemplo, dado que los modelos de LCA son modelos estadísticos, se pueden obtener medidas de ajuste de los modelos obtenidos para cada número *k* de clases, los cuales pueden orientar a la hora de escoger el modelo que mejor se ajusta a los datos. Por tanto, en los modelos de LCA existen criterios objetivos que apoyan la elección del número de clases (19). Además, en contraste con estudios previos, en nuestros estudios utilizamos la escala FAST (*Functional Assessment Short Test*) para

medir funcionamiento psicosocial, la cual ha sido validada en primeros episodios psicóticos (20). Otra de las fortalezas de nuestros estudios respecto a estudios anteriores radica en haber dispuesto de una cohorte muy bien caracterizada, lo que nos permitió evaluar la mayoría de predictores descritos de manera independiente o en grupos más discretos en estudios anteriores. Así, mediante nuestros estudios pudimos definir distintas trayectorias de funcionamiento psicosocial e ideación suicida en pacientes con un primer episodios psicótico y confirmar predictores de evolución funcional y de desarrollo de ideación suicida descritos anteriormente, si bien, de manera importante, observamos que no todos los predictores influyen igual en cada una de las trayectorias, lo que apoya nuestra hipótesis de la necesidad de definir mejor la heterogeneidad observada en PEPs para avanzar hacia una psiquiatría de precisión y más personalizada.

2. INTRODUCCIÓN

2.1. Primer episodio psicótico: generalidades

2.1.1. Definición de un primer episodio psicótico

En 2014, el Grupo de trabajo para la guía clínica y terapéutica de primeros episodios psicóticos en la infancia y adolescencia (21) definió un primer episodio psicótico (PEP) como aquel episodio caracterizado por "la presencia, por primera vez, de sintomatología psicótica definida como la existencia o sospecha clínica (por desorganización conductual, catatonia, etc.) de delirios y/o alucinaciones, independientemente del tiempo de evolución de los síntomas".

2.1.2. Epidemiología

Un PEP es típicamente una enfermedad de la adolescencia tardía o de la edad adulta temprana, si bien debuts más tempranos o en la edad adulta tardía también son posibles (22). En el caso de la esquizofrenia, por ejemplo, aproximadamente el 50% de los pacientes presentarán su primer episodio entre los 15 y los 25 años y aproximadamente el 80% lo presentará entre los 15 y los 35 años (23). La incidencia bruta de los trastornos psicóticos se ha establecido recientemente en 26,6 (intervalo de confianza (IC) del 95%: 22,0-31,7) por 100.000 personas-año (24), algo superior a los que se creía hasta ahora, con un mayor riesgo en hombres (especialmente de psicosis no afectivas) y en minorías raciales/étnicas (25). En general, se ha estimado que un 3% de la población presentará un episodio psicótico a lo largo de su vida (26). Si bien el curso de los PEPs es heterogéneo, como se comentará más adelante, en un porcentaje significativo de casos los trastornos psicóticos se asocian a una mortalidad prematura (27), a una importante morbilidad (2) y una gran carga social y económica (28).

2.1.3. Sintomatología

La sintomatología clásica que se suele observar en un PEP puede dividirse en tres esferas o dominios sintomáticos: los síntomas positivos, los síntomas negativos y los síntomas cognitivos (28). Los síntomas positivos incluyen, por ejemplo, delirios y alucinaciones, así como lenguaje y comportamiento desorganizados. El dominio de síntomas negativos, por su parte, incluye síntomas como el retraimiento social, el aplanamiento afectivo, la

alogia o empobrecimiento del pensamiento y del lenguaje, la anhedonia, y la disminución de la iniciativa (29). La esfera de síntomas cognitivos incluye disfunciones en varios dominios de estrategias mentales, como déficits en la memoria verbal y en la velocidad de procesamiento (30).

También es frecuente observar síntomas afectivos en pacientes con un PEP. El primer episodio de un trastorno bipolar puede ser un PEP, por lo que es posible observar síntomas maníacos en una persona con un debut psicótico (31). Por otro lado, se ha descrito que hasta el 75% de los pacientes con un PEP presentan síntomas depresivos y aproximadamente un 22% cumple criterios de gravedad para un episodio depresivo franco (32).

2.1.4. Fases y curso evolutivo

En la mayoría de casos, un PEP sigue un curso de enfermedad longitudinal bastante prototípica, que se suele dividir en cuatro fases clínicas (23, 33) (**Figura 1**): (i) una fase premórbida clínicamente asintomática; (ii) una fase prodrómica con síntomas progresivos pero inespecíficos; (iii) un primer episodio agudo con síntomas psicóticos francos; y (iv) una fase de recuperación con gran variación a nivel individual.

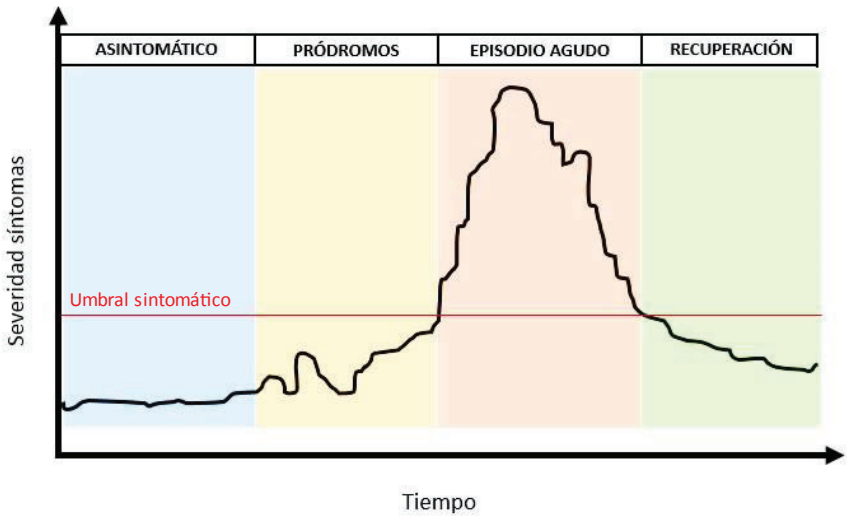

Figura 1. Fases evolutivas de un primer episodio psicótico (23, 33).

La fase prodrómica difiere de paciente a paciente, y también puede variar en función del tipo de psicosis (afectiva vs. no afectiva) (**Tabla 1**) (3, 5). Esta etapa suele caracterizarse por síntomas inespecíficos o atenuados. En muchos casos, los síntomas predominantes son la ansiedad inespecífica o los síntomas depresivos, además de alteraciones conductuales o funcionales (33, 34). Alrededor de un 20% de individuos, sin embargo, no experimenta una fase prodrómica y presenta un inicio abrupto de la clínica psicótica (23). En los demás casos, la duración de la fase prodrómica es variable, de semanas a años. Es importante resaltar que una vez instaurada una sintomatología psicótica más intensa y persistente, pocos pacientes reciben tratamiento para la psicosis de manera inmediata (35). La duración media de la psicosis no tratada (DUP, del inglés *Duration of Untreated Psychosis*), definida como el tiempo que transcurre desde el inicio de los síntomas psicóticos francos hasta la instauración de un tratamiento apropiado, varía de 4 a 50 semanas, según un meta-análisis de Marshall y colaboradores (36). Cuadros más floridos y con más alteraciones conductuales se han asociado con DUPs más cortas (23). La duración de la DUP es de suma relevancia clínica, dado que una mayor duración de la DUP se ha asociado a un peor pronóstico a largo plazo (37).

Tabla 1. Síntomas prodrómicos diferenciales en psicosis afectivas y no afectivas.

Psicosis afectiva	Psicosis no afectiva
Cambios en el estado de ánimo *Etapas iniciales: ansiedad, depresión, insomnio* *Etapas más avanzadas: síntomas maníacos subumbrales*	Cambios en la manera de pensar o sentir *Etapas iniciales: ansiedad, depresión, insomnio* *Etapas más avanzadas: percepciones inusuales, dificultad de comunicación, preocupación por nuevas ideas…*
Alteraciones conductuales *Hiperactividad, locuacidad, indecisión…*	Alteraciones conductuales *Desorganización, aislamiento social* Alteraciones funcionales *Dificultades académicas o laborales* *Dificultades con el autocuidado*

Adaptado de Klosterkötter, 2008 (38); Van Meter y colaboradores, 2016 (39); y Vieta y colaboradores, 2018 (5).

El curso evolutivo a largo plazo es igualmente heterogéneo, tanto a nivel sintomático como funcional (3). A nivel clínico, los pacientes pueden permanecer asintomáticos tras el PEP o la enfermedad puede progresar hacia un trastorno recurrente o persistente. Desde

un punto de vista funcional, la evolución puede variar desde la recuperación completa hasta la necesidad de atención crónica. Debido a esta variabilidad, establecer un pronóstico certero tras un PEP resulta complejo. La evidencia disponible revela que el nivel de funcionalidad tras un PEP, es decir, su capacidad para mantener relaciones sociales, mantener un empleo estable o vivir independientemente, depende en gran medida de la gravedad de los síntomas cognitivos y negativos (28). Así, se ha documentado que las dificultades en la vida cotidiana que presentan estas personas, sobre todo en el área social y laboral, pueden persistir a pesar de haber remitido los síntomas positivos (28). Tras el PEP, un número elevado de recaídas también empeora el pronóstico a nivel laboral y social (40), por lo que un tratamiento adecuado y temprano es fundamental para mejorar el pronóstico funcional a largo plazo. De igual forma, un tratamiento precoz es importante para prevenir las complicaciones a corto y largo plazo que con frecuencia se observan tras un PEP, las cuales incluyen comorbilidades médicas o psiquiátricas, como el abuso de sustancias, o la muerte prematura por suicidio (41). La evolución funcional y el riesgo suicida en PEPs se examinarán con más detalles en secciones posteriores de este trabajo.

2.1.5. Cambio diagnóstico tras un primer episodio psicótico

El diagnóstico de "Primer Episodio Psicótico" es un concepto amplio, que abarca presentaciones clínicas muy heterogéneas (3), por lo que una persona puede recibir diversos diagnósticos tras el debut psicótico, tales como: trastorno psicótico inducido por sustancias, trastorno psicótico breve, psicosis no especificada, trastorno delirante, esquizofrenia, trastorno esquizoafectivo, trastorno bipolar o depresión psicótica.

La estabilidad diagnóstica a nivel longitudinal es variable para cada uno de estos diagnósticos. Un meta-análisis de Fusar-Poli y colaboradores (42) donde se incluyeron 42 estudios con un seguimiento medio de 4,5 años y que englobaban un total de 14.484 pacientes con un PEP estableció la siguiente estabilidad diagnóstica prospectiva: la estabilidad diagnóstica fue elevada en el caso de la esquizofrenia (0,90; IC del 95%: 0,85-0,95) y las psicosis afectivas (0,84; IC del 95%: 0,79-0,89); moderada en el caso del trastorno esquizoafectivo (0,72; IC del 95%: 0,61-0,73); y moderada-baja para el trastorno psicótico inducido por sustancias (0,66; IC del 95%: 0,51-0,81), el trastorno delirante (0,59; IC del 95%: 0,47-0,71) y el trastorno psicótico breve (0,56; IC del 95%

0,62-0,60). La estabilidad diagnóstica fue muy baja para la psicosis no especificada (0,36; IC del 95%: 0,27-0,45) y para el trastorno esquizofreniforme (0,29; IC del 95%: 0,22-0,38).

Las principales características de los distintos tipos de trastornos que pueden debutar como un PEP se describen brevemente a continuación:

- ### Trastorno psicótico inducido por sustancias

El trastorno psicótico inducido por sustancias es un síndrome psicótico breve desencadenado por el consumo de sustancias, tanto drogas ilegales, como el cannabis, como medicamentos de uso habitual, como los corticoesteroides. También se incluyen en este grupo diagnóstico las psicosis inducidas por abstinencia a tóxicos. Los síntomas psicóticos inducidos por sustancias suelen ser de corta duración y reversibles una vez que desaparece el efecto del tóxico. En algunos casos pueden persistir durante días o semanas después de que se haya resuelto la intoxicación por sustancias (43). La incidencia del trastorno psicótico inducido por sustancias oscila entre 1,52 y 6,53 por 100.000 personas-año (24). Hasta el 25% de los primeros ingresos hospitalarios por psicosis pueden incluir un diagnóstico de psicosis inducida por sustancias (43), superando el 40% en poblaciones de alto riesgo, como los consumidores de anfetaminas (43).

- ### Trastorno psicótico breve

El trastorno psicótico breve consiste en la aparición de ideas delirantes, alucinaciones u otros síntomas psicóticos que duran al menos 1 día, pero menos de 1 mes, con retorno final a la funcionalidad normal previa a la enfermedad. Su prevalencia se ha estimado en 0,05% (26).

- ### Trastorno delirante

El trastorno delirante se caracteriza por la presencia de delirios de larga duración como síntoma único o dominante (44). El debut del trastorno delirante suele ser tardío, observándose en personas de mediana edad o de edad avanzada (45). Es menos común que la esquizofrenia y las personas suelen presentar un mejor funcionamiento psicosocial (45). Se ha estimado que su prevalencia a lo largo de la vida en la

población general se sitúa alrededor del 0,02% (46) y constituye entre el 1 y el 4% de todos los ingresos psiquiátricos (45).

○ Esquizofrenia

La esquizofrenia es un síndrome psiquiátrico crónico y complejo, cuya prevalencia se sitúa clásicamente en torno al 1%, aunque se han descrito variaciones en función del sexo y la geografía (28, 47). Se trata de una enfermedad severa, asociada a una importante morbimortalidad y a un elevado impacto en la calidad de vida de las personas que la padecen (48). Según la Organización Mundial de la Salud (OMS), la esquizofrenia representa una de las principales causas de discapacidad a nivel mundial (49). La edad de inicio se sitúa en torno a los 20-24 años (28) y la evidencia indica que la esquizofrenia es más frecuente en hombres que en mujeres (47). En éstas últimas, además, la edad de inicio suele ser más tardía y el curso clínico menos severo (28).

○ Trastorno esquizoafectivo

De acuerdo con los criterios del DSM-5, el diagnóstico de trastorno esquizoafectivo puede realizarse si se produce un episodio maníaco, depresivo o mixto simultáneamente con los síntomas psicóticos característicos de la esquizofrenia, especialmente delirios paranoides, autorreferencialidad y alucinaciones auditivas, y si se produce un episodio con síntomas psicóticos de al menos 2 semanas de duración en ausencia de síntomas afectivos prominentes (46). Además, los síntomas del estado de ánimo deben estar presentes "durante la mayor parte de la duración total de las partes activas y residuales de la enfermedad" (46). Los pacientes esquizoafectivos podrían constituir entre un 10 y un 30% de los cuadros psicóticos que se atienden en las unidades de hospitalización, y su prevalencia a lo largo de la vida podría situarse alrededor de un 0,3-0,5% (3). Desde el punto de vista funcional y neurocognitivo, los pacientes con trastorno esquizoafectivos presentan un deterioro más pronunciado que el de los pacientes con trastorno bipolar (50), pero algo menor que el que suele observarse en los pacientes con esquizofrenia (51).

- Trastorno bipolar

  El trastorno bipolar es un síndrome psiquiátrico caracterizado por la presencia de episodios maníacos o hipomaníacos recurrentes que pueden alternar con episodios depresivos (52). El trastorno bipolar tipo I se define por la presencia de episodios maníacos, que pueden incluir exceso de confianza, grandiosidad, locuacidad, desinhibición extrema, irritabilidad, disminución de la necesidad de dormir, y un estado de ánimo muy elevado. Los síntomas psicóticos, como delirios y alucinaciones, son asimismo frecuentes, pudiendo observarse en hasta el 75% de los episodios maníacos (52). El trastorno bipolar tipo I podría afectar a un 1,6% de la población; si se consideran también las cifras correspondientes al trastorno bipolar II y a la ciclotimia, la prevalencia se situaría entre un 3 y un 6,5% (53).

- Depresión psicótica

  La depresión psicótica es una depresión grave donde se combinan síntomas típicos de un episodio depresivo mayor, como sentimientos de desesperanza, culpa o anhedonia, con características psicóticas (delirios y alucinaciones). Su prevalencia a lo largo de la vida se sitúa entre el 0,35% y el 1% (54). Alrededor de un 8% de los pacientes que presentan depresión psicótica acaban desarrollando un trastorno bipolar (55), si bien también es posible una evolución hacia esquizofrenia, especialmente en hombres (56).

2.2. Intervención precoz y psiquiatría de precisión en primeros episodios psicóticos

2.2.1. Concepto de intervención precoz en psiquiatría

El concepto de intervención precoz en psiquiatría hace referencia al establecimiento de medidas preventivas o de un tratamiento precoz en fases tempranas de la enfermedad, incluida la fase prodrómica, con la idea de mejorar el pronóstico de dicha enfermedad (5) (**Figura 2**).

PREVENCIÓN		
Primaria *(= Prevención)*	**Secundaria** *(= Screening)*	**Terciaria** *(= Tratamiento)*
Antes del inicio de la enfermedad	Durante el desarrollo de la enfermedad	Tras el inicio de la enfermedad
Prevenir enfermedad Reducir factores de riesgo	Screening Detección y tratamiento precoz	Prevenir recaídas y deterioro Reducir complicaciones

Figura 2. Tipos de prevención y etapas para la intervención precoz en primeros episodios psicóticos.

La propuesta de aplicar una intervención precoz en PEPs se sustenta, como se comentaba en secciones anteriores, en la premisa de que tanto las psicosis afectivas como las psicosis no afectivas tienen una naturaleza progresiva (4), con presencia de fases asintomáticas o con síntomas atenuados previos a la presentación clásica de la enfermedad, lo cual abre una ventana de oportunidad para estrategias de prevención. Por ejemplo, para las psicosis no afectivas existen datos que indican que las primeras manifestaciones subclínicas (fase prodrómica) pueden preceder al inicio de los síntomas psicóticos floridos en más de 10 años (28). Ser capaces de prevenir o retrasar el debut psicótico es de suma importancia, ya que el inicio de los síntomas se suele situar en la adolescencia o primera juventud (22), una etapa vital crucial en el desarrollo psicosocial de la persona. Por ejemplo, en el caso del trastorno bipolar, entre el 50% y el 70% de las personas con este trastorno comienzan a manifestar síntomas del estado de ánimo antes de los 21 años (5).

Además, la relevancia de una intervención precoz en PEPs radica también en el hecho de que los trastornos psiquiátricos presentan a menudo un curso neuroprogresivo. El concepto de neuroprogresión implica que una mayor duración de la enfermedad conlleva cambios más pronunciados a nivel clínico y neuropatológico, que pueden conducir a la refractariedad al tratamiento y a déficits neuropsicológicos (57), entre otras complicaciones. Esto traduce la necesidad de intervenciones precoces en etapas tempranas que frenen la progresión de la enfermedad o atenúen su impacto (11).

Así, la intervención precoz en PEPs tiene dos focos principales. Por un lado, la búsqueda de factores de riesgo presentes en etapas premórbidas o en fases precoces de la enfermedad que estén asociados con un resultado de interés; por ejemplo, con deterioro funcional temprano. Estos factores deben ser modificables, es decir, debemos poder actuar sobre ellos, o deben ser útiles como factores pronósticos que guíen la elección del tratamiento. El concepto de intervención precoz también contempla la posibilidad de identificar factores que se puedan fortalecer o mejorar para aumentar la resiliencia de la persona (58). El segundo foco principal de la intervención precoz en PEPs es la búsqueda de signos tempranos o prodrómicos de la enfermedad cuyo tratamiento precoz ayude a prevenir el desarrollo de la enfermedad o favorezca que esta progrese hacia formas clínicas menos severas. Una vez instaurado el PEP, las intervenciones tempranas consistirían en un tratamiento sintomático intensivo para prevenir la progresión de la enfermedad hacia estadios más avanzados, así como en fomentar la resiliencia del individuo, actuar sobre los factores de riesgo asociados a un peor pronóstico y prevenir complicaciones como el desarrollo de comorbilidades médicas y psiquiátricas, el consumo de tóxicos, el deterioro cognitivo, el deterioro funcional o la muerte prematura por suicidio (41, 58).

En un intento por introducir una perspectiva longitudinal de la enfermedad en el proceso diagnóstico y terapéutico que incluyera también las fases más tempranas de las psicosis afectivas y no afectivas y que sirviera para guiar el tratamiento y el pronóstico, hace unos años se propuso introducir el modelo de estadificación en psiquiatría (59, 60). El concepto de estadificación se basa precisamente en la idea de que una determinada enfermedad avanza con una progresión temporal identificable, de una etapa prodrómica a estadios más graves y crónicos de la enfermedad, los cuales a menudo requieren un tratamiento más complejo (61). También sostiene que una intervención eficaz en estadios precoces de la enfermedad puede evitar o retrasar la progresión a estadios más avanzados de la enfermedad o bien, una vez ya instaurada la enfermedad, disminuir la morbimortailidad en caso de progresión (5).

La **Tabla 2** resume los principales factores de riesgo propuestos para un PEP afectivo y no afectivo y las diferentes opciones de intervención precoz según el estadio clínico del paciente.

Tabla 2. Potenciales factores de riesgo para un primer episodio psicótico afectivo y no afectivo y propuestas de intervención precoz en las distintas etapas tempranas de la enfermedad.

Potenciales factores de riesgo	Potenciales intervenciones precoces	
	Estadio clínico	**Tipo de intervención**
Familiares Antecedentes familiares de trastorno psicótico o trastorno afectivo Edad paterna avanzada *Perinatales* Complicaciones perinatales o durante el parto Alteraciones en el neurodesarrollo *Sociales/ambientales* Minoría étnica Migración Urbanidad Uso de sustancias Trauma infantil Eventos estresantes	Etapa asintomática	Educación en salud mental Psicoeducación familiar
	Etapa prodrómica	Educación en salud mental Psicoeducación individual/familiar Disminución uso de sustancias Terapias psicológicas Apoyo social/vocacional
	Primer episodio psicótico	Psicoeducación individual/familiar Disminución uso de sustancias Terapias psicológicas Rehabilitación social Tratamiento farmacológico

Adaptado de Fusar-Poli y colaboradores (40).

2.2.2. Concepto de psiquiatría de precisión

El sistema de estadiaje podría considerarse como el primer paso hacia la psiquiatría de precisión (57, 62), dado que la estadificación permite describir dónde se encuentra un paciente dentro del espectro temporal de progresión del trastorno, y así afinar el diagnóstico, ajustar el pronóstico y ayudar a elegir el tratamiento más adecuado (61). No obstante, no tiene en cuenta la variabilidad interindividual dentro de cada estadio. Considerando la marcada heterogeneidad que se suele observar en los PEPs, tanto a nivel diagnóstico como a nivel de su evolución clínica, funcional o del riesgo suicida, sería necesario avanzar hacia una forma aún más precisa o personalizada de abordar el tratamiento del paciente en estas etapas tempranas (57, 63), lo que se conoce como psiquiatría de precisión (15) (**Figura 3**).

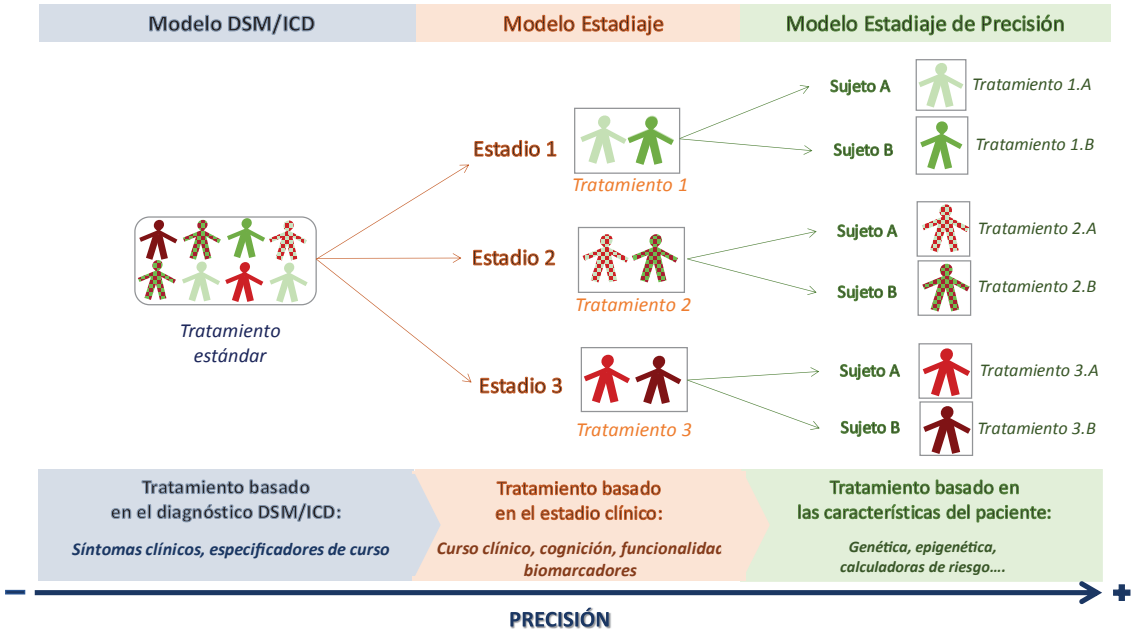

Figura 3. Modelos de estadificación de precisión (adaptado de Salagre y colaboradores, 2018 (57), artículo incluido en esta tesis).

El modelo DSM/ICD clasifica a los pacientes en condiciones particulares de acuerdo con criterios clínicos. El diagnóstico DSM/ICD puede refinarse mediante especificadores de curso. El modelo de estadificación permite ubicar a un paciente dentro del espectro temporal de progresión de la enfermedad, desde las etapas de riesgo (Estadio 1) a las etapas más crónicas (Estadio 3). Sin embargo, todavía puede haber diferencias entre pacientes dentro de una etapa en particular. Un modelo de estadificación de precisión utilizaría los nuevos avances en la psiquiatría de precisión para caracterizar mejor a los pacientes y ofrecerles un tratamiento más personalizado.

La psiquiatría de precisión tiene como objetivo diseñar estrategias terapéuticas y/o preventivas teniendo en cuenta la variabilidad biológica, los factores ambientales y el estilo de vida de cada persona (64, 65). En el caso de la intervención precoz de precisión, el objetivo es proporcionar estas medidas preventivas o terapéuticas "de precisión", es decir, adaptadas de la manera más precisa posible a las necesidades y particularidades de cada paciente, ya en etapas tempranas de la enfermedad. Para alcanzar este objetivo, la psiquiatría de precisión propone combinar información clínica, información sobre factores ambientales, marcadores objetivos y avances estadísticos y tecnológicos de una manera eficiente para crear modelos predictivos multidimensionales que guíen las decisiones clínicas y permitan predecir la vulnerabilidad a la enfermedad, la respuesta al tratamiento, el deterioro funcional o el riesgo de presentar complicaciones clínicas (18, 57). El fin último es lograr un enfoque terapéutico personalizado para cada paciente (66,

67). No obstante, se espera que la evolución de la psiquiatría de precisión sea por etapas caracterizadas por un creciente nivel de sofisticación y de personalización y un mayor papel de la tecnología y los marcadores biológicos (15, 57). Así, un primer paso para avanzar en la psiquiatría de precisión sería la creación de modelos predictivos más clínicos (68), donde posteriormente se podrían añadir factores biológicos. Por ejemplo, ya se han propuesto algunas calculadoras de riesgo preliminares para evaluar el riesgo de conversión a trastorno bipolar en jóvenes con alto riesgo de trastorno bipolar donde se combinan los antecedentes familiares (como proxi de riesgo genético) con medidas psicopatológicas (69).

De igual forma, un paso previo hacia una psiquiatría más personalizada sería la estratificación de los pacientes en diferentes niveles de riesgo para diferentes evoluciones o resultados clínicos según, por ejemplo, sus características clínicas, sociodemográficas y cognitivas (15, 57). El primer paso para llegar a esta estratificación en PEPs podría ser delinear mejor las distintas trayectorias o evoluciones que se pueden presentar tras un PEP mediante la identificación objetiva de subgrupos de pacientes que sean más similares entre ellos a nivel de su evolución para posteriormente examinar si, para cada subgrupo, se puede extraer alguna característica diferencial que pueda servir como futuro predictor de esa determinada evolución.

En los últimos años están ganando protagonismo técnicas estadísticas avanzadas capaces de detectar, dentro de una determinada muestra, subgrupos de pacientes con evoluciones o trayectorias clínicas similares. Entre ellas se encuentra el análisis de modelos de trayectorias de clases latentes (19). Estas técnicas se considerarán en más detalle en secciones posteriores.

2.2.3. Intervención precoz de precisión en primeros episodios psicóticos: potenciales áreas de aplicación

Existen varias áreas de actuación que podrían beneficiarse de una intervención precoz de precisión en pacientes con un PEP y que se desarrollarán a continuación. Por un lado, al tratarse de un diagnóstico transitorio, es importante hallar factores de riesgo, signos o síntomas que nos orienten de manera precoz sobre si un paciente con un PEP mantendrá el diagnóstico de psicosis del espectro no afectivo o evolucionará a una psicosis afectiva, dado que el tratamiento difiere sustancialmente entre estos dos grupos diagnósticos. Estos factores predictores podrían usarse para crear modelos que permitan hacer predicciones a título individual. Asimismo, es necesaria una intervención precoz para evitar complicaciones derivadas de la enfermedad. Entre las más relevantes se encuentran el deterioro funcional y el riesgo suicida. Por ello, se necesita caracterizar mejor las distintas evoluciones que puede presentar un paciente a nivel funcional y de ideación suicida tras un PEP, e identificar aquellos factores de riesgo presentes ya en el debut psicótico que nos ayuden a predecir la evolución más probable del paciente para estas dos potenciales complicaciones. Esta estratificación precoz en función de las características del paciente permitiría potenciar los factores asociados con trayectorias más resilientes y ofrecer un tratamiento intensivo a aquellos pacientes que presenten factores asociados a un mayor riesgo de deterioro funcional o riesgo suicida.

Distinción precoz entre psicosis no afectivas y psicosis afectivas: foco en trastorno bipolar vs. esquizofrenia

El trastorno bipolar es una condición psiquiátrica polimórfica que puede exhibir una sintomatología clínica diversa, particularmente en etapas tempranas (53). De ahí que el diagnóstico de trastorno bipolar en fases iniciales de la enfermedad pueda ser todo un desafío (70, 71), tal y como se refleja en estudios observacionales en pacientes pediátricos (70) y en edad adulta (72-75), donde se describen tasas de diagnóstico erróneo de alrededor del 30-60%.

El primer episodio de trastorno bipolar suele ser depresivo (55), por lo que es frecuente que en un primer momento este trastorno se oriente erróneamente como depresión unipolar (53). También puede confundirse con una psicosis no afectiva, entre las que

destaca la esquizofrenia (70, 76), dado que hasta un 75% de los episodios maníacos puede presentar síntomas psicóticos prominentes, como delirios y alucinaciones (52), que pueden no ser congruentes con el estado del ánimo. De manera ilustrativa, en el *McLean-Harvard International First-Episode Project* (31), se reevaluó el diagnóstico de más de 500 individuos en los dos años siguientes a la presentación de un PEP. Este estudio reportó que cerca del 16% de los pacientes con un diagnóstico final de trastorno bipolar habían sido orientados erróneamente como trastorno psicótico no afectivo al inicio del estudio.

A pesar de haber sido un campo de estudio menos explorado, una distinción temprana entre el trastorno bipolar y los trastornos psicóticos no afectivos, como la esquizofrenia, tiene importantes implicaciones en el tratamiento, ya que los regímenes de tratamiento farmacológico y psicológico difieren entre ambos grupos, así como el pronóstico (3). La confusión diagnóstica con esquizofrenia, por ejemplo, retrasa el inicio de un tratamiento profiláctico eficaz, es decir, un fármaco eutimizante, e implica tratamientos antipsicóticos prolongados, a menudo de manera innecesaria, y que pueden asimismo inducir virajes depresivos. Para un adecuado diagnóstico diferencial entre trastorno bipolar y esquizofrenia es importante evaluar el curso evolutivo de la enfermedad −incluida la fase prodrómica− más allá del cuadro clínico transversal, y no considerar los síntomas psicóticos más floridos, como los de primer rango de Schneider, como específicos de la esquizofrenia. Por ejemplo, los resultados de la revisión incluida en el presente trabajo apuntan a que los síntomas subumbrales (hipo)maníacos son los mayores predictores de conversión a trastorno bipolar (5). Esto se traduce en la necesidad de explorar la presencia de síntomas maníacos atenuados previos al debut psicótico al evaluar a pacientes con un PEP, especialmente en aquellos casos con antecedentes familiares de trastorno bipolar (5) (**Figura 4**). De hecho, según las conclusiones de la revisión incorporada en el presente trabajo, una historia familiar positiva para trastorno bipolar, especialmente en aquellos casos donde uno o ambos progenitores presentaron un trastorno bipolar de inicio temprano, es el factor de riesgo más importante para desarrollar un trastorno del espectro bipolar (5). En cambio, los familiares de pacientes con esquizofrenia suelen presentar con más frecuencia trastornos psicóticos, trastorno de personalidad del Cluster A o trastornos del espectro autista (77).

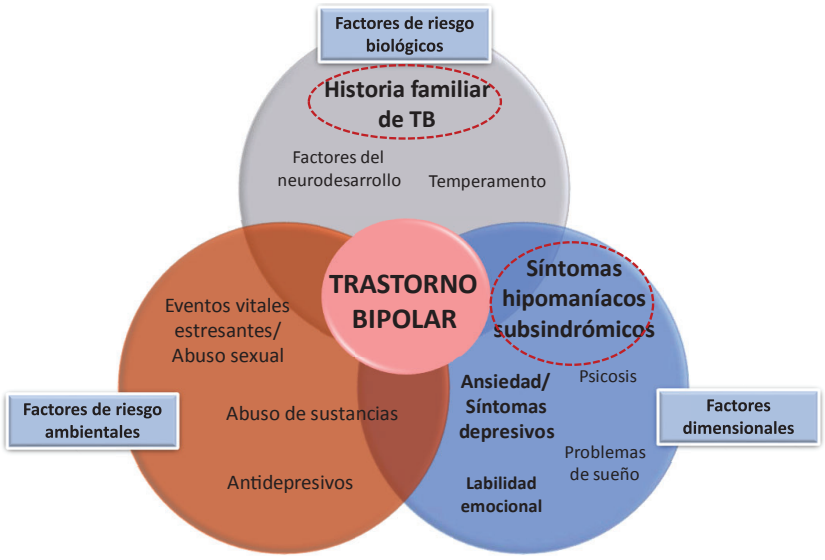

Figura 4. Potenciales factores de riesgo y síntomas prodrómicos en trastorno bipolar (adaptado de Vieta y colaboradores, 2018 (5), artículo incluido en esta tesis). **Abreviaturas:** TB: Trastorno Bipolar**.**

Existen varios estudios que reportan diferencias entre pacientes con un primer episodio bipolar y con un primer episodio de esquizofrenia (**Tabla 3**). Una de las diferencias más replicadas es la distinta distribución de géneros en los PEPs afectivos en comparación con los no afectivos, siendo el género masculino más frecuente en este último grupo (78, 79). También se ha reportado de manera consistente una menor DUP, menor sintomatología negativa en individuos con un PEP afectivo (80, 81) y puntuaciones más altas en el cociente intelectual (78) en pacientes con psicosis afectiva en comparación con los pacientes con psicosis no afectiva.

Tabla 3. Principales diferencias entre primeros episodios bipolares y primeros episodios de esquizofrenia.

	Primeros episodios bipolares	Primeros episodios de esquizofrenia
Género masculino	+	++
DUP	+	++
Sintomatología negativa	-/+	++
Alteraciones neuropsicológicas	-/+	++
Alteraciones neurodesarrollo	+	++
Alteraciones neuroanatómicas	+	++
Alteraciones funcionales	+	++
Antecedente familiares afectivos	++	+/-

Abreviaturas: DUP (del inglés, *Duration of untreated psychosis*): Duración de la psicosis no tratada. De Salagre & Grande, 2020 (82).

Respecto al rendimiento neurocognitivo, Bora y colaboradores (83) analizaron las diferencias neurocognitivas entre pacientes con un PEP de esquizofrenia y un primer episodio bipolar mediante técnicas meta-analíticas, incluyendo velocidad de procesamiento, memoria verbal, memoria visual, atención, razonamiento, memoria de trabajo y fluidez verbal. Sus resultados indicaron que ambos grupos de pacientes presentaban alteraciones en comparación con el grupo de controles sanos, si bien los déficits cognitivos eran más marcados en el grupo con un PEP de esquizofrenia, el cual puntuó peor que los pacientes con un primer episodio bipolar en velocidad de procesamiento, fluencia verbal, memoria verbal y memoria de trabajo**.** Un estudio del grupo PEPs encontró que los pacientes con psicosis afectivas puntuaban mejor que los pacientes con psicosis no afectivas en pruebas cognitivas que miden funciones ejecutivas (81). Algunos estudios apuntan a que en algunos sujetos con esquizofrenia estos déficits neurocognitivos están presentes ya antes del inicio de la enfermedad, mientras que en el trastorno bipolar el rendimiento cognitivo premórbido suele ser igual o incluso superior al de los controles sanos (84).

Más allá de las diferencias descritas entre PEPs afectivos y no afectivos, los datos disponibles sobre factores particulares asociados con el diagnóstico de trastorno bipolar tras un PEP son limitados. Uno de los pocos estudios disponibles fue realizado por Kim y colaboradores (85). En su estudio retrospectivo, encontraron que el género femenino, una DUP más corta, un mejor funcionamiento premórbido y una temática delirante religiosa o con delirios de grandeza se asociaron con el cambio de diagnóstico a trastorno bipolar después de un PEP. Un segundo estudio realizado por Arrasate y colaboradores (86) encontró que la activación y los síntomas maníacos predijeron un diagnóstico de trastorno bipolar a los 5 años de seguimiento tras un PEP. En cuanto al desempeño neurocognitivo, en una muestra de pacientes con un PEP, Peña y colaboradores (87) encontraron que el desempeño en pruebas que miden funciones ejecutivas fue capaz de distinguir a los pacientes con un diagnóstico final de trastorno bipolar de aquellos con un diagnóstico de esquizofrenia u otra psicosis con una tasa general de diagnóstico correcto del 84,4%.

Funcionamiento psicosocial tras un primer episodio psicótico

El concepto de recuperación tras un PEP no solo implica la remisión de los síntomas positivos y negativos [criterios de Andreasen (88)] sino que actualmente incluye también el restablecimiento del funcionamiento social y vocacional del paciente (21). El funcionamiento psicosocial hace referencia a la capacidad para desempeñar las actividades de la vida diaria, como el trabajo, los estudios o las actividades recreativas, y para establecer relaciones interpersonales satisfactorias (89). Así, en los últimos 50 años, la psiquiatría ha pasado progresivamente de una atención basada en el déficit (que se enfoca en la remisión sintomática) a un modelo orientado a la recuperación funcional. Actualmente ayudar al paciente a alcanzar sus metas personales es tan crítico como lograr la remisión sintomática (40). De hecho, cada vez se acepta más que los resultados funcionales son más significativos a la hora de medir la respuesta al tratamiento que simplemente las puntuaciones en escalas que solo califican síntomas psiquiátricos (psicóticos, maníacos o depresivos) (90). También están más alineados con lo que el paciente espera en última instancia del tratamiento (91). Por ello, la remisión funcional completa es actualmente un objetivo preeminente en psiquiatría.

De media, sin embargo, solo una de cada siete personas se recupera completamente tras un PEP a pesar de un tratamiento adecuado, por lo que la psicosis sigue siendo una de las principales causas de discapacidad en todo el mundo (28). La evolución clínica y funcional de los trastornos psicóticos se ha clasificado clásicamente en 4 cuadrantes con fines ilustrativos (**Tabla 4**): 25% de pacientes presentan una recuperación completa sin limitaciones funcionales; un 25% presenta una recuperación parcial con limitaciones funcionales leves; otro 25% presenta una recuperación incompleta con marcados déficits funcionales; y finalmente un 25% presenta un curso crónico, con una severa afectación en su funcionamiento psicosocial (23).

Tabla 4. Clasificación pronóstica clásica tras un primer episodio psicótico.

Pronóstico	Características	Factores asociados
25% Recuperación completa	Recuperación sintomática y funcional completa	**Buen pronóstico:** Inicio agudo (menor duración DUP), aparición tardía, buen ajuste premórbido, mayor nivel educativo
25% Recuperación parcial avanzada	Buena recuperación sintomática pero algún grado de limitación funcional. Los pacientes pueden vivir de forma independiente	
25% Recuperación incompleta	Persistencia de síntomas residuales limitantes entre episodios. Los pacientes necesitan apoyo de la familia o de las instituciones.	**Mal pronóstico:** Inicio insidioso (mayor duración DUP), marcadas alteraciones cognitivas y síntomas negativos severos
25% Curso crónico	Síntomas severos y persistentes con importante repercusión en la funcionalidad del paciente. Requieren de tratamiento intensivo.	

Adaptado de Santesteban-Echarri y colaboradores, 2017 (17), Freudenreich, 2020 (23) y Díaz-Caneja y colaboradores, 2015 (92).

No obstante, estos porcentajes varían de manera marcada entre estudios de cohortes, lo que sugiere que la evolución funcional es mucho más heterogénea y compleja (13, 93). La evidencia disponible también sugiere que lograr la recuperación funcional completa poco después del PEP es un mejor predictor de remisión funcional completa a largo plazo que la remisión sintomática (10, 11). Esta evidencia subraya la necesidad de encontrar factores tempranos y modificables asociados con el deterioro funcional ya desde las primeras etapas. Aunque múltiples estudios han investigado posibles predictores de deterioro en el funcionamiento psicosocial tras el PEP (17, 92) (**Tabla 4**), la mayoría de ellos ha abordado esta cuestión utilizando un resultado dicotómico, es decir, presencia versus ausencia de deterioro funcional. Como se ha comentado, el panorama real parece mucho más complejo que esta aproximación dicotómica, dados los resultados altamente divergentes en el funcionamiento psicosocial que los individuos pueden experimentar después del PEP, los cuales abarcan diversos grados de dificultades funcionales y

diferentes evoluciones a lo largo del tiempo. Algunos pacientes experimentarán una recuperación funcional temprana, mientras otros pueden presentar una mejoría o un empeoramiento funcional más progresivo. Otros pacientes pueden presentar dificultades funcionales graves desde el inicio de la enfermedad y algunos subgrupos pueden experimentar un deterioro funcional más moderado pero persistente, que puede igualmente tener un impacto negativo en su vida diaria. Por lo tanto, el verdadero desafío es predecir en las fases tempranas de la enfermedad qué trayectoria funcional es más probable que presente el individuo tras el PEP. Esto permitiría diseñar tratamientos más tempranos y más personalizados para la recuperación social y personal (5, 40, 94).

Los métodos estadísticos como el análisis de crecimiento de clases latentes (LCGA, del inglés *Latent Class Growth Analisis*) pueden ayudar a proporcionar una imagen más precisa del curso heterogéneo en el funcionamiento psicosocial que se puede observar después de un PEP, pues permiten considerar diferentes resultados de la misma característica simultáneamente (95, 96). Hasta donde sabemos, por ahora solo unos pocos estudios han aplicado estas técnicas estadísticas para evaluar los resultados funcionales en muestras de PEPs (97, 98), con una metodología heterogénea, por lo que la evidencia es todavía muy preliminar. Hodgekins y colaboradores (98), por ejemplo, identificaron tres tipos de perfiles de recuperación social en su muestra de 764 personas con un PEP atendidos en servicios de intervención temprana en psicosis y con un seguimiento a 12 meses: el primer grupo mantuvo dificultades en el funcionamiento psicosocial a lo largo del estudio (66% de la muestra), otro grupo presentó una recuperación funcional moderada con mejoría progresiva a lo largo del estudio (27% de la muestra) y un tercer grupo mostró una mejoría importante inicialmente, pero empeoró a lo largo del estudio (7% de la muestra). Como predictores de una pobre recuperación social encontraron el género masculino, la pertenencia a una minoría étnica, presentar el debut psicótico a una edad más temprana, una sintomatología negativa más pronunciada y un peor ajuste premórbido. Por su parte, Chang y colaboradores (97) examinaron trayectorias de funcionamiento en una muestra de 617 pacientes con un PEP no afectivo atendidos en un servicio de intervención temprana en psicosis y seguidos durante 3 años e identificaron cuatro trayectorias funcionales distintas. El primer grupo mostró déficits funcionales persistentes (48,1% de la muestra), el segundo grupo mostró una mejora temprana (31,3% de la muestra), el tercer grupo una mejora gradual (14,8% de la muestra) y el último grupo una mejora inicial seguida de un deterioro funcional (5,8% de la muestra). En su estudio,

el género masculino, un menor nivel educativo, un diagnóstico de trastorno del espectro de la esquizofrenia y haber necesitado tratamiento en régimen hospitalario en el debut psicótico fueron predictores de la trayectoria caracterizada por déficits funcionales persistentes.

Riesgo suicida tras un primer episodio psicótico

Los trastornos psicóticos presentan un riesgo de mortalidad por todas las causas 2,5 veces mayor que la población general (1). Entre estas causas se encuentra el suicidio. De hecho, está bien establecido que las personas que padecen enfermedades mentales graves tienen un mayor riesgo de intentos de suicidio y muerte por suicidio (99) y que el período inmediatamente posterior al PEP es una etapa donde existe un alto riesgo de presentar ideación suicida e intentos suicidas. Algunos estudios describen tasas de suicidio 2,7 veces más altas entre los pacientes con un PEP en comparación con los pacientes con esquizofrenia crónica (100). La depresión es el principal factor de riesgo de muerte por suicidio consumado en psicosis afectiva y no afectiva (53, 101) y se ha descrito que hasta el 80% de las personas con esquizofrenia sufren como mínimo un episodio depresivo clínicamente significativo en las etapas tempranas de la enfermedad (12).

El riesgo suicida generalmente comienza con la ideación suicida, seguida de un comportamiento preparatorio, y culmina con el intento de suicidio o con un comportamiento autolesivo, que no siempre es letal (99, 102). Por tanto, el estudio y la detección de la ideación suicida es importante porque a menudo precede a los intentos de suicidio (103). Además, la ideación suicida en sí misma –independientemente de si deriva en un intento autolítico– ya debe considerarse un objetivo de tratamiento importante en las personas con un PEP, ya que está relacionado con niveles de angustia y discapacidad significativas (104). Las tasas de ideación suicida entre las personas con un PEP son altas tanto en la presentación inicial (que van del 22 al 47%) como en la fase post-aguda (105-108), si bien la heterogeneidad de las estimaciones entre los estudios sugiere que pueden existir distintos subgrupos de pacientes con un PEP con diferente probabilidad de exhibir ideación suicida.

Se han identificado varios factores de riesgo para la presencia de ideación suicida y comportamiento suicida en cohortes de pacientes con un PEP. Entre estos factores se

encuentran los antecedentes previos de intentos de suicidio (109, 110), una mayor gravedad de los síntomas psicóticos positivos (106, 111), la depresión (110, 112), la desesperanza (109), los antecedentes de trauma (113), una mayor DUP (114), así como un peor funcionamiento cognitivo (115). Sin embargo, la ideación suicida es un fenómeno heterogéneo y, como en el caso del funcionamiento psicosocial, se sabe poco sobre las trayectorias específicas de ideación suicida después de un PEP y sobre posibles factores asociados con cada una de esas posibles trayectorias. Hasta donde sabemos, solo Madsen y colaboradores (116) han explorado trayectorias de ideación suicida después de un PEP. En su estudio identificaron tres subgrupos según sus trayectorias o evoluciones de la ideación suicida durante el seguimiento: un primer subgrupo de pacientes con una ideación suicida inicial poco severa y decreciente (61% de la muestra; n = 317); un segundo subgrupo con ideación suicida frecuente, pero con una intensidad mantenida en el tiempo (33% de la muestra; n = 172); y, por último, un tercer subconjunto que presentaba ideación suicida de manera frecuente y que empeoraba en el tiempo (6% de la muestra; n = 32).

2.3. Herramientas para la intervención precoz de precisión en primeros episodios psicóticos.

2.3.1. Modelos de trayectoria de clases latentes

El análisis de modelos de trayectorias de clases latentes permite identificar subgrupos latentes de individuos que presentan una trayectoria similar a nivel de una característica particular, de manera que la similitud en las trayectorias de los individuos sea máxima dentro del subgrupo y mínima entre subgrupos (96). En otras palabras, se trata de técnicas analíticas que permiten identifican subgrupos de individuos dentro de una determinada muestra que son más similares entre sí en la presentación inicial y en la evolución a lo largo del tiempo de una característica particular (95). En este tipo de análisis, la variable "trayectoria" se considera una variable latente que se estima agrupando probabilísticamente a los individuos que exhiben, respecto a la variable de interés, puntos de partida (intersecciones) y patrones de cambio (pendientes) similares (**Figura 5**).

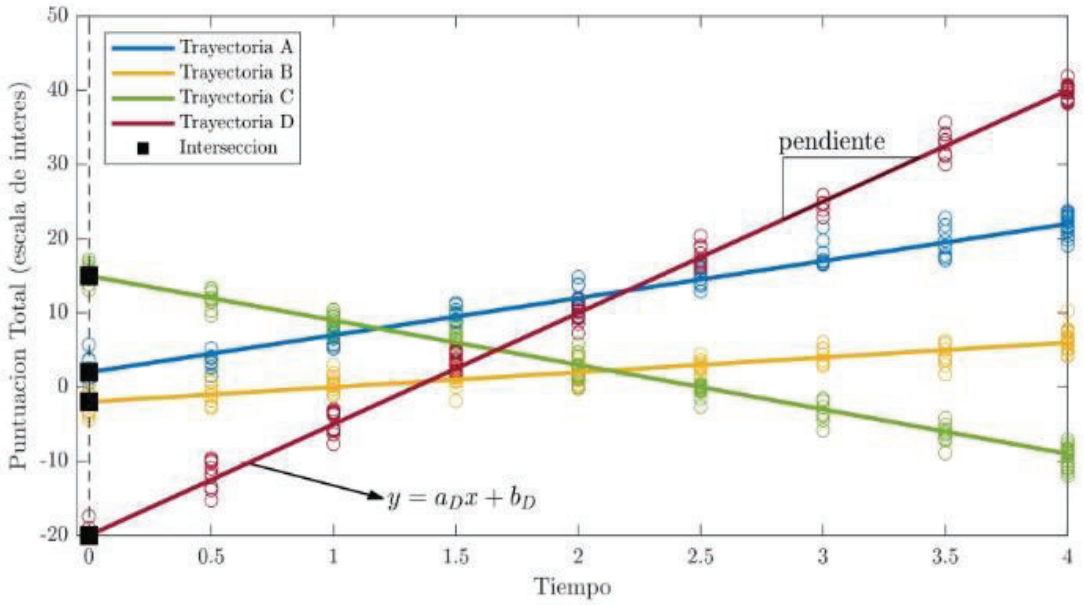

Figura 5. Ejemplo de trayectorias.

a_D = pendiente para la trayectoria D. b_D = intersección para la trayectoria D. Los círculos representan datos individuales. En nuestro ejemplo, los datos representan puntuaciones en una escala de interés que se toman de manera repetida en el tiempo para cada individuo. Cada trayectoria agrupa los datos que presentan una intersección y una evolución en el tiempo (pendiente) más similar.

Este tipo de técnicas están más centradas en la persona, puesto que analizan las similitudes y diferencias entre individuos para identificar estos subgrupos "latentes" según sus trayectorias (19). Estas técnicas enfatizan los "efectos aleatorios", es decir, la variabilidad alrededor de la media muestral, de manera que estas técnicas incorporan la variabilidad individual en los análisis en lugar de tratarla como un error (19). Así, este tipo de análisis asume que la heterogeneidad observada en la muestra se explica mejor por la existencia de dos o más subgrupos dentro de la muestra. Aplicado a la psiquiatría, este enfoque podría proporcionar una imagen más precisa del curso heterogéneo de las enfermedades mentales.

Tanto el análisis de crecimiento de clases latentes (LCGA) como el *Growth Mixture Modeling* (GMM) pertenecen a los modelos de trayectoria de clases latentes (19).

3. HIPÓTESIS Y OBJETIVOS

A partir del marco teórico que se acaba de describir, se establecieron las siguientes **hipótesis** para el presente trabajo:

1. Existirían factores sociodemográficos, premórbidos, clínicos, funcionales o neurocognitivos que podrían predecir de manera temprana un futuro diagnóstico de trastorno bipolar vs. esquizofrenia en pacientes con un PEP.

2. La evolución a nivel de funcionamiento psicosocial tras un PEP sería heterogénea entre pacientes, por lo que se podrían identificar distintas trayectorias funcionales después de un PEP con factores predictores diferenciales.

3. La presencia de ideación suicida tras un PEP sería un fenómeno heterogéneo entre pacientes, por lo que se podrían identificar distintas trayectorias de ideación suicida tras un PEP. Además, se podrían identificar factores predictores durante el primer episodio psicótico que se asociarían con las distintas trayectorias de ideación suicida.

Los **objetivos** del presente trabajo son:

Objetivos principales:

1. Crear un modelo predictivo de diagnóstico de trastorno bipolar vs. esquizofrenia tras un PEP integrando variables sociodemográficas, clínicas y neuropsicológicas.

2. Identificar distintas trayectorias a nivel de funcionamiento psicosocial a lo largo del seguimiento y los factores sociodemográficos, clínicos y neuropsicológicos asociados con la pertenencia a cada una de las trayectorias.

3. Determinar distintas trayectorias a nivel de ideación suicida a lo largo del seguimiento y los factores sociodemográficos, clínicos y neuropsicológicos asociados con la pertenencia a cada una de las trayectorias.

Objetivos secundarios:

1. Definir la distribución de los diagnósticos dentro de las diferentes trayectorias de funcionamiento psicosocial para explorar si los pacientes con un diagnóstico de psicosis afectiva muestran una funcionalidad más conservada a lo largo del tiempo que los pacientes con psicosis no afectiva.

2. Explorar las diferencias entre los sujetos asignados a las diferentes trayectorias de ideación suicida en cuanto a la evolución de la psicopatología y el funcionamiento psicosocial.

De estas hipótesis surgieron los 3 estudios que conforman el presente trabajo:

Hipótesis 1: *"Existirían factores sociodemográficos, premórbidos, clínicos, funcionales o neurocognitivos que podrían predecir de manera temprana un futuro diagnóstico de trastorno bipolar vs. esquizofrenia en pacientes con un PEP."*

Estudio 1: **Salagre E**, Grande I, Vieta E, Mezquida G, Cuesta MJ, Moreno C, et al. **Predictors of Bipolar Disorder Versus Schizophrenia Diagnosis in a Multicenter First Psychotic Episode Cohort: Baseline Characterization and a 12-Month Follow-Up Analysis.** Journal of Clinical Psychiatry. 2020;81(6):19m12996. doi: 10.4088/JCP.19m12996.

Hipótesis 2: *"La evolución a nivel de funcionamiento psicosocial tras un PEP sería heterogénea entre pacientes, por lo que se podrían identificar distintas trayectorias funcionales después de un PEP con factores predictores diferenciales."*

Estudio 2: **Salagre E**, Grande I, Solé B, Mezquida G, Cuesta MJ, Díaz-Caneja CM, et al. **Exploring Risk and Resilient Profiles for Functional Impairment and Baseline Predictors in a 2-Year Follow-Up First-Episode Psychosis Cohort Using Latent Class Growth Analysis.** Journal of Clinical Medicine. 2020;10(1):73. doi: 10.3390/jcm10010073.

Hipótesis 3: *"La presencia de ideación suicida tras un PEP sería un fenómeno heterogéneo entre pacientes, por lo que se podrían identificar distintas trayectorias de ideación suicida tras un PEP. Además, se podrían identificar factores predictores durante el primer episodio psicótico que se asociarían con las distintas trayectorias de ideación suicida."*

Estudio 3: **Salagre E,** Grande I, Jiménez E, Mezquida G, Cuesta MJ, Llorente C, et al. **Trajectories of suicidal ideation after first-episode psychosis: a growth mixture modeling approach**. Acta Psychiatrica Scandinavica. 2021. doi: 10.1111/acps.13279.

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4. METODOLOGÍA

El presente trabajo se basó en datos del proyecto "Fenotipo-genotipo e interacción ambiental. Aplicación de un modelo predictivo en primeros episodios psicóticos" (**Estudio PEPs**) (117). El estudio PEPs es un estudio naturalístico, multicéntrico, y longitudinal con seguimiento a dos años en el que participaron un total de 16 centros de toda España. Catorce de estos centros son miembros del Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM) (118) y dos son centros colaboradores (117).

Este estudio se realizó de acuerdo con los principios éticos de la Declaración de Helsinki y fue aprobado por los comités de ética en investigación de cada centro participante. Se obtuvo un consentimiento informado por escrito de todos los participantes o de sus tutores legales en caso de participantes menores de edad tras proporcionarles una explicación completa del estudio.

4.1. Sujetos

En el Estudio PEPs participaron un total de 335 sujetos con un PEP reclutados por los 16 centros participantes desde abril de 2009 hasta abril de 2012. Los ***criterios de inclusión*** fueron: (i) edad comprendida entre 7 y 35 años en el momento de la primera evaluación; (ii) haber presentado por primera vez síntomas psicóticos de mínimo 1 semana de duración en los últimos 12 meses; (iii) fluidez en castellano; y (iv) firma del consentimiento informado. Los ***criterios de exclusión*** fueron: (i) discapacidad intelectual de acuerdo con los criterios del Manual Diagnóstico y Estadístico de los trastornos mentales, 4ª edición (DSM-IV) (lo que incluye, además de un coeficiente intelectual por debajo de 70, problemas de funcionalidad) (119); (ii) antecedentes de traumatismo craneoencefálico con pérdida del conocimiento; y (iii) presencia de una enfermedad orgánica con repercusión mental.

En el momento de la inclusión en el estudio, los pacientes habían recibido tratamiento antipsicótico durante menos de 12 meses. Las evaluaciones de seguimiento se realizaron a los 2 meses, 6 meses, 12 meses y 24 meses.

4.2. Evaluación

Datos sociodemográficos basales

Al inicio del estudio se recopilaron datos sociodemográficos de todos los participantes, incluidos el sexo, la edad, la etnia, el nivel educativo, el estado civil, la convivencia, la situación laboral y el nivel socioeconómico de los padres. El nivel socioeconómico de los padres se determinó mediante el índice de posición social de dos factores de Hollingshead (120). También se recopilaron antecedentes personales y familiares de trastornos somáticos y psiquiátricos. El historial de abuso de drogas se evaluó mediante una versión adaptada del *Multidimensional Assessment Instrument for Drug and Alcohol Dependence scale* (121). La Escala de Clima Social en la Familia (*Family Environment Scale,* FES), se utilizó para evaluar la percepción de los pacientes del clima social dentro de sus familias (122, 123).

Evaluación clínica y funcional basal

Para todos los sujetos del estudio, el diagnóstico fue establecido por profesionales de la salud mental mediante la Entrevista Clínica Estructurada para los Trastornos del Eje I del DSM-IV (*Structured Clinical Interview for DSM-IV Axis I Disorders*; SCID-I) (119, 124), en el caso de los participantes adultos, y mediante la traducción al español de *Kiddie-Sads-Present and Lifetime Version* (K-SADS-PL) en el caso de los niños y adolescentes (125, 126). El estado psicopatológico se evaluó utilizando las versiones validadas en español de la *Positive and Negative Syndrome Scale* (PANSS) (127, 128), la *Young Mania Rating Scale* (YMRS) (129, 130) y la *Montgomery-Åsberg Depression Rating Scale* (MADRS) (131, 132). La severidad de la ideación suicida en el **Estudio 3** (133) se midió utilizando el ítem "pensamientos suicidas" de la MADRS. Este ítem se puntúa en una escala de 0 ("disfruta de la vida o la toma como viene") a 6 ("planes explícitos de suicidio cuando hay una oportunidad; preparativos activos para el suicidio"). Para determinar la presencia de ideación suicida clínicamente significativa se consideró un punto de corte ≥2 en el ítem "pensamientos suicidas" de la MADRS, en línea con estudios previos (134). En todas las escalas mencionadas, puntuaciones más altas indican una mayor gravedad clínica.

El ajuste premórbido se estimó de manera retrospectiva mediante la Escala de Ajuste Premórbido (*Premorbid Adjustment Scale*; PAS) (135). Para determinar el funcionamiento psicosocial se utilizó la Prueba Breve de Evaluación del Funcionamiento (*Functional Assessment Short Test*; FAST) (89, 136). Esta prueba consta de 24 ítems que evalúan seis dominios de funcionamiento específicos: autonomía, funcionamiento laboral, funcionamiento cognitivo, finanzas, relaciones interpersonales y ocio. Esta escala busca detectar cambios o dificultades en el funcionamiento psicosocial que sean atribuibles a la enfermedad. La puntuación total de la FAST tiene un rango entre 0 y 72. De acuerdo con los puntos de corte propuestos por Bonnín y colaboradores (137), puntuaciones > 40 en la FAST indican un deterioro funcional grave, puntuaciones entre 21 y 40 indican un deterioro funcional moderado, puntuaciones entre 12-20 indican un deterioro funcional leve y puntuaciones ≤11 indican ausencia de deterioro funcional. Esta escala ha demostrado ser sensible a los cambios y ha sido validada para PEPs (20). Tanto en la PAS como en la FAST, puntuaciones más altas indican un mayor deterioro funcional.

Los antecedentes de experiencias traumáticas en el transcurso de la vida se evaluaron mediante la versión española del *Trauma Questionnaire* (TQ) (138, 139). También se registró la duración del ingreso hospitalario motivado por el PEP y la DUP, definida como el número de días transcurridos entre el inicio de los síntomas psicóticos positivos y el inicio del primer tratamiento adecuado para la psicosis. La DUP se calculó utilizando el Inventario de Aparición de Síntomas en Esquizofrenia (*Symptom Onset in Schizophrenia*; SOS) (140).

Primera evaluación neuropsicológica (realizada a los 2 meses de seguimiento)

Los participantes fueron evaluados utilizando una amplia batería neuropsicológica diseñada específicamente para el estudio PEPs y que abarca la mayoría de los dominios cognitivos propuestos por el consenso MATRICS del Instituto Nacional de Salud Mental (NIHM) de Estados Unidos (141). La evaluación fue realizada por neuropsicólogos expertos en los dos primeros meses posteriores a la inclusión del participante en el estudio para evitar la interferencia de manifestaciones psicopatológicas agudas en la evaluación neurocognitiva. La evaluación neuropsicológica incluyó los siguientes dominios cognitivos: (1) Cociente Intelectual (CI) estimado (calculado en función del desempeño

en el subtest de vocabulario de la Escala de Inteligencia para Adultos de Wechsler (*Wechsler Adult Intelligence Scale*; WAIS-III) (142) o de la Escala de Inteligencia de Wechsler para Niños (*Wechsler Intelligence Scale for Children*; WISC-IV) (143)); (2) función ejecutiva (evaluada mediante la Prueba de interferencia del Test de Stroop (144), la Prueba de Clasificación de Tarjetas de Wisconsin (*Wisconsin Card Sorting Test*; WCST) (145) y el Test del Trazo (*Trail Making Test*; TMT), formulario B (146)); (3) atención sostenida/vigilancia (evaluada mediante el Test de Ejecución Continua de Conners-II (*Continuous Performance Test-II*; CPT-II) (147)); (4) velocidad de procesamiento (evaluada mediante el TMT, formulario A (148) y los componentes categóricos (denominación de animales) y fonémicos (F-A-S) del Test de Asociación controlada de palabras (*Controlled Oral Word Association Test,* COWAT) (149)); (5) memoria verbal (evaluada mediante el Test de Aprendizaje Verbal España-Complutense (TAVEC), que es la versión española del *California Verbal Learning Test* (CVLT) (150, 151)); (6) Memoria de trabajo (evaluada mediante las subpruebas 'Dígitos en orden inverso' y 'Letras y números' del WAIS-III (142) o el WISC-IV (143)); y (7) cognición social (Prueba de Inteligencia Emocional de Mayer – Salovey – Caruso (MSCEIT) (152, 153)).

Análisis estadístico

Estudio 1

Para el **Estudio 1** (154), primero analizamos la distribución de los distintos diagnósticos en nuestra muestra a los 12 meses de seguimiento para determinar qué pacientes tenían un diagnóstico confirmado de trastorno bipolar o esquizofrenia en ese momento. Decidimos no incluir en ninguno de los dos grupos a los pacientes que mantenían un diagnóstico de trastorno psicótico no especificado, trastorno psicótico agudo y transitorio, trastorno esquizofreniforme o trastorno psicótico inducido por sustancias a los 12 meses de seguimiento, ya que en estos casos los pacientes todavía podían cambiar su diagnóstico a psicosis afectiva o permanecer como psicosis no afectiva (155). En consecuencia, para este estudio solo nos centramos en aquellos pacientes con diagnóstico confirmado de trastorno bipolar o esquizofrenia a los 12 meses de seguimiento con el fin de obtener grupos más homogéneos. Decidimos centrarnos en la evaluación de seguimiento a los 12 meses para establecer los grupos diagnósticos porque consideramos que era un tiempo de

seguimiento razonable para observar cambios en el diagnóstico y las tasas de retención eran mejores que a los 24 meses de seguimiento.

A continuación, se utilizó la prueba de Kolmogorov-Smirnov para examinar la normalidad de las variables. Las diferencias en las características sociodemográficas, clínicas y neuropsicológicas a nivel basal entre los sujetos con un diagnóstico de trastorno bipolar y esquizofrenia a los 12 meses de seguimiento se evaluaron mediante la prueba de Chi cuadrado para variables categóricas y la prueba *t* o la prueba U de Mann-Whitney, según correspondiese, para variables continuas. En el caso de las variables neurocognitivas, se utilizaron puntuaciones directas para el análisis. Se realizó una regresión logística binaria para determinar el impacto de las variables sociodemográficas, clínicas y neuropsicológicas sobre la probabilidad de tener un diagnóstico de trastorno bipolar vs. esquizofrenia a los 12 meses de seguimiento. Para los análisis de regresión, solo incluimos aquellas variables basales que fueron significativamente diferentes entre los dos grupos en la comparación bivariante inicial y que estuvieran respaldadas por evidencia previa. El diagnóstico de trastorno bipolar se utilizó como variable dependiente. Se crearon modelos según Hosmer y Lemeshow, introduciendo una variable por cada 10 casos observados de la variable dependiente para evitar el sobreajuste de los modelos (156, 157).

Estudio 2

El análisis estadístico del **Estudio 2** (158) consta de varios pasos:

A) Identificación de trayectorias funcionales

En primer lugar, se utilizó la técnica LCGA para identificar distintas trayectorias de funcionamiento a lo largo de los 24 meses de seguimiento. La pertenencia a una determinada clase se asignó en base a las puntuaciones totales de la FAST medidas en 5 puntos temporales distintos durante el seguimiento de 2 años, esto es, en el momento basal y a los 2, 6, 12 y 24 meses de seguimiento. Para este estudio, solo incluimos en el análisis a participantes mayores de 18 años, dado que la escala FAST solo ha sido validada en muestras de individuos adultos, y que tuvieran información de la escala FAST en al menos dos evaluaciones durante el seguimiento. Esto dejó una muestra final de 275 participantes adultos.

Cada modelo se volvió a ejecutar 100 veces utilizando diferentes valores de inicio para evitar la convergencia a un máximo local (159). Para acomodar las fluctuaciones esperadas a lo largo del tiempo, estimamos términos lineales y cuadráticos. Para determinar el número óptimo de clases/trayectorias, se ajustaron a los datos modelos con un número creciente de clases latentes (modelos de 1 a 4 clases latentes) y se seleccionó el modelo con mejor ajuste de acuerdo con las siguientes medidas de bondad de ajuste: criterio de información de Akaike (*Akaike Information Criteria*, AIC), criterio de información bayesiano (*Bayesian Information Criteria*, BIC), BIC ajustado al tamaño de la muestra (*adjusted Bayesian Information Criteria*, aBIC) y entropía. Valores más bajos de AIC, BIC y aBIC sugieren un modelo más parsimonioso, mientras que una entropía más alta también indica un mejor ajuste del modelo. La entropía varía de 0 a 1 y es un indicador de la precisión con la que el modelo clasifica a los individuos en su clase más probable. Una entropía con valores cercanos a 1 indica una clara delimitación de clases (160). La interpretabilidad y la parsimonia del modelo también se tuvieron en cuenta en la selección final del modelo. Asimismo, para identificar las clases clínicamente relevantes, solo se consideraron los modelos con tamaños de clase superiores al 5 % de la muestra (161).

B) Identificación de predictores basales de pertenencia a las distintas trayectorias de funcionamiento psicosocial

Para identificar posibles predictores basales de pertenencia a las distintas trayectorias identificadas, se generó una nueva variable con las clases latentes estimadas (es decir, el grupo de trayectoria estimado) derivadas del LCGA para un análisis de 3 pasos:

Primero creamos siete dominios cognitivos para usar como potenciales predictores basales utilizando datos de la evaluación neurocognitiva realizada en el seguimiento a 2 meses. Para ello, las puntuaciones directas de los pacientes en cada tarea neuropsicológica se estandarizaron a puntuaciones z en base al desempeño de toda la muestra. La selección de las tareas dentro de cada dominio cognitivo se basó en trabajos previos del grupo de PEPs (30, 81, 162). Posteriormente, se sumaron las puntuaciones z de diferentes pruebas y se promediaron para crear los siguientes dominios cognitivos: (1) el dominio "velocidad de procesamiento", basado en la tarea palabra-color del Test de Stroop y en el TMT-A; (2) el dominio "memoria de trabajo", que incluyó las subpruebas "Dígitos en orden

inverso" y "Letras y números" del WAIS-III; (3) el dominio "aprendizaje y memoria verbal", compuesto por el número total de palabras recordadas en los cinco ensayos de la lista A, el número total de palabras recordadas en el recuerdo libre a corto plazo, el número total de palabras recordadas en el recuerdo con claves semánticas a corto plazo, el número total de palabras recordadas en el recuerdo libre a largo plazo, el número total de palabras recordadas en el recuerdo con claves semánticas a largo plazo y los aciertos en la lista de reconocimiento del TAVEC; (4) el dominio "funciones ejecutivas", calculado en base al número de categorías y errores perseverativos del WCST, el test de interferencia del Test de Stroop y el TMT-B; (5) el dominio "atención", que se basó en varias medidas del CPT-II, como la comisión y el tiempo de reacción; (6) el dominio "fluidez verbal", compuesto los componentes categóricos (denominación de animales) y fonémicos (F-A-S) del COWAT; y (7) el dominio "cognición social", que incluyó el 'Manejo emocional' del MSCEIT. En caso de detectar puntuaciones extremas en el desempeño de las pruebas antes mencionada, es decir, más de cuatro desviaciones estándar (DE) por encima o por debajo de la media, las puntuaciones se truncaron a z = + / - 4. Dado que puntuaciones más altas en CPT-II, errores perseverativos WCST y TMT-A y -B indican un rendimiento más bajo, se invirtieron las puntuaciones z obtenidas de estas pruebas antes de construir los dominios cognitivos.

En segundo lugar, se compararon los potenciales predictores (es decir, variables sociodemográficas y clínicas basales, así como los dominios cognitivos creados) entre los participantes agrupados según su trayectoria predicha utilizando pruebas de Kruskal-Wallis y chi-cuadrado, según fuera necesario. Se seleccionó la prueba de Kruskal-Wallis para las variables continuas dado que estas no seguían una distribución normal (evaluada visualmente y mediante la prueba de Kolmogorov-Smirnov). En caso de encontrar diferencias significativas, se realizaron análisis de comparación post-hoc con corrección de Bonferroni para comparaciones múltiples para explorar con más detalle la presencia de diferencias significativas entre los sujetos clasificados en las distintas trayectorias.

En tercer lugar, las variables estadísticamente significativas en el análisis post-hoc en al menos dos comparaciones por pares de trayectorias fueron introducidas en un modelo de regresión multinomial para determinar potenciales predictores de trayectoria, ajustando por edad y sexo. Para la escala PANSS, solo las subescalas PANSS positiva y negativa se ingresaron como variables independientes para evitar la multicolinealidad. El modelo de regresión se construyó mediante la técnica por pasos hacia atrás (163), con el sexo y

la edad como factores fijos. Las clases/trayectorias latentes identificadas se utilizaron como variable dependiente. Como estábamos particularmente interesados en explorar predictores de trayectorias resilientes, seleccionamos el grupo más deteriorado como categoría de referencia.

C) Distribución del diagnóstico dentro de las trayectorias funcionales identificadas

Por último, para explorar si la distribución de los diagnósticos difería dentro de cada trayectoria funcional, y si variaba en el tiempo, comparamos la proporción de individuos con un diagnóstico de esquizofrenia, trastorno bipolar, trastorno esquizoafectivo y otras psicosis (que incluía el trastorno psicótico no especificado, el trastorno psicótico breve, el trastorno esquizofreniforme, el trastorno delirante, y el trastorno psicótico inducido por sustancias) en cada una de las trayectorias funcionales predichas al inicio, a los 12 meses y a los 24 meses de seguimiento mediante pruebas de chi-cuadrado.

Estudio 3

A) Identificación de trayectorias de ideación suicida y predictores de trayectorias

El análisis estadístico se diseñó de forma análoga al paso A del **Estudio 2** (158). Para este estudio, sin embargo, se utilizó la técnica de *growth mixture modeling* (GMM) para determinar el número de clases latentes de ideación suicida. Para el análisis del **Estudio 3** (133), además, se utilizó toda la muestra del estudio PEPs y la pertenencia a una determinada clase se asignó en base a las puntuaciones totales en el ítem "pensamientos suicidas" de la MADRS. Una vez determinado el número de trayectorias latentes, se examinó en qué trayectoria había sido clasificado cada participante según las probabilidades del modelo y esta información se incluyó como una nueva variable en el conjunto de datos original.

Posteriormente, se evaluaron posibles predictores basales de cada trayectoria de ideación suicida utilizando un análisis de regresión multinomial. Para reducir el número de predictores candidatos, primero realizamos un análisis de regresión multinomial univariante para cada predictor candidato, con las trayectorias como variables dependientes. Con respecto a las variables cognitivas, se usaron aquellos dominios

cognitivos creados para el **Estudio 2** (158) que hubieran mostrado asociación con ideación autolítica en la literatura previa o que fueran de especial relevancia en PEPs. Las variables evaluadas fueron: edad, sexo, estado civil, nivel educativo, ocupación, consumo de sustancias, ajuste premórbido, DUP, nivel socioeconómico familiar, subescalas de la FES, ítems de la MADRS, conciencia de enfermedad (medida por la escala PANSS), TQ, CI estimado, el dominio cognitivo "función ejecutiva", la tarea Stroop palabra-color, el dominio cognitivo "cognición social", el dominio cognitivo "aprendizaje y memoria verbal", el dominio cognitivo "memoria de trabajo" y el dominio cognitivo "atención". Las variables asociadas estadísticamente ($p < 0,05$) con las trayectorias identificadas en los análisis de regresión univariante se ingresaron luego en un modelo de regresión multinomial multivariable para determinar qué factores candidatos aún predecían la pertenencia a cada trayectoria al ajustar por la influencia de cada una de ellos. Para la escala MADRS, solo los ítems individuales -y no la puntuación total- se incluyeron como variables independientes. Se identificaron predictores significativos para el modelo multivariable mediante la técnica por pasos hacia atrás, con el sexo y la edad como factores fijos.

B) Comparación de las características de los participantes incluidos en las distintas trayectorias identificadas

Primero, el supuesto de normalidad se evaluó visualmente y utilizando la prueba de Kolmogorov-Smirnov. A continuación, realizamos pruebas de Kruskal-Wallis y chi-cuadrado, según fuera apropiado, para explorar diferencias sociodemográficas, clínicas y funcionales entre los individuos incluidos en las distintas trayectorias en diferentes momentos del seguimiento. Para comparar las variables cognitivas se realizó un análisis multivariado de covarianza (MANCOVA) ajustando el análisis por edad, sexo, nivel educativo y tratamiento antipsicótico. En caso de detectar diferencias estadísticamente significativas mediante las pruebas anteriores, se realizaron comparaciones múltiples por parejas mediante pruebas post-hoc con corrección de Bonferroni para comparaciones múltiples. Las variables sociodemográficas y cognitivas se compararon solo al inicio y a los 2 meses de seguimiento, respectivamente, mientras que las variables psicopatológicas (PANSS, MADRS) y las puntaciones en la FAST se compararon al inicio, a los 12 meses y a los 24 meses de seguimiento.

Los análisis LCGA y GMM se realizaron en la versión 3.6.3 de R, utilizando el paquete "lcmm" [(164); https://cran.r-project.org/web/packages/lcmm/index.html]. El resto de análisis se realizaron con el Statistic Package for Social Sciences (SPSS) v.23 o v.26 de IBM. El nivel de significación estadística para todos los análisis se estableció en un nivel alfa de 0,05.

5. RESULTADOS (RESUMEN)

Estudio 1

Salagre E, Grande I, Vieta E, Mezquida G, Cuesta MJ, Moreno C, et al. **Predictors of Bipolar Disorder Versus Schizophrenia Diagnosis in a Multicenter First Psychotic Episode Cohort: Baseline Characterization and a 12-Month Follow-Up Analysis.** Journal of Clinical Psychiatry. 2020;81(6):19m12996. doi: 10.4088/JCP.19m12996.

En nuestro **Estudio 1** (154) se incluyeron un total de 335 sujetos con un PEP. De estos, 47 sujetos (14,0%) fueron diagnosticados de trastorno bipolar a los 12 meses de seguimiento y 105 sujetos (31,3%) fueron diagnosticados de esquizofrenia. El 29,6% de los sujetos retuvieron un diagnóstico provisional (es decir, un diagnóstico de trastorno psicótico no especificado, trastorno psicótico agudo y transitorio, trastorno esquizofreniforme o trastorno psicótico inducido por sustancias) o recibieron un diagnóstico de trastorno esquizoafectivo. El 25% restante abandonó el estudio.

Comparaciones entre grupos a nivel de las características basales.

Características sociodemográficas

No se encontraron diferencias en las variables sociodemográficas entre los sujetos diagnosticados de trastorno bipolar y los sujetos diagnosticados de esquizofrenia. En cuanto a los antecedentes familiares de trastornos psiquiátricos, se encontró una mayor prevalencia de antecedentes familiares de trastornos del estado de ánimo entre los sujetos con un diagnóstico final de trastorno bipolar (38,2% vs. 18,0%; U de Mann-Whitney: 5,6; $p = 0,02$).

Características clínicas y funcionales

Al inicio del estudio, los pacientes con un diagnóstico final de trastorno bipolar mostraron significativamente más síntomas maníacos (puntuación media en la YMRS (Desviación Estándar, DE): 14,1 (14,1) vs. 7,3 (7,9); U de Mann-Whitney: 1.820; $p < 0,01$) y menos

síntomas negativos (puntuación media en la subescala PANSS negativa (DE): 15,0 (6,7) vs. 22,3 (8,5); U de Mann-Whitney: 3.662,5; $p < 0,001$) que los pacientes con un diagnóstico final de esquizofrenia. No se encontraron diferencias significativas en la puntuación total en la subescala PANSS positiva, aunque, al examinar ítems específicos, los pacientes con un diagnóstico final de trastorno bipolar mostraron puntuaciones significativamente más altas en grandiosidad y puntuaciones significativamente más bajas en conducta alucinatoria. Ambos grupos mostraron deterioro funcional, pero el ajuste premórbido (puntuación media en la escala PAS (DE): 38,4 (19,0) vs. 50,6 (22,9); U de Mann-Whitney: 2.933,5; $p < 0,01$) y el funcionamiento psicosocial (puntuación media en la escala FAST (DE): 23,6 (16,6) vs. 33,7 (15,0); U de Mann-Whitney: 2.993; $p = 0,001$) fueron mejores en el grupo con diagnóstico de trastorno bipolar. La DUP fue más prolongada en el grupo con un diagnóstico final de esquizofrenia (DUP promedio (DE): 144,2 (156,5) vs. 194,7 (133,6); U de Mann-Whitney: 3.037,5; $p < 0,01$). No hubo diferencias entre los dos grupos en el abuso de sustancias.

Medidas neuropsicológicas

Los pacientes con un diagnóstico final de trastorno bipolar y los pacientes con un diagnóstico final de esquizofrenia presentaron diferencias estadísticamente significativas en el CI premórbido estimado, siendo este más alto en los pacientes con un diagnóstico final de trastorno bipolar (CI premórbido estimado medio (DE): 98,7 (17,7) vs. 90,9 (14,5); test de la *t* de Student: 2,78; $p = 0,006$). Ambos grupos también mostraron diferencias significativas en funciones ejecutivas basales, en particular en la flexibilidad cognitiva, ya que los pacientes con un diagnóstico final de trastorno bipolar obtuvieron puntuaciones significativamente mejores en el número de errores perseverativos del WCST (media (DE): 14,2 (8,96) vs. 19,7 (13,4); U de Mann Whitney: 2.609,5; $p = 0,013$).

Factores relacionados con el diagnóstico de trastorno bipolar al año de seguimiento: modelo de regresión logística.

Se realizó un análisis de regresión logística para investigar el impacto de las características basales en el diagnóstico de trastorno bipolar vs. esquizofrenia a los 12 meses de seguimiento. El modelo completo que incluía como predictores los antecedentes

familiares de trastorno afectivo y las puntuaciones basales en la subescala negativa de la PANSS, en la FAST, y en errores perseverativos fue estadísticamente significativo (B = 2,3; p = 0,009; Exp (B) = 9,979). El modelo en su conjunto explicó entre el 21,1% (R cuadrado de Cox y Snell) y el 30,2% (R cuadrado de Nagelkerke) de la varianza y clasificó correctamente el 76,8% de los casos. Los síntomas basales negativos (OR: 0,930; IC del 95%: 0,866-0,999; p = 0,048), el funcionamiento psicosocial (OR: 0,956; IC del 95%: 0,922-0,991; p = 0,015) y el número de errores perseverativos en el WCST (OR: 0,946; IC del 95%:0,899-0,996; p = 0,035) contribuyeron significativamente al modelo (**Tabla 5**), lo que indica que puntuaciones más altas en la subescala negativa de la PANSS, en la FAST, y en errores perseverativos se asociaron con una menor probabilidad de diagnóstico de trastorno bipolar al año de seguimiento.

Tabla 5. Impacto de los factores basales en el diagnóstico de trastorno bipolar al año de seguimiento: modelo de regresión logística.

	Trastorno Bipolar			
	B (EE)	**OR**	**95% IC**	***p***
Constante	2,3 (0,884)	9,979		**0,009**
Puntuación basal PANSS-N	-0,072 (0,036)	0,930	(0,866-0,999)	**0,048**
Puntuación basal FAST	-0,045 (0,018)	0,956	(0,922-0,991)	**0,015**
Errores perseverativos (basal)*	-0,055 (0,026)	0,946	(0,899-0,996)	**0,035**
Historia familiar de ts. afectivos	0,761 (0,533)	2,140	(0,753-6,081)	0,153
R^2 Nagelkerke	0,302			
- 2 log	103,872			

Abreviaturas: EE: Error estándar; OR: Odds Ratio; IC: Intervalo de Confianza; PANSS-N: Positive and Negative Syndrome Scale-Negative scale; FAST: Functioning Assessment Short Test; ts: trastornos. **Valores en negrita** indican significación estadística al nivel de p < 0,05.

Estudio 2

Salagre E, Grande I, Solé B, Mezquida G, Cuesta MJ, Díaz-Caneja CM, et al. **Exploring Risk and Resilient Profiles for Functional Impairment and Baseline Predictors in a 2-Year Follow-Up First-Episode Psychosis Cohort Using Latent Class Growth Analysis.** Journal of Clinical Medicine. 2020;10(1):73. doi: 10.3390/jcm10010073.

Clases latentes de trayectorias funcionales

La muestra final del **Estudio 2** (158) incluyó a 261 participantes adultos. Un total de 14 individuos no fueron considerados para los análisis ya que solo se disponía de información sobre sus puntuaciones en la FAST en una evaluación.

Después de examinar los índices de bondad de ajuste, la entropía, la parsimonia del modelo y la interpretabilidad del modelo, el modelo de 4 clases con el término cuadrático se seleccionó como óptimo para nuestros datos (**Tabla 6**). La entropía fue aceptable (0,76) para el modelo de 4 clases, así como las probabilidades posteriores medias de pertenencia a cada clase (0,81 para la Clase 1, 0,92 para la Clase 2, 0,82 para la Clase 3 y 0,84 para la Clase 4). Esto sugiere que con el modelo de 4 clases probablemente se asigne correctamente a los individuos a su respectiva clase latente.

Tabla 6. Medidas de la bondad de ajuste del LCGA con soluciones de una a cuatro clases de trayectorias de funcionamiento psicosocial.

		Estadísticos de ajuste[a]				% muestra en cada clase			
Nº de clases	**Nº de parámetros**	**AIC**	**BIC**	**aBIC**	**Entropía**	**Clase 1**	**Clase 2**	**Clase 3**	**Clase 4**
1	4	9029,81	9044,07	9031,39	-	100	-	-	-
2	8	8675,19	8703,71	8678,35	0,82	54,02	45,98	-	-
3	12	8639,13	8681,91	8643,86	0,71	41,00	32,18	26,82	-
4	**16**	**8574,11**	**8631,14**	**8580,41**	**0,76**	**38,31**	**18,39**	**12,26**	**31,03**

Abreviaturas: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; aBIC: Bayesian Information Criterion ajustado al tamaño de la muestra. [a]Valores más bajos (AIC, BIC, and aBIC) indican un mejor ajuste del modelo. Una mayor entropía indica un mejor ajuste del modelo. Valores de 0,4, 0,6, y 0,8 representan baja, media y alta entropía (165). **Valores en negrita indican el modelo seleccionado.**

Las puntuaciones medias de la FAST en cada evaluación de los individuos agrupados según su trayectoria prevista se presentan en la **Figura 6**. Un grupo mostró un deterioro funcional leve al inicio del estudio y ausencia de deterioro funcional al final del seguimiento. Esta trayectoria se denominó *Deterioro leve-Mejora* [Clase 1; n = 100 (38,31%)]. Otro grupo mostró un deterioro funcional moderado al inicio y durante todo el seguimiento, y su trayectoria se denominó *Deterioro moderado-Estable* [Clase 2; n = 48 (18,39%)]. Un tercer grupo presentó deterioro funcional severo inicial, que mejoró a lo largo del seguimiento. Esta tercera trayectoria se denominó *Deterioro severo-Mejora* [Clase 3; n = 32 (12,26%)]. El último grupo, cuya trayectoria se denominó *Deterioro severo-Estable*, mostró deterioro funcional severo-moderado durante todo el seguimiento [Clase 4; n = 81 (31,03%)]. Así, el 50,57% de la muestra presentó una trayectoria caracterizada por una mejoría/recuperación funcional, mientras que el 49,42% presentó deterioro funcional persistente durante el seguimiento.

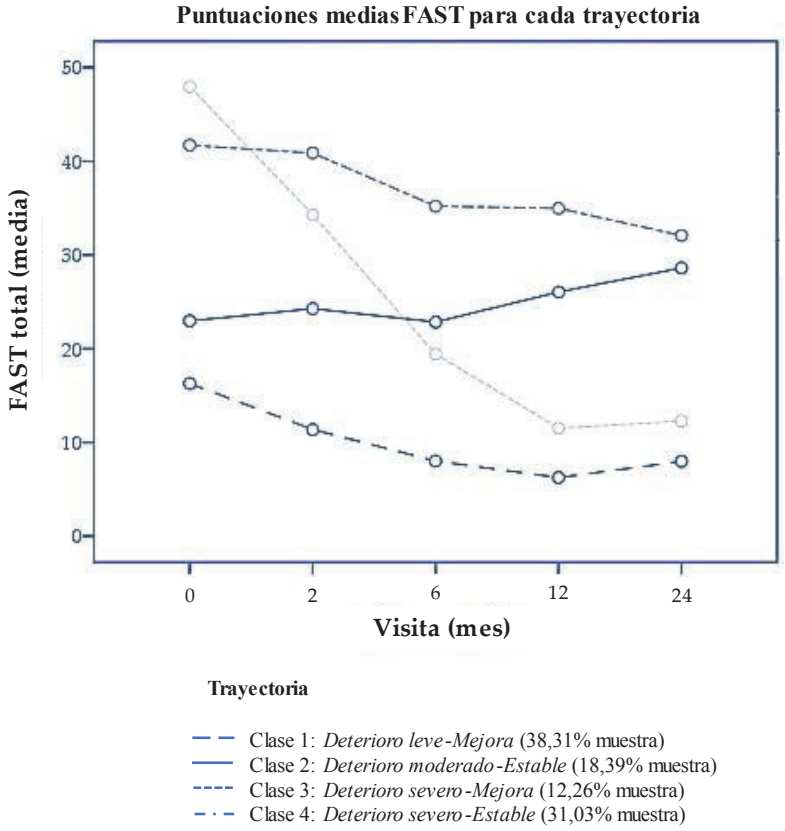

Figura 6. Evolución de las puntuaciones medias de la FAST* para cada una de las trayectorias funcionales derivadas del LCGA. *Puntuaciones más altas en la FAST indican mayor deterioro funcional.

Predictores basales de pertenencia a las trayectorias funcionales identificadas

Se encontraron diferencias estadísticamente significativas entre las 4 trayectorias en al menos dos comparaciones por pares en las siguientes variables: nivel socioeconómico de los padres, consumo de alcohol, puntuación total en la subescala PANSS positivo, puntuación total en la subescala PANSS negativo, puntuación total en la subescala PANSS general, puntuación total en la subescala PANSS total, puntuación total en la YMRS, puntuación total en la MADRS, puntuación total en la PAS, puntuación total en el dominio cognitivo "aprendizaje y memoria verbal" y en el dominio cognitivo "memoria de trabajo". Como se indicó en la metodología, para la escala PANSS solo las subescalas PANSS positiva y negativa se introdujeron como variables independientes en el modelo de regresión multinomial.

El análisis de regresión multinomial (modelo final: R2 Nagelkerke 53%, $\chi 2 = 140{,}26$; grados de libertad = 24; $p < 0{,}001$) indicó que, comparado con los individuos en la trayectoria *Deterioro severo-Estable,* los sujetos incluidos en la trayectoria *Deterioro leve-Mejora* presentaban más probabilidades de tener un nivel socioeconómico familiar medio-alto (OR: 4,14; IC del 95%: 1,65-10,42), síntomas negativos (OR: 0,89; IC del 95%: 0,83-0,96) y depresivos (OR: 0,94; IC del 95%: 0,89-0,99) iniciales menos severos, y mejor ajuste premórbido (OR: 0,96; IC del 95%: 0,94-0,98). Por otro lado, tener un mejor ajuste premórbido (OR: 0,96; IC del 95%: 0,93-0,99) y puntuaciones más altas en el dominio cognitivo "aprendizaje y memoria verbal" (OR: 3,09; IC del 95%: 1,36-7,03) se asoció con una mayor probabilidad de pertenecer a la trayectoria *Deterioro severo-Mejora* que a la trayectoria *Deterioro severo-Estable*. Finalmente, los individuos clasificados en la trayectoria de *Deterioro moderado-Estable* tenían más probabilidades de obtener una puntuación más baja al inicio del estudio en la subescala positiva de la PANSS (OR: 0,93; IC del 95%: 0,87-0,99) que el grupo incluido en la trayectoria *Deterioro severo-Estable*.

Distribución de diagnósticos entre las distintas trayectorias funcionales a lo largo del seguimiento

La distribución de los diagnósticos dentro de cada trayectoria funcional al inicio del estudio, en el seguimiento a 12 meses y en el seguimiento de 24 meses se muestra en la **Figura 7**. La distribución de los diagnósticos fue significativamente distinta entre los individuos clasificados en las distintas trayectorias tanto al inicio del estudio (n = 261; $\chi 2$ = 19,9; p = 0,02), como en el seguimiento a 12 meses (n = 202; $\chi 2$ = 42,6; p <0,001) y en el seguimiento a 24 meses (n = 156; $\chi 2$ = 28,5; p = 0,001). Comparado con la trayectoria de *Deterioro leve-Mejora,* se encontró una mayor proporción de pacientes con un diagnóstico de esquizofrenia entre los individuos clasificados en las trayectorias de *Deterioro severo-Estable* y *Deterioro moderado-Estable*. Por otro lado, los diagnósticos de trastorno bipolar y de otras psicosis fueron más frecuentes entre los individuos clasificados en la trayectoria de *Deterioro leve-Mejora* que entre los individuos clasificados en la trayectoria de *Deterioro severo-Estable*.

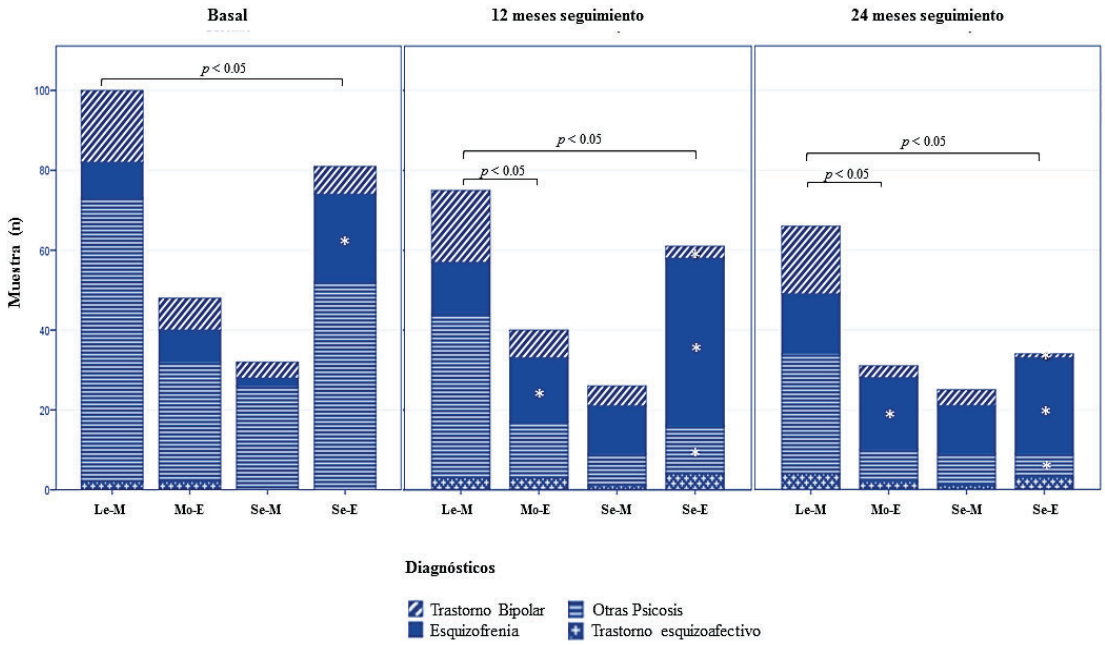

Figura 7. Distribución de los diagnósticos a lo largo del seguimiento para cada una de las trayectorias funcionales identificadas.

Abreviaturas: Le-M: *Deterioro leve-Mejora*; Mo-E: *Deterioro moderado-Estable*; Se-M: *Deterioro severo-Mejora*; Se-E: *Deterioro severo-Estable.* La Figura 7 representa, para cada una de las trayectorias funcionales derivadas del LCGA, el número de individuos con diagnóstico de trastorno bipolar, esquizofrenia, trastorno esquizoafectivo u otras psicosis al inicio, a los 12 y a los 24 meses de seguimiento. Otras psicosis incluyen trastorno psicótico no especificado, trastorno

psicótico breve, psicosis esquizofreniforme, trastorno delirante y psicosis inducida por sustancias. El símbolo (*) indica qué categorías diagnósticas dentro de la trayectoria de *Deterioro severo-Estable* y de la trayectoria de *Deterioro moderado-Estable* muestran una proporción significativamente diferente de individuos en comparación con la trayectoria de *Deterioro leve-Mejora*.

Análisis de mediación post-hoc

Dado que trabajos previos en pacientes con PEPs han sugerido que el ajuste premórbido puede influir en el funcionamiento psicosocial a través de la memoria verbal y los síntomas negativos (166), decidimos explorar mediante un análisis de mediación cómo interactúan los predictores identificados para impactar en el funcionamiento psicosocial en nuestra muestra (167). Los análisis se realizaron con PROCESS (168), con la edad y el sexo introducidos como covariables. El modelo utilizado para explorar la mediación entre los predictores de la trayectoria de *Deterioro severo-Mejora* vs. la trayectoria de *Deterioro grave-Estable* indicó que un mejor ajuste premórbido impacta positivamente en el dominio cognitivo "aprendizaje y memoria verbal", lo que a su vez aumenta la probabilidad de pertenecer a la trayectoria *Deterioro severo-Mejora* (efecto indirecto = -0,011; IC del 95%: -0,030 a -0,001). Sin embargo, nuestros resultados indican una mediación parcial complementaria, ya que tanto los efectos directos como los indirectos fueron significativos y apuntaron en la misma dirección (169). Con respecto a la mediación entre los predictores de las trayectorias de *Deterioro leve-Mejora* vs. *Deterioro grave-Estable*, pudimos establecer que el nivel socioeconómico de los padres media parcialmente sus efectos a través del ajuste premórbido y a través de los síntomas negativos iniciales (efecto indirecto = -0,249; IC del 95%: -0,551 a -0,086).

Estudio 3

Salagre E, Grande I, Jiménez E, Mezquida G, Cuesta MJ, Llorente C, et al. **Trajectories of suicidal ideation after first-episode psychosis: a growth mixture modeling approach**. Acta Psychiatrica Scandinavica. 2021. doi: 10.1111/acps.13279.

Clases latentes de trayectorias de ideación suicida

En el caso del **Estudio 3** (133), la muestra final estuvo compuesta por un total de 334 participantes. Un participante fue excluido de los análisis de GMM ya que no se disponía de información sobre sus puntuaciones en ideación suicida.

Siguiendo la misma metodología que en el **Estudio 2** (158), tras examinar los índices de bondad de ajuste, la entropía, la parsimonia y la interpretabilidad del modelo, se seleccionó el modelo de 3 clases con pendiente e intersección aleatorias y que incluía el término cuadrático como el que mejor se ajustaba a nuestros datos (**Tabla 7**). Aunque el modelo de 4 clases mostró un AIC, BIC y aBIC más bajos que el modelo de 3 clases, una de las clases incluyó menos de un 5% de participantes, por lo tanto, un porcentaje demasiado bajo para representar una clase significativa. Además, una inspección visual de las cuatro trayectorias reveló que la inclusión de una cuarta clase no proporcionaba información adicional sobre las trayectorias, ya que dos de las clases tenían una misma evolución de la ideación suicida (mejoría) y solo diferían en la intensidad de la ideación suicida a nivel basal. Por lo tanto, el modelo de 4 clases parecía desagregar una de las clases identificadas en el modelo de 3 clases, en lugar de proporcionar una clase adicional que incluyera individuos con una trayectoria genuinamente diferente. La entropía fue adecuada (0,85) para el modelo de 3 clases, así como las probabilidades posteriores medias de pertenencia a cada clase (0,96 para la Clase 1, 0,90 para la Clase 2, 0,81 para la Clase 3).

Tabla 7. Estadísticos de bondad de ajuste de GMM con soluciones de una a cuatro clases de trayectorias de ideación suicida.

		Estadísticos de ajuste[a]				% muestra en cada clase			
Nº de clases	**Nº de parámetros**	**AIC**	**BIC**	**aBIC**	**Entropía**	**Clase 1**	**Clase 2**	**Clase 3**	**Clase 4**
1	7	2992,33	3019,00	2996,80	-	100	-	-	-
2	12	2694,32	2740,05	2701,98	0,82	85,93	14,07	-	-
3	**17**	**2617,83**	**2682,62**	**2628,69**	**0,85**	**83,53**	**9,58**	**6,89**	**-**
4	22	2565,71	2649,56	2579,77	0,83	7,78	20,66	68,86	2,69

Abreviaturas: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; aBIC: Bayesian Information Criterion ajustado al tamaño de la muestra. [a]Valores más bajos (AIC, BIC, and aBIC) indican un mejor ajuste del modelo. Una mayor entropía indica un mejor ajuste del modelo. Valores de 0,4, 0,6, y 0,8 representan baja, media y alta entropía (165).

Las tres trayectorias estimadas por el modelo de 3 clases se muestran en la **Figura 8**. La mayoría de la muestra fue clasificada en una trayectoria caracterizada por la ausencia de ideación suicida al inicio y durante todo el período de seguimiento [trayectoria *No ideación suicida*; n = 279 (83,53%)]. El segundo grupo presentó ideación suicida al inicio del estudio, que mejoró durante el seguimiento [trayectoria con *Mejora de la ideación suicida*; n = 32 (9,58%)]. Finalmente, el tercer grupo mostró inicialmente una ideación suicida fugaz o nula, cuya intensidad empeoró levemente durante el seguimiento [trayectoria con *Empeoramiento de la ideación suicida*; n = 23 (6,89%)].

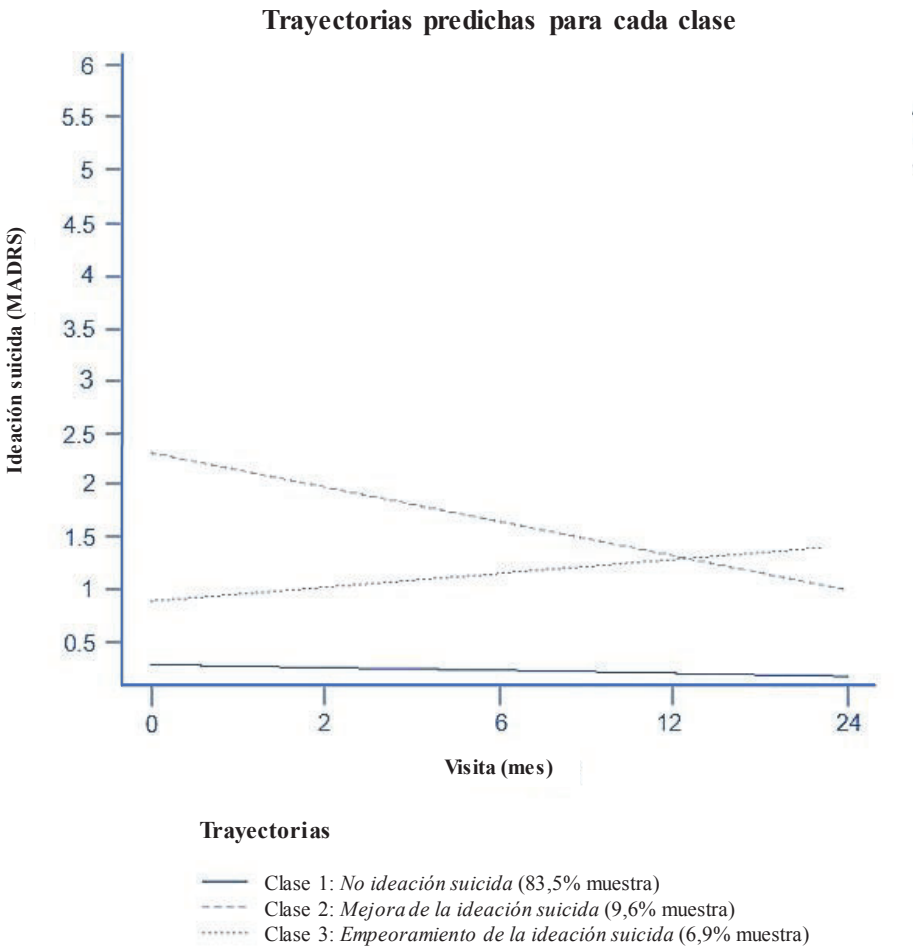

Figura 8. Trayectorias predichas de ideación suicida.

Predictores basales de pertenencia a las trayectorias identificadas

Los resultados del análisis de regresión multinomial univariado identificaron las siguientes características basales asociadas significativamente con las diferentes trayectorias de ideación suicida: DUP, MADRS-Tristeza aparente; MADRS-Tristeza reportada; MADRS-Tensión interior; MADRS-Sueño reducido; MADRS-Apetito reducido; MADRS-Dificultad de concentración; MADRS-Lasitud; MADRS-Incapacidad para sentir, MADRS-Pensamientos pesimistas; Puntuación total PAS; FES-Cohesión; FES-Conflicto; FES-Orientación al logro; FES-Organización.

El análisis de regresión multinomial (modelo final: R2 Nagelkerke 35,2%; $\chi 2 = 82,16$; grados de libertad = 14; $p < 0,001$) indicó que la edad, la DUP, la puntuación en MADRS-

Sueño reducido, MADRS-Incapacidad para sentir, MADRS-Pensamientos pesimistas, FES-Conflicto, FES-Orientación al logro y FES-Organización contribuyeron a diferenciar entre las tres trayectorias de ideación suicida. Específicamente, en comparación con la trayectoria *No ideación suicida*, la trayectoria *Mejora de la ideación suicida* se asoció con puntuaciones basales más altas en MADRS-Incapacidad para sentir (OR: 1,510; IC del 95%: 1,075-2,120) y MADRS-Pensamientos pesimistas (OR: 2,453; IC 95%: 1,681-3,578), con puntuaciones basales más altas en las subescalas FES-Conflicto (OR: 1,083; 95% CI: 1,017-1,154) y FES-Organización (OR: 1,064; 95% CI: 1,002-1,130), y con puntuaciones basales más bajas en la subescala FES-Orientación al logro (OR: 0,932; IC del 95%: 0,875-0,992). Por otro lado, una mayor edad (OR: 1,092; IC 95%: 1,002-1,191), una DUP más larga (OR: 1,004; IC 95%: 1,001-1,007) y unas puntuaciones más altas en la MADRS-Sueño reducido (OR: 1,344; IC del 95%: 1,034-1,747) se asociaron con la trayectoria de *Empeoramiento de la ideación suicida* en comparación con la trayectoria de *No ideación suicida*.

Comparaciones entre trayectorias a nivel de variables sociodemográficas, cognitivas, clínicas y funcionales

No se encontraron diferencias significativas entre los tres grupos en ninguna de las variables sociodemográficas o cognitivas evaluadas. Los sujetos asignados a la trayectoria *Empeoramiento de la ideación suicida* mostraron el peor ajuste premórbido, pero la significación estadística solo se alcanzó en la comparación por pares con los individuos en la trayectoria *No ideación suicida* (mediana de PAS total [IQR]: 52 [32] vs. 41 [36]; p ajustado = 0,036). No se observaron diferencias con respecto a la proporción de participantes con un diagnóstico de psicosis afectivas vs. no afectivas en cada una de las trayectorias.

Con respecto a las características psicopatológicas basales, los tres grupos presentaron diferencias clínicamente significativas en la intensidad de los síntomas depresivos medidos con la MADRS, aunque las diferencias solo alcanzaron significación estadística al comparar las puntuaciones de los sujetos en la trayectoria *No ideación suicida* con los sujetos en las otras dos trayectorias. Los sujetos en la trayectoria *Mejora de la ideación suicida* mostraron síntomas depresivos moderados al inicio del estudio (mediana de la puntuación MADRS total [IQR]: 25 [15]), mientras que los sujetos en la trayectoria *No*

ideación suicida y en la trayectoria *Empeoramiento de la ideación suicida* mostraron síntomas depresivos leves (mediana de la puntuación total de MADRS [IQR]: 10 [13] y 17 [13], respectivamente). En la **Figura 9** se puede encontrar una representación gráfica de la evolución de los síntomas depresivos, los síntomas psicóticos y el funcionamiento psicosocial entre los tres grupos.

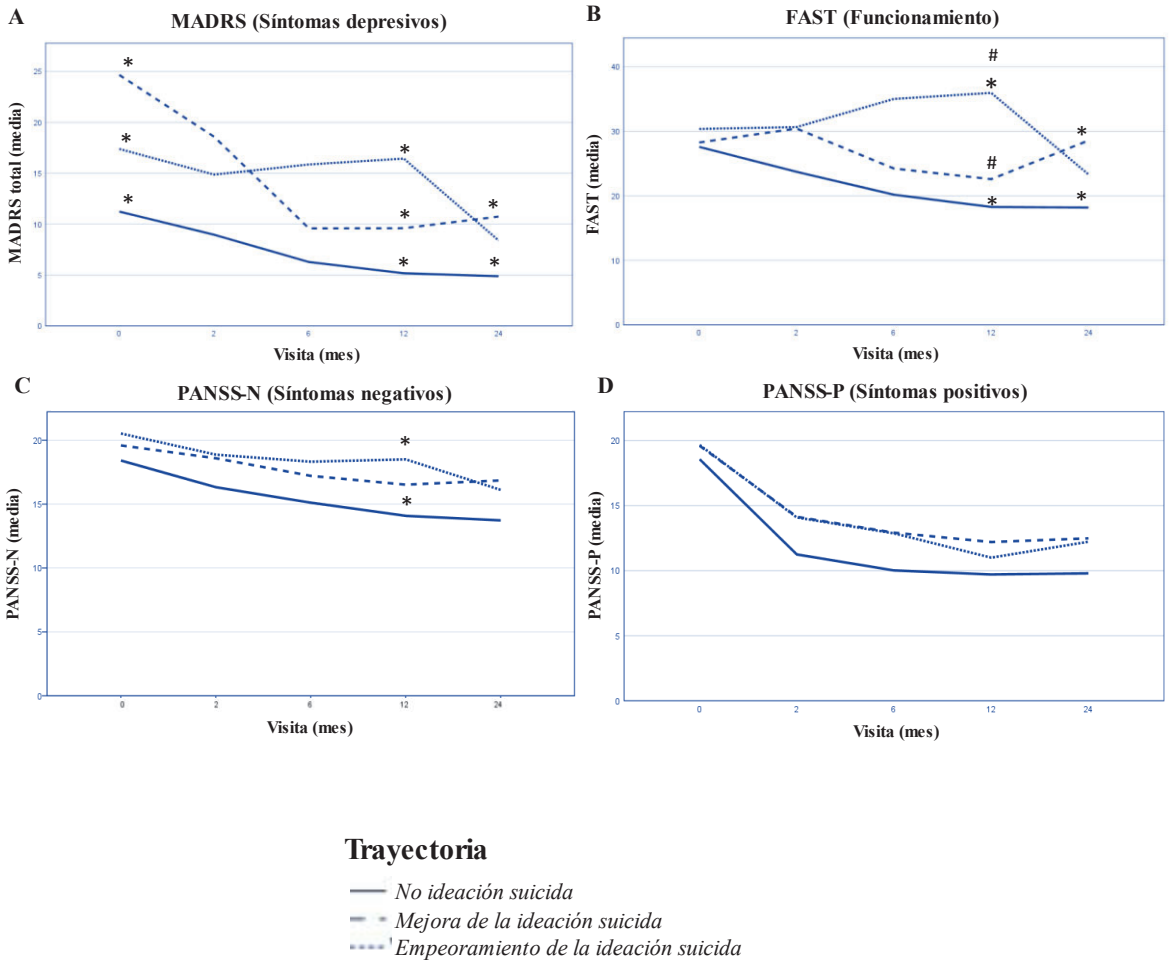

Figura 9. Evolución de las variables clínicas y funcionales a lo largo del estudio para las tres trayectorias de ideación suicida identificadas.

(A) Evolución de los síntomas depresivos, medidos por la MADRS, a lo largo del seguimiento de 24 meses para los individuos agrupados según la trayectoria de ideación suicida donde han sido clasificados. Las puntuaciones medias en la MADRS de los individuos en las trayectorias *Mejora de la ideación suicida* y *Empeoramiento de la ideación suicida* fueron significativamente diferentes de las puntuaciones medias en la MADRS de los individuos en la trayectoria *No ideación suicida* al inicio del estudio y a los 12 meses de seguimiento. A los 24 meses de seguimiento, solo se encontraron diferencias significativas entre los sujetos en la trayectoria *Mejora de la ideación suicida* y la trayectoria *No ideación suicida*. (B) En este panel se describe el funcionamiento psicosocial durante los 24 meses de seguimiento. A los 12 meses de seguimiento se encontraron

puntuaciones medias de la FAST significativamente más altas en los individuos en la trayectoria *Empeoramiento de la ideación suicida* en comparación con los individuos incluidos en las trayectorias *Mejora de la ideación suicida* y *No ideación suicida*. Los paneles (C) y (D) describen, respectivamente, la evolución de los síntomas negativos, evaluados con la subescala negativa de la PANSS, y la evolución de los síntomas psicóticos positivos, medidos con la subescala positiva de la PANSS. (C) En cuanto a los síntomas negativos, a los 12 meses de seguimiento los individuos clasificados en la trayectoria *No ideación suicida* mostraron puntuaciones significativamente más bajas en la subescala negativa de la PANSS que los sujetos en la trayectoria *Empeoramiento de la ideación suicida*. (D) No se encontraron diferencias significativas entre los grupos respecto a las puntuaciones en la subescala positiva de la PANSS en ninguna de las tres evaluaciones.

Las diferencias significativas entre los grupos en diferentes puntos de tiempo están representadas por los símbolos * ($p < 0,01$ frente a trayectoria *No ideación suicida*) o # ($p < 0,01$ frente a trayectoria *Mejora de la ideación suicida*).

6. ARTICULOS

The American Journal of
Psychiatry
175th Year of Publication

Early Intervention in Bipolar Disorder

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Bipolar disorder is a recurrent disorder that affects more than 1% of the world population and usually has its onset during youth. Its chronic course is associated with high rates of morbidity and mortality, making bipolar disorder one of the main causes of disability among young and working-age people. The implementation of early intervention strategies may help to change the outcome of the illness and avert potentially irreversible harm to patients with bipolar disorder, as early phases may be more responsive to treatment and may need less aggressive therapies. Early intervention in bipolar disorder is gaining momentum. Current evidence emerging from longitudinal studies indicates that parental early-onset bipolar disorder is the most consistent risk factor for bipolar disorder. Longitudinal studies also indicate that a full-blown manic episode is often preceded by a variety of prodromal symptoms, particularly subsyndromal manic symptoms, therefore supporting the existence of an at-risk state in bipolar disorder that could be targeted through early intervention. There are also identifiable risk factors that influence the course of bipolar disorder, some of them potentially modifiable. Valid biomarkers or diagnosis tools to help clinicians identify individuals at high risk of conversion to bipolar disorder are still lacking, although there are some promising early results. Pending more solid evidence on the best treatment strategy in early phases of bipolar disorder, physicians should carefully weigh the risks and benefits of each intervention. Further studies will provide the evidence needed to finish shaping the concept of early intervention.

Am J Psychiatry 2018; 175:411–426; doi: 10.1176/appi.ajp.2017.17090972

William J. Mayo (1861–1939) stated that "the aim of medicine is to prevent disease and prolong life; the ideal of medicine is to eliminate the need of a physician" (1). Hence, physicians have been trying for almost a century to find early interventions that would prevent the onset of diseases, or at least change their course. Big steps have been made in several fields of medicine, such as cardiology and oncology. When it comes to psychiatry, although there is ground for optimism, there is still a long way to go (2).

Difficulties concerning primary prevention and intervention in psychiatry arise mainly from the absence of a clear etiology. Consequently, psychiatry has focused more on tertiary prevention, that is, in the use of therapies aiming to minimize the consequences of clinically established disease rather than to prevent its occurrence (3). However, considering the high prevalence of mental illnesses, their significant contribution to global disease burden among young people, and their considerable impact on public health, the implementation of early interventions in psychiatry should be considered a major priority.

To achieve this goal, and since early intervention focuses on known risk factors and early signs of the illness, there is a growing interest in understanding the early course of psychiatric conditions. For bipolar disorder, until recently most information regarding early manifestations came from retrospective and cross-sectional studies, which have a high risk of recall bias and do not allow assessment of temporality. Still, current evidence suggests that bipolar disorder has a progressive nature (4–6), therefore supporting the existence of milder phases of the condition prior to the classic presentation of the illness. This progressive nature makes bipolar disorder an ideal candidate for early intervention strategies, especially considering that 50%–70% of people with bipolar disorder usually start to manifest mood symptoms

AJP AT 175
Remembering Our Past As We Envision Our Future

April 1925: Interpretations of Manic-Depressive Phases

Earl Bond and G.E. Partridge reviewed a number of patients with manic-depressive illness in search of a unifying endo-psychic conflict. They concluded that understanding either phase of illness was "elusive" and "tantalizing beyond reach."

(Am J Psychiatry 1925: 81: 643–662)

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before age 21 (7–12). This highlights the need for early interventions to prevent or at least delay the onset of the full syndromal illness during childhood, which is crucial to avoid impacts on normal developmental tasks and psychosocial or neurobiological deterioration (13) and to prevent future complications, such as the development of psychiatric comorbidities, impaired functioning, or premature death by suicide (14).

Noting that *The American Journal of Psychiatry* is commemorating its 175th year of publication, we see early intervention in bipolar disorder as one of the cutting-edge topics in psychiatry. Although there are limited data based on this concept arising from the area of psychoses, we believe that ongoing and forthcoming research in this field is going to have a long-lasting impact on the field as mental health care increasingly turns its focus to prevention (15). In fact, more than 20 years ago, *The American Journal of Psychiatry* published one of the first articles discussing the role of prodromes and precursors in major depression (16); 10 years later the journal published the first paper proposing early intervention to prevent substance abuse in first-episode bipolar disorder (17) and a landmark trial indicating that first-episode psychosis could be treated with lower dosages of antipsychotics than are used in multiple-episode psychoses (18). Hence, in this review we will focus on the results obtained in longitudinal studies assessing variables considered as predictors of conversion to bipolar disorder or of illness course, conducted in offspring at high familial risk for bipolar disorder, community cohorts, and pediatric populations with diagnoses of bipolar disorder. Finally, the available psychological and pharmacological intervention data in the early stages of bipolar disorder will be covered, as well as the point of view of the authors on future directions of the research on the issue.

IDENTIFYING RISK FACTORS AND PRODROMAL SYMPTOMS AS PREDICTORS OF BIPOLAR DISORDER ONSET AND COURSE

The identification of risk factors or prodromal symptoms defining an at-risk stage has important treatment implications, as early stages are anticipated to be likely to be more responsive to treatment and therefore may need less complex interventions (19, 20). Moreover, psychiatric treatments likely have a more beneficial impact when applied at an earlier stage of the disease (21). A key issue is that the at-risk state in most disorders, including bipolar disorder, is pleomorphic and nonspecific and has the potential to evolve into diverse formed phenotypes or no disorder.

Environmental Risk Factors

Although bipolar disorder has a high genetic loading (22), it is considered a multifactorial disease that is influenced by environmental factors (23), some of which might be used as targets of early intervention strategies since they can be potentially modified (24). Life events have been proposed as triggers of future bipolar disorder (25), but results are controversial. While some studies (26, 27) found a positive association between mean life events and risk of mood disorder, Wals and colleagues (28) found that stressful life events were not related to the onset of mood episodes after adjustment for prior anxious or depressive symptoms. Considering the impact of life events in illness trajectory, lifetime sexual abuse seems to be related to a worse course of bipolar disorder (29–32). Recent public outrage at institutional childhood sexual abuse and campaigns to address this in many countries are an exemplar of a policy approach that may have an impact on a critical risk (33). Antidepressant use in depressed youths also may be a risk factor (34), as antidepressants might induce (hypo)manic symptoms (35).

Substance misuse is a prevalent condition in mood disorders that worsens illness prognosis (36). Moreover, its presence has been related to an increased risk of bipolar disorder at follow-up in patients seeking help for depression, anxiety, or substance use disorder (37). Although some studies have found a lower prevalence of substance use disorder in patients with a first mania episode compared with multiple-episode patients (38–40), this finding suggests that primary prevention of a secondary condition, in this case substance abuse in patients with bipolar disorder, needs to be considered (40). Substance use disorder can be predicted by lifetime alcohol experimentation, lifetime oppositional defiant disorder and panic disorder, family history of substance use disorder, or low family cohesiveness (39); these risk factors show a compounding effect. Presence of mixed features also appears to increase the risk of developing substance use disorder (17). Smoking may be associated with an increased risk of psychiatric disorders from depression to schizophrenia (41). Of concern, even maternal smoking may increase risk in offspring (42, 43).

Biological Risk Factors

Family history of bipolar disorder is one of the more solid risk factors for bipolar disorder (44) and is a primary threshold from universal to indicated prevention strategies. Longitudinal studies conducted in bipolar offspring found that age at onset and mood disorder subtype of the probands influence the heritability and course of bipolar disorder (38, 45, 46). For instance, these studies showed that offspring of early-onset bipolar disorder probands were at an increased risk for any bipolar disorder (45, 46) and that lithium nonresponsiveness in parents was related to a poorer premorbid functioning, a more chronic course, and a higher prevalence of psychotic disorders in their offspring (38).

Neurodevelopmental factors are being studied as potential early markers of specific mental illness. A prebirth cohort study found that child developmental delay assessed with the Denver Developmental Screening Test, which measures fine and gross motor skills, language, and personal–social development, was a predictor of later mania but not of depression or psychosis (47). In the same study, premorbid cognitive ability predicted only psychosis (47). However, there are data indicating that children with the highest academic attainment may be at greatest risk of bipolar disorder, while those with the weakest grades were at moderately increased risk (48) (Table 1).

Prodromal Symptoms

Results from longitudinal studies indicate that bipolar offspring are at a higher risk of developing bipolar disorder than

TABLE 1. Main Preliminary Findings on Bipolar and Psychosis Prodromal Stage

Characteristic	Bipolar Disorder Prodromal Stage	Psychosis Prodromal Stage (145, 157)
Main risk factor	Family history of early-onset bipolar disorder	Family history of psychosis
Early symptoms	Subjective sleep disturbances, anxiety, depression	Attention problems, depression, anxiety, avolition, social difficulties, disorganization, sleep disturbances
Proximal[a] symptoms	Subthreshold (hypo)manic symptoms	Subthreshold psychotic symptoms
Neurodevelopmental profile	Superior or low premorbid cognitive functioning	Verbal memory and processing speed deficits

[a] Proximal symptoms are those that appear closer to conversion to full symptomatic episode.

the general population (46, 49–51), but they are equally at risk of developing other psychopathology, such as major depressive disorder, anxiety disorders, or psychotic disorders (28, 38, 44, 45, 52–54) (Table 2). Similarly, adolescents from community cohort studies who developed bipolar disorder also exhibited significantly high rates of comorbid anxiety disorders and disruptive behavior disorders (55).

As there is strong evidence that the index (hypo)manic episode in both bipolar offspring and community cohorts is frequently preceded by other affective or nonaffective symptoms (38, 49, 52, 55), longitudinal studies have tried to disentangle whether any of these conditions can be considered as early symptoms of bipolar disorder and help to predict future bipolar disorder onset. For instance, in the Dutch bipolar offspring cohort, 88% of the offspring who developed a bipolar spectrum disorder initially presented with a depressive episode, with an average time to bipolar conversion of 5.1 years (52) (Table 2). Subjective sleep problems also may be related to the development of bipolar disorder (56) (Table 2), but more evidence is needed before any firm conclusions can be drawn. Childhood anxiety disorder has been described as a prodromal symptom of major mood disorders, but it seems more related to unipolar depression than to bipolar disorder (44, 54). Anxiety disorders, in turn, seem to be predicted by the temperamental traits of shyness and emotionality (54) (Table 2). In contrast, subthreshold (hypo)manic symptoms have emerged as a key predictor of the development of (hypo)mania in community (37, 57, 58), high-risk (59), and bipolar offspring (45, 49, 50, 60, 61) cohorts (Table 2), even after adjusting for risk factors associated with psychopathology, such as parental psychiatric morbidity (49, 58). Moreover, greater intensity of hypomanic symptoms or earlier age at onset is associated with an increased risk of progressing to bipolar I or II disorder among children and adolescents initially meeting operationalized criteria for bipolar disorder not otherwise specified (62, 63).

Some studies have focused on the predictive value of several dimensional factors and not only in categorical predictors (45, 50, 61). Data emerging from the Pittsburg Bipolar Offspring youth cohort (45) show that offspring of parents with bipolar disorder with significant symptoms of anxiety/depression, affective lability, and subsyndromal manic symptoms were at increased risk of developing bipolar spectrum disorders. While affective lability and anxiety/depression were elevated throughout follow-up in those who later developed bipolar disorder, manic symptoms increased up to the point of conversion. Offspring with all the above risk factors, and particularly those with parents with early-onset bipolar disorder, had a 49% risk of developing bipolar disorder. Similarly, in an Amish cohort of bipolar offspring (50), converters to bipolar disorder showed a higher prevalence of sensitivity, hyperalertness, anxiety, and somatic complaints during the preschool period and more mood and energy fluctuations, tearfulness, sleep disturbances, and fearfulness during school years. However, a meta-analysis reporting data on prodromal symptoms in pediatric and adult samples with bipolar disorder pointed out that even if there are some highly reported prodromal symptoms, the prodromal stage tends to differ between individuals (64).

As bipolar disorder usually first presents with a depressive episode (65), longitudinal studies have assessed the presence of prodromal symptoms of conversion from unipolar depression to bipolar disorder (Figure 1). The main replicated finding is the relationship between diagnosis of psychotic depression and switching to (hypo)mania (66–69). A recent meta-analysis identified a family history of bipolar disorder, an earlier age at depression onset, and the presence of psychotic symptoms as most robustly predicting conversion from depression to bipolar disorder (70). When focusing only on patients diagnosed with psychotic depression, it has been found that conversion to bipolar disorder is mainly related to early age at onset (67, 68), functional impairment (67), mixed features (69, 71), and previous hypomanic symptoms (72).

In summary, parental bipolar disorder, especially early-onset (e.g., <21 years old) parental bipolar disorder, is the most important single risk factor for developing bipolar disorder. In addition, if the youth has subsyndromal manic symptoms, which is the most consistent prodromal factor, and ongoing mood lability or irritability, anxiety, and depression, there is increased likelihood that this youth will develop bipolar disorder (Figure 2). However, the onset and severity of these symptoms are heterogeneous.

HELPING PREDICTION OF BIPOLAR DISORDER ONSET THROUGH SCREENING TOOLS

The above predictors are based on studies that focus on groups as a whole, but they do not inform about the individual risk of developing bipolar disorder. Moreover, the prodromal symptoms are heterogeneous, requiring the assessment of each individual risk (64). Building on accumulated knowledge about early bipolar disorder symptoms, researchers have striven to

TABLE 2. Main Findings of Longitudinal Studies Assessing Prodromal Symptoms in Offspring of Patients With Bipolar Disorder[a]

Authors	Mean Follow-Up	N at Baseline (M/F)	Mean Age at Baseline (years)	Offspring Sample Description	Main Objectives
Pittsburgh Bipolar Offspring Study					
Axelson et al., 2015 (49)	6, 8 years	BO: 391 (200/191), CO: 248 (114/134)	BO: 11.9 (SD 3.7), CO: 11.8 (SD 3.6)	Offspring of patients with BD I or II	To study diagnostic differences between BO and CO; to describe the developmental trajectory of mood episodes and identify diagnostic precursors of full-threshold BD in BO
Levenson et al., 2015 (56)	Not stated	BO: 386 (190/196), CO: 301 (144/157)	BO: 11.4 (SD 3.6), CO: 11.0 (SD 3.5)	Offspring of patients with BD I or II	To evaluate baseline sleep and circadian phenotypes in BO and CO; to evaluate whether baseline sleep and circadian phenotypes in the BO are associated with future conversion to BD
Hafeman et al., 2016 (45)	Not stated	BO: 359 (176/183), CO: 220 (99/121)	BO: 11.6 (SD 3.6), CO: 11.7 (SD 3.4)	Offspring of patients with BD I or II	To assess dimensional symptomatic predictors of new-onset BSD in BO
Dutch Bipolar Offspring Study					
Mesman et al., 2013 (52)	12 years	BO: 108 (58/50)	BO: 16.5 (SD 2.00)	Offspring of parents with BD I or II and age 12 to 21 years	To provide data on the onset and developmental trajectories of mood disorders and other psychopathology in BO
Mesman et al., 2017 (61)	12 years	BO: 107 (57/50)	BO: 16 (range 12–21)	Offspring of parents with BD I or II and age 12 to 21 years	To identify early symptomatic signs of BD in BO with a history of mood disorder (any mood disorder group); to explore the early symptomatic signs of first mood episode development in BO without a history of mood disorder (no mood disorder group)

Assessment Tools	Conversion Rate to BSD	Main Findings	Offspring Exclusion Criteria	Limitations
SCID, K-SADS-PL; subthreshold (hypo)mania was diagnosed using the BDNOS criteria from the COBY study, FH-RDC, the Hollingshead scale (SES)	9.2%	There was a higher prevalence of BSD and MDE in BO as compared with CO. Nearly all non-mood axis I disorders were more prevalent in BO than in CO. Mania/hypomania was almost always preceded by mood and non-mood disorders. Distinct subthreshold episodes of (hypo)mania were the strongest predictor of progression to full threshold mania/hypomania in BO.	Mental retardation	The information collected for the interval between evaluations was retrospective; most offspring were not through the age of risk for onset of BD at their last assessment; low conversion rate; only a small proportion of the biological coparents had direct diagnostic interviews.
SCID, K-SADS-PL; subthreshold (hypo)mania was diagnosed using the BDNOS criteria from the COBY study, PDS, Tanner stages, Hollingshead scale (SES), SSHS	Not stated	Conversion to BSD among BD was significantly predicted by parental and child ratings of child frequent nighttime awakenings, by parental ratings of inadequate sleep, and by child report of time to fall asleep on weekends.	Mental retardation	Use of questionnaire-based proxy measures of sleep and circadian phenotypes; long average time span between baseline SSHS and conversion to BD; low conversion rate; cross-sectional nature of the analyses.
FH-RDC, SCID, K-SADS-PL, CALS, CBCL, CADS, CHI, DBD, MFQ, SCARED, Hollingshead Four-Factor Index (SES); subthreshold (hypo)mania was diagnosed using the BDNOS criteria from the COBY study	14.7%	The most important prospective dimensional predictors of new-onset BSD disorders were anxiety/depressive symptoms (baseline), affective lability (baseline and proximal), and subthreshold manic symptoms (proximal). There was an increased risk of new-onset BSD with earlier parental age at mood disorder onset.	Mental retardation	Follow-up visits every 2 years; low conversion rates; not all offspring were through the age of risk for onset of bipolar illness at their last assessment.
K-SADS-PL, SCID	13% (3% BD I)	72% of BO developed psychopathology. In 88% of offspring with a BSD, the index episode was an MDE. In total, 24% of offspring with a UMD developed a BSD. Mood disorders were often recurrent, with high comorbidity rates, and started before age 25.	Children with a severe physical disease or disability or with an IQ below 70	Small sample size; low generalizability to populations without familial risk; no control group; no data on prepubertal and early adolescent disorders or episodes; not assessing for BDNOS.
K-SADS-PL	2.6% (BD II) in the no mood disorder group, 34% (BD I and II) in the any mood disorder group	Subthreshold manic symptoms were the strongest predictor of BD onset in the any mood disorder BO group. Subthreshold depressive symptomatology was associated with first mood disorder onset.	Children with a severe physical disease or disability or with an IQ below 70	Small sample size; low generalizability to populations without familial risk; only the baseline screen items of the K-SADS-PL were used.

continued

TABLE 2, *continued*

Authors	Mean Follow-Up	N at Baseline (M/F)	Mean Age at Baseline (years)	Offspring Sample Description	Main Objectives
Canadian Bipolar Offspring					
Duffy et al., 2013 (54)	6.23 years	BO: 229 (93/136), CO: 86 (36/50)	BO: 16.35 (SD 5.34), CO: 14.71 (SD 2.26)	Offspring with only one parent with a diagnosis of BD I or II and no other major psychiatric comorbidity	To describe the cumulative incidence of anxiety disorders in BO compared with CO; to identify predictors of anxiety disorders in BO; to determine the association between antecedent anxiety disorders and subsequent mood disorders in BO
Duffy et al., 2014 (38)	6.29 years	BO: 229 (92/137), CO: 86 (36/50)	BO: 16.35 (SD 5.34), CO: 14.71 (SD 2.25)	Offspring with only one parent with a diagnosis of BD I or II and no other major psychiatric comorbidity	To estimate the differential risk of lifetime psychopathology between BO and CO; to compare the clinical course of mood disorders between BO subgroups (defined by the lithium response of the parent)
Other offspring cohorts					
Akiskal et al., 1985 (53)	3 years	BO: 68 (39/29)	Not stated	Individuals with a parent or older sibling with BD I, less than 24 years old at intake, and looking for clinical attention within approximately 1 year of onset of psychopathologic manifestations	To chart the prospective course of early manifestations in the referred juvenile relatives of known bipolar adults
Carlson et al., 1993 (51)	3 years	BO: 125, CO: 108	BO: 7–16 years	Children of parents with BD	To examine the relationship between attention and behavioral disorders in childhood and subsequent BD
Egeland et al., 2012 (50)	16 years	BO: 115, CO: 106	Not stated	BO from the CARE study in preschool or in school (younger than 14 years old)	To identify the pattern and frequency of prodromal symptoms/behaviors associated with onset of BD I during childhood or adolescence

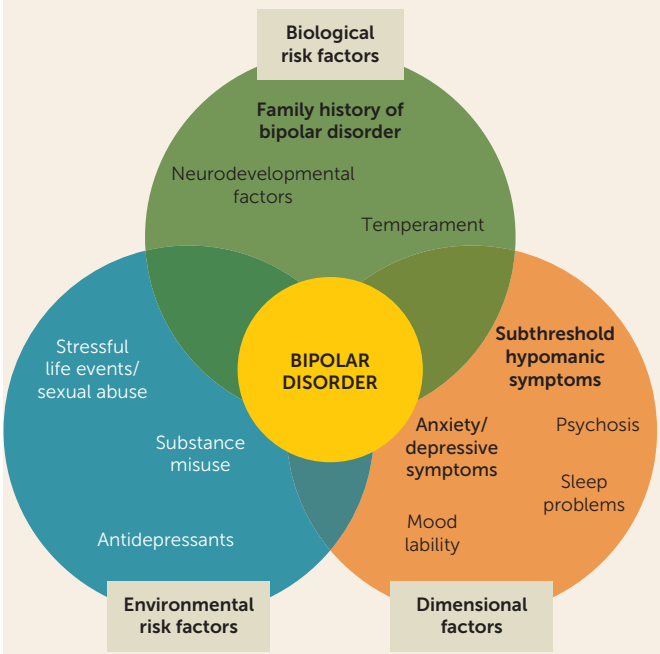
[a] BD=bipolar disorder; BDNOS=bipolar disorder not otherwise specified; BO=bipolar offspring; BSD=bipolar spectrum disorder; CADS=Childhood Affective Dysregulation Scale; CALS=Child Affective Lability Scale; CARE=Children and Adolescent Research Evaluation; CBCL=Child Behavior Checklist; CECA.Q=Childhood Experiences of Care and Abuse Questionnaire; CHI=Children's Hostility Inventory; CO=control offspring; COBY=Course and Outcome of Bipolar Youth; DBD=Disruptive Behavioral Disorders Rating Scale; DBRS=Devereux School Behavior Rating Scales; EAS=Early Adolescent Temperament Scale; FH-RDC=Family History–Research Diagnostic Criteria; GAS=Global Assessment Scale; HARS=Hamilton Anxiety Rating Scale; K-SADS-PL=Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version; MCDQ=Mood Clinic Data Questionnaire; MDD=major depressive disorder; MDE=major depressive episode; MFQ=Mood and Feelings Questionnaire; PDS=Petersen Pubertal Developmental Scale; SADS-L=Schedule for Affective Disorders–Present and Lifetime; SCARED=Screen for Child Anxiety Related Disorders; SCAS=Spence Children's Anxiety Rating Scale; SCID=Structured Clinical Interview for DSM-IV Axis I Disorders; SES=socioeconomic status; SSHS=School Sleep Habits Survey; SUD=substance use disorder; UMD=unipolar mood disorder.

Assessment Tools	Conversion Rate to BSD	Main Findings	Offspring Exclusion Criteria	Limitations
K-SADS-PL, HARS, SCAS, Hollingshead SES scale, EAS, CECA.Q	14%	The cumulative incidence of anxiety disorders was higher and occurred earlier in BO compared with CO. High emotionality and shyness increased the risk of anxiety disorders. Anxiety disorders increased the adjusted risk of mood disorders.	Not stated	Low conversion rate; anxiety disorders preceded mainly MDD; some BO were affected with a mood diagnosis before completing the temperament measure; some offspring were not through the age of risk for onset of bipolar illness at their last assessment.
K-SADS-PL, HARS, SCAS, Hollingshead SES scale, EAS, CECA.Q	13.54%	The adjusted cumulative incidence of BD was higher in BO than CO. There were no differences in lifetime risk of mood disorders between BO subgroups, except for schizoaffective disorder (all cases occurred in BO of lithium nonresponder parents).	Not stated	Retrospective data collection in some offspring; difficult to mask to family affiliation.
MCDQ, the Washington University schema	57%	Acute depressive episodes and dysthymic–cyclothymic disorders are the most common psychopathologic features in the BO. Manic onset occurred after age 13.	Any first-degree relative with schizophrenia	No control group; influence of age at onset of parental illness and type of parental illness not assessed.
Pupil Evaluation Inventory–Peers, ASSESS-Peers, DBRS- Teachers, DBRS- Mother and Father, the distractibility index of the digit span task, SADS-L, SCID (DSM-III), Social and Occupational Competence, GAS, bipolarity rating, SUD rating	4.8%	In childhood, mild to moderate attention and behavior problems were significantly more frequent in BO than in CO. In young adulthood, fewer than half of the BO were free of significant psychopathology.	Not stated	Not stated
CARE Interview instrument	7.8% (BD I)	Higher conversion rates among BO. BO who converted to BD I showed a higher frequency of sensitivity, crying, hyperalertness, anxiety/ worry, and somatic complaints during preschool years and of mood and energy changes, decreased sleep, and fearfulness during school years.		Small sample size; nonstandard interview instrument

FIGURE 1. Main Risk Factors of Conversion From Major Depressive Disorder to Bipolar Disorder

Risk Factors for Conversion
Family History of Bipolar Disorder
Early Onset
Atypical Features
Psychomotor Retardation
Psychotic Symptoms
Functional Impairment
Mixed Features
Previous Hypomanic Symptoms

FIGURE 2. Putative Risk Factors and Prodromal Symptoms of Bipolar Disorder[a]



[a] Several environmental risk factors for bipolar disorder have been proposed, such as stressful life events including sexual abuse, antidepressant use, or substance misuse like cocaine or alcohol misuse. Biological risk factors include family history of bipolar disorder or neurodevelopmental factors such as child developmental delay. Family history of bipolar disorder is one of the strongest risk factors for bipolar disorder, while sexual abuse has been consistently related to a worse illness course. Prodromal symptoms of bipolar disorder can be heterogeneous. Dimensional factors predictive of bipolar disorder include anxiety and depressive symptoms, mood lability, and psychosis or subjective sleep problems, but the most robust predictive factor is the presence of subthreshold (hypo)manic symptoms. Depressive episodes with an early onset and/or psychotic symptoms also seem to predict conversion to bipolar disorder. The interaction between risk factors and prodromal symptoms may lead to bipolar disorder, but the exact mechanisms remain unknown.

design reliable screening tests and screening criteria that could help to predict conversion to bipolar disorder. However, reliable clinical scales to assess prodromal symptoms are still lacking. To date, the predictive value of four clinical scales has been tested in longitudinal studies: the General Behavior Inventory, a self-report measure useful to discriminate between mood and behavioral disorders; the Child Behavior Checklist–Pediatric Bipolar Disorder, a profile consisting of severe aggression, inattention, and mood instability; the Hypomanic Personality Scale; and the Hypomania Checklist–32 Revised scale (73–78). Higher scores on the depression scale of the General Behavior Inventory (74), higher scores on the Hypomanic Personality Scale (75, 76), and positive subthreshold hypomanic symptoms identified by the Hypomania Checklist–32 (77) were related to an increased risk of future mood disorder among bipolar offspring. In turn, the Child Behavior Checklist–Bipolar seems useful for predicting comorbid and impairing psychopathology rather than any one specific DSM-IV diagnosis (73, 78). It is worth mentioning that most participants without the Child Behavior Checklist–Bipolar phenotype did not manifest bipolar disorder, attention deficit hyperactivity disorder (ADHD), cluster B personality disorder, or multiple psychiatric comorbid conditions at young-adult follow-up assessment (negative predictive values of 86% to 95%) (78). An abbreviated version of the General Behavior Inventory, the Seven Up Seven Down, has also been proposed, but it failed to predict new onset of bipolar disorder (79).

Nevertheless, the combination of self-reports and clinical semistructured interviews might be a more accurate approach for clinical decision making than the use of a single scale. Moreover, the assessment of subsyndromal manic symptoms requires trained professionals, as subsyndromal symptoms are difficult to ascertain when assessing children or if comorbid disorders are present. When considering self-report measures, much discussion of the ideal informant has taken place (i.e., parents, offspring, or both), but findings consistently show the greatest validity for parent report, regardless of whether the parent has a diagnosis of mood disorder—one reason being that the degree of awareness of one's own symptoms can influence youth self-report (80).

Besides these proposed screening tests, a set of ultra-high-risk criteria for bipolar disorder exists: the bipolar at-risk criteria developed by Bechdolf et al. (81). They comprise general criteria, such as being in the peak age range for the onset of the disorder, as well as subthreshold clinical and behavioral data and genetic risk. In a sample of help-seeking youths, individuals meeting the bipolar at-risk criteria transitioned significantly more to first-episode (hypo)mania than the group screening negative for the criteria (81). However, important potentially differentiating features such as Mitchell's bipolar signature, including features such as psychomotor-retarded melancholia and atypical depression, are not explored in many risk indices (82). The Early Phase Inventory for Bipolar Disorders criteria (83) and the Bipolar Prodrome Symptom Scale, based on the At Risk for Mania Syndrome criteria (84), are promising screening tools, but they still need to be prospectively tested.

Similar to the existing risk calculators in medicine, the Pittsburgh Bipolar Offspring Study developed a risk calculator to predict the 5-year risk of developing bipolar disorder in offspring of parents with bipolar disorder (85). Including dimensional measures of mania, depression, anxiety, and mood lability; psychosocial functioning; and parental age of mood

disorder, the model predicted onset of bipolar disorder with an area under the curve of 0.76. If replicated, in the future the risk calculator will be instrumental in the development of preventive treatments as well as for biological studies.

HELPING PREDICTION OF BIPOLAR DISORDER ONSET THROUGH BIOMARKERS

Biological and behavioral biomarkers hold promise as objective and useful tools for identifying patients at higher risk of developing bipolar disorder (86). Although biomarkers and staging have not yet had an impact on the official classificatory systems for mental disorders, this is a stated goal of the DSM series (87).

Neuroimaging Biomarkers

In a sample of 98 young unaffected individuals at high familial risk of bipolar disorder and 58 healthy control subjects, the presence of maintained increased insula activation during a task involving executive and language processing could differentiate individuals at high risk of bipolar disorder who later develop depression from healthy control subjects and from those at high familial risk who did not develop a psychiatric disorder (88). Mourão-Miranda et al. (89) showed that the combination of machine learning techniques and functional MRI data collected during an emotional face gender-labeling task could not only discriminate control adolescents from bipolar offspring but also could be helpful in predicting which at-risk adolescents would eventually develop psychiatric disorders. Regarding differences between offspring of parents with schizophrenia and offspring of parents with bipolar disorder, Sugranyes et al. (90) found through repeated neuroimaging measures that schizophrenia offspring displayed cross-sectional reductions in surface area on the occipital lobe compared with bipolar offspring and community control subjects.

Peripheral Biomarkers

Antithyroid peroxidase antibody positivity (91), salivary cortisol levels (92), and cerebral metabolite concentrations measured by proton magnetic resonance spectroscopy (93) could not differentiate high-risk offspring from control offspring or predict conversion to bipolar disorder. However, preliminary findings from the Dutch Bipolar Offspring Study indicate that the monocytes of a large proportion of bipolar patients and their offspring, particularly those who later develop a mood disorder, aberrantly express messenger RNAs of inflammatory, trafficking, survival, and mitogen-activated protein kinase pathway genes compared with healthy control subjects (94). This aberrant neuroimmune state in bipolar offspring was found to be independent of lifetime or future mood disorders; hence, it might reveal a vulnerability for mood disorders rather than being a direct predictor (95, 96). In a prospective general-population U.K. birth cohort childhood study, higher levels of the systemic inflammatory marker IL-6 in childhood were associated with hypomanic symptoms in young adulthood, even after adjusting for sociodemographic variables, past psychological and behavioral problems, body mass index, and maternal postnatal depression (97).

Nevertheless, most of the identified alterations in peripheral blood in ultra-high-risk populations are shared between different psychiatric disorders, potentially predicting the onset of bipolar disorder, depression, or schizophrenia, but alone they are not able to reliably predict occurrence of bipolar disorder over another disorder. One study proposed a blood-based biomarker panel for diagnosing bipolar disorder, employing several different biomarkers. This panel, consisting mostly of immune-related biomarkers, was able to discriminate between recently diagnosed (less than 30 days) bipolar disorder and both recently diagnosed schizophrenia and healthy control subjects (60). This suggests that a single blood biomarker will likely not be useful for ascertaining diagnosis, but that a composite of several biomarkers, and probably other sources of information, will be required in order to achieve sufficient diagnostic properties for clinical utility.

Behavioral Biomarkers

A newly emerging biomarker in the form of ecological momentary assessment is arising from the ability to track behavioral data through mobile devices (98, 99). Hence, big data, such as geolocation, activity, Internet use, calls, and payments, can be analyzed and provide algorithms that might be used through machine learning techniques (100) as sources for risk surveillance and hence early personalized interventions (101).

EXPLORING EARLY TREATMENT STRATEGIES IN BIPOLAR DISORDER

The underlying tenet of early diagnosis is to implement early treatment in order to prevent or delay progression to more advanced stages of the disease associated with greater disability (102). However, there are critical ethical issues pertaining to preventive interventions in at-risk individuals. Potential benefits need to be balanced against risks of preonset interventions. Key considerations include the individual's knowledge, autonomy, and right to choose, ideally in an environment of stigma-free treatment (103).

Effective psychotherapeutic interventions, usually better received by patients and with a more favorable benefit–risk profile, can be an attractive first step in early intervention, although their effectiveness at these early stages needs to be determined (83). Post hoc analysis of many psychosocial interventions for bipolar disorder suggested greater efficacy if used earlier in the illness course (104). Psychoeducation programs have proven effective in preventing relapse in patients with established bipolar disorder and may be more useful earlier in the disorder (105, 106), but they have not been assessed in at-risk populations or pediatric bipolar disorder. Hence, group psychoeducation may be particularly indicated in patients with an established diagnosis of bipolar disorder but with a limited number of recurrences (107). Family-focused therapy, which combines psychoeducation sessions and training in communication and problem-solving skills, is the only psychological

intervention tested in these populations. Results on this therapy are still controversial, although they suggest that it is related to longer affective stability and milder symptoms during follow-up (108, 109) when assessed in youths at high familial risk for bipolar disorder and diagnosis of bipolar disorder not otherwise specified, major depressive disorder, or cyclothymic disorder, or in adolescents with bipolar I or II disorder. Other interventions, such as multifamily psychoeducational psychotherapy (110) or interpersonal and social rhythm therapy (111), have shown some preliminary but promising results in reducing conversion rates and symptom severity among high-risk adolescents with a positive family history of bipolar disorder. Psychotherapies are not free of side effects (112); at early stages, when the diagnosis is not established, emphasis on diagnoses should be avoided, and it is more useful to target identified symptoms and helpful strategies (113). A number of online psychosocial interventions that are increasingly available have tentative data regarding their effectiveness (114, 115).

Choosing preventive pharmacological treatments in at-risk individuals is particularly complex. In the at-risk stage, we may be treating a population that might not convert to bipolar disorder, and the treatment of prodromal symptoms or comorbid conditions may involve medications with a potential risk of precipitating a manic episode, such as psychostimulants or notably antidepressants. Hence, even though some pharmacological treatments, such as lithium, are known to be more effective when started early in the course of the disease (116), the long- and short-term tolerability of each treatment and its potential to prevent bipolar disorder need to be carefully weighed against the individual risk of developing bipolar disorder. Some pilot studies have assessed the protective properties of valproate sodium and quetiapine against the onset of mania, with mixed results (117–119). Moreover, treatment with mood stabilizers or antipsychotics has known short- and long-term adverse effects (120), so their use as first-line treatment in at-risk youths might not be recommendable (121). For instance, valproate sodium has been associated with reproductive–endocrine abnormalities and should be used with caution in women of childbearing age (122, 123). Another scenario is posed when it comes to youths with bipolar disorder not otherwise specified. These youths have as much psychosocial impairment, as many comorbid disorders, and as much risk for suicide and substance abuse as those with bipolar disorder I, and they are at high risk of converting to bipolar I or II disorder (62, 124). Thus, until further research is available, we recommend treating them with the existing psychological and pharmacological treatments for youths with bipolar disorder, depending on factors such as the impact of the symptoms on the youth's functioning and well-being and the individual risk of converting to bipolar I or II disorder.

Considering the feasibility of using nutritional supplements for primary prevention and the reported link between folate deficiency or omega-3 fatty acids and mood symptoms, these compounds have been proposed as a possible treatment in at-risk samples (121, 125). However, in a double-blind parallel-group placebo-controlled trial, Sharpley et al. (125) did not find any impact of folic acid supplementation on the incidence of mood disorder in a youth sample at increased familial risk of mood disorder. Post hoc analysis, though, suggested that folic acid might help to delay the time to onset of mood disorder (125). A recent study reported that omega-3 fatty acids failed to prevent conversion from at-risk mental state to threshold psychosis (126), yet results are limited by the low conversion rate in the placebo group. Thus, the efficacy of omega-3 fatty acids in high-risk populations needs further investigation (127). Anti-inflammatory strategies such as aspirin have demonstrated potential to reduce risk of depression in epidemiological studies. Aspirin is being explored as a potential preventive strategy for depression in a very large clinical trial of over 19,000 people (128). Hence, examining the potential protective effects of nutritional and tolerable pharmacological supplements remains a promising line of research (121). Potential treatments for cognitive dysfunction (cognitive enhancers) might come up in the near future and pose new ethical questions as to when and in whom to use them (129).

Regarding predictors of treatment response, there are no solid results yet (130, 131), but reported results do suggest a number of regions meriting further investigation, such as the gene coding for a subunit of the ligand-gated ionotropic glutamate receptor, GluR2/GLURB (131). A recent genome-wide study from the International Consortium on Lithium Genetics of 2,563 patients found a single locus of four linked single-nucleotide polymorphisms on chromosome 21 that met genome-wide significance criteria for association with lithium response (132). Furthermore, in an independent prospective study of 73 patients treated with lithium monotherapy for a period of up to 2 years, carrying the response-associated alleles was associated with a significantly lower rate of relapse (132). The pharmacogenetics of pharmacodynamic pathways, such as P450 enzymes and blood-brain barrier polymorphisms, is being explored as a predictor of antidepressant response (133), although not yet for mood stabilizers. However, sensitivity and specificity limitations mean that these genetic findings are not yet robust enough to guide treatment decisions.

SUMMARY AND FUTURE DIRECTIONS

The findings of this review support the notion of a prodromal state and a progressive course in bipolar disorder. This dynamic course fits in the model of clinical staging proposed by several authors (14, 134–137), which assumes that illnesses progress from an at-risk stage to a late and resistant stage.

A positive family history of bipolar disorder, particularly if the parents have early-onset bipolar disorder, is the most significant risk factor for developing a bipolar spectrum disorder. Regarding prodromal symptoms, the most robust result is that subthreshold (hypo)manic symptoms are the strongest predictor of bipolar conversion, both in studies focusing on bipolar offspring and in community youths. Consequently, this translates into a need for screening for attenuated mania-like symptoms when assessing young patients seeking help for mood lability, anxiety, depression, or

behavioral disorders, especially among bipolar offspring (138). Moreover, preliminary findings indicate that bipolar offspring with an aberrant inflammatory state or changes in the volume or activity of the amygdala may be more vulnerable to developing a mood disorder, suggesting a potential role for these alterations as putative biomarkers for disease prediction in individuals at genetic risk (121, 139).

However, even if there is a promising emerging set of putative prodromal symptoms, biomarkers, and environmental risk factors, the possible additive or synergistic associations between all these factors remains a mystery (121). Therefore, more studies are needed to build a clear picture of high-risk bipolar states that can help clinicians differentiate genuinely at-risk individuals from persons with benign and self-limiting states (140, 141). Moreover, since prodromal symptoms are highly heterogeneous and particular to each individual, individualized risk assessment is needed. Novel bioinformatic techniques, such as machine learning approaches, present a valuable ally in the field of early intervention to overcome such limitations (142, 143).

Early intervention is an ideal breeding ground for new randomized clinical trials looking for the most efficacious treatment strategy for early stages. Currently there are no specific treatments for symptomatic youths who do not fulfill diagnostic criteria for bipolar disorder not otherwise specified but are at very high risk of developing bipolar disorder because one or both of the parents are diagnosed with bipolar disorder, particularly early-onset bipolar disorder. Since these children already present psychopathology in the form of symptoms of depression, anxiety, mood lability, or subsyndromal mania, they require existing treatments to target these symptoms—either pharmacotherapy or psychological therapies such as cognitive-behavioral therapies, family-focused therapy, self-help programs, or mental health first aid. What we do not know yet is whether these treatments will also prevent the onset of bipolar disorder. Thus, the need to perform studies to prevent or at least delay the onset of bipolar disorder should be considered a priority in psychiatry, especially in countries with a higher prevalence of pediatric bipolar disorder (144). Furthermore, as pointed out by Lambert et al. (145), once the most efficacious therapy is identified, further efforts should be made to ensure that at-risk populations have access to these interventions. Providing specialty care in youth mental health clinical services may be preferable to standard outpatient care, as evidence suggests that specialized treatment is more clinically effective and cost-effective (146, 147). Very gradual dosage escalation and cautious use of pharmacotherapy, potentially augmented by pharmacogenetics if positive data emerge, may help treatment choice when pharmacological treatment becomes necessary. In the early stages, prevention of potential side effects is paramount, since an initial adverse experience primes beliefs about medication and powerfully influences future adherence and engagement (148). In the case of bipolar disorder, there is some indication that critical factors for illness outcome, such as cognitive impairment, are heavily influenced by illness course and morbidity (149, 150). Hence, the early implementation of prevention strategies as appropriate according to illness stage and clinical phenotype may already help in preventing functional impairment. For very early stages, promoting and enhancing cognitive reserve may be one way to go (151–154).

Early intervention strategies in bipolar disorder face the lack of specificity of prodromal symptoms, as evidence emerging from studies performed in populations at ultra-high risk for psychosis indicate that there might be a common risk syndrome for diverse major psychiatric illnesses prior to the development of full symptoms more characteristic of any particular disease (141). Fernandes and Berk (142) hypothesized that this might also be true for biomarkers, with biomarkers useful for staging being common across different psychiatric disorders. Indeed, many of the biomarkers found in populations at risk for bipolar disorder are predictive for major psychiatric disorders in general and are common across commonly comorbid noncommunicable medical disorders, such as diabetes and cardiovascular disorders. This raises the question of whether more general interventions oriented toward enhancing stress-management strategies or reducing the proinflammatory state identified in at-risk individuals should be preferable. Findings concerning neurodevelopment, though, indicate that there may already be subtle potential differences between some psychiatric diseases at the earliest stages (155). In any case, this highlights the urgency of performing studies to test whether any given early intervention would help reduce vulnerability to psychiatric illnesses in general and not only to bipolar disorder, as bipolar offspring are at high risk of developing a wide range of psychiatric illnesses. As mentioned before, testing the protective potential of a variety of psychological interventions such as cognitive-behavioral therapies, family-focused therapy, self-help programs, or mental health first aid, or compounds such as omega-3 fatty acids, *N*-acetylcysteine, or minocycline, might be a feasible line of research. Lifestyle modifications such as smoking cessation, encouragement of physical activity, and healthy diet are indicated across the psychiatric spectrum and commonly comorbid medical disorders as well (156).

Overall, this review supports the idea of the existence of an at-risk state in bipolar disorder, thereby laying the foundations for bringing early intervention to life. However, we cannot deny that further efforts are required to advance on the difficult road of primary prevention. Given that psychiatric and commonly comorbid medical disorders share common risk determinants and operative biological pathways, a shared framework for disease prevention and control is warranted. A cross-disciplinary, multitarget approach is essential for wide-scale implementation in real-world settings (156). The need for new prospective studies with a larger sample size and standardized recruitment criteria and assessment tools is unquestionable. These studies should assess the validity of the proposed predictive factors to better determine which individuals are at highest risk for conversion and therefore more likely to benefit from early interventions. Further studies

on early psychological and pharmacological interventions, either alone or in combination, are equally warranted.

In conclusion, considering that the onset of bipolar disorder usually occurs during adolescence—a period of personal, social, and professional development that is often truncated by the illness—introducing early interventions in psychiatry is imperative. By the time *The American Journal of Psychiatry* commemorates its 200th year of publication, we look forward to seeing that early intervention in psychiatry has been integrated in common clinical practice.

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REVIEW
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Toward Precision Psychiatry in Bipolar Disorder: Staging 2.0

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Personalized treatment is defined as choosing the "right treatment for the right person at the right time." Although psychiatry has not yet reached this level of precision, we are on the way thanks to recent technological developments that may aid to detect plausible molecular and genetic markers. At the moment there are some models that are contributing to precision psychiatry through the concept of staging. While staging was initially presented as a way to categorize patients according to clinical presentation, course, and illness severity, current staging models integrate multiple levels of information that can help to define each patient's characteristics, severity, and prognosis in a more precise and individualized way. Moreover, staging might serve as the foundation to create a clinical decision-making algorithm on the basis of the patient's stage. In this review we will summarize the evolution of the bipolar disorder staging model in relation to the new discoveries on the neurobiology of bipolar disorder. Furthermore, we will discuss how the latest and future progress in psychiatry might transform current staging models into precision staging models.

Keywords: bipolar disorder, staging, biomarkers, personalized psychiatry, prevention

INTRODUCTION

Bipolar disorder is a chronic psychiatric condition characterized by mood swings with both manic and depressive symptoms (1). Despite this general picture, bipolar disorder is a highly heterogeneous condition regarding clinical presentation, response to treatment and functional outcome (2, 3). Subsequent DSM and ICD versions have increasingly reflected this heterogeneity, for instance, by adding diagnosis and course specifiers (4). Still, the focus of current systems of classification remains largely cross-sectional and limited to clinical features (5). Moreover, these criteria apply to people with established disorder, but miss people in the prodromal phases of the illness (4).

Emerging data points to the need of a broader approach to bipolar disorder. There is increasing evidence that bipolar disorder is a neuroprogressive disorder, meaning that longer duration of the disease entails more pronounced changes at the clinical and neuropathological level, which may lead to treatment refractoriness and neuropsychological deficits (6, 7). Moreover, several studies support the notion of a prodromal stage before illness onset (8). In an attempt to introduce a longitudinal perspective of the illness in the diagnostic process which would include the earliest phases of bipolar disorder and guide treatment and prognosis, some authors have suggested incorporating the staging model in psychiatry (9–13).

The staging model is based on the concept that an illness progresses following an identifiable temporal progression, from at-risk or prodromal stages to chronic ones (10). Moreover, considering the neuroprogressive course of psychiatric disorders, the staging model assumes that treatment needs and response may differ according to stage. While early stages of the disease might show a better response to simpler treatment regimens, chronic stages might need more complex treatments and still show less clinical improvement (14). Consequently, defining the stage in which the patient is located may help clinicians to choose the treatment that is better adapted to the patient's needs (14). Additionally, the administration of a timely treatment precisely adapted to the stage in which the patient is located might modify or even prevent the progression to subsequent stages of the disease (10).

The staging model in bipolar disorder has been in constant development since its introduction in psychiatry. As new evidence on bipolar disorder has emerged, staging models were refined according to these new findings. In spite of this, experts supporting the staging model still warn that this model gives a standard vision of the progression of the disorder that might not suit every patient (15, 16).

New advances in the field of biological markers (e.g., molecular and neuroanatomical markers of illness vulnerability and/or progression), genetics (e.g., genetic markers or pharmacogenomics) or computer science (e.g., machine learning approaches) might provide current staging models of a higher level of precision regarding diagnosis, prognosis, and treatment choice (15, 16), allowing a more personalized approach to the patient.

The aim of this review is to summarize the evolution of the staging model in bipolar disorder in relation to the new discoveries on the course and neurobiology of the disease. Furthermore, we will discuss how the latest and ongoing progresses in psychiatry might transform current staging models into precision staging models.

THE EVOLUTION OF STAGING MODELS IN BIPOLAR DISORDER

The Dawn of Staging in Psychiatry: Fava and Kellner Staging Model (1993)

Fava and Kellner, in 1993, first proposed the application of the concept of staging to psychiatric disorders (9), as staging had shown to be useful in other complex diseases potentially severe if untreated, such as diabetes mellitus, cardiovascular diseases and neoplastic diseases. However, their staging model faced a major limitation in psychiatry research, which was the dearth of longitudinal studies assessing the progression of psychiatric disorders and the scarce data available on prodromal symptoms.

As a result, the staging model proposed by Fava and Kellner did not focus on the longitudinal course of bipolar disorder, but described the different stages that can be seen in a manic episode based on symptom severity (**Table 1**). Although their model referred only to the manic phase of the disease, Fava and Kellner provided the basis for future staging models in psychiatry.

The Spread of the Concept of Staging in Psychiatry: McGorry et al. (10)

In 2006, McGorry and colleagues introduced a staging model which highlighted the longitudinal course of psychiatric diseases in the psychotic spectrum, also integrating mood disorders (10). They underlined that the staging model does not imply that every patient needs to go through every stage. The main characteristic of McGorry and colleagues' model is that it is built on evidence on major psychiatric disorders jointly and not exclusively on data on bipolar disorder. Importantly, compiling evidence emerging from research on neurobiological correlates of psychotic disorders, allowed McGorry and colleagues to go one step forward and include some biological and endophenotypic markers in the earlier stages of their model (**Table 1**). They warned, though, that evidence on biological markers arose from studies that evaluated patients with long-established disease, raising the question whether these biological markers were inherent to psychiatric disorders or a consequence of illness duration.

They also incorporated some indicators of illness extent and progression -that is, functioning and cognitive impairment- in their staging model. They defended the importance of addressing social adaptation when assessing patients, as they noted that a person who already presents a great deal of collateral academic or social damage at illness onset may be less likely to respond to treatment and hence is more prone to have a worse prognosis. McGorry and colleagues have continued to progress a transdiagnostic staging model, arguing that the early stages are non-specific, although the later courses of different major psychiatric disorders can have divergent course and outcome patterns (17).

New Insights on Bipolar Disorder Progression: Berk et al. (11)

Although similar to and adapting from McGorry and colleagues' model (10), Berk and colleagues' model focused exclusively on bipolar disorder (11). At that moment, a growing body of evidence on a prodromal state for bipolar disorder started to appear (11). Besides identifying risk factors for bipolar disorder, mainly a positive family history of mood disorder and stressful life events (18–20), emerging studies on high-risk youth described a series of prodromal symptoms (21–23), therefore supporting the notion of a traceable at-risk stage.

TABLE 1 | Stage definition according to each staging model.

	Clinical stage definition				
	Fava and Kellner (9)	**McGorry et al. (10)**	**Berk et al. (11)**	**Kapczinski et al. (12)**	**Duffy (13)**
At-risk stages	**Stage 1:** Prodromal manic symptoms (increased self-confidence, energy and elated mood)	**Stage 0:** Increased risk of psychotic or severe mood disorder without symptoms *BIOMARKERS: Trait marker candidates and endophenotypes*, e.g., *Smooth Pursuit Eye Movements, P 50, Niacin sensitivity, Binocular rivalry, Prepulse Inhibition, Mismatch Negativity, Olfactory deficits, etc.*	**Stage 0:** Increased risk of severe mood disorder (e.g., family history, abuse, substance use) No specific symptoms currently	**Latent Stage:** At risk for developing BD, positive family history, mood or anxiety symptoms without criteria for threshold BD	**Stage 0:** **a) Classical Episodic Bipolar:** asymptomatic individuals + familial risk for classical BD or recurrent affective disorders **b) Spectrum bipolar:** asymptomatic individuals + familial risk for chronic psychotic disorders or atypical bipolar disorder.
		Stage 1a: Mild or non-specific symptoms, mild functional change or decline	**Stage 1a:** Mild or non-specific symptoms of mood disorder		**Stage 1:** **a) Classical Episodic Bipolar:** non-specific syndromes + familial risk for classical BD or recurrent affective disorders. **b) Spectrum bipolar:** non-specific syndromes and neurodevelopmental disorders + familial risk for chronic psychotic disorders or atypical BD.
		Stage 1b: Ultra high risk: moderate but subthreshold symptoms, moderate neurocognitive changes and functional decline (GAF<70) *BIOMARKERS: Niacin sensitivity, folate status, MRI and MRS changes, HPA axis dysregulation*	**Stage 1b:** Prodromal features: ultra-high risk		
Early stages	**Stage 2:** Hypomania	**Stage 2:** First episode of psychotic or severe mood disorder Full threshold disorder with moderate-severe symptoms, neurocognitive deficits and functional decline (GAF 30-50)	**Stage 2:** First-episode threshold mood disorder	**Stage I**: Well-defined periods of euthymia without overt psychiatric symptoms *BIOMARKERS:* ↑ *TNF-α,* ↓ *3-NT*	**Stage 2:** **a) Classical Episodic Bipolar:** minor mood and single episode depressive disorder + familial risk for classical BD or recurrent affective disorders. **b) Spectrum bipolar disorder:** negative syndrome + familial risk for chronic psychotic disorders or atypical BD.
Mid-stages	**Stage 3:** Manic episode without psychotic features	**Stage 3a:** Incomplete remission from first episode	**Stage 3a:** Recurrence of sub-threshold mood symptoms	**Stage II:** Symptoms in interepisodic periods related to comorbidities *BIOMARKERS:* ↓ *TNF-α,* ↓ *BDNF,* ↑ *3-NT*	**Stage 3:** **a) Classical Episodic Bipolar:** recurrent major depressive disorder. **b) Spectrum Bipolar:** attenuated psychotic syndrome.

(Continued)

TABLE 1 | Continued

	Clinical stage definition				
	Fava and Kellner (9)	**McGorry et al. (10)**	**Berk et al. (11)**	**Kapczinski et al. (12)**	**Duffy (13)**
		Stage 3b: Recurrence/relapse of psychotic/mood disorder which stabilizes with treatment at a level of GAF, residual symptoms, or neurocognition below the best level achieved following remission from first episode	**Stage 3b:** First threshold relapse		
		Stage 3c: Specialist care services	**Stage 3c:** Multiple relapses		
Late stages	**Stage 4:** Manic episode with psychotic features	**Stage 4:** Severe, persistent or unremitting illness as judged on symptoms, neurocognition and disability criteria.	**Stage 4:** Persistent unremitting illness	**Stage III:** Marked impairment in cognition and functioning *BIOMARKERS: Morphometric changes in brain may be present,* ↑ *TNF-α,* ↓*BDNF,* ↑ *3-NT*	**Stage 4a:** **a) Classical Episodic Bipolar:** classic BD. **b) Spectrum bipolar:** mixed mania, psychotic/cyclic mania
					Stage 4b: **a) Classical Episodic Bipolar:** BD with residual symptoms. **b) Spectrum bipolar:** psychotic disorders.

BD, bipolar disorder; BDNF, brain-derived neurotrophic factor; GAF, Global Assessment of Functioning; HPA, hypothalamic–pituitary–adrenal; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; TNF-α, tumor necrosis factor alpha; 3-NT, 3-nytrotyrosine.

Moreover, at that moment there was increasing evidence emerging from clinical, neuroimaging and neurocognitive studies that supported a progressive and deteriorating course of bipolar disorder (11). For instance, it had been reported that inter-episode periods were longer after the first episodes, but tended to shorten as the number of episodes increased (24). It had also been found that longer duration of the illness with multiple relapses seemed to be associated with increased medical comorbidities and increased suicidal risk (25). Furthermore, available evidence suggested that response to psychological and pharmacological treatments might not be the same over the illness course (26–29). Response to lithium, for example, seemed to be better if started early after illness onset (30, 31) and before multiple relapses had taken place (32). The number of episodes had also been found to be related to neuroanatomic changes in the brain (33). In 2002, Strakowski et al. (33) described increased lateral ventricular size in bipolar patients with multiple manic episodes, but not in first-episode patients. Likewise, evidence supported that a longer duration of illness and a larger number of episodes was associated with cognitive dysfunction which, in turn, seemed to involve a worse clinical course and functional disability (34). The authors hypothesized that all those alterations observed in the later stages of bipolar disorder were a consequence of progressive changes in the central nervous system due to subsequent mood episodes (6, 7). This phenomenon was called neuroprogression (6). Berk and colleagues suggested several possible pathways involved in neuroprogression including inflammation, oxidative stress, neurotrophins imbalance, mitochondrial dysfunction and epigenetics (6, 7).

Drawing all this evidence together, Berk and colleagues described a staging model with a special focus on the initial phases of the disease and number of episodes (**Table 1**).

The Ascendance of Biological Psychiatry: Kapczinski et al. (12)

Kapczinski and colleagues' model appeared at a moment when biological explanations gained prominence and risk phases were explained based on a gene-environmental (GxE) approach (12). For early stages, the GxE perspective suggested that individual genetic differences determine distinct resilience or vulnerability to environmental stress, placing individuals at different risk levels to develop bipolar disorder (35, 36). For late stages, this approach suggested that every individual has a different neuronal resilience to the deleterious effect of repetitive mood episodes (12). Along this line, Kapczinski et al. (37) adapted McEwens' notion of allostatic load to bipolar disorder (38). This concept implies that the interaction of neuroprogressive changes, somatic comorbidities and substance abuse leads to a dwindling resilience to life stress, especially if coping skills are poor (37). Hence, according to Post's kindling hypothesis (36), while stressful life events are an important trigger for first affective episodes, later on the course of the disease recurrences might take place without a clear environmental factor (37).

At that time, studies focusing on the pathophysiology of bipolar disorder reported a deregulation of oxidative and inflammatory pathways in bipolar disorder, especially during mood episodes (39–43), which came with a decrease in neurotrophic factors, like brain-derived neurotrophic factor (BDNF) (44–46). Importantly, it was also described that levels of neurotrophins, oxidative and inflammatory markers differed depending on illness stage (47, 48). For instance, compared to controls, the serum levels of the pro-inflammatory cytokine IL-6 were increased both in the early and late stages of bipolar disorder, while levels of BDNF and the anti-inflammatory cytokine IL-10 were decreased in late stages (meaning patients with 10–20 years of illness duration) but not in early stages (47). TNF-alpha levels appeared to be elevated throughout the illness course but were even higher in later stages (47). In addition, some parameters of oxidative stress, such as 3-nitrotyrosine, were found to be altered in the early and late stages of bipolar disorder, but not in controls (48). The activity of key enzymes in the glutathione pathway was found to be increased in late-stage patients compared with early-stage patients and controls (48). Hence, these data supported the hypothesis presented by Berk and colleagues indicating that neurotrophic, inflammatory and oxidative pathways may be involved in neuroprogression (6). Furthermore, neuroimaging findings also supported the concept of neuroprogression, as although some cerebral structures were shown to be already altered in early stages (49–51), longitudinal studies indicated that patients with repetitive mood episodes showed a progressive brain gray matter loss (52, 53). All these findings implied the identification of putative biomarkers that could be useful to distinguish between patients in early and late stages of bipolar disorder (54).

Psychosocial functioning was also gaining momentum as an outcome measure in bipolar disorder, since it had been demonstrated that symptomatic recovery is not equivalent to functional recovery (55). Psychosocial functioning involves domains such as work and education, leisure time, social and affective relationships or independent living (56), and it can be negatively affected by clinical variables and neurocognitive impairments (57).

Accordingly, Kapczinski and colleagues presented a model based on functioning that, moreover, incorporated cognition and biomarkers (12) (**Table 1**).

A Broader Vision of Bipolar Disorder: Duffy (13)

Duffy proposed a more integrative clinical staging model which described the natural history of bipolar disorder according to illness subtypes: the classical form of bipolar disorder (alternant manic-depressive episodes) vs. the broader bipolar spectrum (13). Duffy claimed that, while the classical form of bipolar disorder tended to follow the progressive course described in previous staging models (i.e., a recurrent and deteriorating course with an increasingly shorter inter-episodic period), other subtypes of bipolar disorder might present a different evolution (13). Evidence, for instance, supported that lithium non-responders showed a more chronic course and a higher-risk of non-affective disorders in family members (58, 59). Neuroimaging and genetic differences between classical lithium

responsive bipolar patients and lithium non-responsive bipolar patients were also reported (60, 61). Moreover, her model was supported by longitudinal data showing differences between offspring of lithium responders and lithium non-responders regarding the prodromal period and longitudinal course of bipolar disorder. Offspring of lithium responders had a personal history of anxiety and sleep disorders before illness onset and, once bipolar disorder was established, tended to show an episodic remitting course with good response to lithium (62–64). In contrast, offspring of lithium non-responders manifested higher rates of early developmental alterations, attention deficits and cluster A personality traits (62–64) and, for those who developed bipolar disorder, illness course tended to be more torpid and response to anticonvulsant or atypical antipsychotic seemed to be better than to lithium (63). Thus, Duffy aimed to present an integrative staging model that describes the expected longitudinal course of classical episodic bipolar disorder and of bipolar spectrum disorder (**Table 1**).

WHEN STAGING IS NOT ENOUGH

Although different staging models have been proposed in bipolar disorder over the last 25 years, they still need to be better operationalized and validated by empirical research (14). The idea behind the different staging models is to allow defining, for every individual, the extent of illness progression in the moment of the evaluation (65). This can help to refine diagnosis, adjust prognosis and choose the best treatment according to illness stage (66). In this regard, authors have suggested some treatment approaches adapted to every stage: most models agree that prodromal stages would benefit from interventions targeted toward reducing stressors and increasing coping skills; early stages would benefit from patient and family psychoeducation and simpler pharmacological regimens; while mid-stages would need more intensive psychotherapies and more complex pharmacotherapies (12, 15). Clozapine or functional remediation therapies would be reserved for more chronic stages (15). Some individuals with highly refractory illness may need more "palliative" approaches focusing on reduction of side-effects and unnecessary polypharmacy, limited symptom control, identifying and targeting psychological and social problems, and setting realistic goals to aim for the best quality of life for people and their families within the envelope of their disability (67).

However, even if the staging model proposes stage-targeted treatments that might provide a better clinical outcome with less side effects, there are still differences among the patients of a particular stage. In consequence, "standard stage-adapted treatments" may not be useful for every patient at a particular stage (15) and increasing the level of precision in every stage would be desirable in order to achieve an even more personalized way of approaching the patient (16) (**Figure 1**).

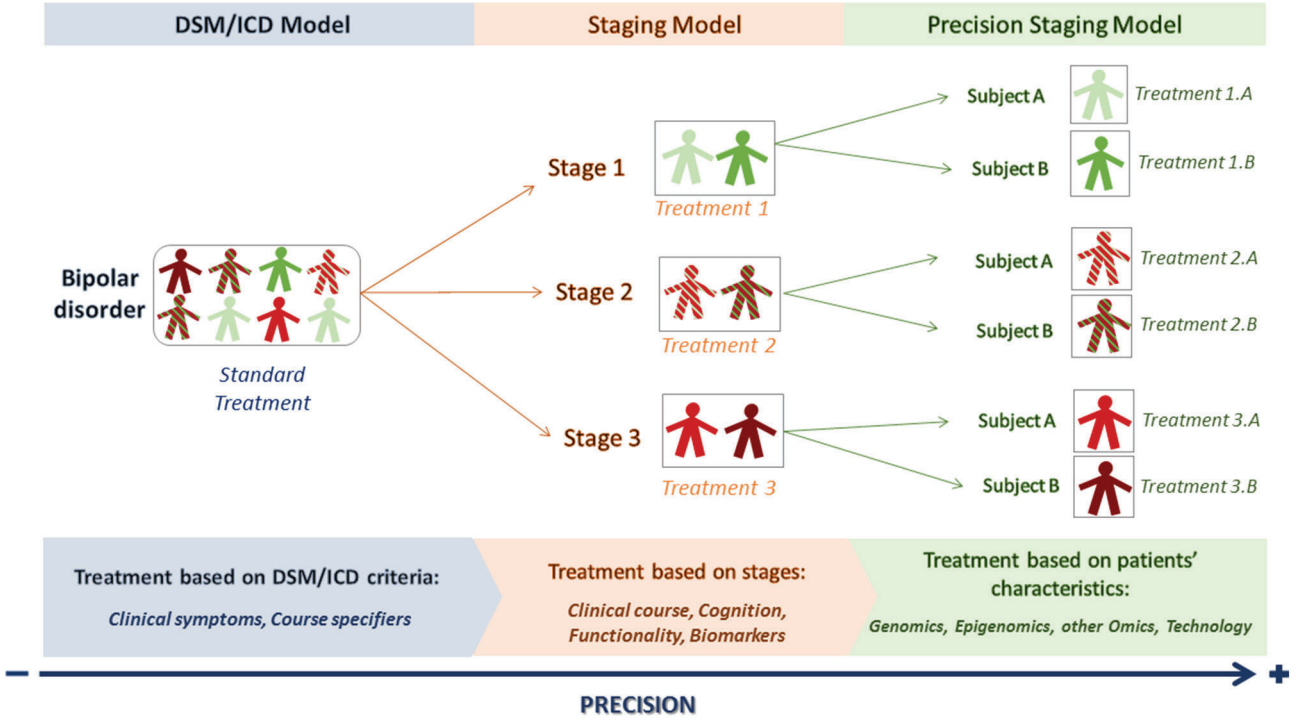

FIGURE 1 | From DSM/ICD to precision staging models. The DSM/ICD model classifies patients into particular conditions according to clinical-based criteria. DSM/ICD diagnosis can be refined by course specifiers. The staging model allows placing the patient in a particular stage according to the extent of illness progression, starting from at-risk stages (stage 1) to more chronic ones (stage 3). However, there can still be differences between patients within a particular stage. A precision staging model would then use the new advances on precision medicine to better characterize the patients and offer them a more personalized treatment.

FROM STAGING TO PRECISION STAGING MODELS

The aim of precision psychiatry is to offer the patient tailored medical decisions and treatments (68). For that purpose, precision psychiatry needs to integrate biographical, clinical and biological information regarding each individual (69). In addition, precision psychiatry is envisaged to benefit from the coming advances in technological, data, and computer science to aid diagnostic processes and treatment provision. A precision staging model would ideally incorporate all these recent progresses into the appropriate stage (**Table 2**).

Many advances in precision medicine are related to genomics. Genomics have led to improvements in staging models in some branches of medicine, especially cancer (70). However, psychiatric disorders are genetically complex conditions and their genetic underpinnings remain to be determined. Still, international consortia that comprise samples from several countries have brought some light on risk loci associated with bipolar disorder (71, 72). These collaborative genome-wide association studies (GWAS) allow overcoming replication difficulties often seen in genetic studies due to small sample sizes. One of these studies analyzed genomic data on a sample of 40,000 bipolar patients and replicated the discoveries of previous GWAS studies regarding several single-nucleotide polymorphisms (SNPs) statistically associated with the disease, including variants within the genes CACNA1C, ANK3, MAD1L1, and SYNE1 (73). Two new risk loci were also identified (73). Moreover, the Psychiatric Genomics Consortium has recently identified specific loci that distinguish between bipolar disorder and schizophrenia (74). Genetic markers promise to be valuable at the earliest stages of bipolar disorder, as the main aim of mental health approaches at at-risk and early stages is to predict disease vulnerability and make accurate diagnosis. So far, though, little of the advances in genomics have translated into clinically useful tools.

Besides genetic markers, screening for risk factors and epigenetic modifications may be another useful tool at at-risk stages of the disease, given that stressful life events, particularly childhood trauma, can alter DNA methylation and may increase the risk of developing mood disorders (75). Concordant with this, childhood verbal, physical, or sexual abuse has been related to a worse illness course (76).

Risk calculators are another promising tool for at-risk stages (77), as the multifactorial and polygenic nature of bipolar disorder makes it improbable that a single factor can accurately predict its onset (78). The Pittsburgh Bipolar Offspring Study group (BIOS) has recently developed a risk calculator to predict the 5-year risk of bipolar disorder onset in offspring of parents with bipolar disorder combining dimensional measures of mania, depression, anxiety, mood lability, psychosocial functioning, and parental age of mood disorder onset (79). Although their findings need to be replicated, the model seemed to be able to predict onset of bipolar disorder with an area under the curve (AUC) in the receiver operating characteristic curve analysis of 0.76 and might be of potential value for youth at ultra-high risk for BD. Machine learning, a field of computer science that studies and constructs

TABLE 2 | Potential precision staging model in bipolar disorder.

Clinical stage	Definition	Potential precision tools and precision interventions	Domains to be assessed and general interventions
At-risk stages	Increased risk of severe mood disorder (e.g., family history, abuse, substance use) Asymptomatic or non-specific symptoms of mood disorder	Individualized evaluation of risk/protective factors Genetic and epigenetic markers	a) Clinical domain b) Cognitive domain c) Functional domain d) Comorbidities domain: - Substance use - Physical comorbidities - Psychological comorbidities
	Prodromal features: ultra-high risk	Genetic and epigenetic markers Risk Calculator Risk biomarkers (molecular, neuroimaging) Machine learning approaches (risk for bipolar disorder) Cognitive enhancers	
Early stages	First-episode threshold mood disorder	Genetic markers of treatment response Epigenetics (illness course) Biomarkers of treatment response and illness progression Machine learning approaches (suicide risk) mHealth (Psychoeducation, monitoring)	Pharmacotherapy and psychological interventions adapted to each individual physical and psychological comorbidities
Mid stages	Clinical relapse	Pharmacogenetic tests Biomarkers of treatment response and illness progression Machine learning approaches (suicide risk) mHealth (psychoeducation, monitoring) Functional remediation tailored to patients' profile, cognitive enhancers	Substance use intervention
Late stages	Persistent unremitting illness	Functional remediation tailored to patients' profile	

algorithms that can learn from large number of data, find patterns and make predictions (80), might also be useful to estimate the individual probability of a particular outcome (80, 81). Mourao-Miranda et al. (82), for instance, found that machine learning approaches using functional magnetic resonance imaging (fMRI) data could differentiate between adolescents genetically at-risk for mood disorders and healthy controls with a 75% accuracy (sensitivity = 75%, specificity = 75%). Moreover, those at-risk adolescents who developed an anxiety or depressive disorder at follow-up showed significantly higher predictive probabilities, therefore suggesting that predictive probabilities could be used as a score to predict which at-risk adolescents would develop a mood disorder in the future (82).

Early and middle stages of bipolar disorder may benefit from progress in the field of pharmacogenomics. This is the study of genetic variations that affects individual response to drugs and vulnerability to adverse effects (83). After the first acute episode, selecting the best treatment for the patient, both in terms of efficacy and tolerability is a necessary but complex task. International consortiums in genetics, such as the International Consortium of Lithium Genetics (ConLiGen) (71), have worked to disentangle genetic variants associated with treatment response, mainly response to lithium. In 2016, the ConLiGen consortium uniformly phenotyped 2,563 bipolar patients and reported a genome-wide significant association with a locus of four linked SNPs on chromosome 21 and lithium response (84). Another recent GWAS performed by the ConLiGen consortium displayed that bipolar patients with a low genetic load for schizophrenia showed a better response to lithium (85). Pharmacogenetic screening for hepatic cytochrome P450 genetic polymorphisms can also be helpful in the near future to predict tolerability and side effects of psychiatric treatments (86). While the precise patient profile that would benefit from these tests remains to be elucidated, pharmacogenetic tests are kept for selected patients with unusual patterns of drug response or unexpected adverse reactions (83, 87).

Less progress has been made in the field of biological markers in the last few years and data on molecular and neuroimaging biomarkers is still contradictory and limited by the heterogeneity between studies and the poor specificity of the putative biomarkers (88). Although evidence is not yet compelling, some biological markers have been suggested to be associated with increased risk of conversion to bipolar disorder, and therefore may be useful when assessing subjects at at-risk stages. fMRI studies report that frontal hyperactivation during working memory paradigms may be associated with genetic risk for bipolar disorder (89, 90). In more established stages, neuroimaging might be useful to monitor treatment response (91). Also, a preliminary study using a voxel-based morphometry-pattern classification approach was able to distinguish between patients with unipolar and bipolar depression based on structural gray matter differences (92). Studies on biological markers have also suggested that peripheral concentrations of BDNF could be used to discriminate unipolar depression from bipolar depression (93, 94), but evidence is not clear (95). This would be of the utmost importance in the earliest stages of the disease, considering that bipolar disorder is often misdiagnosed since the index episode is frequently depressive. In consequence, patients are treated with antidepressants and the introduction of a mood stabilizer is delayed until the first manic episode is detected, which may negatively affect illness course and prognosis (8).

Regarding other molecular markers, hypothalamic-pituitary-adrenal (HPA) axis dysfunction is thought to be one of the pathways involved in neuroprogression in bipolar disorder (96), but it has also been suggested to be a useful trait marker in high-risk individuals (97, 98). Alterations in neurotransmitters transporters have been suggested as markers of bipolar disorder (96), but there is no evidence on changes in neurotransmitters according to illness stage. Regarding later stages of bipolar disorder, recent studies have reported higher levels of TNF-alpha and IL-6 in late stages of bipolar disorder (99, 100). Similarly, Soeiro-de Souza and colleagues described that patients with recurrent episodes showed increased oxidative and inflammatory markers, which were related to the number of manic episodes (101). Further, increased inflammation, increased oxidative stress and reduced telomere length have been suggested as possible mechanistic links between psychiatric diseases like bipolar disorder and other systemic diseases, such as endocrine or cardiovascular diseases (102–105). Hence, the identification of a deregulation on those pathways related to both psychiatric and somatic diseases may have therapeutic implications (106). For instance, bipolar patients exhibiting persistently increased low-grade inflammation (107) might benefit from anti-inflammatory treatment strategies and from periodic screening of systemic conditions like metabolic syndrome (106). Considering these data, screening for physical comorbidities seems especially important in middle and late stages of the disease, albeit protecting against complications like physical comorbidities or substance abuse should be a priority at every stage of the disease.

Cognition is another important domain that needs an individualized evaluation throughout all the stages of bipolar disorder (108). On one hand, cognitive reserve, defined as the ability of a brain to cope with brain pathology in order to minimize symptoms (109), may be useful in early stages to predict neurocognitive performance in patients with bipolar disorder (110), as it has been found that lower estimated cognitive reserve is associated with worse performance in neuropsychological tests and more functional impairment (110, 111). Similarly, a recent study on first-episode psychosis has found that those patients with affective psychosis with a greater cognitive reserve showed a higher socioeconomic status, better functioning and greater verbal memory performance (112). This study also emphasizes the need to explore the impact of specific interventions, like physical activities and hobbies, on cognitive reserve, since it could be useful to guide the development of personalized treatment programs (112). Therefore, cognitive enhancing strategies might be key in the early stages and not necessarily in the late stages of the disease. On the other hand, evidence points to a heterogeneous cognitive profile in bipolar patients both in "cold" and "hot" cognition (113–115). The presence of such heterogeneous cognitive profiles among patients with bipolar disorder might be taken into account to

design more tailored cognitive remediation therapies adapted to each individual needs (116–118). Cognitive deficits may also limit long-term psychosocial functioning, which means that patients with greater cognitive impairment are more likely to experience poorer outcomes. Previously, we showed that patients in stage I and healthy controls had similar functioning patterns. In addition, a strong linear association was found between functioning and clinical stages, suggesting a progressive functional decline from stage I through to stage IV of bipolar disorder. These findings provide further support to the clinical staging model in bipolar disorder, indicating that bipolar patients lie on a continuum of disorder progression ranging from periods of favorable functioning to others of incomplete functional recovery (118). The link between variables related to the course of the illness, cognitive deficits and functioning suggests that early intervention is crucial to prevent illness progression and to improve cognitive/functional outcome. Some studies have also found different profiles of psychosocial functioning in patients with bipolar disorder, which should also be taken into consideration in the framework of a personalized approach (3, 119).

All these advances should complement regular clinical practice, which already contains elements of staging and precision psychiatry. The assessment of the patient's particular symptoms, such as his/her distinctive early signs of relapse, predominant polarity (i.e., the "tendency" to present more depressive or manic relapses) (120) or individual suicide risk (121) is regularly done in clinical settings and is essential to monitor the patient evolution and guide treatment selection. Technological advances used in everyday life, encompassed in the concept of mobile Health (mHealth), might be a valuable tool to help clinicians to collect individualized data on illness course and monitor illness progression (122). For instance, changes in activity, geolocation or sleep patterns may help to detect early signs of mood relapse (123, 124). Additionally, smartphone apps can be used to empower patients with bipolar disorder to detect prodromal symptoms of relapse by providing them personalized psychoeducational messages (125, 126). New methods like machine learning approaches might also be useful in the future to help predict suicide risk (127, 128).

DISCUSSION

In this review we describe the evolution of the staging model in bipolar disorder since its introduction into psychiatry. The first staging models in bipolar disorder were initially based on evidence derived from cross-sectional studies, but longitudinal studies and data on neuroimaging, peripheral biomarkers, cognition, psychosocial functioning, and prodromal symptoms have successively enriched the staging models (66). We have also described several elements of precision psychiatry that could be incorporated in future precision staging models.

The main advantage of staging and precision medicine is the recognition that a reductionist clinical approach based on the presence or absence of a series of symptoms is not enough to design an adequate therapeutic strategy. These symptoms need to be considered in the light of the illness progression and, most importantly, of the patient's own clinical evolution. For instance, the presence of a switching or non-switching pattern should be considered when evaluating a patient, as it has prognostic implications and therefore might impact staging. As highlighted in a review by Salvadore et al. (129), patients showing a switching pattern [i.e., patients showing a "sudden transition from a mood episode to another episode of the opposite polarity" (129)] usually spend less time in remission, show higher comorbidity rates and substance abuse and are at a higher risk of suicide attempt (129). While mood symptoms will of course still be the cornerstone of bipolar disorder diagnosis, other elements should be likewise considered as they can be as informative as clinical symptoms (9, 10, 12, 15). As such, everyday difficulties, cognitive complains, substance abuse or comorbidities can be markers of illness severity or stage specifiers and merit an individualized assessment and treatment. Social and personal losses due to the illness and previous personality should also be included in a standard evaluation throughout the stages and be given the attention they deserve (10). Patients' insight and perception of the disease should be carefully assessed, as these are important prognosis and therapeutic factors, especially in early stages (8). Medication load, treatment satisfaction, and compliance should be also carefully assessed, as it might influence disease progression. While this way of approaching the patient is naturally adopted by most clinicians and many guidelines, it remains underrepresented in diagnostic manuals (5). In any case, this approach is more in line with the World Health Organization definition of health: "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"[1]. The inclusion of self-report measures of well-being in research and clinical care in bipolar disorder may contribute to take into consideration the patient's perspective when assessing the efficacy and usefulness of pharmacological and psychological interventions (130).

Another important point of clinical staging is the assumption that prodromal phases of the disease can be also identified and targeted. The possibility of making an early diagnosis radically changes the way how bipolar disorder in particular, and psychiatric diseases in general, have hitherto been managed. At-risk stages are rather non-specific, though. In consequence, the prodromal period has also been preferably defined as "at risk mental states" (17), as a prodrome is defined as "any symptom that signals the impending onset of a disease" (131) and evidence does not support this definition. On one hand, data from the field of ultra-high risk in psychosis shows that disease onset is not deterministic and a significant proportion of the at-risk youth show a remission of these early symptoms (132). On the other hand, these early symptoms are not specific to any disease but can progress into several possible psychiatric conditions (64). In the absence of specific genetic markers for bipolar disorder or very precise risk calculators, transdiagnostic preventive interventions aimed to reduce stress, educate on mental-well-being and prevent substance abuse are preferable at these at-risk stages (133). Implementing early interventions that include enhancing

[1]WHO. http://apps.who.int/gb/bd/PDF/bd47/EN/constitution-en.pdf?ua=1. 1946

cognitive reserve by increasing mental stimulation (reading and cognitive exercises), introducing physical exercise and leisure activities or building social skills and social interaction, may provide a set of skills that can help to cope better with the disease (134–136). This kind of preventive interventions or "positive habits" could even be implemented at school or primary care, which could help to reduce stigma on mental health by educating the population on the importance of taking care of mental well-being (133).

In this regard, it has been suggested that a transdiagnostic staging model might be more adequate for the study of at-risk phases, while disorder-specific models are more useful once the fully-develop disorder emerges (15). It is necessary to bear in mind that psychiatric disorders are dynamic and clinical symptoms may evolve over time, requiring a change in diagnosis (137). Nevertheless, the general staging approach supported by stage specifiers should still be useful to assess illness severity regardless of changes in DSM or ICD diagnosis.

Biomarkers also face the problem of lack of specificity. Alterations in the inflammatory or oxidative systems have been found across several psychiatric and medical diagnoses (138). Again, biomarkers could be more stage-specific than illness-specific and be conceived as an additional tool for the assessment of illness risk or treatment outcome. Low sensitivity and replicability seems a bigger handicap. Moreover, most published data on biomarkers are based on the currently commercially available ELISA kits, which is also a limiting factor. State-of-the-art techniques widely used in precision medicine might help to overcome these limitations. A multi-omic approach, meaning using genomic, epigenomics, transcriptomics, proteomics, metabolomics, metagenomics, and lipidomics data, combined with environmental information gathered, for instance, through mobile devices, could help to identify more sensitive biomarkers panels to guide diagnosis and treatment choice (69). However, as these "omic" platforms cannot be used in regular clinical practice, the potential discoveries arising from these platforms need to be translated into an immuno-based assay, which is a more viable option. New strategies with a more integrative approach between clinical factors and biological markers are being proposed in biomarker research of lithium response, which are expected to shed some light on precision drug prescription (139).

Precision in psychiatry implies embracing the multifactoriality of psychiatric diseases and the need to incorporate in the patient's assessment a range of biological and environmental factors that interact with each other in a dynamic way. Moreover, the biological and environmental factors involved in illness onset and progression are particular to every patient, as it is the way they interact (17). The use of personal devices to monitor the trajectories of patients at anytime and anywhere might help to deepen our knowledge on the complex interaction between biological and environmental factors. They can also allow evaluating less studied markers, such as sleep or chronobiological markers, which may turn out to be very informative (140). Moreover, further studies on epigenetics or mitochondrial genomes might identify novel factors involved in this complex disease (141). Similar to what is being developed in the field of psychosis, research on bipolar disorder could benefit from consortia sharing data to develop machine learning algorithms to help the prediction of bipolar disorder onset (17, 142).

A major limitation of current staging models is the absence of an agreement on the definition of stages. Moreover, operationalized cut-off points are lacking, probably due to the lack of longitudinal studies assessing patients according to stages, the absence of clear and reproducible neurobiological markers defining every stage and the intrinsic heterogeneity of psychiatric illnesses (15, 16, 143). Therefore, the current proposed models of staging are mainly theoretical and need to be validated for the moment. Additionally, participants of the available studies assessing differences between early and late stages of bipolar disorder include subjects attending specialized clinics, hence probably representing more severe forms of bipolar disorder (16). Moreover, it should be noted that precision medicine is still in its early beginnings, meaning that findings on genomics, genetic markers, and epigenetics are preliminary and need to be replicated before being integrated in any model of classification.

Until more solid information is available on the biology of the disease, though, the staging models can be based on pragmatic variables, like number of episodes and impact on cognition and functionality. A staging system based on characteristics that can be easily measured allows to standardize it and make it available and applicable in a broader number of clinical settings and countries worldwide (144).

Regardless of what the future brings, personalized medicine means "patient-centered care," therefore the choice among those new diagnostic techniques or treatments should be subject to a consensus between the clinician and the patient, especially considering the new ethical challenges that precision psychiatry brings with it (145). While psychiatrists can offer their expertise, patients opinions and preferences should play a central role in treatment decisions through shared decision-making (145).

AUTHOR CONTRIBUTIONS

ES was responsible for conception and design as well as initial drafting of the manuscript. All other authors (SD, AA, AR, SA, JP, MR, MB, FK, EV, and IG) were responsible for revising the manuscript critically for important intellectual content of the version of the manuscript to be published. All authors read and approved the final manuscript.

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After studying this article, you should be able to:

- Identify patients with first-episode psychosis who have clinical features that are associated with a diagnosis of bipolar disorder as opposed to schizophrenia

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Predictors of Bipolar Disorder Versus Schizophrenia Diagnosis in a Multicenter First Psychotic Episode Cohort: Baseline Characterization and a 12-Month Follow-Up Analysis

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ABSTRACT

Objective: The aim of this study was to identify predisposing factors and clinical features at baseline that might help predict diagnosis of bipolar disorder vs schizophrenia in a first-episode psychosis (FEP) cohort.

Methods: In this prospective, naturalistic study, we evaluated a cohort of 335 subjects with FEP recruited from April 2009 to April 2012. Baseline features were compared between subjects with a final *DSM-IV* diagnosis of bipolar disorder and schizophrenia at 12-month follow-up. A binary logistic regression model was used to assess predictors of diagnosis of bipolar disorder at follow-up.

Results: At 12-month follow-up, 47 of the 335 subjects included in the study received the diagnosis of bipolar disorder and 105, of schizophrenia. Subjects with a final diagnosis of bipolar disorder had a higher prevalence of family history of mood disorders (38.2% vs 18.0%, $P = .02$), better baseline premorbid adjustment (Premorbid Adjustment Scale [PAS]: 38.4 vs 50.6, $P < .01$) and psychosocial functioning (Functional Assessment Short Test [FAST]: 23.6 vs 33.7, $P = .001$), better cognitive flexibility (number of perseverative errors on the Wisconsin Card Sorting Test [WCST]: 14.2 vs 19.7, $P = .01$), more manic symptoms (Young Mania Rating Scale [YMRS]: 14.1 vs 7.3, $P < .01$), lesser negative symptoms (Positive and Negative Syndrome Scale negative scale [PANSS-N]: 15.0 vs 22.3, $P < .001$), and shorter duration of untreated psychosis (144.2 vs 194.7 days, $P < .01$) than subjects with a schizophrenia diagnosis. Binary logistic regression model revealed that lower FAST scores (odds ratio [OR] = 0.956; $P = .015$), lower PANSS-N scores (OR = 0.93; $P = .048$), and lower number of perseverative errors on the WCST (OR = 0.946; $P = .035$) were significantly related to diagnosis of bipolar disorder at follow-up.

Conclusions: In our FEP cohort, better psychosocial functioning, lesser negative symptoms, and better cognitive flexibility were related to diagnosis of bipolar disorder at 12-month follow-up.

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Clinical Points

- Early diagnosis in bipolar disorder can be challenging due to its heterogeneous clinical presentation, which can be in the form of first-episode psychosis (FEP).
- In those FEP patients presenting with good baseline psychosocial functioning, less severe negative symptoms, and less cognitive impairment, differential diagnosis with bipolar disorder should be considered.

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Bipolar disorder is a polymorphic psychiatric condition that can exhibit diverse clinical symptomatology, particularly in its early stages.[1] Therefore, the diagnosis of bipolar disorder at these stages can be extremely challenging,[2,3] as reflected in previous reports describing misdiagnosis rates of around 30%–60% in pediatric[2] and adult bipolar samples.[4–7] In its early stages, bipolar disorder is most commonly misdiagnosed as major depressive disorder when the onset of the disorder is a depressive episode.[2,8,9] However, bipolar disorder can also be misdiagnosed as schizophrenia when incongruent psychotic symptoms are evident in first-episode psychosis (FEP).[2,10,11] In the McLean-Harvard International First-Episode Project,[12] more than 500 patients with a first-lifetime psychotic episode had their diagnosis reassessed over 2 years, and it was reported that around 16% of the patients with a final diagnosis of bipolar disorder had been diagnosed with a nonaffective psychotic disorder at baseline.

An early distinction between bipolar disorder and nonaffective psychotic disorders has important treatment implications, as pharmacologic and psychological treatment regimens, as well as prognoses, differ between the groups.[13] Moreover, an early start of mood stabilizers in bipolar disorder is usually associated with a better response to treatment.[14,15] Research efforts to date in FEP samples have mainly focused on the identification of those factors related to conversion to schizophrenia.[16–19] However, fewer available data exist on particular factors related to the diagnostic shift to bipolar disorder. One of the few studies was carried out by Kim et al.[20] In their retrospective study, they found that female gender, shorter duration of untreated psychosis (DUP), better premorbid functioning, and religious or grandiose delusions were associated with diagnostic shift to bipolar disorder after FEP. A second study done by Arrasate et al[21] found that activation and manic symptoms predicted a diagnosis of bipolar disorder at 5 years of follow-up and that the presence of depressive symptoms predicted misdiagnosis. Due to the limited prospective data on the topic, the aim of the present study was to investigate baseline differences in sociodemographic, clinical, and neuropsychological variables between schizophrenia and psychotic bipolar disorder subjects included in a FEP cohort. Moreover, we sought to identify baseline features potentially useful to predict diagnosis of bipolar disorder at 12-month follow-up.

METHODS

The current work is part of the project "Phenotype-Genotype and Environmental Interaction: Application of a Predictive Model in First Psychotic Episodes" (PEPs study). The detailed protocol of the study has been published elsewhere.[22] The PEPs study was a multicenter, longitudinal, naturalistic follow-up study with a total of 16 participating centers throughout Spain. Fourteen of these centers are members of the Biomedical Research Networking Center for Mental Health (CIBERSAM),[23] and 2 are collaborator centers.[22]

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. It was approved by the investigation ethics committees of each participating center. Written, informed consent was obtained from all participants, or their legal guardians in case of underage participants, after providing them with a full explanation of the study.

Sample

A total of 335 subjects with FEP were recruited by the 16 participating centers, from April 2009 to April 2012. The inclusion criteria were (1) age between 7 and 35 years; (2) presence of first lifetime psychotic symptoms for at least

1 week in the last 12 months; (3) fluency in the Spanish language; and (4) provision of signed informed consent. The exclusion criteria were (1) intellectual disability according to the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition (*DSM-IV*) criteria[24]; (2) history of head trauma with loss of consciousness; and (3) presence of an organic disease with mental repercussions.

Patients had been receiving antipsychotic treatment for less than 12 months at study entry. Follow-up evaluations were performed at 2 months, 6 months, 12 months, and 24 months. For the purpose of the present study, we decided to focus on the 12-month follow-up assessment to establish the diagnostic groups, as we considered it a reasonable time frame to observe changes in diagnosis with better retention rates than at 24-month follow-up.

Diagnostic and Sociodemographic Assessment

Adults were evaluated using the Structured Clinical Interviews for *DSM-IV* Axis I and II Disorders (SCID-I and -II),[24–26] and children and adolescents were evaluated using the Spanish translation of the Kiddie-SADS-Present and Lifetime Version (K-SADS-PL).[27,28] Sociodemographic data, including gender, age, education, current living situation, and occupation, were gathered from all participants at baseline. Parental socioeconomic status was recorded using the Hollingshead Two-Factor Index of Social Position.[29] A complete personal and family history of psychiatric disorders was also compiled.

Clinical and Functional Assessment

Psychopathology was evaluated using the Spanish validated versions of the Positive and Negative Syndrome Scale (PANSS),[30,31] the Montgomery-Asberg Depression Rating Scale,[32,33] and the Young Mania Rating Scale (YMRS).[34,35] The retrospective Premorbid Adjustment Scale (PAS)[36] was used to estimate premorbid adjustment. Functional outcome was determined using the Functional Assessment Short Test (FAST).[37,38] In all scales, higher scores are indicative of greater clinical severity or functional impairment.

Days spent in the hospital and DUP were also registered. DUP was defined as the number of days elapsed between the onset of positive psychotic symptoms and the initiation of the first appropriate treatment for psychosis. Apart from the interviews with the patient, multiple sources of information (including medical records and interviews with relatives) were used to establish the onset of positive psychotic symptoms (defined as the first week with the PANSS items P1, P3, P5, P6, or G9 scoring 4 or more).

Neuropsychological Assessment

Trained neuropsychologists evaluated cognition in the first 2 months after the inclusion of the participant in the study to ensure clinical stability. No minimum years of education were required. The neuropsychological assessment included the following cognitive domains: (1) estimated Intelligence Quotient (IQ) (calculated based on the performance on the Vocabulary subtest from the Wechsler Adult Intelligence Scale [WAIS-III][39] or from the Wechsler Intelligence Scale for Children [WISC-IV][40]); (2) executive function (Stroop Color-Word Interference Test,[41] Wisconsin Card Sorting Test [WCST],[42] and Trail Making Test, form B[43]); (3) attention (Continuous Performance Test-II[44]); (4) processing speed (categorical [Animal Naming] and phonemic [F-A-S] components of the Controlled Oral Word Association Test[45] and Trail Making Test, form A[46]); (5) verbal memory (Spanish version of the California Verbal Learning Test, the Test de Aprendizaje Verbal España-Complutense[47,48]); (6) working memory (Digit and Letters and Numbers subtests of WAIS-III[39] and WISC-IV[40]); and (7) social cognition (Mayer-Salovey-Caruso Emotional Intelligence Test[49,50]). Direct scores were used for the analysis. The battery is explained in detail in the PEPsCog study.[51]

Statistical Analysis

First, we analyzed diagnosis distribution in our sample at 12-month follow-up in order to determine which patients had a well-established diagnosis of bipolar disorder or schizophrenia (determined by expert clinicians using *DSM-IV* criteria) at that point. We decided not to include in either group (bipolar disorder or schizophrenia) patients keeping a provisional diagnosis (ie, psychotic disorder not otherwise specified, acute and transient psychotic disorder, schizophreniform disorder, or substance-induced psychotic disorder) at 12-month follow-up, as we could not be certain whether their diagnosis would shift to affective psychosis or stay as nonaffective psychosis. In consequence, for subsequent analyses we only focused on those patients with a confirmed diagnosis of bipolar disorder or schizophrenia at 12-month follow-up in order to obtain more homogeneous groups.

Next, the Kolmogorov-Smirnov test was used to examine the normality of variables. Differences in baseline sociodemographic, clinical, and neuropsychological features between FEP subjects with a diagnosis of bipolar disorder and schizophrenia at 12-month follow-up were assessed using the χ^2 test for categorical variables and the *t* test or the Mann-Whitney *U* test, as appropriate, for continuous variables. A binary logistic regression was performed to determine the impact of sociodemographic, clinical, and neuropsychological variables on the likelihood of having a diagnosis of bipolar disorder vs schizophrenia at 12-month follow-up. For the regression analyses, we only entered those baseline variables that were significantly different between the 2 groups in the initial bivariate comparison and supported by prior evidence. Diagnosis of bipolar disorder was used as the dependent variable. Models were created according to Hosmer and Lemeshow, introducing a variable for every 10 observed cases of the dependent variable to avoid overfitting.[52,53] A direct approach was used to build the models. Data were analyzed using the IBM Statistic Package for Social Sciences (SPSS) v.23. Significance level was set at $P < .050$.

Table 1. Comparison of Sociodemographic Characteristics at Baseline

Characteristic	Bipolar Disorder (n = 47) Mean	SD	Schizophrenia (n = 105) Mean	SD	Mann-Whitney *U*	*P*[a]
Age, y	22.34	6.3	23.94	5.8	2,856.5	.12
	n	%	n	%	χ^2	
Gender					0.72	.79
Female	12	25.5	29	27.6		
Male	35	74.5	76	72.4		
Civil status					2.63	.11
Single	40	85.1	98	93.3		
Other	7	14.9	7	6.7		
Education					2.47	.12
Basic education	27	57.4	74	70.5		
Bachelor's degree or university degree	20	42.6	31	29.5		
Living situation					1.13	.57
Family of origin	36	77.0	88	83.8		
Independent	9	19.1	14	13.3		
Other	2	4.3	3	2.9		
Employment situation					3.61	.16
Student	26	55.3	44	41.9		
Active	8	17.0	15	14.3		
Other	13	27.7	46	43.8		
Parental socioeconomic status					2.52	.77
High	9	19.2	20	19.0		
Medium-high	5	10.6	9	8.6		
Medium	14	29.8	24	22.8		
Medium-low	12	25.5	36	37.0		
Low	7	14.9	14	13.3		
Unknown	0	0.0	2	1.9		
Previous psychiatric diagnoses	n = 19		n = 28			
Anxiety disorders	3	15.8	9	32.1	1.59	.31
Affective disorders	9	47.4	9	34.6	0.74	.54
Behavioral/learning disorders	4	21.1	5	17.9	0.08	1.00
Others[b]	3	15.8	7	25.0	0.57	.72
Family history of psychiatric disorder	n = 34		n = 89			
Affective disorders	13	38.2	16	18.0	5.6	**.02**
Anxiety disorders	5	14.7	11	12.4	0.12	.73
Psychotic disorders	4	11.8	14	15.7	0.31	.58
Substance misuse	4	11.8	12	13.5	0.06	.80
Others[c]	4	11.8	7	7.9	0.46	.50

[a]Boldface indicates statistical significance at the $P < .05$ level.
[b]Includes eating disorders, personality disorders, or substance use.
[c]Includes eating disorders, personality disorders, or autism spectrum disorder.

RESULTS

A total of 335 subjects with FEP were included in the study. Of these, a total of 47 subjects (14.0%) were diagnosed with bipolar disorder at 12-month follow-up, and 105 subjects (31.3%) were diagnosed with schizophrenia. 29.6% of subjects retained a provisional diagnosis or received a diagnosis of schizoaffective disorder, and the remaining 25% of the sample dropped out of the study. The most frequent diagnoses in the dropout group were psychotic disorder not otherwise specified, acute and transient psychotic disorder, and schizophreniform disorder. No significant differences were found between those subjects who remained in the study and those who dropped out except for civil status and living situation (patients who were in the dropout group lived more often independently from their families of origin), the number of days in the hospital (lower in the dropout group), and the number of perseverative errors in the WCST (again, lower in the dropout group). These differences suggest that the dropout group might be a better preserved group.

Comparisons Between Groups on Baseline Characteristics

Sociodemographic characteristics. As displayed in Table 1, no differences in sociodemographic variables were found between both groups. Among those patients with a positive personal history of psychiatric disorders, the prevalence of previous diagnoses did not differ between both groups. With regard to family history of psychiatric disorder, the prevalence of mood disorders encompassing major depressive disorder and bipolar disorder was higher among patients diagnosed with bipolar disorder (38.2% vs 18.0%; $P = .02$).

Clinical and functioning features. At baseline, patients diagnosed with bipolar disorder exhibited significantly more manic symptoms (mean YMRS score: 14.1 vs 7.3; $P < .01$) and lesser negative symptoms (mean PANSS negative

Table 2. Comparison of Clinical Characteristics and Functioning at Baseline

	Bipolar Disorder (n = 47) n (%)	Schizophrenia (n = 105) n (%)	χ^2	P^a
Substance misuse	36 (77.0)	80 (76.0)		
Tobacco use	30 (63.8)	65 (61.9)	0.05	.86
Cannabis use	14 (29.8)	43 (40.9)	1.72	.19
Alcohol use	27 (57.4)	45 (42.9)	2.77	.10
Cocaine use	3 (6.4)	12 (11.4)	0.93	.34
	Mean (SD)	Mean (SD)	Mann-Whitney *U*	
PANSS				
Total positive	19.0 (8.5)	18.7 (7.2)	2,466	.99
Total negative	15.0 (6.7)	22.3 (8.5)	3,662.5	**<.001**
Total general	36.7 (14.1)	39.7 (13.2)	2,774	.22
Total PANSS	70.7 (24.5)	80.7 (24.4)	3,007	**.03**
YMRS	14.1 (14.1)	7.3 (7.9)	1,820	**<.01**
MADRS	12.6 (11.7)	13.5 (9.3)	2,752	.26
FAST				
Autonomy	3.6 (3.1)	5.4 (3.5)	2,843.5	**<.01**
Occupational functioning	5.4 (5.3)	8.3 (5.9)	2,821	**<.01**
Cognitive functioning	5.5 (3.9)	6.6 (3.8)	2,581.5	.10
Financial issues	1.7 (1.9)	2.0 (1.9)	2,389	.41
Interpersonal relationships	5.6 (5.1)	8.5 (4.7)	2,963.5	**.001**
Leisure time	1.7 (1.9)	2.9 (1.9)	3,001.5	**<.001**
FAST total	23.6 (16.6)	33.7 (15.0)	2,993	**.001**
PAS				
Childhood	6.2 (4.5)	6.0 (4.1)	2,261.5	.96
Early adolescence	7.8 (4.7)	9.0 (5.1)	2,449.5	.22
Late adolescence	7.9 (5.1)	10.8 (6.2)	2,313	**.03**
Adulthood	2.4 (2.3)	3.9 (3.3)	1,757.5	**.03**
General questions	15.9 (8.1)	22.9 (10.9)	3,067.5	**<.001**
PAS total	38.4 (19.0)	50.6 (22.9)	2,933.5	**<.01**
Duration of untreated psychosis, d	144.2 (156.5)	194.7 (133.6)	3,037.5	**<.01**
No. of days spent in the hospital	23.7 (14.6)	31.6 (26.5)	1,743.5	.20

[a]Boldface indicates statistical significance at the $P < .05$ level.
Abbreviations: FAST = Functioning Assessment Short Test, MADRS = Montgomery-Asberg Depression Rating Scale, PANSS = Positive and Negative Syndrome Scale, PAS = Premorbid Adjustment Scale, YMRS = Young Mania Rating Scale.

scale [PANSS-N] score: 15.0 vs 22.3; <.001) than patients diagnosed with schizophrenia (Table 2). No significant differences were found in the total PANSS positive scale (PANSS-P), although, when focusing on specific items, patients diagnosed with bipolar disorder showed higher scores in grandiosity and lower scores in hallucinatory behavior (data not presented). Both groups showed functional impairment, but premorbid adjustment (mean PAS score: 38.4 vs 50.6; $P < .01$) and psychosocial functioning (mean FAST scale score: 23.6 vs 33.7; $P = .001$) were better in the group diagnosed with bipolar disorder, in particular in the areas of autonomy, interpersonal relationships, and leisure time. DUP was longer in the group diagnosed with schizophrenia (mean DUP: 144.2 vs 194.7 days; $P < .01$). There were no differences in substance misuse between both groups.

Neuropsychological measures. As described in Table 3, patients diagnosed with bipolar disorder and patients diagnosed with schizophrenia differed in the estimated premorbid IQ, with patients diagnosed with bipolar disorder exhibiting a mean estimated premorbid IQ of 98.7 compared to 90.9 in the patients diagnosed with schizophrenia ($P = .01$). Both groups also showed differences in the executive function domain in the first neuropsychological assessment (2-month follow-up), in particular in cognitive flexibility, as patients diagnosed with bipolar disorder performed significantly better in the perseverative error measure of the WCST.

Factors Related to Diagnosis of Bipolar Disorder at Follow-Up: Logistic Regression Model

A logistic regression analysis was performed to investigate the impact of baseline characteristics in the diagnostic group membership at 12-month follow-up. The full model containing the variables baseline PANSS-N, FAST, perseverative errors, and family history of affective disorder as predictors was statistically significant ($B = 2.3$; $P = .009$; $\text{Exp}(B) = 9.979$). The model as a whole explained between 21.1% (Cox and Snell R^2) and 30.2% (Nagelkerke R^2) of the variance and correctly classified 76.8% of cases. Baseline negative symptoms (OR = 0.930 [0.866–0.999]; $P = .048$), functioning (OR = 0.956 [0.922–0.991]; $P = .015$), and the number of perseverative errors on the WCST (OR = 0.946 [0.899–0.996]; $P = .035$) significantly contributed to the model (Table 4), indicating that higher scores on the PANSS-N, FAST, and perseverative errors were associated with a lower probability of bipolar disorder diagnosis.

As included subjects had a wide age range, we decided to explore whether predictors of bipolar disorder would be different in subjects < 18 years old (pediatric sample) and in subjects ≥ 18 years old (adult sample). In the pediatric

Table 3. Comparison of Neuropsychological Characteristics at 2-Month Follow-Up

	Bipolar Disorder (n = 47) Mean (SD)	Schizophrenia (n = 105) Mean (SD)	Statistic	P[a]
Estimated premorbid IQ				
WAIS vocabulary	98.7 (17.7)	90.9 (14.5)	2.78[b]	**.01**
Executive function				
WCST				
Errors	29.3 (16.1)	34.9 (16.9)	2,466[c]	.05
Perseverative responses	17.5 (11.4)	23.1 (17.3)	2,395[c]	.08
Perseverative errors	14.2 (9.0)	19.7 (13.4)	2,609.5[c]	**.01**
Categories	4.98 (1.7)	4.6 (1.8)	1,743.5[c]	.13
SCWT				
Interference	1.4 (13.3)	−1.1 (11.7)	164[c]	.74
TMT				
Trails B	93.3 (41.4)	97.5 (49.1)	2,243.5[c]	.75
Attention				
CPT-II				
Omissions	9.2 (14.4)	10.9 (13.1)	1,873.5[c]	.42
Commissions	16.1 (8.2)	16.5 (8.2)	−0.26[b]	.80
Mean hit RT	386.7 (98.3)	405.0 (62.7)	−1.1[b]	.28
Mean hit RT SE	8.6 (5.9)	7.9 (3.1)	0.69[b]	.50
Processing speed				
COWAT				
FAS	30.2 (10.6)	27.0 (9.4)	1.74[b]	.08
Animal naming	18.1 (5.2)	16.4 (4.2)	1,694.5[c]	.08
TMT				
Trails A	38.9 (22.4)	42.4 (19.9)	2,637[c]	.09
Verbal learning and memory				
TAVEC				
List A (total)	46.2 (12.5)	45.0 (12.8)	0.5[b]	.60
Free short-recall	9.9 (3.6)	9.2 (3.4)	1.15[b]	.25
Cued short-recall	10.5 (3.4)	10.0 (3.4)	1,855.5[c]	.46
Free delayed-recall	10.2 (3.8)	9.6 (3.4)	1[b]	.32
Cued delayed-recall	10.4 (3.4)	10.3 (3.5)	0.25[b]	.80
Recognition	14.6 (1.5)	14.0 (2.1)	1,588[c]	.10
Working memory				
WAIS-III				
Digit-symbol coding	14.4 (3.3)	13.7 (2.9)	1.27[b]	.21
Letter-number sequencing	9.6 (3.4)	8.9 (3.1)	1,852[c]	.19
Emotional intelligence				
MSCEIT				
Managing emotions	93.2 (8.5)	93.3 (10.0)	−0.75[b]	.94

[a]Boldface indicates statistical significance at the $P < .05$ level.
[b]Student t test.
[c]Mann-Whitney U.
Abbreviations: COWAT = Controlled Oral Word Association Test, CPT-II = Conners Continuous Performance Test, Mean hit RT = mean hit reaction time, Mean hit RT SE = mean hit RT standard error, MSCEIT = Mayer-Salovey-Caruso Emotional Intelligence Test, SCWT = Stroop Color and Word Test, TAVEC = Test de Aprendizaje Verbal España-Complutense, TMT = Trail Making Test, WAIS = Wechsler Adult Intelligence Scale, WCST = Wisconsin Card Sorting Test.

Table 4. Impact of Baseline Factors in Diagnosis of Bipolar Disorder at Follow-Up: Logistic Regression Model

	B (SE)	OR	95% CI	P[a]
Constant	2.3 (0.884)	9.979		**.009**
Negative symptoms[b] (baseline PANSS-N score)	−0.072 (0.036)	0.930	0.866–0.999	**.048**
Functioning[b] (baseline FAST score)	−0.045 (0.018)	0.956	0.922–0.991	**.015**
Perseverative errors (baseline)[b]	−0.055 (0.026)	0.946	0.899–0.996	**.035**
Family history of affective disorders	0.761 (0.533)	2.140	0.753–6.081	.153
R^2 Nagelkerke	0.302			
−2 log	103.872			

[a]Boldface indicates statistical significance at the $P < .05$ level.
[b]The results show that higher scores in the PANSS-N, FAST, and perseverative errors are associated with a lower probability of bipolar disorder diagnosis.
Abbreviations: FAST = Functioning Assessment Short Test, OR = odds ratio, PANSS-N = Positive and Negative Syndrome Scale–Negative scale, SE = standard error.

sample, only the model containing the variable baseline FAST as predictor of bipolar disorder was statistically significant ($B = 1.875$; $P = .040$; $\text{Exp}(B) = 6.523$). Regarding the adult sample, the full model containing the variables baseline PANSS-N, FAST, and DUP as predictors was statistically significant ($B = 2.079$; $P = .005$; $\text{Exp}(B) = 8.000$). Baseline negative symptoms (OR = 0.913 [0.857–0.972]; $P = .004$) and DUP (OR = 0.995 [0.992–0.999]; $P = .020$) significantly contributed to the model.

DISCUSSION

Our results indicate that subjects with FEP and further diagnosed with bipolar disorder or schizophrenia at 12-month follow-up display some clinical and cognitive differences from early baseline. Better baseline psychosocial functioning, lower PANSS negative score, and better executive performance—specifically, better cognitive flexibility, as measured by the perseverative errors on the WCST—were related to diagnosis of bipolar disorder at 12-month follow-up. Identification of features suggesting the diagnosis of bipolar disorder in a person with FEP has important clinical implications, as mood stabilizers and nonpharmacologic interventions like psychoeducation have proven to be more effective when started earlier in the course of bipolar disorder.[54,55] In addition, early interventions such as those aimed at improving cognitive reserve might need to be designed differently for patients with bipolar disorder and patients with schizophrenia.[56]

These results replicate previous findings from FEP samples, where better psychosocial functioning, less severe negative symptoms, or better executive functions were associated with a future diagnosis of bipolar disorder.[20,57–59] Besides, the relationship between more negative symptoms, lower functioning, and diagnosis of schizophrenia at follow-up has been consistently reported in previous studies examining diagnosis stability in adult and pediatric FEP samples.[2,16–19,59] Moreover, our results support the findings from Peña et al[57] on the potential of executive functioning to predict diagnostic shift to bipolar disorder or schizophrenia after FEP. Using a multinomial logistic regression model, they found that baseline performance on the WCST tasks "number of categories completed" and "perseverative errors" was able to distinguish between those patients with a final diagnosis of schizophrenia, those with a final diagnosis of other psychoses, and those with a final diagnosis of bipolar disorder with an overall accuracy rate

of 84.4%.[57] The findings of better cognitive flexibility in FEP patients with a final diagnosis of bipolar disorder compared to FEP patients with a final diagnosis of schizophrenia, along with higher IQ in the former group, may be linked to findings from neuroimaging studies that reported more pronounced and generalized gray matter deficits in patients with schizophrenia compared to patients with bipolar disorder,[60] suggesting that more severe neuronal alterations in frontotemporal brain regions in schizophrenia can be considered a biological trait related to the poor cognitive performance and clinical negative symptoms typical of the schizophrenia diagnosis.

In contrast to previous FEP studies, we found neither gender differences[61,62] nor differences in educational level[61] or age at onset[58] between the 2 groups. Yet, our findings confirm the presence of more manic symptoms and lesser negative symptoms in FEP patients with a final diagnosis of bipolar disorder, in consonance with prior studies comparing first-episode schizophrenia and first-episode psychotic bipolar disorder.[58,63,64] We did not find differences in the PANSS-P between the 2 groups except for grandiosity and hallucinatory behavior, on which the patients diagnosed with bipolar disorder scored higher and lower, respectively. This finding reflects the overlap between the PANSS-P and the YMRS—as does the fact that the group diagnosed with schizophrenia showed YMRS scores compatible with subclinical manic symptoms—and may suggest that the PANSS-P might not be sensitive enough to distinguish when positive symptoms like excitement or irritability are due to manic symptoms or due to psychotic symptoms. As so, it highlights the importance of completing the evaluation of subjects with FEP by carefully checking for the presence of "core" manic symptoms using the YMRS, especially among those subjects with high scores in grandiosity and low scores in negative symptoms and hallucinatory behavior. Our results are in consonance with those reported by Jauhar et al,[65] who found that clinical psychopathology syndromes could differentiate affective vs nonaffective psychosis with reasonable accuracy using machine learning techniques. These novel techniques are expected to better capture the complex relationship between variables included in prediction models than traditional statistical models, especially in large data sets.

We also found a shorter DUP in patients diagnosed with bipolar disorder compared to patients diagnosed with schizophrenia, in keeping with the results of previous reports.[20,58,64] The shorter DUP in patients diagnosed with bipolar disorder might be a consequence of more abrupt and noticeable behavioral changes in this group, with lesser predominance of negative symptoms, hence motivating an earlier contact with mental health services. Together with the fact that longer DUP has been related to a future diagnosis of schizophrenia spectrum disorder after FEP,[16,66] our evidence suggests that DUP might be a useful measure to differentiate between schizophrenia and bipolar disorder.

In our cohort, family history of affective disorder was more frequent in patients diagnosed with bipolar disorder than in patients diagnosed with schizophrenia. Nevertheless, this significance was not maintained in the regression model, even though a positive family history of bipolar disorder—especially early onset bipolar disorder—has been found as the strongest predictive factor for bipolar disorder in bipolar offspring cohort studies.[14,67] We did not find any differences in personal history of psychiatric disorder between the 2 groups. Caution is needed in interpreting these results due to the small number of patients reporting previous psychiatric disorders. Still, evidence arising from high-risk populations suggests that subjects at high risk for bipolar disorder and for schizophrenia might initially present with rather unspecific symptoms,[65] whereas more specific symptoms would appear shortly before the development of the full-blown bipolar or psychotic syndrome.[68,69] Thus, the presence or absence of a particular premorbid psychiatric disorder might be less informative than the evolution of psychiatric symptoms over time.

Lastly, previous studies have already reported that subjects with schizophrenia present a more marked premorbid deterioration in functionality than subjects with bipolar disorder,[36] as supported by our findings. In relation to the fact that common and different neural bases between schizophrenia and bipolar disorder have been identified,[70] some authors theorize that both disorders might share developmental pathologies, though of different nature and more severe or frequent in schizophrenia.[71] Taking that into account, although differences in premorbid adjustment and psychosocial functioning could be a consequence of an earlier start of attenuated clinical symptoms in the group of patients diagnosed with schizophrenia, as suggested by a longer DUP, they might also be due to more pronounced neurodevelopmental vulnerability in this group.

Strengths and Limitations

Some limitations should be mentioned when interpreting these results. First, the follow-up period was short, and only a small percentage of subjects received a diagnosis of bipolar disorder or schizophrenia at 12-month follow-up. Additionally, the sample size in the group of patients diagnosed with bipolar disorder was half of that in the group of patients diagnosed with schizophrenia. Third, due to this short follow-up, the subgroup of nonaffective psychosis patients included in the study might comprise those with a more severe clinical course, and, therefore, differences between patients diagnosed with bipolar disorder and patients diagnosed with schizophrenia might be more pronounced, influencing our results. Still, our findings are in line with other studies with longer follow-up.[20,59] Fourth, we cannot rule out that some of the patients diagnosed with bipolar disorder or schizophrenia might still change diagnosis, for instance, to schizoaffective disorder. However, a high diagnostic stability for both bipolar disorder and schizophrenia has been reported,[9,59,72] suggesting that the numbers of diagnostic shifts in both groups are expected to be minimal. Also, the significance threshold of our model was not corrected for multiple testing, which may be taken

into account when interpreting it. Nevertheless, this is a controversial issue due to the risk of increasing β error,[73] and our results are supported by previous literature, which makes them less likely to be due to chance. Lastly, as the study design was constructed prior to 2009, specific scales for negative symptoms such as the Brief Negative Symptom Scale or the Clinical Assessment Interview for Negative Symptoms were not used.

Despite these limitations, it must be underlined that this is a naturalistic study that includes a large sample of patients with a wide age range of inclusion, from adolescence to mid-adulthood, recruited in multiple Spanish psychiatric admission centers for acute psychosis. As such, the sample is expected to be representative of the FEP population in Spain. Furthermore, subjects included in the study were very well characterized, as they underwent a comprehensive protocol that explored in detail sociodemographic, clinical, and neuropsychological variables. Moreover, psychopathology was assessed with well-validated instruments, and cognition was measured using an extensive neuropsychological battery based on the National Institute of Mental Health MATRICS consensus.[74]

CONCLUSIONS

Our results indicate that subjects meeting diagnostic criteria for bipolar disorder or schizophrenia after FEP differ in clinical and neuropsychological variables from patients in the early phases of illness. In particular, we found that better psychosocial functioning, lesser negative symptoms, and better executive performance are related to diagnosis of bipolar disorder at 12-month follow-up. Future prediction models would ideally use a combination of clinical and biological factors. Meanwhile, disentangling which clinical features represent the most differential elements between affective and nonaffective psychosis even at early stages may represent a starting point to guide research in biological markers.

Further studies with larger sample sizes and longer follow-up periods are needed to confirm our results. Even so, our findings support the notion that there are some baseline features that are easily measurable in a clinical setting and useful for identifying patients at high risk of a shift in diagnosis to bipolar disorder after FEP, hence making it possible to design early interventions tailored to these patients.

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POSTTEST

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1. **Bipolar disorder is associated with initial misdiagnosis rates in pediatric and adult samples of around:**
   a. 1–2%
   b. 5–10%
   c. 30–60%
   d. 80–90%

2. **Which of the following neurocognitive tests/tasks would you preferentially administer to a patient after a first psychotic episode to help you in the differential diagnosis between bipolar disorder and schizophrenia?**
   a. Conners' Continuous Performance Test-II
   b. Wisconsin Card Sorting Test perseverative error measure
   c. Stroop Color-Word Interference Test
   d. Wechsler Adult Intelligence Scale III Letter-Number Sequencing

3. **When assessing a patient with first-episode psychosis, which of the following scales would prove less informative for the differential diagnosis between bipolar disorder and schizophrenia?**
   a. Young Mania Rating Scale
   b. Functional Assessment Short Test
   c. Positive and Negative Syndrome Scale-Negative Symptoms Subscale
   d. Positive and Negative Syndrome Scale-Positive Symptoms Subscale

4. **Marquita, a 23-year-old woman, was admitted 2 months ago for a first psychotic episode characterized by delusional ideation without hallucinatory behavior. She was diagnosed with schizophrenia. In the last 2 weeks, Marquita has shown low mood, insomnia, clinophobia, refusal to shower or eat, ideas of guilt, and slowness of movement and speech. Current symptomatology, together with a family history of affective disorder, makes you rethink the diagnosis. To evaluate Marquita for a possible diagnosis of bipolar disorder, based on the results of this study, you should collect information on all of the following items *except*:**
   a. Severity of negative symptoms during the first-episode psychosis
   b. Psychosocial functioning prior to the first psychotic episode
   c. Manic symptoms during the first-episode psychosis
   d. History of cocaine use

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Article

Exploring Risk and Resilient Profiles for Functional Impairment and Baseline Predictors in a 2-Year Follow-Up First-Episode Psychosis Cohort Using Latent Class Growth Analysis

Estela Salagre [1], Iria Grande [1,*], Brisa Solé [1], Gisela Mezquida [2], Manuel J. Cuesta [3], Covadonga M. Díaz-Caneja [4], Silvia Amoretti [2], Antonio Lobo [5], Ana González-Pinto [6,7], Carmen Moreno [4], Laura Pina-Camacho [4], Iluminada Corripio [7,8], Immaculada Baeza [9], Daniel Bergé [10], Norma Verdolini [1], André F. Carvalho [11,12], Eduard Vieta [1,*], Miquel Bernardo [2] and PEPs Group [†]

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Abstract: Being able to predict functional outcomes after First-Episode Psychosis (FEP) is a major goal in psychiatry. Thus, we aimed to identify trajectories of psychosocial functioning in a FEP cohort followed-up for 2 years in order to find premorbid/baseline predictors for each trajectory. Additionally, we explored diagnosis distribution within the different trajectories. A total of 261 adults with FEP were included. Latent class growth analysis identified four distinct trajectories: Mild impairment-Improving trajectory (Mi-I) (38.31% of the sample), Moderate impairment-Stable trajectory (Mo-S) (18.39%), Severe impairment-Improving trajectory (Se-I) (12.26%), and Severe impairment-Stable trajectory (Se-S) (31.03%). Participants in the Mi-I trajectory were more likely to have higher parental socioeconomic status, less severe baseline depressive and negative symptoms, and better premorbid adjustment than individuals in the Se-S trajectory. Participants in the Se-I trajectory were more likely to have better baseline verbal learning and memory and better premorbid adjustment than those in

the Se-S trajectory. Lower baseline positive symptoms predicted a Mo-S trajectory vs. Se-S trajectory. Diagnoses of Bipolar disorder and Other psychoses were more prevalent among individuals falling into Mi-I trajectory. Our findings suggest four distinct trajectories of psychosocial functioning after FEP. We also identified social, clinical, and cognitive factors associated with more resilient trajectories, thus providing insights for early interventions targeting psychosocial functioning.

Keywords: first-episode psychosis; functional outcomes; risk factors; early intervention; neurocognition; latent class analysis; precision medicine

1. Introduction

Psychosocial functioning refers to the ability to perform in daily living activities such as work, studies or recreational activities, and to establish satisfying interpersonal relationships with others [1]. In the last 50 years, psychiatry has progressively moved from a deficit-based care (which focuses on symptomatic remission), to a model oriented towards functional recovery, meaning that helping the patient to meet his/her personal goals has become as critical as achieving symptomatic remission [2,3]. In fact, it is increasingly accepted that functional outcomes are more meaningful when measuring treatment response than are scores on various scales rating only psychiatric symptoms [4]—and more aligned with what the patient ultimately expects from treatment [5]. Therefore, full functional remission is currently a preeminent goal in psychiatry.

Prior evidence suggests that achieving full functional recovery short after first-episode psychosis (FEP) is a stronger predictor of long-term full functional remission than symptomatic remission [6,7]. This evidence underscores the need to find early and modifiable factors associated with functional impairment already from early stages. Although multiple studies have investigated putative predictors of poor psychosocial functioning after FEP [8], most of them have approached this question using a dichotomous outcome, that is, presence vs. absence of functional impairment. The real picture seems far more complex, though, given the highly divergent outcomes in psychosocial functioning that individuals can experience after FEP, which encompass varying degrees of functional difficulties and different evolutions over time. Some patients will experience an early functional recovery, others might exhibit severe functional difficulties from illness onset and some subgroups might experience (persistent or transitory) mild to moderate functional impairment, which still have a negative impact on their daily life. Hence, the real challenge is to predict early in the course of the disease which individual will fall into each of these trajectories in order to be able to design earlier and more tailored treatments for social and personal recovery [2,9–11].

Statistical methods like latent class growth analysis (LCGA) can help to provide a more accurate picture of the heterogeneous course in psychosocial functioning that can be observed following FEP, as it allows considering different outcomes of the same characteristic simultaneously [12,13]. To our knowledge, only few studies so far have applied these statistical techniques to assess functional outcomes in FEP samples [14–16], and none of them has considered simultaneously sociodemographic variables, clinical features and an extensive set of cognitive domains, all of them previously related to poor functional outcomes [17]. Therefore, our main aim was to identify different trajectories of functional impairment in the 24-month follow-up of a FEP cohort and to assess putative predictors of these diverse trajectories, with a special focus on resilient trajectories. As a secondary objective, we aimed to explore diagnoses distribution within the different trajectories.

2. Experimental Section

2.1. Participants

The current study is based on data from the project 'Phenotype–genotype and environmental interaction. Application of a predictive model in first psychotic episodes' (PEPs

study), a multicenter, longitudinal, naturalistic follow-up study [18]. A total of 16 centers throughout Spain participated in this study; fourteen of them were members of the Biomedical Research Networking Center for Mental Health (CIBERSAM) [19] and two were collaborator centers [18]. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. It was approved by the ethics committees at each participating center (project identification code: 2008/4232). All participants or their legal guardians signed an informed consent after providing them a full explanation of the study's procedures.

The detailed protocol of the PEPs study was published elsewhere [18,20]. Briefly, a total of 335 subjects with FEP were recruited by all the participating centers, from April 2009 to April 2012. Individuals were included in the PEPs study if they were between 7 and 35 years old, presented first lifetime psychotic symptoms for at least one week in the last 12 months, were fluent in Spanish language, and were willing to sign the informed consent. Intellectual disability according to the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV) criteria [21], history of head trauma with loss of consciousness, and presence of an organic disease with mental repercussions constituted exclusion criteria. Patients had been under antipsychotic treatment for less than 12 months at study entry. Follow-up assessments were conducted at 2 months, 6 months, 12 months and 24 months following inclusion.

2.2. Assessment

2.2.1. Baseline Sociodemographic Data

Sociodemographic data were collected from all participants at baseline, including sex, age, ethnicity, educational level, marital status, current living situation, occupation, and parental socioeconomic status (SES). Parental SES was determined using the Hollingshead Two-Factor Index of Social Position [22]. Personal and family history of somatic and psychiatric disorders was also compiled. History of drug misuse was evaluated using the adapted version of a Multidimensional Assessment Instrument for Drug and Alcohol Dependence scale [23]. The Family Environment Scale (FES), a self-report instrument, was used to assess the patients' perception of the social climate within their families [24,25].

2.2.2. Baseline Clinical and Functional Assessment

For all subjects in the study, diagnosis was established by experienced mental health professionals using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) [21,26]. Psychopathology was evaluated using the Spanish validated versions of the Positive and Negative Syndrome Scale (PANSS) [27,28], the Young Mania Rating Scale (YMRS) [29,30], and the Montgomery–Åsberg Depression Rating Scale (MADRS) [31,32]. Premorbid adjustment was estimated by means of the retrospective Premorbid Adjustment Scale (PAS) [33]. The Functional Assessment Short Test (FAST) [1,34] was used to determine psychosocial functioning. It comprises 24 items, which evaluate six specific functioning domains: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships, and leisure time. This scale seeks to identify changes or difficulties in functionality attributable to the illness. The FAST scores range from 0 to 72. According to the cut-off classification as proposed by Bonnín et al. [35], FAST scores > 40 are indicative of severe functional impairment, FAST score between 21 and 40 indicate moderate functional impairment, FAST scores between 12–20 indicate mild impairment, and $\leq$11 points in the FAST reflect no functional impairment. This scale has shown to be sensitive to change and has been validated for FEP [36]. In all the aforementioned scales, higher scores are indicative of greater clinical severity or functional impairment. History of traumatic life events was assessed through the Spanish version of the Trauma Questionnaire (TQ) [37,38]. Duration of untreated psychosis (DUP), defined as the number of days elapsed between the onset of positive psychotic symptoms and the initiation of the first appropriate treatment for psychosis, was also registered. It was estimated using the Symptom Onset in Schizophrenia (SOS) inventory [39].

2.2.3. 2-Month Follow-Up Neuropsychological Assessment

Participants were likewise evaluated using a comprehensive neuropsychological battery encompassing most of the cognitive domains proposed by the National Institute of Mental Health MATRICS consensus [40]. The evaluation was performed by trained neuropsychologists in the first two months after the inclusion of the participant in the study to avoid the interference of acute psychopathological manifestations on neurocognitive assessments. The neuropsychological assessment comprised the following cognitive domains: (1) estimated Intelligence Quotient (IQ) (calculated based on the performance on the Vocabulary subtest from the Wechsler Adult Intelligence Scale (WAIS-III) [41]); (2) executive function (Stroop Color-Word Interference Test [42], Wisconsin Card Sorting Test (WCST) [43] and Trail Making Test (TMT), form B [44]); (3) attention (Continuous Performance Test-II (CPT-II) [45]); (4) processing speed (TMT, form A [46] and categorical (Animal Naming) and phonemic (F-A-S) components of the Controlled Oral Word Association Test (COWAT) [47]); (5) verbal memory (Spanish version of the California Verbal Learning Test, the *Test de Aprendizaje Verbal España-Complutense* (TAVEC) [48]); (6) working memory (Digit span and Letter-Number sequencing subtests of WAIS-III [41]); and (7) social cognition (Mayer–Salovey–Caruso Emotional Intelligence Test (MSCEIT) [49,50]). The neuropsychological battery is described in further detail in the PEPsCog study [51].

2.3. Statistical Analysis

2.3.1. Identification of Functional Trajectories: Latent Class Growth Analysis

LCGA was used to identify distinct functioning trajectories over the 24-month follow-up. In the current analysis, individual class membership was assigned on the basis of FAST total scores measured at five time points over the two-year follow-up period, namely at baseline, 2-, 6-, 12-, and 24-month follow-up. We only included in the analysis individuals over 18 years old, as the FAST scale has only been validated in adult samples, and with information on the FAST scale in at least two follow-up assessments. This left a sample of 275 adult participants.

Each model was rerun 100 times using different start values to avoid converging to local maxima [52]. To accommodate expected fluctuations over time, we estimated linear and quadratic terms. In order to determine the optimal number of trajectory classes, models with increasing number of latent classes (from 1- to 4-class models) were fitted to the data and the best-fitting model was selected according to the following goodness-of-fit indices: Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), samples-size-adjusted BIC (aBIC), and entropy. Lower values of AIC, BIC, and aBIC suggest a more parsimonious model, while higher entropy also indicates better model fit. Entropy ranges from 0 to 1 and is a summary indicator of the accuracy with which models classify individuals into their most likely class. Entropy with values approaching 1 indicate clear delineation of classes [53]. Interpretability and parsimony of the model were also taken into consideration in the final selection of the model. LCGA analyses were performed on R version 3.6.3, using the *'lcmm'* package ([54]; https://cran.r-project.org/web/packages/lcmm/index.html).

2.3.2. Identification of Baseline Predictors of Functional Trajectory Membership

To identify putative baseline predictors of trajectory membership, the estimated latent classes (i.e., the estimated trajectory group) derived from LCGA were imported to SPSS, version 23 (SPSS Inc., Chicago, IL, USA), for a three-step analysis:

First, we created seven cognitive composites to be used as putative baseline predictors using data from the two-month follow-up neurocognitive assessment. To do so, patients' raw scores on each neuropsychological task were standardized to z-scores based on the performance of the whole sample. The selection of the tasks within each cognitive domain was based on previous works from the PEPs group [51,55,56]. Afterwards, z-scores of different tests were summed and averaged to create the following seven cognitive composites: (1) the processing speed composite, based on the word–color task from the Stroop Test

and the TMT-A; (2) the working memory composite, which included the Letter-Number Sequencing and the Digit-Span WAIS-III subtests; (3) the verbal learning and memory index, which was composed of the total trials 1–5 list A, short free recall, short cued recall, delayed free recall, delayed cued recall, and recognition scores of the TAVEC; (4) the executive function composite, calculated based on the number of categories and perseverative errors of the WCST, the Stroop Interference Test, and the TMT-B; (5) the attention composite score, which was based on several measures of the CPT-II, such as commission and reaction time; (6) the verbal fluency composite which was composed of the Category Fluency (Animal Naming) and the F-A-S Test of the COWAT; and (7) the social cognition composite, which included the Emotional Management of the MSCEIT. Whenever extreme scores in the performance of the aforementioned test were detected (i.e., more than four standard deviations (SD) above or below the mean), the scores were truncated to $z = +/- 4$. Since higher scores in CPT-II, WCST perseverative errors, and TMT-A and -B indicate poorer performance, z-scores obtained from measures of these tests were reversed before constructing the corresponding composite scores.

Second, candidate predictors (i.e., baseline sociodemographic and clinical variables as well as the created cognitive composites) were compared between trajectory classes using Kruskal-Wallis and chi-square tests, as appropriate. The Kruskal–Wallis test was selected for continuous variables since they did not follow a normal distribution, as assessed visually and by the Kolmogorov–Smirnov test. When applicable, post-hoc comparison analyses with Bonferroni correction for multiple comparisons were performed to further clarify the presence of significant differences between trajectory classes.

Third, those variables found to be statistically significant in the post-hoc analysis in at least two pair-wise comparisons were then entered into a multinomial regression model to determine which candidate factors independently predicted trajectory membership, adjusting for age and sex. For the PANSS scale, only the PANSS positive and negative subscales were entered as independent variables to avoid multicollinearity. Significant putative predictors for the multivariable model were identified using a stepwise backwards elimination process [57], with sex and age entered as fixed factors. The identified latent classes were used as the dependent variable. Since we were interested in exploring predictors of resilient trajectories, we selected the most impaired group as the reference category.

2.3.3. Diagnosis Distribution within the Identified Functional Trajectories

Lastly, to explore whether diagnosis distribution differed within each functional trajectory and how it changed over time, we compared using chi-square tests the proportion of individuals with a diagnosis of Schizophrenia, Bipolar disorder, Schizoaffective disorder, and Other psychoses (including psychotic disorder not-otherwise specified, brief psychotic disorder, schizophreniform psychosis, delusional disorder, substance-induced psychosis) in each of the predicted functional trajectories at baseline, 1-year and 2-year follow-up.

The level of statistical significance for all analyses was set at $p < 0.05$.

3. Results

3.1. Sample Characteristics and Attrition Analysis

The final sample included 261 participants. A total of 14 individuals were not considered for the analyses since information on their FAST scores was only available at one time point. Therefore, they were treated as drop-outs. The baseline characteristics of the final sample are presented in Table 1. A comparison between drop-outs and non-drop-outs at baseline, 12-month, and 24-month follow-up can be found in the Supplementary Table S1. The median age of the final sample was 25.05 years old (Interquartile Range: 9) and 33% of the participants were female. Among those subjects that dropped out from the study, there was a lower proportion of Caucasian participants and of participants with a family history of psychiatric disorders. Subjects that dropped out from the study reported more frequently substance misuse at baseline too.

Table 1. Baseline characteristics of the final sample (n = 261).

Characteristics	Median (IQR)/*n* (%)
Age (Years)	25.05 (9)
Sex (Female)	87 (33.3)
Marital status (Single)	222 (85.1)
Ethnicity (Caucasian)	228 (87.4)
Parental socioeconomic status (Medium-high)	141 (54.6)
Living situation (Living independently)	55 (21.1)
Educational level (Higher education)	115 (44.2)
Occupational status (Active *)	136 (52.1)
Somatic comorbidity (Yes)	73 (28.0)
Family history of psychiatric disorder (Yes)	146 (55.9)

* Active includes workers and students.

3.2. Latent Classes of Functional Trajectories

After examining fit indices, entropy, parsimony, and interpretability of the model, the 4-class model including the quadratic term was selected as optimal for our data (Table 2). Entropy was acceptable (0.76) for the 4-class model as well as post mean class probabilities (0.81 for Class 1, 0.92 for Class 2, 0.82 for Class 3, and 0.84 for Class 4). This suggests that with the 4-class model individuals were likely to be correctly assigned to their respective latent class.

Table 2. Goodness-of-fit statistics of latent class growth analysis with one-to-four class solutions of psychosocial functioning trajectories.

		Fit Statistics [a]				% of the Sample in Each Class			
Number of Classes	**Number of Parameters**	**AIC**	**BIC**	**aBIC**	**Entropy**	**Class 1**	**Class 2**	**Class 3**	**Class 4**
1	4	9029.81	9044.07	9031.39	-	100	-	-	-
2	8	8675.19	8703.71	8678.35	0.82	54.02	45.98	-	-
3	12	8639.13	8681.91	8643.86	0.71	41.00	32.18	26.82	-
4	**16**	**8574.11**	**8631.14**	**8580.41**	**0.76**	**38.31**	**18.39**	**12.26**	**31.03**

Abbreviations: AIC: Akaike's Information Criterion; BIC: Bayesian Information Criterion; aBIC: sample size–adjusted Bayesian Information Criterion. [a] Lower values (AIC, BIC, and aBIC) indicate a better model fit. Higher entropy indicates better model fit. Values of 0.4, 0.6, and 0.8 represent low, medium, and high entropy [58]. Bold is used here to indicate which model was selected.

The mean FAST scores at each assessment point of individuals grouped according to their predicted trajectory are presented in Figure 1. One group showed mild impairment at baseline and no impairment by the end of the follow-up, and was referred to as *Mild impairment-Improving trajectory* (Class 1; n = 100 (38.31%)). Another group, denominated as *Moderate impairment-Stable trajectory* (Class 2; n = 48 (18.39%)) exhibited moderate functional impairment at baseline and throughout the follow-up. A third group presented with severe functional impairment that improved along the follow-up. It was referred as *Severe impairment-Improving trajectory* (Class 3; n = 32 (12.26%)). The last group, termed as *Severe impairment-Stable trajectory*, displayed severe-moderate functional impairment throughout the follow-up (Class 4; n = 81 (31.03%)). Thus, 50.57% of the sample showed a trajectory characterized by a functional improvement/recovery ("*Improving trajectories*"), while 49.42% exhibited persistent functional impairment during follow-up ("*Stable trajectories*").

3.3. Baseline Predictors of Trajectory Membership

The comparison between the four psychosocial functioning trajectories on sociodemographic, clinical, and neuropsychological variables is presented in Table 3. The baseline variables found to be statistically different between groups in at least two pairwise comparisons were: parental SES, alcohol use, PANSS positive, PANSS negative, PANSS general, PANSS total, Young total, MADRS total, PAS total, verbal learning, and memory and working memory. As previously stated, for the PANSS scale, only the PANSS positive and negative subscales were entered as independent variables in the multinomial regression model.

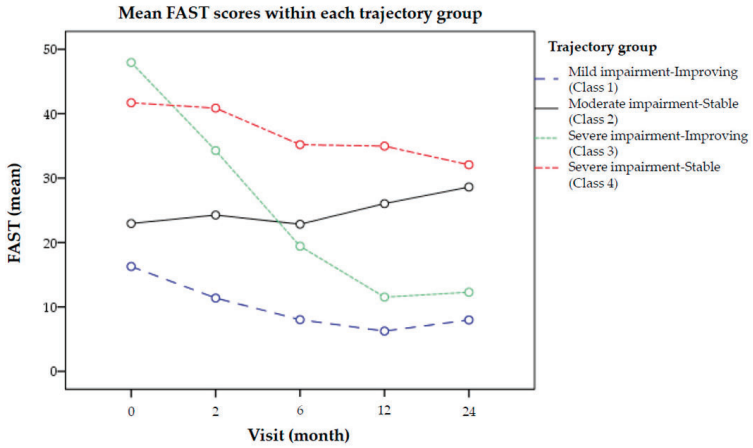

Figure 1. Evolution of mean FAST scores within each of the functional trajectory groups derived from the latent class growth analysis. Higher scores in the FAST are indicative of greater functional impairment.

Multinomial regression analysis (final model: R^2 Nagelkerke 53%, $X^2 = 140.26$; df = 24; $p < 0.001$) indicated that parental SES, total baseline scores in PANSS positive subscale, PANSS negative subscale, MADRS, and PAS, as well as verbal learning and memory contributed to differentiate among the four functional trajectories (Table 4). Specifically, subjects falling into the *Mild impairment-Improving* group were more likely to have a medium-high parental SES (OR: 4.14, 95% CI 1.65–10.42), lower severity of baseline negative symptoms (OR: 0.89, 95% CI 0.83–0.96) and of depressive symptoms (OR: 0.94, 95% CI 0.89–0.99), and better premorbid adjustment (OR: 0.96, 95% CI 0.94–0.98). On the other hand, compared to individuals in the *Severe impairment-Stable* trajectory, better premorbid adjustment (OR: 0.96, 95% CI 0.93–0.99) and higher scores in the verbal learning and memory domain (OR: 3.09, 95% CI 1.36–7.03) increased the probability of belonging to the *Severe impairment-Improving trajectory* group. Finally, individuals falling in the *Moderate impairment-Stable* trajectory were more likely to score lower in the PANSS positive subscale (OR: 0.93, 95% CI 0.87–0.99) at baseline than the *Severe impairment-Stable* group.

3.4. Exploring Diagnoses Distribution among Functional Trajectories throughout the Follow-Up

The diagnoses distribution within each functional trajectory at baseline, one-year follow-up and two-year follow-up is depicted in Figure 2. Diagnosis distribution significantly differed between trajectory groups at baseline ($n = 261$; $X^2 = 19.9$; $p = 0.02$), 1-year follow-up ($n = 202$; $X^2 = 42.6$; $p < 0.001$) and at 2-year follow-up ($n = 156$; $X^2 = 28.5$; $p = 0.001$). A higher proportion of patients with a diagnosis of Schizophrenia was found among individuals falling into the *Severe impairment-Stable* and *Moderate impairment-Stable* trajectories compared to the *Mild impairment-Improving trajectory*. On the other hand, the diagnoses of Bipolar disorder and Other psychosis were more frequent among individuals falling into the *Mild impairment-Improving trajectory* compared to the *Severe impairment-Stable* trajectory. Abbreviations: Mi-I: Mild impairment-Improving; Mo-S: Moderate impairment-Stable; Se-I: Severe impairment-Improving; Se-S: Severe impairment-Stable.

Figure 2 represents, for each of the functional trajectories derived from the Latent class growth analysis, the number of individuals with a diagnosis of Bipolar disorder, Schizophrenia, Schizoaffective disorder, or Other psychoses at baseline, 12-month and 24-month follow-up. Other psychoses include psychotic disorder not-otherwise specified, brief psychotic disorder, schizophreniform psychosis, delusional disorder, and substance-induced psychosis. (*) symbol indicates which diagnostic categories within the *Severe impairment-Stable* trajectory and the *Moderate impairment-Stable* trajectory show a significantly different proportion of individuals compared to the *Mild impairment-Improving* trajectory group. Abbreviations: Mi-I: Mild impairment-Improving; Mo-S: Moderate impairment-Stable; Se-I: Severe impairment-Improving; Se-S: Severe impairment-Stable

Table 3. Comparison between groups derived from the identified functional trajectories.

	Mi-I (1) *n* = 100	Mo-S (2) *n* = 48	Se-I (3) *n* = 32	Se-S (4) *n* = 81	Kruskal–Wallis/X^2	*p*-Value	Post-Hoc [a]					
							1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Sociodemographic characteristics												
Age (years) [b]	25.8 (10)	24.9 (8)	24.4 (8)	24.8 (8)	1.44	0.70						
Sex (Female) [c]	29 (29.0)	18 (37.5)	10 (31.2)	30 (37.0)	1.78	0.62						
Ethnicity (Caucasian) [c]	91 (91.0)	41 (85.4)	27 (84.4)	69 (85.2)	1.97	0.58						
Marital status (Single) [c]	83 (83.0)	42 (87.5)	29 (90.6)	68 (83.9)	1.42	0.70						
Living situation (Living independent) [c]	30 (30.0)	4 (8.3)	7 (21.9)	14 (17.3)	10.19	**0.02**	**<0.05**					
Educational level (Higher education) [c]	55 (55.0)	20 (41.7)	16 (50.0)	24 (29.6)	12.71	**<0.01**			**<0.05**			
Occupational status (Active [d]) [c]	63 (63.0)	26 (54.2)	18 (56.2)	29 (35.8)	13.68	**<0.01**			**<0.05**			
Socioeconomic status (Medium-high) [c]	72 (72.0)	22 (45.8)	18 (56.2)	29 (35.8)	24.06	**<0.001**	**<0.05**		**<0.05**			
Family history of psychiatric disorders (Yes) [c]	53 (53.0)	33 (68.7)	17 (53.1)	43 (53.1)	3.92	0.27						
Previous psychiatric diagnoses (Yes) [c]	24 (24.0)	13 (27.1)	8 (25.0)	29 (35.8)	4.65	0.59						
Substance use [c]												
Tobacco	70 (70.0)	33 (68.7)	24 (75.0)	55 (67.9)	0.57	0.90						
Alcohol	60 (60.0)	25 (52.1)	24 (75.0)	32 (39.5)	14.05	**<0.01**			**<0.05**			**<0.05**
Cannabis	44 (44.0)	22 (45.8)	13 (40.6)	36 (44.4)	0.22	0.97						
Cocaine	9 (9.0)	8 (16.7)	6 (18.7)	12 (14.8)	3.04	0.39						
Clinical measures												
DUP (days) [b]	85.0 (165)	133.0 (263)	110.0 (168)	162.0 (216)	14.36	**<0.01**			**<0.05**			
PANSS [b]												
PANSS positive	14.0 (14)	16.0 (10)	23.5 (10)	21.0 (9)	32.14	**<0.001**		**<0.05**	**<0.05**	**<0.05**	**<0.05**	
PANSS negative	14.0 (11)	19.0 (13)	19.5 (11)	23.0 (9)	57.27	**<0.001**	**<0.05**	**<0.05**	**<0.05**		**<0.05**	
PANSS general	29.5 (19)	34.5 (17)	45.5 (19)	43.0 (14)	58.89	**<0.001**		**<0.05**	**<0.05**	**<0.05**	**<0.05**	
PANSS total	57.5 (39)	72.0 (28)	86.5 (29)	88.0 (24)	65.12	**<0.001**		**<0.05**	**<0.05**	**<0.05**	**<0.05**	
Young total [b]	2.0 (14)	2.0 (14)	13.5 (19)	7.0 (18)	15.26	**<0.01**		**<0.05**		**<0.05**		
MADRS total [b]	6.0 (10)	13.0 (12)	16.0 (17)	16.0 (12)	39.05	**<0.001**	**<0.05**	**<0.05**	**<0.05**			
PAS total [b]	30.0 (24)	43.0 (27)	36.0 (31)	57.0 (33)	51.58	**<0.001**	**<0.05**		**<0.05**			**<0.05**
TQ [b]	1.0 (2)	0.0 (1)	0.0 (2)	0.0 (2)	2.69	0.44						
FES [b]												

Table 3. *Cont.*

	Mi-I (1) *n* = 100	Mo-S (2) *n* = 48	Se-I (3) *n* = 32	Se-S (4) *n* = 81	Kruskal–Wallis/X^2	*p*-Value	Post-Hoc [a]					
							1 vs. 2	1 vs. 3	1 vs. 4	2 vs. 3	2 vs. 4	3 vs. 4
Cohesion	52.0 (13)	52.0 (13)	52.0 (15)	47.0 (17)	5.30	0.15						
Expressiveness	53.0 (16)	50.0 (16)	53.0 (14)	47.0 (16)	4.14	0.25						
Conflict	49.0 (9)	49.0 (9)	49.0 (9)	49.0 (17)	7.19	0.07						
Independence	51.0 (11)	51.0 (11)	51.0 (14)	51.0 (17)	3.50	0.32						
Achievement-orientation	47.0 (10)	47.0 (10)	47.0 (15)	47.0 (16)	1.35	0.72						
Intellectual-cultural orientation	51.0 (23)	47.0 (14)	47.0 (14)	42.0 (19)	5.78	0.12						
Active-recreational orientation	53.0 (14)	48.0 (19)	48.0 (21)	44.0 (4)	19.69	<0.001			**<0.05**			
Moral-religious emphasis	44.0 (10)	49.0 (15)	44.0 (10)	44.0 (15)	3.34	0.34						
Organization	54.0 (10)	51.5 (19)	49.0 (20)	49.0 (15)	4.51	0.21						
Control	45.0 (14)	49.0 (14)	49.0 (14)	49.0 (14)	4.06	0.25						
Cognitive measures												
	n = 93	*n* = 44	*n* = 28	*n* = 76								
IQ [b]	100 (20)	92.5 (24)	93.5 (19)	90.0 (20)	10.18	**0.02**			**<0.05**			
	n = 91	*n* = 43	*n* = 25	*n* = 67								
Verbal Fluency [b]	0.20 (1.2)	−0.08 (1.4)	0.25 (1.1)	−0.50 (0.9)	20.69	**<0.001**			**<0.05**			
	n = 85	*n* = 36	*n* = 23	*n* = 53								
Attention [b]	0.18 (0.4)	0.03 (0.7)	0.10 (0.6)	−0.11 (0.5)	13.54	**<0.01**			**<0.05**			
	n = 94	*n* = 43	*n* = 28	*n* = 73								
Working memory [b]	0.14 (1.1)	−0.01 (1.3)	0.15 (0.9)	−0.17 (1.2)	14.10	**<0.01**			**<0.05**			**<0.05**
	n = 92	*n* = 40	*n* = 25	*n* = 67								
Verbal Learning and Memory [b]	0.38 (1.2)	0.20 (1.3)	0.25 (0.9)	−0.43 (1.4)	24.18	**<0.001**			**<0.05**			**<0.05**
	n = 93	*n* = 41	*n* = 30	*n* = 70								
Processing Speed [b]	0.32 (0.8)	0.14 (0.9)	−0.11 (1.4)	−0.16 (1.0)	14.78	**<0.01**			**<0.05**			
	n = 92	*n* = 40	*n* = 28	*n* = 58								
Executive function [b]	0.29 (0.7)	−0.03 (0.8)	0.14 (0.8)	0.00 (1.0)	13.26	**<0.01**			**<0.05**			
	n = 89	*n* = 43	*n* = 26	*n* = 66								
Social cognition [b]	−0.33 (1.3)	−0.01 (1.4)	0.04 (1.3)	−0.07 (1.4)	3.47	0.32						

[a] Tukey or Z statistic, as appropriate. Significance values have been adjusted using the Bonferroni correction for multiple tests. Bold type indicates $p < 0.05$. [b] Values are indicated as median (Interquartile Range). [c] Values are indicated as *n* (%). [d] Active includes workers and students. Abbreviations: Mi-I: Mild impairment-Improving; Mo-S: Moderate impairment-Stable; Se-I: Severe impairment-Improving; Se-S: Severe impairment-Stable; DUP: Duration of Untreated Psychosis; PANSS: Positive and Negative Syndrome Scale; MADRS: Montgomery–Åsberg Depression Scale; YMRS: Young Rating Mania Scale; PAS: Premorbid Adjustment Scale; TQ: trauma questionnaire; FES: Family Environment Scale; IQ: Intelligence Quotient.

Table 4. Multinomial logistic regression [a]: baseline predictors of functional trajectories.

	B	SE	Wald [c]	Sig.	Adjusted Exp(B) [b]	95% Interval Confidence Exp(B)	
						Lower Limit	Upper Limit
Mild impairment-improving trajectory *							
Intersection	4.95	1.62	9.35	**<0.01**			
Parental SES (medium-high)	1.42	0.47	9.14	**<0.01**	4.14	1.65	10.42
PANSS positive (baseline score)	−0.05	0.03	2.94	0.09	0.95	0.89	1.01
PANSS negative (baseline score)	−0.12	0.04	9.75	**<0.01**	0.89	0.83	0.96
MADRS total (baseline score)	−0.06	0.03	4.44	**0.03**	0.94	0.89	0.99
PAS total (baseline score)	−0.04	0.01	10.91	**<0.01**	0.96	0.94	0.98
Verbal learning & memory	0.39	0.28	1.89	0.17	1.47	0.85	2.55
Moderate impairment-stable trajectory *							
Intersection	3.58	1.65	4.71	**0.03**			
Parental SES (medium-high)	0.58	0.48	1.48	0.22	1.78	0.70	4.54
PANSS positive (baseline score)	−0.07	0.03	4.94	**0.03**	0.93	0.87	0.99
PANSS negative (baseline score)	−0.07	0.05	2.44	0.12	0.93	0.85	1.02
MADRS total (baseline score)	0.06	0.03	2.99	0.08	1.06	0.99	1.13
PAS total (baseline score)	−0.02	0.01	2.83	0.09	0.98	0.96	1.00
Verbal learning & memory	0.29	0.28	1.08	0.30	1.33	0.77	2.30
Severe impairment-improving trajectory *							
Intersection	−1.44	2.12	0.46	0.50			
Parental SES (medium-high)	0.81	0.61	1.76	0.18	2.25	0.68	7.46
PANSS positive (baseline score)	0.05	0.04	1.76	0.18	1.06	0.97	1.14
PANSS negative (baseline score)	−0.07	0.05	2.44	0.12	0.93	0.85	1.02
MADRS total (baseline score)	0.06	0.03	2.99	0.08	1.06	0.99	1.13
PAS total (baseline score)	−0.04	0.01	7.56	**<0.01**	0.96	0.93	0.99
Verbal learning & memory	1.13	0.42	7.25	**<0.01**	3.09	1.36	7.03

[a] Nagelkerke $R^2 = 0.53$, Model $\chi^2 = 140.26$, df = 24, $p < 0.001$. [b] Adjusted by age and sex. [c] Degrees of freedom: 1. * Reference category is *Severe impairment-Stable* trajectory. Abbreviations: SE: Standard Error; SES: Socioeconomic status; PANSS: Positive and Negative Syndrome Scale; MADRS: Montgomery–Åsberg Depression Scale; PAS: Premorbid Adjustment Scale. Bold type indicates $p < 0.05$.

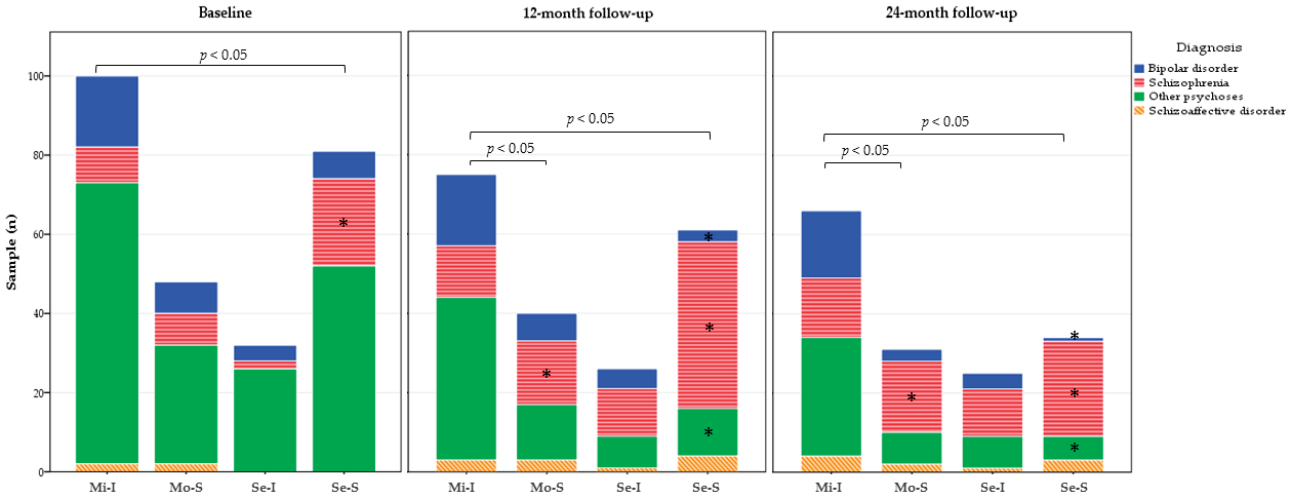

Figure 2. Diagnoses distribution within each of the identified functional trajectories.

3.5. Post-Hoc Mediation Analysis

Given that previous works on FEP samples have suggested that premorbid adjustment may influence psychosocial functioning through verbal memory and negative symptoms [59], we decided to test how the identified predictors interact to impact functioning in our sample. For that, we examined mediation using a regression-based bootstrapping approach [60]. Analyses were performed with PROCESS [61], with age and sex introduced as covariables (see Appendix A for a more detailed explanation). The model used to explore mediation between predictors of the *Severe impairment-improving trajectory* vs. *Severe impairment-Stable trajectory* indicated that better premorbid adjustment positively impacts verbal learning and memory, which in turn increases the probability of belonging to the *Severe impairment-improving* trajectory (indirect effect = −0.011; 95% CI, −0.030 to −0.001). However, our results indicate complementary partial mediation since both direct and indirect effects were significant and pointed in the same direction [62]. Regarding mediation between predictors of *Mild impairment-Improving* vs. *Severe impairment-Stable* trajectories, we could establish that parental SES partially mediates its effects through premorbid adjustment and through baseline negative symptoms (indirect effect = −0.249; 95% CI, −0.551 to −0.086).

4. Discussion

In this study, we used LCGA to investigate trajectories of psychosocial functioning following FEP. In line with previous studies using the same approach [14–16], our results indicate a heterogeneous pattern of psychosocial functioning in the first years after FEP. Specifically, we found four distinct functional trajectories. The largest number of subjects in our sample showed mild functional impairment at baseline and experienced functional recovery short after FEP. The second largest group experienced severe functional impairment at baseline which persisted, although more moderately, throughout the study period. A third group displayed a moderate and persistent functional impairment throughout the 24-month follow-up. Finally, a minority of patients exhibited severe functional impairment at baseline, which subsequently improved almost to the point of no functional impairment by the end of the follow-up. Importantly, around 50% of the sample exhibited a marked functional improvement by the end of follow-up. Baseline factors associated with functional improvement were parental medium-high SES, less severe negative, and depressive symptoms (for individuals in the *Mild impairment-Improving* trajectory), better scores in the verbal learning and memory domain (for individuals in the *Severe impairment-Improving* trajectory) and better premorbid adjustment (for both

the *Mild impairment-Improving* and *Severe impairment-Improving* trajectory groups). Less severe positive symptoms at baseline predicted a *Moderate impairment-Stable* trajectory vs. a *Severe impairment-Stable* trajectory. These results are in agreement with previous studies performed in FEP and chronic psychiatric samples, where parental SES [17,63], negative [14,64,65] and depressive symptoms [66,67], verbal memory [64], and premorbid adjustment [14,68] were predictors of functional outcomes. To our knowledge, however, this is the first study to simultaneously analyze such a large panel of potential predictors of mid-term psychosocial functioning trajectories identified using an LCGA approach, which included sociodemographic, clinical, and neurocognitive variables, and to further examine the interaction between the identified predictors.

Regarding diagnosis distribution among classes, our findings are in keeping with previous research [20,69]. All diagnoses were represented in the four trajectories, yet the proportion of patients with a diagnosis of Schizophrenia was higher among individuals showing persistent functional difficulties, whereas a higher proportion of patients with Bipolar disorder or Other psychoses fell into the group showing the most favorable functional trajectory. Despite these results need to be interpreted with caution due participants drop-out during follow-up, we found the same pattern at 12-month and 24-month follow-up.

In our study, medium-high parental SES appeared as one of the main predictors of the trajectory characterized by mild functional impairment at first assessment followed by an early functional recovery. The association between higher parental SES and better functional outcomes is probably a complex one. Our mediation analysis, indeed, suggests that parental SES partially mediate its influence on functionality through premorbid adjustment and negative symptoms. However, other factors not included in the mediation analysis also seem to play a role. For instance, families with a higher SES might provide more cognitive stimulation to their offspring [70], for example, involving them in more intellectual, artistic, or cultural leisure activities, hence enhancing their cognitive reserve, which has been associated with better functional outcomes [56,71,72]. In fact, we found that subjects within the *Mild impairment-Improving* trajectory reported to be involved in more social and recreational activities than the *Severe impairment-Improving* trajectory group, as reflected by higher scores in the Active-recreational orientation subscale of the FES. These families may likewise have more resources to identify the first psychotic symptoms and enable an earlier engagement with mental health services [73]. It could also translate more family support or means to provide better care in the post-FEP period [74]. In any case, our results emphasize the need for social interventions to promote and educate on mental health and facilitate the access to mental health services in the pre- and post-FEP period [75,76], as it has been done in Australia through the headspace initiative (https://www.headspace.org.au).

Several studies have consistently reported a relationship between verbal learning and memory and functional outcomes, both in affective and non-affective samples [51,67,77–79]. For instance, more preserved verbal learning before enrolling to functional remediation, a psychological therapy specifically targeting functional impairments, is associated with better long-term functional outcomes after this therapy [80]. Negative symptoms are also well-known predictors of poor functional outcomes [81–83] and the interrelationship between negative symptoms and cognition as predictors of functionality has been a matter of intense debate and study in prior works [84,85]. In the study by Milev et al. [64], performed in a sample of 99 subjects followed for seven years after FEP, verbal memory appeared as a strong predictor of global functioning in univariate logistic analysis. However, when the effect of verbal memory was examined together with negative symptoms in a multivariate multinomial logistic regression, negative symptoms took precedence over verbal memory as a predictor of global functioning, since the latter was no longer significant. In their three years follow-up study, Simons et al. [86] likewise found that the association between the performance in most cognitive domains, including verbal memory, and social functioning in the long-term was fully mediated by negative symptoms. Finally, Jordan et al. [59] showed that verbal memory predicted length of negative symptoms remission in FEP patients, which in turn predicted better functional performance. According to this evidence,

negative symptoms might play a more predominant role predicting functional outcomes than verbal memory. That might explain why, when comparing those groups exhibiting significantly different severity of negative symptoms at baseline (i.e., *Severe impairment-Stable* vs. *Mild impairment-Improving*), negative symptoms but not verbal memory appeared as a predictor of poorer functional trajectory. In contrast, when comparing groups with similar negative symptoms at baseline (i.e., *Severe impairment-Stable* vs. *Severe impairment-Improving trajectory*), more preserved verbal memory arose as a significant predictor of better functional recovery. Consequently, our findings confirm the importance of negative symptoms as a treatment target for functional recovery and suggest that assessing performance in verbal learning and memory might be especially useful as a differential factor of future functional outcome in FEP subjects presenting with severe functional impairment and similar negative symptoms. On the contrary, for those subjects showing mild negative symptoms at baseline, assessing verbal memory and learning might not provide additional information on their functional prognosis.

Better premorbid adjustment also appeared as a predictor of a more favorable functional trajectory in our analysis, in keeping with prior evidence [81,87]. As suggested by Hodgekins et al. [14], the persistence in functional impairment after FEP in those subjects with poorer premorbid adjustment might just reflect a functional disability that was already present before the onset of the full-blown psychotic episode, then rendering it difficult for these patients to achieve a functional remission—hence, the importance of intervening early in the course of the disease with specific interventions designed to improve functionality [75,88,89]. Considering that the effects of premorbid adjustment on psychosocial functioning might be partially mediated by verbal learning and memory, as further supported by Jordan et al. [59], those individuals at high-risk for affective and non-affective psychosis who exhibit poor social adjusted (and especially those with low parental SES) might benefit from an adapted version of functional remediation, which improves functionality but also enhances verbal memory [90,91]. Randomized clinical trials in early-stage samples will be needed to test the real benefit of early functional remediation interventions (ideally adapted to high-risk samples) in long-term psychosocial outcomes. To date, evidence coming from randomized clinical trials is only available on the effect of cognitive remediation in individuals at ultra-high risk for psychosis, which points to a positive impact on cognitive measures, including verbal memory, but less clear effects on psychosocial functioning [92].

Finally, our results indicate that less severe depressive symptoms at baseline are associated with a *Mild impairment-Improving* trajectory. Persistent depressive symptoms have been shown to worsen functional prognosis after FEP [93,94]; however, in our study, we were evaluating the putative predictive role of baseline depressive symptoms and therefore it can be that our findings just reflect a less severe clinical presentation in the *Mild impairment-Improving* trajectory compared to the *Severe impairment-Stable* trajectory. Additionally, the *Severe impairment-Stable* trajectory was characterized by more severe negative symptoms, and we cannot rule out some overlap between scores in the MADRS and the PANSS negative subscale [95]. A similar explanation can be applied to our findings of lower scores at baseline in the PANSS positive subscale being predictors of a *Moderate impairment-Stable* trajectory compared to the *Severe impairment-Stable* trajectory. They may reflect that the differences in functionality observed between the two groups in the first assessment are driven by more severe psychotic symptoms at baseline.

Future works with greater sample size, including variables not available in this study (such as cognitive reserve scores or biological markers) and taking into account longitudinal factors that can also influence functioning (such as persistent substance abuse or therapeutic non-compliance) would be needed to confirm and refine our findings. Furthermore, our findings that all diagnoses are represented in all trajectories support the idea that there are transdiagnostic subgroups that are alike in clinical presentation and outcomes. According to previous research [96], these subsets of patients might represent specific biotypes that are not governed by classical diagnostic criteria. Therefore, future studies that analyze

whether patients falling in resilient vs. persistent functional trajectories are characterized by a differential set of biomarkers would be interesting to develop precise models of risk stratification of functional impairment. For now, our results already suggest that more preserved verbal learning and memory could be used as a marker of functional resilience in those FEP patients with a more severe clinical and functional presentation.

5. Limitations

The current study presents several limitations to be noted. Firstly, as a sub-analysis of a prior study not primarily designed for the purpose of the present work, sample size might be too small and follow-up too short to capture all the potential trajectories for psychosocial functioning. Secondly, trajectory "naming" is a subjective process; in our case, it was based on what we considered the most important information to be extracted from the observed trajectories. Some might not agree with the chosen labels for each trajectory. Nevertheless, we consider our approach to be pragmatic and clinically useful, as it delineates two subsets of patients: those at risk of sustained functional difficulties and those more resilient, that is, showing more improvement during follow-up. Thirdly, we focused on baseline predictors and did not take into account variables like treatment compliance or substance abuse during follow-up, which might also contribute to functional outcomes in the period after FEP. Fourthly, as the study design was constructed prior to 2009, specific scales for negative symptoms such as the Brief Negative Symptom Scale (BNSS) [97] or the Clinical Assessment Interview for Negative Symptoms (CAINS) [98] were not used. The same applies to cognitive reserve, with scales such as the CRASH not being available at that time [99]. Lastly, results regarding diagnosis distribution need to be interpreted with caution due to the small sample size in some of the diagnostic categories, which may render X^2 results non-valid.

6. Conclusions

In our study, we identified four trajectories of psychosocial functioning following FEP, two of them indicative of a persistent functional impairment course and two describing a more resilient course. Additionally, our findings give some clues on putative factors that might mediate functional resilience, such as better socioeconomic status and premorbid adjustment, lesser negative symptoms, and more preserved verbal learning and memory. They also highlight that final functional outcomes are the result of the additive effects of a variety of factors. Hence, an integrative approach from very early stages is needed to target functional impairments, especially among those in a more vulnerable psychosocial situation.

Supplementary Materials: The following are available online at https://www.mdpi.com/2077-0383/10/1/73/s1, Table S1: Comparison between participants who completed the assessment and those who dropped-out.

Author Contributions: Conceptualization, E.S., I.G., and E.V.; methodology and formal analysis, E.S.; writing—original draft preparation, E.S., I.G., B.S., and E.V.; writing—review and editing, E.S., I.G., B.S., E.V., G.M., M.J.C., C.M.D.-C., S.A., A.L., A.G.-P., C.M., L.P.-C., I.C., I.B., D.B., N.V., A.F.C., M.B. and PEPs Group; project coordinator: M.B. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by Ethics Committee of Hospital Clinic de Barcelona (project identification code: 2008/4232; 17/04/2008).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available from the corresponding author on reasonable request.

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Appendix A

Post-hoc mediation analyses

Given that previous works on FEP samples have suggested that premorbid adjustment may influence psychosocial functioning through verbal memory and negative symptoms [59], we decided to test how the identified predictors interact to impact functioning in our sample. For that, we examined mediation using a regression-based bootstrapping approach [60]. Analyses were performed with PROCESS [61]. Before beginning the analyses, two dummy variables for trajectory membership were created, one including only *Mild impairment-Improving* and *Severe impairment-Stable* trajectories and another including only *Severe impairment-Improving* and *Severe impairment-Stable* trajectories.

First: we used PROCESS model 4 to test a simple mediation model with trajectory membership (*Severe impairment-Improving* vs. *Severe impairment-Stable*, with *Severe impairment-Stable* trajectory as the reference category) as the outcome variable (Y), baseline PAS score as the predictor variable (X) and baseline verbal learning and memory as the mediator variable (M) (Figure A1). Age and sex were included as covariates. The data are consistent with the claim that better premorbid adjustment positively impacts verbal learning and memory, which in turn increases the probability to belong to the severe and improving functional impairment trajectory (indirect effect = −0.011; 95% CI = −0.030 to −0.001). The mediation partially explains the effect of premorbid adjustment on trajectory membership; in addition, premorbid adjustment influences class membership independently from the proposed mechanism (b = −0.05, p = 0.002). Hence, we infer complementary partial mediation [62].

Second: we used a series mediation model to assess mediation between predictors of *Mild impairment-Improving* vs. *Severe impairment-Stable* trajectory. In this model, trajectory membership (*Mild impairment-Improving* vs. *Severe impairment-Stable*, with *Severe impairment-Stable* trajectory as the reference category) was the outcome variable (Y) and parental SES the predictor variable (X). Baseline PAS score (M1) and baseline PANSS negative subscale scores (M2) were included, in this order, as mediator variables. Total MADRS score was not considered as a mediator as no association with parental SES was found in a preliminary analysis. We could establish a serial mediation from parental SES through premorbid adjustment and through baseline negative symptoms to trajectory membership (indirect effect = −0.249; 95% CI: −0.551 to −0.086). In addition, parental SES had an indirect effect on class membership only through premorbid adjustment (indirect effect = −0.525, 95% CI: −1.097 to −0.171) and only through baseline negative symptoms (indirect effect = −0.504, 95% CI: −1.076 to −0.135). Finally, there was a direct effect of parental SES on trajectory membership (b = −0.932, p = 0.029), indicating complementary partial mediation.

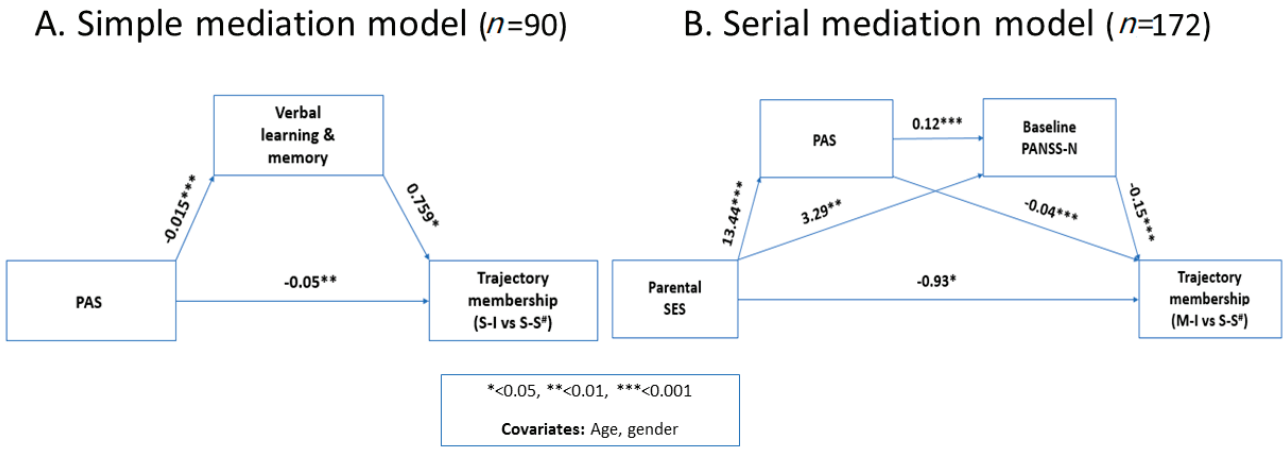

Figure A1. Mediation analyses. #: S-S was used as the reference category. Abbreviations: S-I: *Severe impairment-Improving;* S-S: *Severe impairment-Stable;* M-I: *Mild impairment-Improving.* PAS: Premorbid Adjustment Scale; SES: Socioeconomic Status, PANSS-N: Positive and Negative Syndrome Scale-Negative Subscale.

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ORIGINAL ARTICLE

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Trajectories of suicidal ideation after first-episode psychosis: a growth mixture modeling approach

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Abstract

Objective: The period immediately after the onset of first-episode psychosis (FEP) may present with high risk for suicidal ideation (SI) and attempts, although this risk may differ among patients. Thus, we aimed to identify trajectories of SI in a 2-years follow-up FEP cohort and to assess baseline predictors and clinical/functional evolution for each trajectory of SI.

Methods: We included 334 FEP participants with data on SI. Growth mixture modeling was used to identify trajectories of SI. Putative sociodemographic, clinical, and cognitive predictors of the distinct trajectories were examined using multinomial logistic regression.

*PEPS group members are presented in Appendix 1.

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Results: We identified three distinct trajectories: *Non-SI* trajectory (85.53% sample), *Improving SI* trajectory (9.58%), and *Worsening SI* trajectory (6.89%). Multinomial logistic regression model revealed that greater baseline pessimistic thoughts, anhedonia, and worse perceived family environment were associated with higher baseline SI followed by an *Improving* trajectory. Older age, longer duration of untreated psychosis, and reduced sleep predicted *Worsening SI* trajectory. Regarding clinical/functional evolution, individuals within the *Improving SI* trajectory displayed moderate depression at baseline which ameliorated during the study period, while the *Worsening SI* subgroup exhibited persistent mild depressive symptoms and greater functional impairment at follow-up assessments.

Conclusion: Our findings delineated three distinct trajectories of SI among participants with FEP, one experiencing no SI, another in which SI might depend on acute depressive symptomatology, and a last subset where SI might be associated with mild but persistent clinical and functional impairments. These data provide insights for the early identification and tailored treatment of suicide in this at-risk population.

KEYWORDS

suicidal ideation, psychotic disorders, risk factors, follow-up studies, precision medicine

1 | INTRODUCTION

It is well established that people suffering from severe mental illness are at an increased risk for suicidal attempts and deaths because of suicide.[1,2] It has been shown that the period immediately after the onset of first-episode psychosis (FEP) may be particularly associated with a higher vulnerability to suicide attempts,[3,4] with some studies reporting suicide rates to be 2.7 times higher among patients with FEP compared with patients with chronic multi-episode schizophrenia.[5]

Suicidal ideation (SI) often precedes suicide attempts.[6] Rates of SI among individuals with FEP are high both at its initial presentation (ranging from 22% to 47%) and in the post-acute phase.[7-10] The heterogeneity of estimates across studies suggests that distinct subgroups of patients with FEP with different likelihood to exhibit SI may occur. In addition, suicidality by itself is an important treatment target among people with FEP since it is related to significant distress and disability,[11] and it is also a known source of death in this at-risk population.

Several risk factors for SI and suicidal behavior have been identified in FEP cohorts, such as previous history of suicide attempts,[12,13] severity of positive psychotic symptoms,[10,14] depression,[15,16] hopelessness,[13] trauma history,[17] longer duration of untreated psychosis (DUP),[18] as well as worse cognitive functioning.[19] However, SI is a heterogeneous phenomenon, and little is known about specific trajectories of SI after FEP and putative risk factors associated with those different trajectories. To our knowledge, to date, only Madsen

Significant outcomes

- We found three trajectories of suicidal ideation after first-episode psychosis: "Nonsuicidal ideation," "Improving suicidal ideation," and "Worsening suicidal ideation."
- These trajectories were associated with distinct baseline risk factors and a different evolution of psychopathology and functioning during follow-up, suggesting the need for different tailored interventions for tackling suicidal ideation in this at-risk population.
- Baseline depressive symptoms and worse family functioning were associated with suicidal ideation at baseline ("Improving suicidal ideation" trajectory), while older age, longer duration of untreated psychosis and insomnia predicted a "Worsening suicidal ideation" trajectory.

Limitations

- Modest sample size.
- No data were available on suicidal attempts or completed suicides during follow-up.
- Causality could not be assessed because of the design of our study, and we could not evaluate how variables like treatment adherence might have influenced the evolution of suicidal ideation.

et al.[20] have explored trajectories for SI after FEP. Using latent growth mixture modeling analysis, a statistical technique that can be applied to longitudinal data to identify unique latent trajectories of a particular characteristic taking into account individual variability over time,[21] they identified one subgroup of patients with FEP with a baseline low and decreasing SI; a second subgroup presenting with frequent and stable SI; and, lastly, a third subset presenting with a frequent and increasing SI.

1.1 | Aims of the study

The main aims of the study are (i) to investigate the existence of discrete trajectories of suicidal ideation in a 24-month follow-up cohort of first-episode psychosis patients and (ii) to examine which baseline sociodemographic, clinical, and cognitive features could predict those possible distinct trajectories. As a secondary aim, we explored differences between the subjects assigned to the different trajectories concerning the evolution of psychopathology and psychosocial functioning.

2 | MATERIAL AND METHODS

2.1 | Patients

The current work is a post hoc analysis of the project "Phenotype-genotype and environmental interaction. Application of a predictive model in first psychotic episodes" (PEPs study), which is a multicenter, prospective, and naturalistic follow-up study encompassing 16 participating centers across Spain.[22] Fourteen of these centers are members of the Biomedical Research Networking Center for Mental Health (CIBERSAM)[23] and two are collaborator centers.[22] The PEPS study was conducted in accordance with the ethical principles stated on the Declaration of Helsinki. The protocol was approved by ethics committees at each participating center. A written and signed informed consent was obtained from all participants or their legal guardians after providing a full explanation of the study's procedures.

The detailed protocol of this study was published elsewhere.[22,24] In brief, a total of 335 subjects with FEP were recruited from April, 2009 to April, 2012. The inclusion criteria were as follows: (i) age between 7 and 35 years old; (ii) presence of first lifetime psychotic symptoms for at least 1 week in the previous 12 months; (iii) fluency in Spanish language; and (iv) provided signed informed consent. The exclusion criteria were as follows: (i) presence of intellectual disability according to the Diagnostic and Statistical Manual of mental disorders, 4th edition (DSM-IV) criteria[25]; (ii) history of head trauma with loss of consciousness; and (iii) organic disease with possible mental health repercussions. For all subjects enrolled in the current study, diagnoses were established using the Structured Clinical Interview for DSM Disorders (SCID) parts I and II (SCID-I & II)[25-27] for adults and the Spanish translation of the Kiddie-Sads-Present and Lifetime Version (K-SADS-PL)[28,29] for children and adolescents. Follow-up assessments were conducted after 2, 6, 12, and 24 months following inclusion.

2.2 | Assessment

Individuals included in the PEPs study underwent an exhaustive clinical and neuropsychological evaluation. For the present post hoc analysis, we focused on those variables already established as possible risk factors for SI or behavior in the scientific literature[30,31]:

(i) *Baseline sociodemographic data*: We collected information on gender, age, educational level, marital status, current living situation, occupation, and parental socioeconomic status (SES). Parental SES was determined by means of the Hollingshead Two-Factor Index of Social Position.[32] Personal and family history of psychiatric disorders were also obtained, as well as information on substance misuse, which was collected using an adapted version of the Multidimensional Assessment Instrument for Drug and Alcohol Dependence scale.[33] The Family Environment Scale (FES) was also completed. This is a self-report instrument which assesses the patients' perceptions of the social climate within their families.[34,35]

(ii) *Baseline clinical and functional assessment*: Psychopathology was evaluated employing the Spanish validated versions of the Positive and Negative Syndrome Scale (PANSS)[36,37] and the Montgomery-Åsberg Depression Rating Scale (MADRS).[38,39] The MADRS is a ten-item clinician-administered diagnostic questionnaire used to measure severity of depressive symptoms. It assesses the following symptoms: apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic thoughts, and suicidal thoughts. Each item is rated on a 0–6 continuum, where 0 represents absence of the evaluated symptom and 6 indicates maximum severity. Overall MADRS scores range from 0 to 60, and cut-off points include: 0 to 6—symptom absent, 7 to 19—mild depression, 30 to 34—moderate depression, and 35 to 60—severe depression. Psychosocial functioning was determined by the Functional Assessment Short Test (FAST).[40,41] Data on premorbid adjustment were estimated using the retrospective rating scale Premorbid Adjustment Scale (PAS).[42] In all scales, higher scores are indicative of higher clinical severity or functional

impairment. Additionally, we obtained the lifetime history of exposure to traumatic events by means of the Trauma Questionnaire (TQ),[43,44] and DUP, defined as the number of days that have elapsed between the onset of positive psychotic symptoms and the initiation of the first appropriate treatment for psychosis based on clinical discretion given the naturalistic design of the study. DUP was determined using the Symptom Onset in Schizophrenia (SOS) inventory.[45]

(iii) *Neuropsychological assessment at 2-month follow-up*: A detailed explanation of the neuropsychological battery employed in this study can be found in the PEPsCog study.[46] Cognitive performance was evaluated by trained neuropsychologists in the first two months after inclusion of participants in the study to avoid the interference of acute psychopathological manifestations on neurocognitive assessments. Since SI and behavior have been associated with higher Intelligence Quotient (IQ) and cognitive rigidity,[13,47] we estimated IQ and executive function for each participant. The IQ was calculated based on the performance on the vocabulary subtest from the Wechsler Adult Intelligence Scale (WAIS-III)[48] or from the Wechsler Intelligence Scale for Children (WISC-IV),[49] while executive function was measured with the Stroop Color-Word Interference Test,[50] the Wisconsin Card Sorting Test (WCST),[51] and the Trail Making Test, form B (TMT-B).[52] The word-color task from the Stroop Test was included as a neurocognitive measure of impulsivity. Social cognitive biases have been recently related to SI.[53] Therefore, social cognition scores on the Mayer-Salovey-Caruso Emotional Intelligence Test[54,55] were also obtained. We likewise included other important cognitive domains in FEP: verbal learning, working memory, and attention.[56] Verbal memory was assessed using the Spanish version of the California Verbal Learning Test, the *Test de Aprendizaje Verbal España-Complutense* (TAVEC),[57,58] while working memory was measured by the digit and letters and numbers subtest of WAIS-III[48] and WISC-IV[49] and attention was evaluated using the Continuous Performance Test-II (CPT-II).[59]

(iv) *Suicidal ideation*: SI was measured using the "suicidal thoughts" item of the MADRS. This item is rated on a scale of 0 ("enjoys life or takes it as it comes") to 6 ("explicit plans for suicide when there is an opportunity; active preparations for suicide"). A MADRS "suicidal thoughts" score ≥2 was considered the cut-off to determine the presence of any SI, as described in previous studies.[60]

(v) *Follow-up clinical and functional assessment*: In order to explore the evolution of psychopathology and psychosocial functioning of individuals within each of the identified trajectories, we also included information on the PANSS, MADRS, and FAST scores of participants at 12-month and 24-month follow-up.

2.3 | Statistical analysis

2.3.1 | Trajectories of suicidal ideation and predictors of trajectories

Statistical analysis was designed according to a standard three-step method previously described.[61]

First, we determined the number of latent classes of SI using growth mixture modeling (GMM) without including any predictor for putative class membership (Step 1). GMM is a person-centered statistical approach used to delineate homogenous subgroups (latent classes) of individuals with similar patterns of change in a variable of interest over time. For the current analysis, individual class membership was assigned on the basis of scores on the "suicidal thoughts" item of the MADRS measured at 5 time points over the 2-year follow-up, namely at baseline, 2-month, 6-month, 12-month, and 24-month follow-up periods. Missing data were omitted by default. We estimated linear and quadratic terms to allow for curved trajectories. To determine the optimal number of trajectory classes, models with increasing number of latent classes (from 1- to 4-class models) were fitted to the data, and the best-fitting model was selected according to the following goodness-of-fit indices: Akaike's Information Criterion (AIC), Bayesian Information Criterion (BIC), samples-size-adjusted BIC (aBIC), and entropy. Lower values of AIC, BIC, and aBIC suggest a more parsimonious model, while higher entropy indicates a better model fit. Entropy ranges from 0 to 1; values approaching 1 indicate a clear delineation of classes.[62,63] Aside from fit statistics, interpretability and parsimony of the model were also taken into consideration in model selection. To identify clinically relevant classes, only models with class sizes greater than 5% were considered.[64] GMM analyses were performed on R version 3.6.3, using the *"lcmm"* package[65] (https://cran.r-project.org/web/packages/lcmm/index.html).

Secondly, the most likely class (i.e. trajectory) membership for every participant based on model probabilities was examined and imported to SPSS, version 26 (SPSS Inc., Chicago, II, USA), to be included as a new variable in the original dataset (Step 2).

Finally, baseline predictors of each SI trajectory were tested using a multinomial regression analysis (Step 3). In order to narrow down the number of candidate predictors, we first performed univariate multinomial regression analysis for each candidate predictor, with class trajectories as dependent variables. Regarding cognitive variables, we created cognitive composites to be used as baseline predictors using data from the 2-month neurocognitive assessment (see *Supplementary methods*). The variables tested were as follows: age, gender, marital status, educational level, occupation, substance use, premorbid adjustment, DUP, SES, FES subscales, MADRS items, insight (measured by the PANSS scale), TQ, estimated IQ, executive function composite (Stroop Color-Word

Interference task, WCST, TMT-B), Stroop word-color task, social cognition (MSCEIT Emotional Management), verbal learning and memory composite (TAVEC total trials 1–5 list A, short free recall, short cued recall, delayed free recall, delayed cued recall and recognition scores), working memory composite (WAIS-III Letter-Number Sequencing and Digit-Span), and attention composite (CPT-II commission and reaction time). Those variables statistically ($P < 0.05$) associated with class trajectories in the univariate regression analyses were then entered into a multivariable multinomial regression model to determine which candidate factors still predicted membership in each previously determined trajectory when accounting for the shared variance between variables. For the MADRS scale, only the individual items—and not the total score—were entered as independent variables. Significant predictors for the multivariable model were identified using a stepwise backwards elimination process,[61] with gender and age entered as fixed factors. In order to test for multicollinearity among predictors, we assessed correlations between the variables in the model.

Each step carried out in this analysis is presented in more detail in Supplementary methods.

2.3.2 | Comparison of characteristics of participants across identified trajectories

First, normality assumption was assessed visually and using the Kolmogorov-Smirnov test. Next, we performed Kruskal-Wallis and chi-square tests, as appropriate, to explore sociodemographic, clinical, and functional outcome differences between individuals included in distinct trajectories at different time points. Multivariate analysis of covariance (MANCOVA) was carried out to compare cognitive variables adjusting the analysis for age, sex, educational level, and antipsychotic treatment. Post hoc comparison analyses with Bonferroni correction for multiple comparisons were performed to further elucidate correlates of each trajectory classes. Sociodemographic and cognitive variables were compared only at baseline and at 2-month follow-up, respectively, while psychopathology and functioning were compared at baseline, 12-month, and 24-month follow-up.

Statistical significance for all analyses was set at an alpha level of 0.05.

3 | RESULTS

3.1 | Sample characteristics and attrition analysis

The final sample comprised a total of 334 participants. One participant was excluded from the GMM analyses since no information on SI was available. Therefore, this participant was treated as a drop-out. Baseline characteristics of the final sample are described in Table 1. Median age was 23.1 [Interquartile Rage (IQR) = 9], and 32.6% of the participants were females. Regarding attrition analysis, a total of 315 subjects participated in the 2-month follow-up, 282 subjects in the 6-month follow-up, 259 subjects participated in the 12-month follow-up, and 209 participants were assessed at 24-month follow-up. No significant differences emerged between completers and noncompleters in terms of age, gender, DUP, somatic comorbidities, current living situation, educational level, parental SES, family history of affective, anxiety or psychotic disorders, personal history of affective disorder or learning/behavior disorder, cannabis or alcohol use, or baseline diagnosis (affective vs nonaffective psychosis). Significant differences in ethnicity, urbanicity, marital status, occupation, family history of addictive disorders, or personal history of anxiety disorders between completers and noncompleters at the different follow-up points are shown in the Supplementary results (Table S1).

3.2 | Latent classes of suicidal ideation trajectories

After examining fit indices, entropy, parsimony, and interpretability of the model, the 3-class GMM model with both random slope and intercept and including a quadratic function of time was selected as the best fit of our data (Table 2). Although the 4-class model showed a lower AIC, BIC, and aBIC than the 3-class model, one of the classes included less than 5% of participants, hence, a too low percentage to represent a meaningful class. Furthermore, a visual inspection of the four trajectories revealed that the inclusion of a fourth class did not provide additional information on trajectories, since two of the classes had an improving trajectory of SI and only differed in the intensity of SI at baseline. Hence, the 4-class model seemed to disaggregate one of the classes identified in the 3-class model, rather than provide an additional class including individuals with a genuinely different trajectory. Entropy was adequate (0.85)[66] for the 3-class model, as well as post mean class probabilities (0.96 for Class 1, 0.90 for Class 2, and 0.81 for Class 3).

The three mean trajectories estimated by the 3-class model are depicted in Figure 1. The majority of the sample fell into a trajectory characterized by the absence of SI at baseline and throughout the follow-up period [*Non-SI* trajectory; $n = 279$ (83.53%)]. The second group presented SI at baseline, which improved during follow-up [*Improving SI* trajectory; $n = 32$ (9.58%)]. Finally, the third group initially displayed no or fleeting SI, the magnitude of which

TABLE 1 Baseline sociodemographic, clinical, and cognitive characteristics of the final sample and the three suicidal ideation trajectory groups.

	Total sample	Nonsuicidal Ideation (1)	Improving Suicidal Ideation (2)	Worsening Suicidal Ideation (3)	Kruskal-Wallis/ χ^2/F[a]		Post hoc[b]		
	N = 334	*N* = 279	*N* = 32	*N* = 23		*P* value	1 vs 2	1 vs 3	2 vs 3
Sociodemographic measures									
Age (years)	23.1 [9]	23.2 [9]	21.1 [11]	26.2 [11]	3.83	0.15			
Preadolescent (10–12), *n* (%)	4 (1.2)	3 (1.1)	1 (3.1)	0 (0.0)					
Adolescent (13–18), *n* (%)	56 (16.8)	45 (16.2)	10 (31.2)	1 (4.3)					
Adult (≥18), *n* (%)	274 (82.0)	231 (82.8)	21 (65.6)	22 (95.7)					
Gender (Female)	109 (32.6)	84 (30.1)	15 (46.9)	10 (43.5)	4.99	0.08			
Marital status (Single)	293 (87.7)	245 (87.8)	30(93.8)	18 (78.3)	2.99	0.22			
Coexistance (Living independent)	59 (17.7)	53 (19.0)	2 (6.3)	4 (17.4)	3.21	0.20			
Educational level (University)	51 (15.3)	44 (15.8)	2 (6.3)	5 (21.7)	2.81	0.24			
Occupation (Active[c])	199 (59.6)	168 (60.2)	21 (65.6)	10 (43.5)	3.01	0.22			
Socioeconomic status (Medium-high)	178 (54.4)	150 (54.9)	19 (61.3)	9 (39.1)	2.79	0.25			
Substance use									
Alcohol	172 (51.8)	147 (52.9)	17 (54.8)	8 (34.8)	2.91	0.23			
Cannabis	146 (44.0)	122 (43.9)	16 (51.6)	8 (34.8)	1.52	0.47			
Family history of psychiatric disorders	*N* = 272	*N* = 227	*N* = 27	*N* = 18					
Psychotic disorder	35 (12.9)	31 (13.6)	2 (7.4)	2 (11.1)	0.82	0.66			
Affective disorder	71 (26.1)	60 (26.4)	7 (25.9)	4 (22.2)	0.15	0.93			
Anxiety disorder	30 (11.0)	24 (10.6)	4 (14.8)	2 (11.1)	0.44	0.80			
Substance use disorder	40 (14.7)	31 (13.6)	3 (11.1)	6 (33.3)	5.29	0.07			
Clinical measures									
DUP (days)	131.5 [193]	124.0 [198]	130.0 [138]	193.0 [249]	13.62	0.06			
PAS total	42 [36]	41.0 [36]	42.0 [32]	52.0 [32]	6.74	**0.03**		**0.04**	
PANSS positive	19.0 [13]	18.0 [14]	20.0 [15]	19.0 [9]	0.91	0.64			
PANSS negative	18.0 [12]	18.0 [12]	20.0 [13]	23.0 [11]	2.30	0.32			
PANSS total	75.0 [34]	75.0 [33]	82.0 [36]	77.0 [23]	3.11	0.21			
MADRS items									
Apparent sadness	1.0 [2]	1.0 [2]	3.0 [3]	2.0 [3]	24.12	**<0.001**	**<0.001**		
Reported sadness	1.0 [2]	0.0 [2]	3.0 [2]	2.0 [3]	38.87	**<0.001**	**<0.001**		**<0.001**
Inner tension	2.0 [3]	2.0 [3]	2.0 [2]	2.0 [2]	13.03	**0.001**	**0.001**		
Reduced sleep	0.0 [3]	0.0 [2]	0.0 [4]	3.0 [4]	9.46	**0.01**		**0.01**	
Reduced appetite	0.0 [1]	0.0 [0]	0.5 [2]	0.0 [2]	13.85	**0.001**	**0.001**		
Concentration difficulty	2.0 [2]	2.0 [2]	3.0 [2]	2.0 [1]	8.76	**0.01**	**0.014**		
Lassitude	1.0 [2]	1.0 [2]	2.0 [3]	2.0 [2]	21.29	**<0.001**	**0.001**	**<0.01**	
Inability to feel	1.0 [2]	0.5 [2]	2.5 [4]	2.0 [3]	26.33	**<0.001**	**<0.001**	**<0.01**	

(Continues)

TABLE 1 Continued

	Total sample	Nonsuicidal Ideation (1)	Improving Suicidal Ideation (2)	Worsening Suicidal Ideation (3)	Kruskal-Wallis/ χ^2/F[a]		Post hoc[b]		
	N = 334	*N* = 279	*N* = 32	*N* = 23		*P* value	1 vs 2	1 vs 3	2 vs 3
Pessimistic thoughts	0.0 [2]	0.0 [1]	2.5 [2]	2.0 [2]	47.83	**<0.001**	**<0.001**	**<0.01**	
Suicidal thoughts	0.0 [1]	0.0 [1]	2.5 [2]	1.0 [0]	105.08	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Total	12.0 [14]	10.0 [13]	25.0 [15]	17.0 [13]	42.98	**<0.001**	**<0.001**	**0.01**	
FAST total	26.5 [23]	26.0 [24]	26.0 [29]	30.0 [16]	1.38	0.50			
FES subscales									
Cohesion	52.0 [13]	52.0 [13]	47.0 [9]	47.0 [15]	7.17	**0.03**			
Expressiveness	53.0 [16]	53.0 [16]	47.0 [16]	47.0 [16]	1.07	0.58			
Conflict	49.0 [13]	49.0 [9]	54.0 [9]	54.0 [13]	14.36	**0.001**	**<0.01**		
Independence	51.0 [11]	51.0 [11]	46.0 [17]	51.0 [20]	1.53	0.47			
Achievement orientation	47.0 [10]	47.0 [10]	42.0 [11]	47.0 [16]	5.99	0.05			
Intellectual-cultural orientation	47.0 [19]	47.0 [19]	47.0 [14]	37.0 [23]	2.08	0.35			
Active-recreational orientation	48.0 [14]	48.0 [14]	48.0 [19]	44.0 [14]	2.36	0.31			
Moral-religious emphasis	44.0 [15]	44.0 [10]	49.0 [10]	39.0 [15]	2.35	0.31			
Organization	49.0 [15]	54.0 [10]	44.0 [15]	44.0 [20]	5.44	0.07			
Control	49.0 [14]	49.0 [14]	49.0 [14]	45.0 [17]	0.26	0.88			
Previous psychiatric diagnoses	*N* = 302	*N* = 251	*N* = 29	*N* = 22					
Affective disorder	41 (13.6)	31 (12.4)	6 (20.7)	4 (18.2)	1.97	0.37			
Anxiety disorder	25 (8.3)	20 (8.0)	4 (13.8)	1 (4.5)	1.60	0.45			
Learning/Behavior disorder	25 (8.3)	19 (7.6)	3 (10.3)	3 (13.6)	1.16	0.			
Psychiatric diagnosis at baseline					1.37	0.50			
Affective psychosis	59 (17.7)	51 (18.3)	6 (18.7)	2 (8.7)					
Nonaffective psychosis	275 (82.3)	228 (81.7)	26 (81.2)	21 (91.3)					
Pharmacological treatment									
Clozapine	8 (2.4)	6 (2.1)	0 (0.0)	2 (8.7)	4.76	0.09			
Other antipsychotics	291 (87.1)	245 (87.8)	29 (90.6)	17 (73.9)	4.05	0.13			
Antidepressant	42 (12.6)	26 (9.3)	11 (34.4)	5 (21.7)	18.28	**<0.001**	**<0.001**		
Mood stabilizer	44 (13.2)	37 (13.3)	5 (15.6)	2 (8.7)	0.57	0.75			
Cognitive measures									
Frontal executive function	−0.03 (0.7)	−0.02 (0.6)	−0.15 (0.7)	−0.00 (0.7)	0.10	0.90			
Stroop Word-Color	0.06 (1.0)	0.06 (1.0)	−0.25 (0.9)	0.41 (1.1)	1.43	0.24			
Social cognition	0.02 (1.0)	0.03 (1.0)	0.21 (1.2)	−0.41 (0.7)	0.90	0.41			
Verbal learning and memory	0.06 (0.9)	0.07 (0.9)	0.10 (1.0)	−0.08 (0.8)	0.77	0.46			
Working memory	0.05 (0.9)	0.06 (0.8)	0.01 (1.0)	0.04 (0.9)	0.04	0.96			

(Continues)

TABLE 1 Continued

	Total sample	Nonsuicidal Ideation (1)	Improving Suicidal Ideation (2)	Worsening Suicidal Ideation (3)	Kruskal-Wallis/ χ^2/F[a]		Post hoc[b]		
	N = 334	*N* = 279	*N* = 32	*N* = 23		*P* value	1 vs 2	1 vs 3	2 vs 3
Attention	0.03 (0.4)	0.04 (0.4)	−0.03 (0.3)	0.06 (0.5)	0.03	0.97			
IQ	92.35 (14.9)	92.49 (14.9)	91.84 (18.1)	91.33 (10.8)	0.12	0.88			

Values are indicated as median [Interquartile Range] or *N* (%). For cognitive measures, values are indicated as mean (standard deviation).

Abbreviations: DUP, Duration of untreated psychosis; FAST, Functional Assessment Short Test; FES, Family Environment Scale; IQ, Intelligence Quotient; MADRS, Montgomery-Åsberg Depression Scale; PANSS, Positive and Negative Syndrome Scale; PAS, Premorbid Adjustment Scale.

[a]Adjusted by age, sex, educational level, and antipsychotic use.

[b]Tukey or Z statistic, as appropriate. Significance values have been adjusted using the Bonferroni correction for multiple tests. Bold type indicates $P < 0.05$.

[c]Active includes workers and students.

worsened slightly during follow-up [*Worsening SI* trajectory; $n = 23$ (6.89%)]. A graphical representation of the evolution of mean MADRS "suicidal thoughts" scores within each of the functional trajectory groups derived from the GMM can be found in the Supplementary results (Figure S1), together with information on the actual proportion of patients showing substantial SI (mean MADRS "suicidal thoughts" scores ≥ 2) in each of the predicted trajectory groups at different time points (Figure S2).

3.3 | Baseline predictors of trajectory membership

Results from the univariate multinomial regression analysis identified the following baseline characteristics significantly associated with different SI trajectories: DUP, MADRS-Apparent sadness; MADRS-Reported sadness; MADRS-Inner tension; MADRS-Reduced sleep; MADRS-Reduced appetite; MADRS-Concentration difficulty; MADRS-Lassitude; MADRS-Inability to feel, MADRS-Pessimistic thoughts; PAS total score; FES-Cohesion; FES-Conflict; FES-Achievement orientation; and FES-Organization (see *Supplementary results* Table S2).

Multinomial regression analysis (final model: R2 Nagelkerke 35.2%; $\chi^2 = 82.16$; df = 14; $P < 0.001$) indicated that age, DUP, MADRS-Reduced sleep, MADRS-Inability to feel, MADRS-Pessimistic thoughts, FES-Conflict, FES-Achievement orientation, and FES-Organization contributed to differentiate among the three SI trajectories (Table 3). Specifically, compared with the *Non-SI* trajectory, the *Improving SI* trajectory was associated with higher baseline scores in the MADRS-Inability to feel (OR: 1.510; 95% CI: 1.075–2.120) and MADRS-Pessimistic thoughts (OR: 2.453; 95% CI: 1.681–3.578) items, higher baseline scores in the FES-Conflict (OR: 1.083; 95% CI: 1.017–1.154) and FES-Organization (OR: 1.064; 95% CI: 1.002–1.130) subscales, and with lower baseline scores in FES-Achievement orientation (OR: 0.932; 95% CI: 0.875–0.992). On the other hand, older age (OR: 1.092; 95% CI: 1.002–1.191), longer DUP (OR: 1.004; 95% CI: 1.001–1.007), and higher scores in the MADRS-Reduced sleep (OR: 1.344; 95% CI: 1.034–1.747) were associated with the *Worsening SI* trajectory compared with the *Non-SI* trajectory.

Because of the wide age range in our sample, we re-run the analyses including only the adult sample. This yielded very similar results to the ones with the whole sample (see *Supplementary results* Table S3). Only the variables "MADRS-Inability to feel" and "age" were no longer predictors of the *Improving SI* trajectory and the *Worsening SI* trajectory, respectively. Unfortunately, the small number of pre-adolescents and adolescents in our study prevented us from performing separate analysis for the sample of individuals <18 years old.

3.4 | Between-trajectory group comparisons on sociodemographic, cognitive, clinical, and functional variables

As shown in Table 1, no significant differences between the three groups were found in any of the assessed sociodemographic or cognitive variables. Subjects assigned to the *Worsening SI* trajectory showed the worst premorbid adjustment, but statistical significance was only reached when compared with individuals in the *Non-SI* trajectory (median total PAS [IQR]: 52 [32] vs 41 [36]; adjusted $P = 0.036$). Subjects falling into the *Improving SI* trajectory were more likely to be treated with antidepressants than subjects in the *Non-SI* trajectory (34.4% vs 9.3%, adjusted $P < 0.001$). No differences were observed concerning the proportion of participants diagnosed with affective vs. nonaffective psychoses.

With regards to baseline psychopathological features, the three groups differed clinically in the intensity of depressive symptoms as measured with the MADRS, although

TABLE 2 Goodness-of-fit statistics of GMM with one-to-four class solutions of suicidal ideation trajectories.

		Fit statistics[a]				% of the sample in each class			
Number of classes	Number of parameters	AIC	BIC	aBIC	Entropy	Class 1	Class 2	Class 3	Class 4
1	7	2992.33	3019.00	2996.80	–	100	–	–	–
2	12	2694.32	2740.05	2701.98	0.82	85.93	14.07	–	–
3	**17**	**2617.83**	**2682.62**	**2628.69**	**0.85**	**83.53**	**9.58**	**6.89**	–
4	22	2565.71	2649.56	2579.77	0.83	7.78	20.66	68.86	2.69

Abbreviations: aBIC, sample size-adjusted Bayesian Information Criterion; AIC, Akaike's Information Criterion; BIC, Bayesian Information Criterion.

[a]Lower values (AIC, BIC, and aBIC) indicate better model fit. Higher entropy indicates better model fit. Values of 0.4, 0.6, and 0.8 represent low, medium, and high entropy.

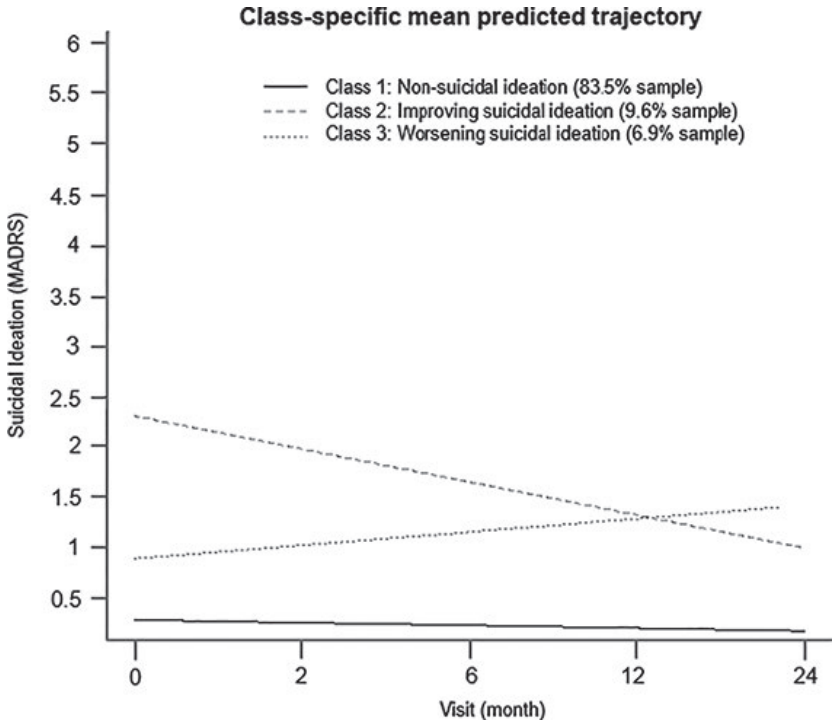

FIGURE 1 Predicted trajectories of suicidal ideation.

differences only reached statistical significance when comparing the *Non-SI* group with subjects in the other two predicted trajectories (Table 1). Subjects in the *Improving SI* trajectory showed moderate depressive symptoms at baseline (median total MADRS score [IQR]: 25 [15]), while subjects in the *Non-SI* trajectory and *Worsening SI* trajectory showed mild depressive symptoms (median total MADRS score [IQR]: 10 [13] and 17 [13], respectively). A graphical representation of the evolution of depressive symptoms, psychotic symptoms, and psychosocial functioning among the three groups can be found in Figure 2.

4 | DISCUSSION

Our results point to the existence of three discrete trajectories for SI in a FEP population which was followed up for 24 months: (i) one trajectory characterized by the absence of SI at baseline and throughout the follow-up visits, which included the largest proportion of participants; (ii) a second trajectory characterized by the presence of SI at baseline that ameliorated in subsequent follow-up visits, and (iii) a third one characterized by the absence or by only sporadic SI at baseline that slightly worsened during follow-up period, which encompassed the smallest number of participants. These results are in line with the findings reported by Madsen et al.[20] In their work, the most common trajectory was composed by patients with a low and decreasing SI while a minority of patients showed a frequent and increasing SI trajectory.

When considering predictors of different trajectories, the *Improving SI* trajectory was associated with higher presence of depressive symptoms, more specifically "pessimistic thoughts" and "inability to feel," at baseline assessment. In this sense, it should be taken into account

TABLE 3 Multinomial logistic regression[a]: baseline predictor variables for suicidal ideation trajectories.

	B	SE	Wald[b]	Sig.	Exp(B)	Exp (B) 95% Confidence Interval	
						Lower limit	Upper limit
Improving suicidal ideation							
Intersection	−8.681	3.115	7.766	0.005			
Sex (female)	0.592	0.534	1.227	0.268	1.808	0.634	5.152
Age	0.008	0.046	0.031	0.860	1.008	0.920	1.104
DUP	−0.001	0.002	0.399	0.528	0.999	0.994	1.003
MADRS-Reduced sleep	0.078	0.131	0.356	0.551	1.081	0.837	1.397
MADRS-Inability to feel	0.412	0.173	5.655	**0.017**	1.510	1.075	2.120
MADRS-Pessimistic thoughts	0.897	0.193	21.689	**<0.001**	2.453	1.681	3.578
FES-Conflict	0.080	0.032	6.114	**0.013**	1.083	1.017	1.154
FES-Achievement orientation	−0.071	0.032	4.867	**0.027**	0.932	0.875	0.992
FES-Organization	0.062	0.031	4.043	**0.044**	1.064	1.002	1.130
Worsening suicidal ideation							
Intersection	−6.776	2.867	5.588	0.018			
Sex (female)	0.102	0.518	0.039	0.844	1.107	0.401	3.059
Age	0.088	0.044	3.978	**0.046**	1.092	1.002	1.191
DUP	0.004	0.002	6.015	**0.014**	1.004	1.001	1.007
MADRS-Reduced sleep	0.296	0.134	4.894	**0.027**	1.344	1.034	1.747
MADRS-Inability to feel	0.318	0.165	3.738	0.053	1.375	0.996	1.898
MADRS-Pessimistic thoughts	0.144	0.204	0.498	0.481	1.155	0.774	1.723
FES-Conflict	0.035	0.033	1.145	0.285	1.036	0.971	1.105
FES-Achievement orientation	−0.019	0.029	0.429	0.512	0.981	0.927	1.038
FES-Organization	−0.014	0.028	0.251	0.616	0.986	0.932	1.042

Abbreviations: DUP, Duration of untreated psychosis; FES, Family Environment Scale; MADRS, Montgomery-Åsberg Depression Scale; S.E., Standard Error.

[a]Model information: Nagelkerke $R^2 = 0.352$, Model $\chi^2 = 82.16$, degrees of freedom = 14; $p < 0.001$. *Nonsuicidal Ideation* trajectory was used as the reference group. Bold type indicates $p < 0.05$.

[b]Degrees of freedom = 1.

that "hopelessness," included in the MADRS-pessimistic thoughts item, has been proven to be a relevant risk factor for the emergence of both SI and suicidal behavior in FEP population, as well as in other psychiatric samples.[67,68] However, in our sample, higher scores in pessimistic thoughts were not found to be associated to the *Worsening SI* trajectory. Similarly, Madsen et al.[20] did not find hopelessness to be related to their frequent and increasing SI trajectory. Of note, a work by Kivelä et al.[69] applying linear mixed-effects growth models to data from the Netherlands Study of Depression and Anxiety (NESDA) provided results similar to ours. Although they did not focus on a FEP sample, they likewise found that hopelessness was related to more severe SI at study inclusion in individuals with depression and anxiety. Furthermore, those participants presenting with greater hopelessness at baseline experienced a higher decline in SI over time.[69] This might indicate that hopelessness may actually be a risk factor for acute and/or more severe SI, while the presence of persistent SI or the development of subacute SI might be mediated by other factors. Higher baseline scores in "inability to feel" were associated with the *Improving SI* trajectory. Interestingly, a positive correlation between anhedonia and SI scores has been described in subjects at ultra-high risk of psychosis.[70] Although we did not find statistically significant differences in gender or substance use, it is interesting to note that the percentage of females and alcohol/cannabis use—two important risk factors for SI—was higher in the *Improving SI* group.[2,71]

Improving SI trajectory was likewise associated with worst perceived family environment at baseline, that is, higher scores in conflict and organization (the latter reflects greater importance to order, planning, and rules within the family) and lower scores in achievement-orientation. However, participants presenting this trajectory also exhibited more depressive symptoms at baseline. This aspect could have biased their answers when asked about their family environment. Nevertheless, family interventions including sessions where

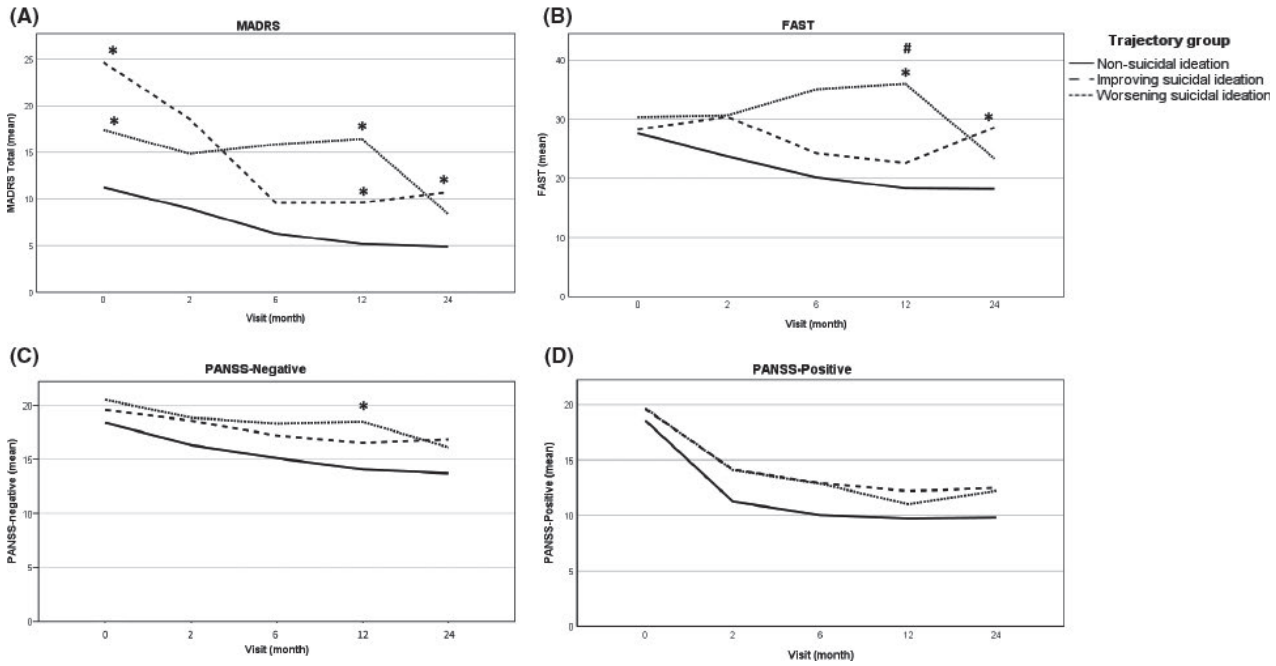

FIGURE 2 Evolution of clinical and functional variables throughout the study for the three predicted suicidal ideation trajectories. (A) Evolution of depressive symptoms, measured by the Montgomery-Åsberg Depression Rating Scale (MADRS), throughout the 24-month follow-up for each of the three suicidal ideation (SI) trajectory groups. Mean MADRS scores of individuals falling into the *Improving SI* trajectory and *Worsening SI* trajectory were significantly different from mean MADRS scores of individuals in the *Non-SI* subgroup at baseline and at 12-month follow-up. At 24-month follow-up, significant differences were only found between subjects in the *Improving SI* trajectory and the *Non-SI* trajectory. (B) Psychosocial functioning throughout the 24-month follow-up is depicted here. At 12-month follow-up, significantly higher mean FAST scores were found in the *Worsening SI* trajectory subgroup compared with both the *Improving SI* trajectory and the *Non-SI* trajectory subgroups. Panel (C) and (D) describe, respectively, the evolution of negative symptoms, assessed with the Positive and Negative Syndrome Scale (PANSS) Negative subscale, and the evolution of positive psychotic symptoms, measured by the PANSS-Positive subscale. (C) As for negative symptoms, individuals falling into the *Non-SI* trajectory showed significantly lower scores in the PANSS Negative subscale than subjects in the *Worsening SI* trajectory group at 12-month follow-up. (D) No significant between-group differences were found for the PANSS-Positive subscale at any time point. For all variables, the mean values at each follow-up point are presented in the figures. Significant differences between groups at different time points are represented by the symbols *($P < 0.01$ *vs Non-SI* trajectory) or # ($P < 0.01$ *vs Improving SI* trajectory).

families are provided with tools to recognize and act in the event of suicidal risk could be an additional intervention to prevent suicides in this population, especially for preadolescent/adolescent patients.[72]

Our finding indicating that older age is associated with a *Worsening SI* trajectory contrasts with previous literature where younger age at FEP was reported to confer a higher risk for SI.[9,67] As in the case of hopelessness, this discrepancy may respond to differences in the methodological approach of our study compared with others. However, older age has also been related to higher risk of suicidal behavior after FEP, as well as longer DUP.[30,71,73] Notwithstanding that the final mechanism through which longer DUP is associated with an increased risk of suicidal behavior remains unknown, our findings highlight the importance of an early detection and intervention in psychotic disorders, along with a close monitoring of SI in those patients presenting with a longer DUP. In line with previous studies, our results also reveal that higher baseline scores in MADRS-reduced sleep is associated with *Worsening SI* trajectory. Insomnia has been widely related to the acute emergence and persistence of suicidal thoughts.[69,74-76] In keeping with this view, this symptom is a modifiable risk factor. Therefore, the early identification and treatment of even mild sleep disruptions might provide a meaningful benefit for patients with FEP presenting with fluctuating SI.

After exploring predictors of trajectories and comparing the evolution of clinical and functional characteristics between the individuals falling into each of the predicted trajectories, our findings suggest two differential profiles of patients with FEP showing SI. Subjects within the *Improving SI* trajectory present with moderate depressive symptoms at baseline that rapidly improve in subsequent follow-up assessments. Conversely, participants with a predicted *Worsening SI* trajectory exhibit mild depressive symptoms at baseline and during the first follow-up year, while SI worsens over the same period. This group, which is also older, presents the most severe functional impairment according to FAST scores, and is likewise characterized by longer DUP and poor premorbid adjustment. Importantly, individuals from these two trajectories did not

differ in terms of severity of positive psychotic symptoms, negative symptoms, or total PANSS scores. This finding might indicate that while there is a group where the presence and severity of SI seems closely related to the severity of depressive symptoms, there is another group where the emergence of suicidal thoughts may be mediated by a multitude of other factors such as persistence of mild depressive symptoms over time, difficulties in psychosocial functioning, older age, and more pronounced premorbid vulnerability. If replicated in future studies specifically designed to assess SI, those findings may have important clinical implications, since these two groups will require different treatment approaches. The first profile may benefit more from an adequate treatment focused on the acute treatment and the prevention of depressive symptoms. On the contrary, the second group might likely benefit from a more integrative approach. In this second group, therapies focused on managing SI and improving functional outcomes may be needed additionally to symptomatic treatment.[77] Furthermore, this subgroup may also benefit from psychopharmacological therapies with evidence of specific antisuicidal effects, such as lithium or clozapine.[78-80] Long-acting antipsychotics might also prove beneficial in reducing suicidal risk already in these early stages. In addition to improving adherence, which can lead to better clinical and functional outcomes, treatment administration involves a frequent contact with mental health services. This can prevent social isolation and provide more support to counteract potential negative beliefs about psychosis, two factors associated with suicide risk.[81] Importantly, in both groups, it is paramount to offer enough education about suicide to families and health professionals so that they can detect and respond adequately to direct or indirect suicidal communication, since about half of all suicides communicate their suicidal intentions prior to committing suicide.[82]

Overall, our results confirm previous risk factors for SI, but highlight that not all risk factors apply to all patients presenting with SI. Interestingly, in this same line, a recent work with FEP population found distinct risk factors for suicide depending on the illness stage at which suicidal behaviors had emerged. In this study, the authors reported that history of suicide attempt prior to the onset of FEP was related to a higher risk to commit suicide early after FEP, while premorbid occupational impairment, poor treatment adherence, and a higher number of relapses during the first 3 years of the psychotic illness were associated with the emergence of suicidal behaviors in later stages of the illness.[83]

4.1 | Strengths and limitations

The current study presents some limitations that require consideration. Firstly, it is a post hoc of a prior study that was not primarily designed to detect SI. Thus, our sample size might have been insufficient to capture all potential trajectories for SI. Additionally, one of the trajectories included just 6.89% of the sample, thus, challenging the identification of specific predictors for that trajectory. Hence, we cannot rule that the lack of significant differences in univariate analyses might be because of lack of power. That could have been the case, for instance, of cognitive variables. Secondly, SI was not measured using a suicide-specific scale, which might have reduced our sensitivity to detect SI. Nevertheless, some authors have reported an adequate agreement between the "suicidal thoughts" item of the MADRS and the first five items of the Scale for Suicide Ideation (SSI), which serve as a first screening for SI.[60] Thirdly, there was an absence of data on suicidal attempts or completed suicides during follow-up. As such, we could not assess whether the *Worsening SI* trajectory was associated with higher rates of suicide attempts, as reported in previous studies.[20] Fourthly, notwithstanding some information on family history of completed suicide was available, the reduced number of cases (n = 4) prevented us from including it as a putative predictor variable, despite the fact that it is clearly one of the major risk factors for suicidality. On the other hand, none of the participants in the study reported having a personal history of suicidal behavior. However, as the study was not specifically designed for assessing suicidality, it may well be that this information was not actively sought for. Fifthly, attrition rate at 24-month follow-up was 38%. Therefore, the sub-analyses involving comparisons of clinical and functional outcomes between trajectory groups at the 24-month follow-up period have been underpowered providing the relatively small samples sizes, especially in the *Worsening SI* trajectory group. Taking into account the higher attrition rate in this group, we cannot rule out the possibility that clinical and functional improvements observed in this subset may be because of the fact that the final sample in this trajectory group is biased toward less severe individuals. Sixthly, the design of our study prevents us from assessing causality, and we did not evaluate how variables like treatment adherence, relapses, or social support after the FEP might have influenced the evolution of SI or psychopathology. Future studies with different methodological design are needed to overcome this issue. Seventhly, although our methodology is analog to other studies of the kind, it might not have been optimum to explore the complex phenomenon that is SI. Eighthly, SI severity was positively skewed, meaning that most participants reported none or mild SI. Lastly, because of the exploratory nature of our analysis, we only corrected for multiple comparisons when performing post hoc comparisons.

Despite those limitations, our study has some worth-mentioning strengths. Since participants underwent exhaustive clinical and cognitive assessments, most of the putative predictors of SI and behaviors could be incorporated in the current analysis. Most previous studies were able to simultaneously

explore only a handful of potential predictors of SI. Moreover, information on clinical and functional outcomes was available at several time-points, predominantly during the first year. In contrast to previous studies, the presence of SI was not investigated using subjective scales, but it was objectively assessed by experienced mental health professionals.

In conclusion, our findings delineate three profiles of patients with FEP regarding SI, one experiencing no SI after FEP, another in which SI might depend on acute depressive symptomatology and, lastly, a group where SI might respond to mild but persistent clinical symptoms, along with psychosocial impairments that seem to be present already in the premorbid period. Future studies are needed to confirm these hypotheses. Nevertheless, our results suggest that tailored identification and management of SI may be possible with implications for suicide prevention in FEP.

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CONFLICTS OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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APPENDIX 1

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Supplementary Results

Table S1. Baseline differences between study completers and non-completers throughout the 24-month follow-up period.

	Follow-up visit							
	2-month		6-month		12-month		24-month	
	Completers	Non-completers	Completers	Non-completers	Completers	Non-completers	Completers	Non-completers
	N=315	N=20	N=282	N=53	N=259	N=76	N=209	N=126
Ethnicity [Caucasian; n(%)]	272(86.3)	12(60.0)	246(87.2)	38(71.7)	225(86.9)	59(77.6)	-	-
	X^2=10.12; **p=0.001**		X^2=8.34; **p=0.004**		X^2=3.89; **p=0.049**			
Urbanicity [Capital city; n(%)]	-	-	-	-	-	-	121(57.9)	53(42.1)
							X^2=7.52; **p=0.016**	
Marital status [Single; n(%)]	-	-	252(89.4)	41(77.4)	233(90)	60(78.9)	-	-
			X^2=5.86; **p=0.015**		X^2=6.5; **p=0.011**			
Working status [Student; n(%)]	135 (42.9)	4 (20.0)	-	-	115(44.4)	24(31.6)	96(45.9)	43(34.1)
	X^2=4.05; **p=0.044**				X^2=3.98; **p=0.046**		X^2=4.51; **p=0.034**	
Family history of addictive disorders [Yes; n(%)]	-	-	-	-	-	-	20(11.3)	20(21.7)
							X^2=5.21; **p=0.022**	
Personal history of anxiety disorder [Yes; n(%)]	-	-	17(19.3)	8(50.0)	-	-	-	-
			X^2=6.98; **p=0.008**					

Notes: Only significant differences are presented. Bold type indicates P<0.05.

Table S2. Results from the univariate multinomial logistic regression analyses.

			Model information			
	Improving Suicidal Ideation N=32	Worsening Suicidal Ideation N=23	X^2	df	P value	R2 Nagelkerke
Age (years)	-	-	2.890	2	0.236	
Gender (Female)	-	-	4.785	2	0.091	
Marital status (Single)	-	-	2.893	2	0.235	

Educational level (Higher education)	-	-	0.059	2	0.971	
Occupation (Active*)	-	-	2.958	2	0.228	
Socioeconomic status (Medium-high)	-	-	2.789	2	0.248	
Substance use						
Alcohol	-	-	2.943	2	0.230	
Cannabis	-	-	1.535	2	0.464	
DUP (days)	OR: 1	**OR: 1.003**	6.409	2	**0.041**	2.9%
MADRS						
Apparent sadness	**OR=1.866**	OR=1.250	29.113	2	**<0.001**	12.4%
Reported sadness	**OR=2.097**	OR=1.274	41.843	2	**<0.001**	17.5%
Inner tension	**OR=1.511**	OR=1.117	11.043	2	**0.004**	4.8%
Reduced sleep	OR=1.165	**OR=1.323**	8.974	2	**0.011**	3.9%
Reduced apetite	**OR=1.551**	OR=1.204	11.720	2	**0.003**	5.1%
Concentration difficulty	**OR=1.378**	OR=1.138	7.536	2	**0.023**	3.3%
Lassitude	**OR=1.548**	**OR=1.468**	18.545	2	**<0.001**	8%
Inability to feel	**OR=1.691**	**OR=1.461**	26.872	2	**<0.001**	11.5%
Pessimistic thoughts	**OR=2.319**	**OR=1.502**	49.067	2	**<0.001**	20.3%
PAS total	OR=1.007	**OR=1.023**	6.736	2	**0.034**	3.1%
FES						
Cohesion	**OR=0.929**	**OR=0.953**	7.125	2	**0.028**	3.5%
Expressiveness	**-**	**-**	1.517	2	0.468	
Conflict	**OR=1.072**	OR=1.050	13.217	2	**0.001**	6.4%
Independence	**-**	-	2.039	2	0.361	
Achievement orientation	**OR=0.954**	OR=0.966	6.549	2	**0.038**	3.2%
Intellectual-cultural orientation	**-**	-	2.038	2	0.361	

Active-recreational orientation	-	-	1.857	2	0.395	
Moral-religious emphasis	-	-	1.800	2	0.407	
Organization	OR=0.978	**OR=0.954**	6.477	2	**0.039**	3.2%
Control	-	-	0.543	2	0.762	
TQ	-	-	2.287	2	0.319	
Cognitive measures						
Executive function	-	-	0.754	2	0.686	
Stroop Word-Color	-	-	3.545	2	0.170	
Social cognition	-	-	3.390	2	0.184	
Verbal learning and memory	-	-	0.704	2	0.703	
Working memory	-	-	1.088	2	0.580	
Attention	-	-	1.113	2	0.573	
IQ	-	-	0.247	2	0.884	

Notes: Only significant differences are presented. Bold type indicates P < 0.05. *Non-Suicidal Ideation* trajectory was used as the reference group.

Abbreviations: MADRS: Montgomery–Åsberg Depression Scale; PAS: Premorbid Adjustment Scale; FES: Family Environment Scale; TQ: Trauma Questionnaire; IQ: Intelligence Quotient.

Table S3. Multinomial logistic regression†: baseline predictor variables for suicidal ideation trajectories (only adult sample).

	B	S.E.	Wald ‡	Sig.	Exp(B)	Exp (B) 95% Confidence Interval	
						Lower limit	Upper limit
Improving suicidal ideation							
Intersection	-10.125	3.620	7.821	**0.005**			
Sex (female)	0.522	0.593	0.775	0.379	1.686	0.527	5.395
Age	0.028	0.056	0.243	0.622	1.028	0.921	1.148
DUP	0.000	0.003	0.005	0.941	1.000	0.995	1.005
MADRS-Reduced sleep	0.112	0.149	0.556	0.452	1.119	0.835	1.499

MADRS-Inability to feel	0.353	0.216	2.658	0.103	1.423	0.931	2.174
MADRS-Pessimistic thoughts	1.056	0.251	17.711	**<0.001**	2.874	1.758	4.700
FES-Conflict	0.094	0.037	6.546	**0.011**	1.099	1.022	1.182
FES-Achievement orientation	-0.093	0.037	6.488	**0.011**	0.911	0.848	0.979
FES-Organization	0.076	0.035	4.572	**0.032**	1.079	1.006	1.156
Worsening suicidal ideation							
Intersection	-6.528	3.011	4.699	0.030			
Sex (female)	0.048	0.531	0.008	0.927	1.050	0.371	2.970
Age	0.045	0.051	0.801	0.371	1.046	0.948	1.155
DUP	0.004	0.002	7.831	**0.005**	1.005	1.001	1.008
MADRS-Reduced sleep	0.344	0.139	6.136	**0.013**	1.410	1.074	1.851
MADRS-Inability to feel	0.327	0.181	3.271	0.071	1.387	0.973	1.977
MADRS-Pessimistic thoughts	0.238	0.225	1.119	0.290	1.269	0.816	1.973
FES-Conflict	0.040	0.034	1.420	0.233	1.041	0.974	1.112
FES-Achievement orientation	-0.014	0.030	0.234	0.628	0.986	0.930	1.045
FES-Organization	-0.011	0.029	0.129	0.720	0.990	0.934	1.048

† Model information: Nagelkerke $R^2 = 0.385$, Model $\chi 2 = 68.85$, degrees of freedom = 18; $p < 0.001$. *Non-Suicidal Ideation* trajectory was used as the reference group. Bold type indicates $p < 0.05$.

‡ Degrees of freedom = 1

Abbreviations: S.E.: Standard Error; DUP: Duration of untreated psychosis; MADRS: Montgomery–Åsberg Depression Scale; FES: Family Environment Scale.

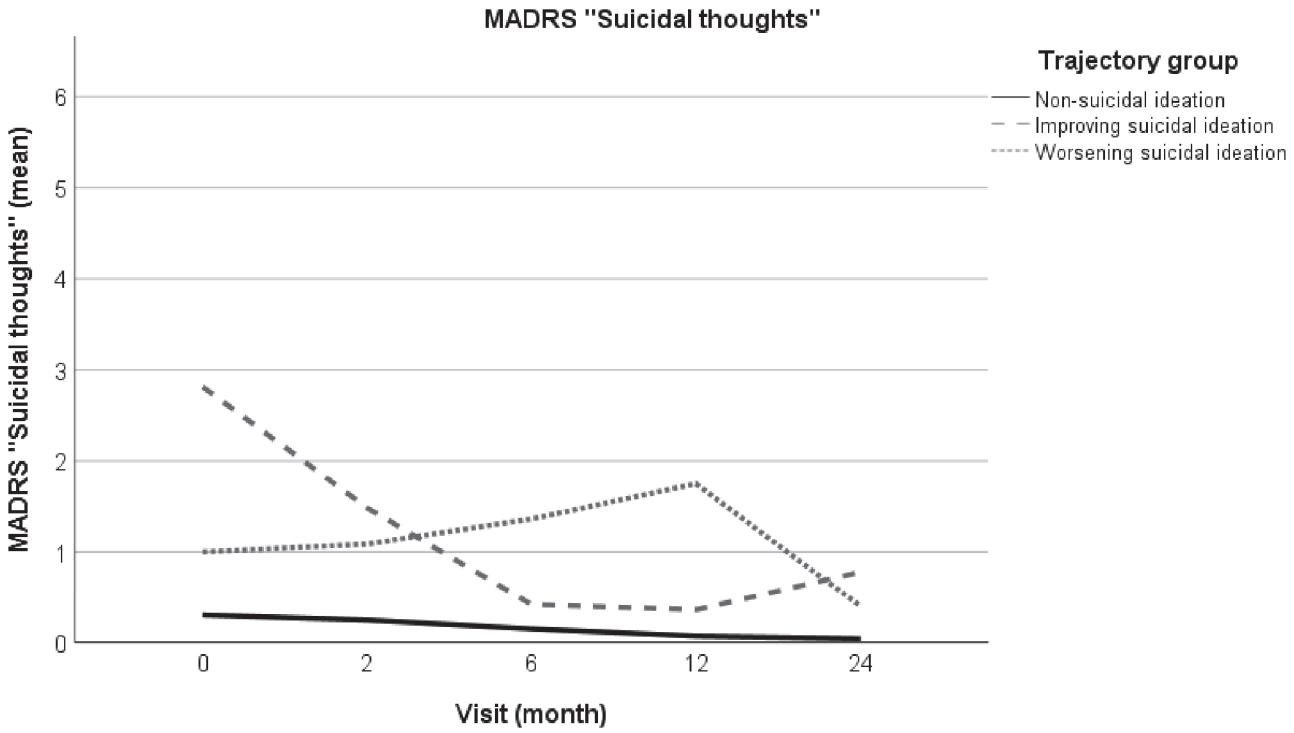

Figure S1. Evolution of mean MADRS "suicidal ideation" scores within each of the functional trajectory groups.

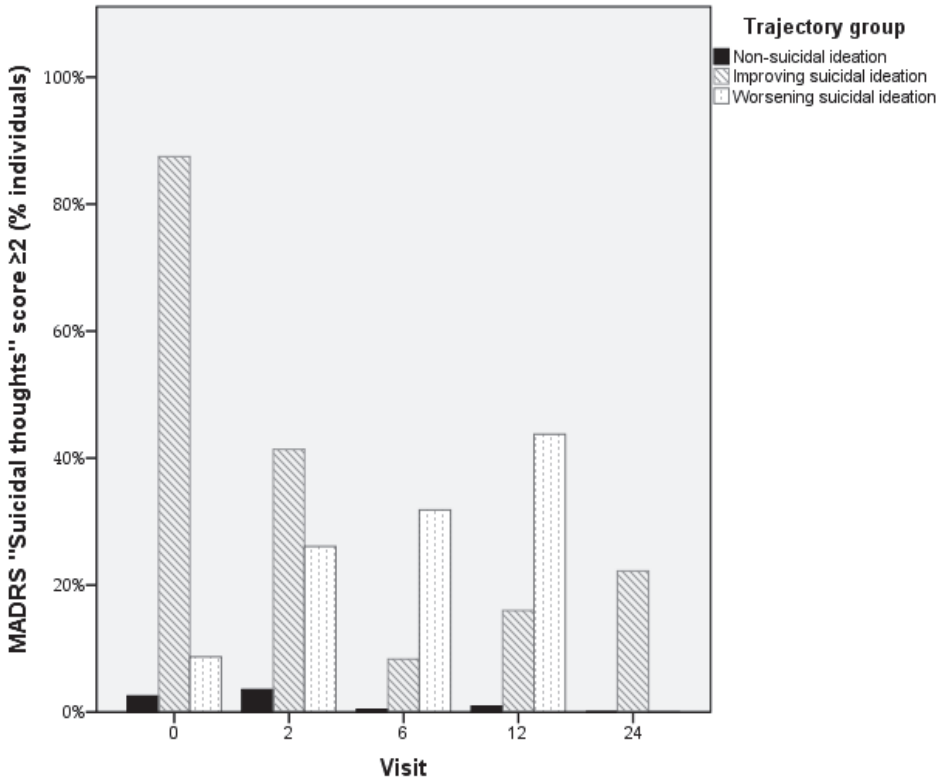

Figure S2. Evolution of the proportion of individuals showing clinical suicidal ideation (MADRS "suicidal thoughts" scores ≥2) during follow-up in each of the predicted trajectories.

A MADRS "suicidal thoughts" score ≥2 was considered the cut-off to determine the presence of any suicidal ideation, as described in previous studies.[1]

1. Ballard ED, Luckenbaugh DA, Richards EM, et al. Assessing measures of suicidal ideation in clinical trials with a rapid-acting antidepressant. *Journal of psychiatric research.* 2015;68:68-73.

7. DISCUSIÓN

Los resultados del presente trabajo apoyan la presencia de una marcada heterogeneidad en la evolución funcional y de la ideación suicida en pacientes con un PEP, así como la existencia de marcadores pronósticos presentes en etapas tempranas de los trastornos psicóticos que pueden servir para crear modelos predictivos de diagnóstico de psicosis afectiva vs. no afectiva y para estratificar a los pacientes en subgrupos de riesgo según su evolución más probable a nivel funcional y de ideación suicida.

Los marcadores pronósticos identificados en nuestros estudios fueron factores premórbidos, clínicos y cognitivos. En cuanto a los factores premórbidos, hallamos que un nivel socioeconómico familiar más bajo y un peor ajuste premórbido estarían asociados con un peor pronóstico funcional a largo plazo. En nuestra muestra, además, los pacientes con un diagnóstico de trastorno bipolar al año de seguimiento presentaron mejor ajuste premórbido que los pacientes diagnosticados de esquizofrenia durante el primer año de seguimiento. Asimismo, al comparar a los pacientes clasificados en las distintas trayectorias de ideación suicida, el subgrupo de pacientes con una trayectoria caracterizada por un empeoramiento de la ideación autolítica también fue el grupo con un peor ajuste premórbido. En cuanto a los marcadores pronósticos clínicos, nuestros resultados subrayan la importancia de los síntomas negativos, los síntomas depresivos y la funcionalidad como principales factores pronósticos de diagnóstico de psicosis afectiva (trastorno bipolar), de evolución funcional y/o de desarrollo de ideación autolítica, en línea con trabajos anteriores. Una DUP más prolongada también se asoció con un mayor riesgo de presentar ideación autolítica subaguda. Por último, respecto a los factores cognitivos, nuestros hallazgos apuntan a la función ejecutiva como factor pronóstico de futuro diagnóstico de trastorno bipolar vs. esquizofrenia y a la memoria y aprendizaje verbal como marcador diferencial de resiliencia funcional entre pacientes que presentan dificultades funcionales marcadas en el debut psicótico. Asimismo, nuestros resultados subrayan que, si bien los síntomas positivos son los síntomas que más se exploran en la clínica durante el episodio agudo y el seguimiento para valorar la respuesta al tratamiento y monitorizar recaídas, estos síntomas parecen ser menos relevantes a la hora de predecir la evolución a medio plazo del paciente en las áreas de funcionalidad e ideación suicida exploradas en el presente trabajo. De hecho, hoy en día está aceptado que la medicación antipsicótica –que principalmente actúa sobre los síntomas positivos– es útil para controlar los síntomas agudos de la enfermedad y prevenir recaídas, pero su influencia directa en el funcionamiento psicosocial y laboral es limitada, ya que este parece asociarse

más a síntomas negativos y cognitivos (28, 170). Por esta razón cada vez está más clara la necesidad de una aproximación holística que combine intervenciones psicológicas, sociales y farmacológicas para reducir el deterioro funcional que a menudo se observa en pacientes con trastornos psicóticos (28, 170).

Los resultados del presente trabajo apuntan a que esta aproximación holística debe ser personalizada ya que nuestros hallazgos también reflejan que la evolución de los pacientes tras un PEP puede ser muy heterogénea. Por ello se podrían establecer planes terapéuticos individualizados desde etapas tempranas en función de los factores de riesgo (o de resiliencia) que presenten los pacientes. Por ejemplo, un tratamiento más intensivo podría reservarse para los pacientes con peor ajuste premórbido, un nivel socioeconómico más bajo, y dificultades cognitivas y síntomas negativos más marcados desde el inicio de la enfermedad.

Por último, cabe destacar que los distintos subgrupos identificados en los análisis de trayectorias no se corresponden con grupos diagnósticos definidos (psicosis afectiva vs. no afectiva), sino que todos los diagnósticos estuvieron representados en todas las evoluciones funcionales y de ideación suicida. Este hallazgo puede estar influido por la inestabilidad diagnóstica en las primeras etapas de la enfermedad, aunque también puede ser indicador de que hay dimensiones transdiagnósticas que pueden aportar mayor información pronóstica en etapas tempranas que el diagnóstico en sí.

Los hallazgos más relevantes de este trabajo se analizarán en más detalle a continuación.

Distinción precoz entre psicosis no afectivas y psicosis afectivas: foco en trastorno bipolar vs esquizofrenia

Respecto al primer objetivo, abordado en el **Estudio 1** (154), nuestros resultados indican que los sujetos que reciben una orientación diagnóstica de trastorno bipolar durante el año siguiente al PEP parecen mostrar ya algunas diferencias clínicas, funcionales y cognitivas en el debut psicótico con respecto a los sujetos que reciben una orientación de esquizofrenia tras el PEP. En nuestra muestra, un mejor funcionamiento psicosocial basal, una puntuación más baja en la subescala negativa de la PANSS y un mejor rendimiento en funciones ejecutivas –específicamente, una mejor flexibilidad cognitiva, medida por

los errores perseverativos en el WCST–, resultaron variables predictoras del diagnóstico de trastorno bipolar a los 12 meses de seguimiento en nuestro modelo predictivo. Estos resultados replican hallazgos previos de estudios realizados en pacientes con un PEP, donde un mejor funcionamiento psicosocial, menos síntomas negativos o mejores funciones ejecutivas se habían asociado con un futuro diagnóstico de trastorno bipolar (85, 87, 171, 172). Estos resultados tienen importantes implicaciones clínicas, puesto que tanto los estabilizadores del estado de ánimo como intervenciones psicológicas como la psicoeducación han demostrado ser más efectivas cuando se inician de manera temprana en el curso del trastorno bipolar (6, 173, 174). Además, otros trabajos del grupo PEPs apuntan a que intervenciones psicológicas tempranas destinadas a mejorar la reserva cognitiva deben diseñarse de manera distinta para los pacientes con trastorno bipolar y para los pacientes con esquizofrenia (30, 81, 162).

Funcionamiento psicosocial tras un PEP

El segundo objetivo de este trabajo fue investigar trayectorias de funcionamiento psicosocial tras un PEP. En nuestro **Estudio 2**, tratamos de alcanzar este objetivo utilizando la técnica estadística LCGA y nuestros resultados indicaron un patrón heterogéneo de funcionamiento psicosocial en los dos primeros años después del PEP, en consonancia con estudios previos que utilizaron el mismo enfoque (97, 98). Específicamente, encontramos cuatro trayectorias funcionales distintas. La mayoría de sujetos de nuestra muestra mostró un deterioro funcional leve al inicio del estudio y experimentó una recuperación funcional poco después del PEP. El segundo grupo más numeroso experimentó un deterioro funcional severo al inicio del estudio que persistió, aunque de forma más moderada, durante todo el período de estudio. Un tercer grupo mostró un deterioro funcional moderado y persistente durante los 24 meses de seguimiento y, por último, una minoría de pacientes presentó un deterioro funcional grave al inicio del estudio, que posteriormente mejoró hasta casi una recuperación funcional completa al final del seguimiento. Es importante destacar que alrededor del 50% de la muestra exhibió una marcada mejoría funcional al final del seguimiento. En línea con nuestras hipótesis, encontramos factores basales asociados con las distintas trayectorias. Los factores basales asociados con la mejoría funcional fueron un nivel socioeconómico medio-alto de los padres, síntomas negativos y depresivos menos severos al inicio del estudio (para los individuos en la trayectoria *Deterioro leve-Mejora*), mejores

puntuaciones en el dominio de aprendizaje y memoria verbal (para los individuos en la trayectoria *Deterioro severo-Mejora*) y un mejor ajuste premórbido (tanto para los individuos en la trayectoria *Deterioro leve-Mejora* como para los individuos en la trayectoria *Deterioro severo-Mejora*). Síntomas positivos menos severos al inicio del estudio predijeron una trayectoria estable de deterioro moderado frente a una trayectoria estable de deterioro severo. Estos resultados concuerdan con estudios previos realizados tanto en pacientes con un PEP como en pacientes con una forma crónica de la enfermedad, donde el nivel socioeconómico de los padres (41, 175), los síntomas negativos (97, 98, 176) y depresivos (177, 178), la memoria verbal (176) y el ajuste premórbido (98, 179) fueron predictores de evolución funcional. Hasta donde sabemos, sin embargo, nuestro estudio es el primero en analizar simultáneamente un panel tan amplio de potenciales predictores de trayectorias de funcionamiento psicosocial –que incluyó variables sociodemográficas, clínicas y neurocognitivas– identificadas mediante un enfoque de LCGA, y en examinar posteriormente la interacción entre los predictores identificados.

Con respecto a la distribución del diagnóstico entre clases, nuestros hallazgos están en consonancia con investigaciones anteriores (154, 180). Todos los diagnósticos estuvieron representados en las cuatro trayectorias, sin bien la proporción de pacientes con un diagnóstico de esquizofrenia fue mayor entre los individuos que mostraron dificultades funcionales persistentes, mientras que encontramos una mayor proporción de pacientes con diagnóstico de trastorno bipolar u otras psicosis en el grupo que mostró la trayectoria funcional más favorable.

En nuestro estudio, un nivel socioeconómico familiar medio-alto apareció como uno de los principales predictores de la trayectoria más resiliente, caracterizada por un deterioro funcional leve en la primera evaluación seguida de una recuperación funcional precoz. La asociación entre un mayor nivel socioeconómico de los padres y mejores resultados funcionales es probablemente compleja. Nuestro análisis de mediación, de hecho, sugiere que el nivel socioeconómico de los padres media parcialmente su influencia en la funcionalidad a través del ajuste premórbido y los síntomas negativos. Pero otros factores no incluidos en el análisis de mediación también parecen influir. Por ejemplo, las familias con un nivel socioeconómico más alto podrían proporcionar más estimulación cognitiva a su descendencia (181), por ejemplo, involucrándolos en actividades de ocio más intelectuales, artísticas o culturales. Esto podría mejorar su reserva cognitiva, lo que se ha asociado con mejores resultados funcionales (162, 182, 183). Asimismo, estas familias

podrían tener más recursos para identificar los primeros síntomas psicóticos –fomentando así una vinculación más temprana con los servicios de salud mental (184) – o quizás más capacidad para brindar una mejor atención en el período posterior al PEP (185). Por otro lado, también se han descrito mayores tasas de jóvenes que no estudian ni trabajan en familias con niveles socioeconómicos más bajos (93). En cualquier caso, nuestros resultados enfatizan la necesidad de intervenciones sociales para promover y educar en salud mental, reducir el estigma y facilitar el acceso a los servicios de salud mental en el período pre y post-PEP (40, 58).

Varios estudios han reportado de manera consistente una relación entre el aprendizaje y memoria verbal y los resultados funcionales, tanto en pacientes con trastornos afectivos como no afectivos (30, 177, 186-189). Los síntomas negativos son también predictores bien conocidos de un mayor deterioro funcional (190-192).La interrelación entre los síntomas negativos y la cognición como predictores de la funcionalidad ha sido un tema de intenso debate y estudio en diversos trabajos (193-195). Varios de estos trabajos apuntan a que los síntomas negativos prevalecerían sobre la memoria verbal como predictores de funcionalidad (176, 196). Jordan y colaboradores (166), por ejemplo, mostraron que la memoria verbal predijo la duración de la remisión de los síntomas negativos en pacientes con un PEP, lo que a su vez predijo un mejor rendimiento funcional. Esto podría explicar por qué en nuestro estudio una sintomatología negativa más marcada apareció como predictora de una peor trayectoria funcional al comparar los grupos que exhibieron diferencias significativas en la gravedad de los síntomas negativos al inicio del estudio (es decir, los grupos en las trayectorias *Deterioro severo-Estable* vs. *Deterioro leve-Mejora*), pero el dominio "aprendizaje y memoria verbal" no apareció como un factor predictor relevante. Por el contrario, al comparar grupos con síntomas negativos similares al inicio del estudio (es decir, los grupos *Deterioro severo-Estable* vs. *Deterioro severo-Mejora* en la trayectoria), mejores puntuaciones en el dominio cognitivo "aprendizaje y memoria verbal" surgieron como un predictor significativo de una mejor recuperación funcional. En consecuencia, nuestros hallazgos confirman la importancia de los síntomas negativos como un objetivo de tratamiento para la recuperación funcional y sugieren que evaluar el desempeño en el dominio cognitivo "aprendizaje y memoria verbal" podría ser especialmente útil como un factor diferencial para predecir qué pacientes tendrían más probabilidades de presentar una mejoría

funcional entre los sujetos con un PEP que presentan un deterioro funcional severo y síntomas negativos marcados en el debut psicótico.

Un mejor ajuste premórbido también apareció como un predictor de una trayectoria funcional más favorable en nuestro análisis, de acuerdo con la evidencia previa (190, 197). Como sugirieron Hodgekins y colaboradores (98), la persistencia de deterioro funcional después de un PEP en aquellos sujetos con un ajuste premórbido más deficiente podría simplemente reflejar una discapacidad funcional que ya estaba presente antes del inicio del PEP, por lo que resulta difícil que estos pacientes logren una remisión funcional tras el PEP. De ahí la importancia de intervenir ya en etapas de riesgo con intervenciones específicas dirigidas a mejorar la funcionalidad (57, 58, 198). Teniendo en cuenta que los efectos del ajuste premórbido sobre el funcionamiento psicosocial podrían estar parcialmente mediados por el aprendizaje y memoria verbal, como apoyan los resultados de Jordan y colaboradores (166), aquellos individuos con alto riesgo de psicosis afectiva y no afectiva que exhiben un ajuste social pobre (y especialmente aquellos con bajo nivel socioeconómico de los padres) podrían beneficiarse de una versión adaptada de rehabilitación funcional, la cual ha mostrado tener efectos beneficiosos sobre el funcionamiento psicosocial y la memoria verbal (199, 200).

Por último, nuestros resultados indican que síntomas depresivos menos severos al inicio del estudio se asocian con una trayectoria de *Deterioro leve-mejora*. Si bien se ha demostrado que los síntomas depresivos persistentes empeoran el pronóstico funcional después de un PEP (201, 202), se debe tener en cuenta que en nuestro estudio evaluamos el potencial papel predictivo de los síntomas depresivos basales y, por tanto, puede ser que nuestros hallazgos solo reflejen una presentación clínica menos grave en la trayectoria *Deterioro leve-mejora* en comparación con la trayectoria *Deterioro severo-estable*.

Riesgo suicida tras un PEP

Respecto a nuestro tercer objetivo, que abordamos en el **Estudio 3** (133), nuestros análisis revelaron la existencia de tres trayectorias de ideación suicida en nuestra muestra de pacientes con un PEP seguida durante 24 meses. Se identificó una trayectoria caracterizada por la ausencia de ideación suicida al inicio y a lo largo de las visitas de

seguimiento, donde se clasificaron la mayor parte de los participantes del estudio, una segunda trayectoria caracterizada por la presencia de ideación suicida clínicamente significativa al inicio del estudio que mejoró en las visitas de seguimiento posteriores, y una tercera trayectoria caracterizada por la ausencia o por la presencia esporádica de ideación suicida al inicio del estudio que empeoró levemente durante el período de seguimiento. Esta última trayectoria incluyó el menor número de participantes. Estos resultados están en línea con los hallazgos reportados por Madsen y colaboradores (116) en su muestra de sujetos con un PEP. En su trabajo, la trayectoria más común estuvo compuesta por pacientes con una ideación suicida leve y decreciente, mientras que una minoría de pacientes mostró una trayectoria caracterizada por una ideación suicida frecuente y de intensidad creciente. Al evaluar potenciales predictores de las diferentes trayectorias, encontramos que la trayectoria *Mejora de la ideación suicida* se asoció con una mayor presencia de síntomas depresivos, más específicamente "pensamientos pesimistas" e "incapacidad para sentir", en la evaluación inicial. En este sentido, se debe tener en cuenta que la "desesperanza", incluida en el ítem de la MADRS "pensamientos pesimistas", ha demostrado ser un factor de riesgo relevante para la aparición tanto de ideación suicida como de conducta suicida en poblaciones con un PEP, así como en otros trastornos psiquiátricos (203, 204). Sin embargo, en nuestra muestra, puntuaciones más altas en el ítem de la MADRS "pensamientos pesimistas" no se asociaron con la trayectoria *Empeoramiento de la ideación suicida*. De manera similar, Madsen y colaboradores (116) no encontraron en su estudio que la desesperanza estuviera relacionada con la trayectoria caracterizada por una ideación suicida frecuente y de intensidad creciente. Esto podría indicar que la desesperanza puede ser en realidad un factor de riesgo para la ideación suicida aguda y/o más grave, mientras que la presencia de ideación suicida leve pero persistente o el desarrollo de ideación suicida subaguda podría estar mediada por otros factores.

La trayectoria *Mejora de la ideación suicida* también se asoció con una peor percepción del entorno familiar a nivel basal, reflejada por puntuaciones más altas en las subescalas "conflicto" y "organización" de la FES (esta última podría reflejar una mayor preocupación por el orden, la planificación y las reglas dentro de la familia) y puntuaciones más bajas en "orientación al logro". A la hora de interpretar estos resultados hay que tener en cuenta que los participantes que presentaron esta trayectoria también exhibieron síntomas depresivos más severos al inicio del estudio, lo que podría haber

sesgado sus respuestas cuando se les preguntó sobre su entorno familiar. No obstante, en sujetos con ideación suicida marcada en el PEP que reporten una mala percepción del clima familiar se podrían plantear intervenciones familiares que incluyeran sesiones donde se proporcionara a las familias herramientas para reconocer y actuar en caso de riesgo suicida como una intervención adicional para la prevención de la conducta suicida (205).

Nuestros resultados indicaron que una edad más avanzada y una DUP más prolongada se relacionan con un mayor riesgo de presentar ideación suicida subaguda después del PEP, en línea con estudios previos (16, 206, 207). Si bien se desconoce el mecanismo final a través del cual una DUP más prolongada se asocia con un mayor riesgo de presentar ideación suicida subaguda tras el PEP, nuestros hallazgos destacan la importancia de detectar e intervenir precozmente en los trastornos psicóticos, y de monitorizar estrechamente el desarrollo de ideación suicida en aquellos pacientes que presentan una DUP más prolongada. Puntuaciones iniciales más altas en el ítem "sueño reducido" de la MADRS también se asociaron con la trayectoria *Empeoramiento de la ideación suicida* en nuestro estudio. El insomnio se ha relacionado ampliamente con la aparición aguda y la persistencia de pensamientos suicidas (208-211). De acuerdo con esto, este síntoma es un factor de riesgo modificable. Por lo tanto, la identificación y el tratamiento tempranos de incluso alteraciones del sueño leves, podrían proporcionar un beneficio significativo para los pacientes con PEP que presentan una ideación suicida fluctuante.

Tras examinar los predictores de trayectorias identificados en nuestro estudio y comparar la evolución de las características clínicas y funcionales entre los individuos clasificados en cada una de las trayectorias predichas, nuestros hallazgos parecen sugerir dos perfiles diferenciales de pacientes con PEP que muestran ideación suicida. Los sujetos clasificados en la trayectoria de *Mejora de la ideación suicida* presentaron síntomas depresivos moderados al inicio del estudio que mejoraron rápidamente en las evaluaciones de seguimiento posteriores; es decir, los síntomas depresivos y la ideación suicida parecieron mostrar una evolución paralela. Por el contrario, los participantes clasificados en la trayectoria *Empeoramiento de la ideación suicida* presentaron síntomas depresivos leves al inicio del estudio y durante el primer año de seguimiento, mientras que la ideación suicida empeoró durante ese mismo período. Este grupo presentó el deterioro funcional más severo tras el PEP según las puntuaciones de la FAST y se

caracterizó igualmente por una DUP más prolongada y un peor ajuste premórbido. Es importante destacar que los individuos de estas dos trayectorias no difirieron en la gravedad de los síntomas psicóticos positivos, los síntomas negativos o las puntuaciones totales de la PANSS. Así, estos hallazgos podrían indicar que, si bien hay un grupo en el que la presencia y gravedad de la ideación suicida parece estar estrechamente relacionada con la gravedad de los síntomas depresivos (con un posible efecto también del funcionamiento familiar), hay otro grupo en el que la aparición de pensamientos suicidas podría estar mediada por una multitud de factores, como la persistencia de síntomas depresivos leves a lo largo del tiempo, dificultades en el funcionamiento psicosocial, una mayor edad y una vulnerabilidad premórbida más pronunciada. De replicarse en futuros estudios específicamente diseñados para evaluar ideación suicida, estos hallazgos podrían tener importantes implicaciones clínicas, dado que estos dos perfiles de pacientes requerirían diferentes enfoques de tratamiento. El primer perfil podría beneficiarse más de un tratamiento centrado en el tratamiento agudo y posterior prevención de los síntomas depresivos. Por el contrario, el segundo grupo probablemente se beneficiaría de un enfoque más integrador, que incluyera terapias centradas en el manejo de la ideación suicida, terapias de rehabilitación funcional y tratamientos psicofarmacológicos para abordar los síntomas depresivos (212, 213). Asimismo, este subgrupo podría beneficiarse de terapias psicofarmacológicas con evidencia de efectos anti-suicidas específicos, como el litio o la clozapina (214-216). Los antipsicóticos de acción prolongada también podrían resultar beneficiosos para reducir el riesgo de suicidio ya en estas primeras etapas. Además de mejorar la adherencia, que puede conducir a mejores resultados clínicos y funcionales, la administración del tratamiento conlleva un contacto frecuente con los servicios de salud mental lo que puede prevenir el aislamiento social y brindar más apoyo para contrarrestar potenciales creencias negativas sobre la psicosis, dos factores asociados con el riesgo de suicidio (217). Es importante destacar que en ambos grupos es fundamental ofrecer a las familias y a los profesionales de la salud suficiente educación sobre el suicidio para que puedan detectar y responder adecuadamente a la comunicación suicida directa o indirecta, ya que aproximadamente la mitad de todos los suicidios comunican sus intenciones suicidas antes de cometer suicidio (218).

Las principales conclusiones del presente trabajo y sus implicaciones clínicas se resumen en la **Tabla 8.**

Tabla 8. Potenciales implicaciones clínicas de los hallazgos del presente trabajo.

EVALUACIÓN PEP		RELEVANCIA	POTENCIALES INTERVENCIONES
DOMINIO CLÍNICO	Síntomas negativos	DD TB vs. ESQ	Explorar síntomas maníacos subumbrales en pacientes con un PEP que presenten poca sintomatología negativa. Post PEP: Cuidadoso diagnóstico diferencial entre depresión y síntomas negativos.
		Funcionamiento psicosocial	Intervenciones de rehabilitación funcional tempranas, sobre todo si déficits en el dominio cognitivo "aprendizaje y memoria verbal".
	Síntomas depresivos	Riesgo suicida	Pensamientos pesimistas ++: Tratamiento agudo de síntomas depresivos y prevención de recaídas depresivas como prevención de ideación suicida
			Vigilar aparición de ideación suicida en pacientes con DUPs largas, dificultades funcionales y síntomas depresivos leves persistentes tras el PEP. Tratamiento intensivo de las alteraciones del sueño y de los síntomas depresivos leves, valorar terapias psicológicas para el manejo de la ideación suicida y las dificultades funcionales. Valorar fármacos con acción anti-suicida, antipsicóticos inyectables de liberación prolongada.
		Funcionamiento psicosocial	Tratamiento de síntomas depresivos para disminuir riesgo de dificultades funcionales.
	DUP	DD TB vs. ESQ*	Explorar síntomas maníacos subumbrales en pacientes con un PEP y DUP más corta.
		Riesgo suicida	Vigilar aparición de ideación suicida en pacientes con DUPs largas, dificultades funcionales y síntomas depresivos leves persistentes tras el PEP.
DOMINIO FUNCIONALIDAD	Ajuste premórbido	DD TB vs. ESQ*	Explorar síntomas maníacos subumbrales en pacientes con un PEP y buen ajuste premórbido.
		Funcionamiento psicosocial	Intervenciones de rehabilitación funcional tempranas, sobre todo si bajo nivel socioeconómico.

	Funcionamiento psicosocial pre/post PEP	DD TB vs. ESQ	Explorar síntomas maníacos subumbrales en pacientes con un PEP y buena funcionalidad.
		Riesgo suicida*	Vigilar aparición de ideación suicida en pacientes con DUPs largas, dificultades funcionales y síntomas depresivos leves persistentes tras el PEP. Tratamiento de las dificultades funcionales.
DOMINIO COGNITIVO	Funciones ejecutivas	DD TB vs. ESQ	Explorar síntomas maníacos subumbrales en pacientes con un PEP y funciones ejecutivas más preservadas.
	Aprendizaje y memoria verbal	Funcionamiento psicosocial	Explorar para DD en caso de síntomas negativos prominentes en el PEP. Si déficits, intervenciones de rehabilitación funcional tempranas.
DOMINIO FACTORES AMBIENTALES	Funcionamiento familiar	Riesgo suicida	Evaluar funcionamiento familiar percibido en pacientes con ideación suicida en el PEP. Intervenciones familiares donde se faciliten herramientas para reconocer y actuar en caso de riesgo suicida.
	Nivel socioeconómico	Funcionamiento psicosocial	Intervenciones sociales para promover y educar en salud mental y facilitar el acceso a los servicios de salud mental en el período pre y post-PEP (idealmente servicios especializados en estadios tempranos de la enfermedad).

*Resultados del análisis univariante.

Abreviaturas: PEP: Primer episodio psicótico. DD: Diagnóstico Diferencial; TB: trastorno bipolar; ESQ: esquizofrenia; DUP (del inglés, *Duration of untreated psychosis*): Duración de la psicosis no tratada.

7.1. Limitaciones

A la hora de interpretar los resultados, se deben considerar algunas limitaciones.

1. Primero, el período de seguimiento fue corto y la tasa de abandono a los 24 meses de seguimiento fue del 38%, lo que puede haber disminuido el poder estadístico de los análisis realizados con datos de la evaluación a 2 años.

2. Respecto al **Estudio 1** (154), solo un pequeño porcentaje de sujetos recibió un diagnóstico de trastorno bipolar o esquizofrenia a los 12 meses de seguimiento. Además, el tamaño de la muestra en el grupo de pacientes que recibió un diagnóstico de trastorno bipolar fue la mitad que en el grupo de pacientes con un diagnóstico de esquizofrenia. Asimismo, debido al corto tiempo de seguimiento, el subgrupo de pacientes con esquizofrenia considerados en el **Estudio 1** podría incluir aquellos con un curso clínico más grave y, por lo tanto, las diferencias entre los pacientes diagnosticados con trastorno bipolar y los pacientes diagnosticados de esquizofrenia podrían ser más pronunciadas, influyendo así en nuestros resultados. Aun así, nuestros hallazgos están en línea con otros estudios con un seguimiento más prolongado (85, 171).

3. Respecto al **Estudio 1** (154), no podemos descartar que algunos de los pacientes diagnosticados de trastorno bipolar o esquizofrenia cambiaran de diagnóstico a posteriori, por ejemplo, a trastorno esquizoafectivo. Sin embargo, varios estudios apuntan hacia una alta estabilidad diagnóstica tanto para trastorno bipolar como para esquizofrenia (31, 42, 171), por lo que se espera que el número de cambios de diagnóstico sea mínimo en ambos grupos.

4. Respecto al **Estudio 1** (154), el umbral de significación de nuestro modelo no se corrigió para múltiples pruebas, lo que debe tenerse en cuenta al interpretarlo. Este es un tema controvertido debido al riesgo de aumento del error β (219) y nuestros resultados están respaldados por la literatura previa, lo que hace menos probable que sean un hallazgo fortuito.

5. Respecto a los **Estudios 2 y 3** (133, 158), como subanálisis de un estudio anterior no diseñado específicamente para el propósito de estos dos trabajos, el tamaño de

la muestra podría ser demasiado pequeño y el seguimiento demasiado corto para capturar todas las trayectorias potenciales de funcionamiento psicosocial o de ideación suicida. En segundo lugar, la denominación de trayectorias es un proceso subjetivo; en nuestro caso, la elección se basó en la información que consideramos más importante de extraer de las trayectorias observadas, usando un enfoque pragmático y clínicamente útil.

6. Respecto a los **Estudios 2 y 3** (133, 158), el diseño de ambos estudios impide evaluar causalidad. Además, dado que nuestro mayor interés fue detectar factores basales que sirvieran como predictores de futuras trayectorias, no tuvimos en cuenta variables como el cumplimiento del tratamiento o el abuso de sustancias durante el seguimiento, que también podrían contribuir a los resultados funcionales o a la presencia de ideación suicida en el período posterior al PEP.

7. Respecto al **Estudio 2** (158), se utilizaron los puntos de corte de la FAST validados para el trastorno bipolar, dado que los puntos de cortes específicos para PEPs no estaban disponibles en el momento de publicación del estudio (220). Sin embargo, las diferencias son mínimas.

8. Respecto al **Estudio 3** (133)**,** la ideación suicida no se midió utilizando una escala específica de suicidio, lo que podría haber reducido nuestra sensibilidad para detectar la ideación suicida. No obstante, algunos autores han reportado una adecuada concordancia entre el ítem "pensamientos suicidas" de la MADRS y los primeros cinco ítems de la Escala de Ideación Suicida (*Scale for Suicide Ideation*, SSI), que sirven de primer cribado para detectar ideación suicida (134). Por otro lado, al no disponer de datos sobre intentos suicidas o suicidios consumados durante el seguimiento, no pudimos evaluar si la trayectoria *Empeoramiento de la ideación suicida* se asoció con tasas más altas de intentos de suicidio, como se había descrito en estudios anteriores (116). Además, a pesar de que se disponía de cierta información sobre antecedentes familiares de suicidio consumado, el reducido número de casos (n = 4) nos impidió incluirlo como potencial variable predictora, si bien es claramente uno de los principales factores de riesgo de suicidio. De manera similar, ninguno de los participantes en el estudio reportó antecedentes personales de comportamiento suicida. Como el estudio no fue diseñado específicamente para evaluar riesgo suicida, es posible que los pacientes

no fueran interrogados activamente sobre este punto. Otra limitación a considerar es que la tasa de abandono a los 24 meses fue especialmente alta en el grupo con una trayectoria de *Empeoramiento de la ideación suicida,* por lo que no podemos descartar la posibilidad de que la mejoría clínica y funcional observada en este subgrupo en el seguimiento a 24 meses puedan deberse al hecho de que la muestra final de individuos en esta trayectoria esté sesgada hacia individuos con una forma de enfermedad menos severa. Por último, las puntuaciones en ideación suicida presentaron una asimetría positiva, lo que significa que la mayoría de los participantes reportaron ausencia de ideación suicida o ideación suicida leve.

9. Para los tres estudios, dado que el diseño del estudio fue anterior a 2009, no se utilizaron escalas específicas para síntomas negativos, como la Escala Breve de Síntomas Negativos (BNSS) o la Entrevista de Evaluación Clínica para Síntomas Negativos (CAINS). Lo mismo aplica a la reserva cognitiva, con escalas como CRASH que no estaban disponibles en ese momento (221).

A pesar de esas limitaciones, el presente trabajo tiene varias **fortalezas** dignas de mención. Hay que subrayar que el estudio PEPs es un estudio naturalístico que incluyó una muestra de pacientes considerable y con un amplio rango de edad de inclusión, desde la preadolescencia hasta la edad adulta, reclutados en múltiples centros españoles. Se espera por tanto que la muestra sea representativa de la población con un PEP en España. Además, los sujetos incluidos en el estudio fueron sometidos a un protocolo integral que exploró en detalle variables sociodemográficas, clínicas y neuropsicológicas. La psicopatología se evaluó mediante instrumentos bien validados y la cognición se midió utilizando una extensa batería neuropsicológica basada en el consenso MATRICS del Instituto Nacional de Salud Mental. Precisamente por el hecho de que los participantes se sometieron a evaluaciones clínicas y cognitivas exhaustivas, pudimos evaluar de manera conjunta la mayoría de predictores de cambio diagnóstico, ideación suicida y alteraciones funcionales identificados de manera aislada (o en combinaciones más reducidas) en otros estudios. Además, el carácter longitudinal del estudio PEPs permitió evaluar cambios clínicos y funcionales a lo largo del tiempo. Por último, a diferencia de estudios anteriores, la presencia de ideación suicida no se investigó mediante escalas subjetivas, sino que fue evaluada objetivamente por profesionales de la salud mental con amplia experiencia en psicopatología.

7.2. Implicaciones Futuras

En el presente trabajo se han intentado crear modelos predictivos de cambio diagnóstico a trastorno bipolar tras un PEP y de pertinencia a las distintas trayectorias funcionales y de ideación suicida identificadas combinando factores clínicos y cognitivos. Sin embargo, son necesarios futuros trabajos con un mayor tamaño muestral, periodos de seguimiento más prolongados, que incluyan variables no disponibles en este estudio (como puntuaciones de reserva cognitiva o marcadores biológicos) y que tengan en cuenta factores longitudinales que también pueden influir en el funcionamiento o la ideación suicida (como el abuso persistente de sustancias o el incumplimiento terapéutico) para confirmar y perfeccionar nuestros hallazgos y valorar su utilidad clínica.

Así, por ejemplo, los modelos predictivos de diagnóstico de psicosis afectiva vs. no afectiva podrían idealmente utilizar una combinación de factores sociodemográficos, clínicos y biológicos. Las técnicas de aprendizaje automático o *machine learning* podrían ser buenas aliadas para crear este tipo de modelos "mixtos" (14, 222), los cuales ya se están explorando en pacientes en fases más avanzadas de la enfermedad (223). A falta de marcadores biológicos bien definidos, nuestros hallazgos ilustran que existen algunas características clínicas fácilmente explorables en un entorno clínico que pueden ser útiles para identificar a los pacientes con alto riesgo de cambiar su diagnóstico a trastorno bipolar después de un PEP. Por otro lado, la identificación de las características clínicas más diferenciales entre la psicosis afectiva y no afectiva ya desde etapas tempranas puede representar un punto de partida para orientar la investigación en marcadores biológicos, que podrían incorporarse *a posteriori* en modelos predictivos inicialmente más clínicos. Los marcadores biológicos podrían también ser útiles para para afinar las predicciones en pacientes que ya han sido estratificados según criterios clínicos. Los resultados de un estudio reciente de Musliner y colaboradores (224) podrían considerarse un ejemplo ilustrativo de este último enfoque. En este estudio se evaluó la asociación entre puntuaciones de riesgo poligénico (PRS, del inglés *poligenic risk scores*) para trastorno bipolar y esquizofrenia y conversión a trastorno bipolar o esquizofrenia en pacientes con un episodio depresivo. Los autores hallaron que los antecedentes psiquiátricos de los padres fueron predictores más potentes de cambio diagnóstico que los PRS, especialmente en el caso del trastorno bipolar. Por su parte, los PRS parecerían

especialmente útiles para afinar el riesgo de progresión a esquizofrenia o trastorno bipolar entre aquellos pacientes con antecedentes familiares positivos.

De manera importante, una vez identificados un potencial conjunto de factores predictores de distinta naturaleza (síntomas clínicos, biomarcadores, factores ambientales…) que ayuden a diferenciar psicosis afectivas y no afectivas o a predecir la evolución más probable del paciente a nivel de un resultado clínico particular, el siguiente paso sería explorar las posibles asociaciones aditivas o sinérgicas entre todos estos factores (5, 225). Otro reto para estudios futuros será pensar en estrategias para facilitar la implementación de estos modelos predictivos en la práctica clínica, por ejemplo, mediante calculadoras de riesgo disponibles a través de páginas web (69, 226).

Por otro lado, nuestros hallazgos de que todos los diagnósticos están representados en todas las trayectorias funcionales y de ideación suicida apoyarían la existencia de subgrupos transdiagnósticos que son similares en su presentación y evolución clínica a nivel de factores clínicos dimensionales, es decir, constructos psicopatológicos que son comunes a varias entidades diagnósticas (227, 228). Estos factores dimensionales pueden ser importantes para predecir el pronóstico o guiar el tratamiento más allá del diagnóstico específico del individuo. Así, para avanzar en la estratificación de los pacientes en psiquiatría a nivel de estos factores clínicos dimensionales, podría ser útil mantener este enfoque centrado en intentar identificar subgrupos similares independientemente del diagnóstico DSM, especialmente si se tiene en cuenta la heterogeneidad clínica dentro de un mismo diagnóstico DSM y el frecuente solapamiento clínico entre diagnósticos DSM. De hecho, esta aproximación ha sido fructífera en estudios de genética (229). Además, según investigaciones anteriores (230), estos subconjuntos de pacientes podrían representar biotipos específicos que no se rigen por los criterios diagnósticos clásicos. Serían por ejemplo interesantes estudios futuros que analicen si los pacientes clasificados en trayectorias funcionales resilientes presentan un conjunto diferencial de biomarcadores que los diferencien de los pacientes clasificados en trayectorias caracterizadas por déficits funcionales persistentes, para así desarrollar modelos más precisos y objetivos de estratificación de riesgo de deterioro funcional. Por ahora, nuestros resultados sugieren que el presentar un aprendizaje y memoria verbal más preservada podría usarse como un marcador de resiliencia funcional en aquellos pacientes con PEP con una presentación clínica y funcional más severa. De manera más general, cabría considerar si futuros

estudios encaminados a avanzar en la psiquiatría de precisión podrían necesitar reconsiderar los sistemas de diagnóstico categórico actuales y enfocarse en subgrupos más homogéneos a nivel de estas dimensiones transdiagnósticas. Esta aproximación podría ayudar a comprender la base biológica de los síntomas individuales y aumentar la probabilidad de identificar genes de interés, y estaría más alineada con el enfoque personalizado.

La **Tabla 9** presenta un modelo de estadiaje clínico transdiagnóstico para psicosis afectivas y no afectivas donde se incorporarían los avances en la psiquiatría de precisión, que incluirían estos marcadores biológicos.

Tabla 9. Potencial modelo de estadiaje de precisión, enfocado en primeros episodios psicóticos (adaptado de Salagre y colaboradores, 2018 (57)).

<table>
<tr><th>Estadio clínico</th><th>Definición</th><th>Potenciales herramientas de precisión e intervenciones de precisión</th><th>Dominios a evaluar en todos los estadios e intervenciones generales</th></tr>
<tr><td rowspan="2">Estadios “de riesgo”</td><td>Asintomáticos o síntomas inespecíficos, pero riesgo aumentado de psicosis afectiva/no afectiva (antecedentes familiares, uso de sustancias, etc.)</td><td>Evaluación individualizada de factores de riesgo/protectores

Marcadores genéticos o epigenéticos</td><td rowspan="4">a) Dominio clínico
b) Dominio cognitivo
c) Dominio funcional
d) Dominio comorbilidades:
- Uso sustancias
- Comorbilidades físicas
- Comorbilidades psicológicas

Terapias farmacológicas y psicológicas adaptadas a cada paciente en función de los dominios anteriores

Prevención o Intervención en caso de uso de sustancias

Intervenciones familiares</td></tr>
<tr><td>Síntomas prodrómicos: estadios de muy alto riesgo</td><td>Calculadoras de riesgo

Biomarcadores de riesgo (genéticos, epigenéticos, etc.)</td></tr>
<tr><td>Estadios tempranos</td><td>Primer episodio psicótico</td><td>Evaluación individualizada de factores de riesgo/protectores de complicaciones clínicas o deterioro funcional.

Biomarcadores de respuesta al tratamiento y progresión de la enfermedad

Modelos predictivos de evolución clínica/funcional o cambio diagnóstico (IA)

mHealth (psicoeducación, monitorización)</td></tr>
<tr><td>Estadios medios</td><td>Recaídas clínicas</td><td>Tests farmacogenéticos

Biomarcadores de respuesta a tratamiento y progresión de la enfermedad

Modelos predictivos de riesgo suicida, etc. (IA)

mHealth (monitorización)</td></tr>
<tr><td>Estadios avanzados</td><td>Enfermedad persistente, cronicidad</td><td>Modelos predictivos de riesgo suicida, etc. (IA)</td></tr>
</table>

Abreviaturas: IA= inteligencia artificial

En la misma línea, nuestros resultados también apuntan a la existencia de factores de "alerta" en la etapa premórbida que parecen relacionarse con un desenlace clínico particular independientemente del diagnóstico del paciente, como son el ajuste premórbido o el nivel socioeconómico de los padres. Sumado a los estudios que sugieren que los síntomas prodrómicos tienen una escasa especificidad diagnóstica (4, 228), nuestros hallazgos apoyarían que en los estadios "de riesgo" podrían ser más útiles intervenciones transdiagnósticas orientadas a fomentar la resiliencia y a actuar sobre los factores de mal pronóstico de manera individualizada, como podrían ser las intervenciones familiares o la prevención del uso de sustancias. Dado el papel del aprendizaje y la memoria verbal en los resultados funcionales, terapias como la rehabilitación funcional (idealmente adaptadas a PEPs y pacientes de alto riesgo) o estrategias procognitivas también podrían estar indicadas en estas etapas (162, 188, 231). El potencial beneficio de estas intervenciones en etapas tempranas debería explorarse idealmente mediante ensayos clínicos aleatorizados con seguimiento longitudinal. Como se ha comentado anteriormente en la discusión, además de identificar las terapias más eficaces para las etapas más tempranas, se deben realizar más esfuerzos a nivel de políticas sociales para garantizar el acceso de las poblaciones en riesgo a estas intervenciones (5). Brindar atención especializada en servicios clínicos de salud mental para jóvenes puede ser preferible a la atención ambulatoria estándar, ya que la evidencia sugiere que el tratamiento especializado tendría mejores resultados en térmicos clínicos, funcionales y de adherencia al tratamiento que el tratamiento habitual (232), sobre todo entre pacientes con DUPs más cortas (233). Además, permiten un enfoque multidisciplinario y con objetivos múltiples, por lo que es el entorno ideal para combinar estrategias más generales con una evaluación individualizada, por ejemplo, para identificar síntomas prodrómicos más específicos de conversión a psicosis del espectro afectivo vs. no afectivo, para poder ajustar el tratamiento de manera acorde (5, 234).

8. CONCLUSIONES/CONCLUSIONS

Conclusiones

Las principales conclusiones de esta tesis que se derivan del **Estudio 1** (154), **Estudio 2** (158) y **Estudio 3** (133) se detallan a continuación:

1. Los sujetos que cumplen criterios diagnósticos para trastorno bipolar o esquizofrenia tras un PEP difieren en variables clínicas y neuropsicológicas ya desde las fases iniciales. En concreto, encontramos asociación entre el diagnóstico de trastorno bipolar tras un PEP y:
    a. un mejor funcionamiento psicosocial basal
    b. menos síntomas negativos
    c. un mejor desempeño en pruebas que evalúan funciones ejecutivas.

2. El nivel de funcionalidad tras un PEP es heterogéneo. En nuestro estudio, identificamos cuatro trayectorias de funcionamiento psicosocial tras un PEP, dos de ellas indicativas de un curso de deterioro funcional persistente y dos correspondientes a un curso más resiliente. Además, hallamos que:
    a. la resiliencia funcional estaría mediada por un mejor nivel socioeconómico familiar, un mejor ajuste premórbido, menos síntomas negativos y una memoria y aprendizaje verbal más conservados.
    b. la evolución funcional es el resultado de los efectos aditivos de una variedad de factores. Por lo tanto, se necesita un enfoque integrador desde etapas muy tempranas de los trastornos psicóticos para prevenir o abordar los déficits funcionales, especialmente entre aquellos sujetos en una situación psicosocial más vulnerable.
    c. los pacientes con psicosis afectiva, en concreto con trastorno bipolar, presentan mejor funcionamiento psicosocial tras el PEP que los pacientes con esquizofrenia, pero no mejor que los pacientes diagnosticados de "Otras psicosis".

3. La evolución a nivel de ideación suicida tras un PEP difiere entre pacientes:
    a. teniendo en cuenta la evolución clínica, funcional y de ideación suicida, nuestros hallazgos delinean tres perfiles de pacientes con PEP con respecto a la ideación suicida, uno que no experimenta ideación

suicida después del PEP, otro en el que la ideación suicida podría depender de la sintomatología depresiva aguda y, por último, un perfil de pacientes donde la ideación suicida podría responder a síntomas depresivos leves pero persistentes, junto con dificultades psicosociales que parecen estar ya presentes en el período premórbido. En cuanto a los predictores de cada trayectoria, hallamos que:

b. los pensamientos pesimistas, la incapacidad para sentir y un peor clima familiar percibido se asociaron con la presencia de ideación suicida aguda en el debut psicótico, con mejoría durante el seguimiento.
c. una edad más avanzada, una DUP más prolongada y las dificultades para dormir se relacionaron con un mayor riesgo de presentar ideación suicida subaguda después del PEP.
d. Así, nuestros resultados sugieren que la identificación y el manejo personalizados de la ideación suicida pueden ser posibles, con implicaciones para la prevención del suicidio en PEPs.

Conclusions

The main conclusions of this thesis derived from **Study 1** (154), **Study 2** (158) and **Study 3** (133) are detailed below:

1. Subjects who meet diagnostic criteria for bipolar disorder or schizophrenia after FEP differ in clinical and neuropsychological variables already from the initial stages. Specifically, we found an association between the diagnosis of bipolar disorder after FEP and:
    a. better psychosocial functioning at baseline
    b. fewer negative symptoms
    c. better performance on tests that assess executive functions.

2. The degree of impairment in psychosocial functioning is heterogeneous in individuals with FEP. In our study, we identified:
    a. four trajectories of psychosocial functioning following FEP, two of them indicative of a persistent functional impairment course and two describing a more resilient course.
    b. Better paternal socioeconomic status, better premorbid adjustment, lesser negative symptoms, and more preserved verbal learning and memory could mediate functional resilience.
    c. Final functional outcomes are the result of the additive effects of several factors. Therefore, an integrative approach from the very early stages of psychotic disorders is needed to prevent or address functional deficits, especially among those in a more vulnerable psychosocial situation.
    d. Patients with affective psychosis, specifically with bipolar disorder, present better psychosocial functioning after FEP than patients with schizophrenia, but not better than patients diagnosed with "Other psychoses".

3. The evolution of suicidal ideation after FEP differs between patients:
    a. Considering the clinical, functional and suicidal ideation evolution, our findings delineate three profiles of FEP patients regarding suicidal

ideation, one experiencing no suicidal ideation after FEP, another in which suicidal ideation might depend on acute depressive symptomatology and, lastly, a group where suicidal ideation might respond to mild but persistent clinical symptoms, along with psychosocial impairments that seem to be present already in the premorbid period.

b. Pessimistic thoughts, inability to feel, and a worse perceived family climate were associated with acute suicidal ideation, which improved during follow-up.
c. Older age, longer DUP, and sleeping difficulties were associated with an increased risk of presenting subacute suicidal ideation after PEP.
d. Thus, our results suggest that tailored identification and management of suicidal ideation may be possible, with implications for suicide prevention in FEP.

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