UNIVERSIDADE DE LISBOA

Faculdade de Medicina

Fatores de risco para mortalidade precoce: Estudos de trajetórias e preditores no primeiro episódio psicótico

RICARDO MOUTINHO COENTRE

Orientadores: Professora Doutora Maria Luísa Caruana Canessa Figueira da Cruz Filipe

Professor Doutor Carlos José Fernandes da Conceição Góis

Tese especialmente elaborada para obtenção do grau de Doutor em Medicina, Especialidade de Psiquiatria e Saúde Mental

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Abreviaturas

BDI – Inventário de Depressão de Beck

DSM-IV - Manual de Diagnóstico e Estatística das Perturbações Mentais, 4ª edição

DSM-5 - Manual de Diagnóstico e Estatística das Perturbações Mentais, 5ª edição

DUP - Duração de Psicose não tratada

CAD-SAS – *Classification Algorithm for Determination of Suicide Attempted and Suicide*

CASH – *Comprehensive Assessment of Symptoms and History*

CDSS – *Calgary Depression Scale for Schizophrenia*

CGI-BP – *Clinical Global Impression for Bipolar Disorder*

CID – Classificação Internacional de Doenças

CSF – *Cerebrospinal fluid*

EPHPP – *Effective Public Health Practice Project*

FEP – *First-episode psychosis*

GAF – Escala de Avaliação Global do Funcionamento

HARM2009 – *Harmonizing Metabolic Syndrome Definition*

HDL – *High density lipoprotein*

HDRS – *Hamilton Depression Rating Scale*

5-HIAA – Ácido 5-hidroxi-indolacético

IC – Intervalo de confiança

ICD-10 - *International Classification of Diseases, 10th Revision*

ICD-11 – *International Classification of Diseases, 11th Revision*

IDF – Federação Internacional de Diabetes

IMC – Índice de Massa Corporal

LDL – *Low-density lipoprotein*

MAST - *Michigan Alcohol Screening Test*

MetS – Síndroma Metabólica

NCEP-ATP III – *National Cholesterol Education Program Adult Treatment Panel III*

NHANES - *National Health and Examination Survey*

NOS - *Nottingham Onset Schedule*

OMS – Organização Mundial de Saúde

OPCRIT – *Operational Criteria Checklist for Psychotic Illness and Affective Illness*

OR – *Odds ratio*

PA – Pressão arterial

PANSS – *Positive and Negative Syndrome Scale*

PEP – Primeiro episódio psicótico

PORMETS – *The Portuguese Metabolic Syndrome Study*

PPD – *Post Psychotic Depression*

PPEP – Programa do Primeiro Episódio Psicótico, Hospital Vila Franca de Xira

PRISMA – *Preferred Reporting Items for Systematic Reviews and Meta-Analyses*

PROFIP – Programa de Intervenção nas Fases Iniciais da Psicose, Hospital de Santa Maria

SCID-I – *Strutural Clinical Interview for DSM-IV*

SD – Desvio padrão

SPSS – *Statistical Package for Social Science*

TG - Triglicéridos

UHR – *Ultra-high risk of psychosis*

VLDL – *Very-low-density lipoprotein*

ÍNDICE

RESUMO

As perturbações psicóticas são, pelo seu quadro clínico e impacto na vida dos doentes, as mais graves perturbações em Psiquiatria, com uma prevalência de cerca de 3%. Estudos demonstram que as taxas de mortalidade nestes doentes estão aumentadas 2 a 3 vezes em relação à população geral, vivendo os doentes psicóticos entre 10 a 25 menos anos em comparação com a população geral. O risco de mortalidade nas perturbações psicóticas é particularmente elevado nos primeiros anos de perturbação. As principais causas deste excesso de mortalidade incluem as doenças cardiovasculares, nomeadamente doença isquémica coronária, e o suicídio. Este trabalho investigou a prevalência, evolução e possíveis fatores preditores do comportamento suicida e síndroma metabólica, reconhecidos fatores de risco para suicídio e doença cardiovascular respetivamente, nos 12 meses seguintes a um primeiro episódio psicótico. Trata-se de um estudo longitudinal, que incluiu doentes com primeiro episódio psicótico afetivo e não afetivo de duas equipas de intervenção precoce na psicose na área metropolitana de Lisboa, Portugal. Os doentes foram submetidos a uma avaliação compreensiva que incluiu dados socio-demográficos e clínicos, em dois momentos distintos: uma avaliação realizada na *baseline*, logo que existiam condições clínicas para esta durante o primeiro episódio psicótico, e uma segunda avaliação 12 meses após a primeira. O comportamento suicida foi investigado por um questionário sobre ideação suicida, plano suicida e tentativa de suicídio. A síndroma metabólica foi avaliada usando os critérios da definição modificada da *National Cholesterol Education Program Adult Treatment Panel III* (NCEP-ATP III).

Os resultados mostraram uma prevalência de comportamento suicida de 25,4% na avaliação *baseline*, com uma significativa redução para 13,3% (p=0,035) na avaliação a 12 meses. A análise logística binária multivariada mostrou que a história prévia de comportamento suicida e diagnóstico de depressão no primeiro episódio psicótico foram preditores de comportamento suicida no momento da avaliação *baseline*, e a história prévia de comportamento suicida e baixos níveis de colesterol total na *baseline* mostraram ser preditores de comportamento suicida 12 meses após o primeiro episódio psicótico. Em relação à prevalência da síndroma metabólica encontrou-se um aumento de 6,7% na avaliação *baseline* para 11,7% na avaliação a 12 meses (p=0,250) As prevalências de valores não normais de perímetro abdominal (p=0,039), triglicéridos (p=0.040) e HDL (p=0,019) aumentaram significativamente da avaliação *baseline* para a avaliação a 12 meses. Todos os parâmetros metabólicos e antropométricos estudados (triglicéridos, HDL, pressão arterial, perímetro abdominal e glucose em jejum) agravaram durante o período de *follow-up*, mas apenas de forma estatisticamente significativa o perímetro

abdominal, triglicéridos e HDL. Apenas o valor médio do perímetro abdominal foi na avaliação a 12 meses não normal (valor médio: 102,50cm±99,41; valores não normais: homem≥102 cm e mulheres≥88cm). Não se identificaram preditores na *baseline* para o desenvolvimento de síndroma metabólica na avaliação a 12 meses.

Este trabalho mostrou uma prevalência elevada de comportamento suicida no ano seguinte ao primeiro episódio psicótico, com uma redução durante o período de *follow-up*, mas ainda com uma taxa significativa aos 12 meses. Os nossos resultados também mostraram valores elevados das alterações metabólicas com rápido agravamento no primeiro ano após o primeiro episódio psicótico, apesar da não existência de significância estatística para a síndroma metabólica. O perímetro abdominal, indicador de obesidade, foi o parâmetro metabólico estudado que mais significativamente aumentou durante os 12 meses de *follow-up*, parecendo indicar que este é um fator primário da síndroma metabólica, sendo os restantes elementos secundários aquele.

Os nossos resultados mostram que doentes com primeiro episódio psicótico com história prévia de comportamento suicida, depressão e baixos níveis de colesterol total no primeiro episódio psicótico estão em risco particularmente elevado de comportamento suicida, e consequentemente de suicídio, nos 12 meses seguintes ao primeiro episódio psicótico. Este grupo de doentes beneficiará potencialmente de tratamento adequado no sentido da sua proteção e redução do risco de suicídio. Os nossos resultados indicam também que deve existir uma cuidadosa monitorização dos parâmetros metabólicos nos primeiros 12 meses após o primeiro episódio psicótico, aqueles que apresentem critérios de síndroma metabólica, devem ser submetidos a um plano de intervenção sobre os estilos de vida e tratamento. A investigação futura deve procurar replicar os resultados encontrados e ampliar o conhecimento em relação a intervenções que sejam particularmente eficazes neste grupo de doentes com primeiro episódio psicótico e risco elevado de doença cardiovascular e/ou suicídio. Os estudos futuros devem ainda avaliar se estas intervenções têm impacto, como esperado, na redução da mortalidade dos doentes psicóticos, nomeadamente nas fases iniciais destas perturbações.

Palavras-chave: primeiro episódio psicótico; síndroma metabólica; comportamento suicida; esquizofrenia;

ABSTRACT

Psychotic disorders are, for their clinical picture and impact on patients' lives, the most serious disorders in Psychiatry, with a prevalence of around 3%. Studies show that mortality rates in these patients are 2 to 3 times higher than in the general population, with psychotic patients living 10 to 25 years less than the general population. The risk of mortality in psychotic disorders is particularly high in the first years of the disorder. The main causes of this excess of mortality include cardiovascular disease, notably coronary ischaemic disease, and suicide. This study investigated the prevalence, evolution and possible predictors of suicidal behaviour and metabolic syndrome, recognized risk factors for suicide and cardiovascular disease respectively, in the 12 months following a first-episode psychosis. This is a longitudinal study, which included patients with affective and non-affective first-episode psychosis from two early psychosis intervention teams in the metropolitan area of Lisbon, Portugal. Patients were submitted to a comprehensive assessment including socio-demographic and clinical data, at two distinct moments: an assessment carried out at baseline, as soon as clinical condition for this assessment existed during the first-episode psychosis, and a second assessment 12 months after the first one. Suicidal behaviour was investigated by a questionnaire on suicide ideation, suicide planning and suicide attempt. Metabolic syndrome was assessed using the criteria of the modified definition of the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III).

Results showed a prevalence of suicidal behaviour of 25.4% at baseline assessment, with a significant reduction to 13.3% ($p=0.035$) at 12 months assessment. The multivariate binary logistic analysis showed that previous history of suicidal behaviour and diagnosis of depression at the first-episode psychosis were predictors of suicidal behaviour at baseline assessment, and previous history of suicidal behaviour and low total cholesterol levels at baseline were predictors of suicidal behaviour 12 months after the first-episode psychosis. The prevalence of metabolic syndrome increased from 6.7% at baseline to 11.7% at 12 months ($p=0.250$). The prevalence of abdominal circumference ($p=0.039$), triglyceride ($p=0.040$) and HDL ($p=0.019$) non-normal values increased significantly from baseline to 12 months. All metabolic and anthropometric parameters studied (triglycerides, HDL, blood pressure, abdominal circumference and fasting glucose) worsened during the follow-up period, but only abdominal circumference, triglycerides and HDL were statistically significant. Only the mean abdominal circumference value was at the 12-month assessment non-normal (mean value: 102.50cm±99.41; non-normal values: men≥102cm and women≥88cm). No predictors

were identified at baseline for the development of metabolic syndrome at 12-month assessment.

This work showed a high prevalence of suicidal behaviour in the year following the first-episode psychosis, with a reduction during the follow-up period, but still a significant rate at 12 months. Our results also showed high values of metabolic changes with rapid worsening in the first year after first-episode psychosis despite of non-significance on statistical analysis on metabolic syndrome. Abdominal circumference, an indicator of obesity, was the metabolic parameter studied which increased most significantly during the 12 months of follow-up, seeming to indicate that this is a primary factor of the metabolic syndrome, the other elements being secondary to it.

Our results show that first-episode psychosis patients with a previous history of suicidal behaviour, depression and low total cholesterol levels in the first-episode psychosis are at particularly high risk of suicidal behaviour, and consequently of suicide, in the 12 months following the first psychotic episode. This group of patients will potentially benefit from appropriate treatment in order to protect them and reduce their risk of suicide. Our results also indicate that there should be careful monitoring of metabolic parameters in the first 12 months after the first-episode psychosis, those with criteria for metabolic syndrome should undergo a lifestyle and treatment intervention plan. Future research should seek to replicate the results found and expand knowledge regarding interventions that are particularly effective in this group of patients with first-episode psychosis and high risk of cardiovascular disease and/or suicide. Future studies should also assess whether these interventions have an impact, as expected, on reducing mortality in psychotic patients, particularly in the early stages of these disorders.

Keywords: first-episode psychosis; metabolic syndrome; suicidal behaviour; schizophrenia;

INTRODUÇÃO

Psicose: Definição, breve revisão histórica e conceptualização

Classicamente a psicose é uma síndroma clínica caracterizada por uma significativa perda do contacto com a realidade. Os sintomas principais das psicoses são os delírios, alucinações e perturbações da forma do pensamento e as consequentes alterações de comportamento que estes sintomas originam [1]. Aos designados sintomas psicóticos positivos mencionados existem associados frequentemente outros sintomas como sintomas negativos, cognitivos e afetivos.

A introdução do conceito de psicose na nomenclatura psiquiátrica foi efetuada pelo médico Canstatt em 1841 como sinónimo do termo neurose psíquica [2]. O significado inicial de neurose foi de associação a todas as perturbações do sistema nervoso, com a designação psíquica Canstatt enfatizou a sua manifestação como uma doença do cérebro [3]. Todavia durante muito tempo foi atribuída a primeira utilização da designação psicose, efetuada num livro publicado em 1845, ao médico Austríaco Ernst von Feuchtersleben [4]. Este autor usou o termo psicose como sinónimo de psicopatia, sublinhando a alteração da personalidade e uma complexa recíproca interação entre o físico e o psíquico. Ambos os autores, Canstatt e Feuchtersleben, apesar dos seus conceitos diferentes de psicose, viam a etiologia das psicoses como entre uma fraqueza somática e uma vulnerabilidade psíquica. Esta base orgânica para as perturbações psicóticas explica a continuação da classificação das psicoses como neuroses até ao final do século XIX. Em 1859 Fleming usou o termo psicose numa visão mais abrangente, identificando perturbações mentais com base orgânica, mas também aquilo a que designou perturbações da alma que eram assumidas como tendo base orgânica [5]. As psicoses eram vistas por Fleming como o aspeto psicológico de uma neurose [6].

Ao longo da segunda metade do século XIX o termo psicose ficou ligado ao conceito orgânico da mesma, tal como defendido por Psiquiatras como Wernicke, Meynert e Koeppe. Também Griesinger, como Fleming, defendeu que as perturbações cerebrais têm a sua contrapartida nas doenças dos nervos. As perturbações cerebrais seriam o reino da Psiquiatria enquanto as perturbações dos nervos constituíam a Neurologia. Todavia este autor sublinhava também a dificuldade na separação das doenças mentais de outras doenças nervosas, sublinhando a artificialização desta distinção entre as psicoses e outras doenças nervosas [7].
Mais tarde em 1875 Möbius fez referência às designadas psicoses endógenas que cobriam

um espectro largo de perturbações, nomeadamente a histeria, melancolia, mania e paranoia [8]. O termo exógeno foi usado inicialmente por vários autores para caracterizar a causalidade da perturbação mental por uma influência estranha, quer somática quer psíquica na sua natureza.

O primeiro Psiquiatra a usar o termo "psicose funcional" foi Fuerstner, por contraste com a psicose orgânica [9]. Contudo alguns Psiquiatras como Nissl sublinharam que em todas as psicoses existem sempre achados corticais [10]. As doenças funcionais teriam sempre origem física, mas em que esta ainda não tinha sido descoberta. A mudança no significado do termo psicose derivou grandemente da alteração do conceito de neurose. O desenvolvimento da neuropatologia e da psicanálise conduziu à restrição do conceito de neurose às perturbações puramente psicogénicas. Foi este o tempo da descrição de doenças diversas como, por exemplo, a doença de Alzheimer, esclerose múltipla ou a neurosífilis. No famoso Manual de Medicina Interna de Strümpell de 1887 as neuroses foram finalmente definidas como "doenças do sistema nervoso sem base anatómica conhecida" [11]. O desenvolvimento posterior da psicanálise, nomeadamente de Freud (1895), sublinhou o significado da biografia individual e sexualidade na etiologia de alguns tipos de neurose [12].

Também Jaspers, na primeira edição da sua obra "Psicopatologia Geral" (1913), descreveu em parte a evolução do conceito de psicose [13]. Para Jaspers as psicoses são sempre o resultado de doença somática e são assim um *processo*, as neuroses têm causas psicológicas biográficas e são um *desenvolvimento* num continuum com a saúde. Esta dicotomia entre *processo* e *desenvolvimento*, conduziu à explicação causal das psicoses, não passiveis de compreensibilidade psicológica, característica das neuroses, e apenas passiveis de explicação. Esta separação dos métodos facilitava o diagnóstico diferencial entre as duas entidades. Este conceito de diagnóstico diferencial, que permitiria uma clara prescrição de medidas terapêuticas, formou a base para o princípio hierárquico de Jaspers, bem descrita no capítulo da "Classificação das Psicoses", da primeira edição do já mencionado livro de "Psicopatologia Geral" deste mesmo autor. Para Jaspers os sintomas patológicos estão dispostos em camadas como uma cebola, sendo a camada mais exterior formada por sintomas degenerativos (psicopatias, mas também a designada à época insanidade maníaco-depressiva de Kraeplin), seguida pela camada dos sintomas processuais (esquizofrenias) e nas camadas mais interiores os sintomas orgânicos. Para Jaspers o exame individual de cada caso é fundamental e permite atingir as camadas mais profundas.

A origem do termo endógeno está no trabalho do Psiquiatra Francês Benedict Morel [14,15]. Este autor aplicou a teoria da degeneração à Psiquiatria e propôs a hereditariedade transformacional (ou polimórfica). Morel defendeu que de uma geração para a seguinte ocorria a transformação cada vez mais grave de uma perturbação mental. O que podia começar como uma fobia ou compulsão numa geração, poderia passar para cleptomania na geração seguinte, na terceira geração poderia surgir a *demência precoce* e na quarta geração a demência e a morte prematura. Com base nesta teoria muitas perturbações mentais foram designadas de endógenas, por serem consideradas degenerativas, isto é, causadas pela predisposição individual para a doença mental. Foi o caso do Alemão Moebius que defendeu esta ideia nas suas publicações [16]. Este autor distinguiu as perturbações mentais em doenças exógenas, em que as causas são por exemplo o álcool ou toxinas, e as endógenas onde existe uma única causa, a "predisposição".

Mais tarde, Emil Kraeplin não faz referência clara à dicotomia psicose-neurose, considerou sim a dicotomia da psicose em "*dementia praecox*" e "insanidade maníaco-depressiva" que se tornou aceite como regra. A designação *dementia praecox* enfatizava a alteração na cognição (demência) e inicio precoce *(precox*) da doença que mais tarde se chamou esquizofrenia. Estes doentes teriam uma doença crónica, deteriorante do ponto de vista cognitivo, e com sintomas clínicos, como as ideias delirantes e alucinações. Para Kraeplin estes doentes distinguiam-se de outros com períodos de doença alternados com intervalos livres de sintomas que designou de "insanidade maníaco-depressiva" [17–19]

A designação do termo esquizofrenia foi dada por Eugene Bleuler, que repôs o nome *dementia praecox* por esquizofrenia. Este termo sublinha a presença de *schisms* ou clivagem entre o pensamento, emoção e comportamento nos doentes com esta perturbação. Ao contrário do conceito de Kraeplin, Bleuler sublinhou que a esquizofrenia não tem um curso necessariamente deteriorante [20].

Na primeira metade do século XX a psicose foi amplamente estudada nas diversas dimensões da sua definição. Reflexo da diversidade e variabilidade clínica, Kurt Schneider introduziu uma hierarquia nos sintomas psicóticos, dividindo-os em primeira e segunda ordem. Este autor considerava que alguns sintomas psicóticos seriam mais importantes do que outros [21]. Contudo enfatizou que os sintomas de primeira ordem não eram específicos da esquizofrenia, sendo úteis no seu diagnóstico, não deviam ser aplicados de forma rígida. Assim para Kurt Schneider a doença poderia ser diagnosticada com base na existência dos sintomas de segunda ordem e noutros aspetos típicos desta.

No século XX o debate sobre a psicose unitária foi permanecendo associado à psicose atípica. Mesmo Kraepelin afirmou que nem sempre era possível distinguir entre as duas psicoses (demência precoce e insanidade maníaco-depressiva). Kraepelin defendeu que se as manifestações da doença apenas forem examinadas entre estas duas entidades por vezes podem não ser distinguíveis [17]. Kleist usou o termo psicose atípica para se referir às designadas "psicoses degenerativas benignas" que incluíam não apenas a "insanidade maníaco-depressiva" e paranoia, mas também histeria [22]. A Psiquiatria Escandinava enfatizou a designação psicose "psicogénica" e "reativa". August Wimmer descreveu em 1916 a psicose psicogénica adaptando em parte a psicose reativa de Jaspers [23]. Para Wimmer as psicoses psicogénicas cumpririam cinco critérios: 1)eram causadas por agentes mentais ("traumas mentais"); 2)a forma e conteúdo das psicoses poderiam ser compreendidas em termos de fatores precipitantes mentais; 3)habitualmente terminavam em recuperação e nunca em deterioração; 4) os doentes tinham uma "fundação predisposição"; 5)estas psicoses eram clinicamente independentes de outras doenças. Também McCabe e Stroemgren descreveram com pormenor a psicose reativa, onde a distinção para a esquizofrenia e psicose maníaco-depressiva está descrita de forma pormenorizada com respeito ao tratamento, história natural e prognóstico [24].

Uma outra categoria que pode ser vista como uma psicose atípica é a psicose cicloide. Esta foi introduzida por Kleist como uma forma atípica benigna da categoria maníaco-depressiva de Kraepelin [22]. Mais tarde, Karl Leonhard, pupilo de Kleist, desenvolveu a classificação de Kleist e fez das psicoses cicloides um dos seus maiores grupos diagnósticos [25]. Para Kleist estas psicoses nunca conduziriam a detioração o que as distinguia da esquizofrenia, apesar de alguns aspetos clínicos sobreponíveis a esta. Foram descritos três tipos de psicoses cicloides: ansiedade-elação, psicose confusional e psicose motilidade. Mais recentemente (1974) Perris descreveu com bastante pormenor as psicoses cicloides como condições agudas, sem precipitantes e com sintomatologia polimórfica [26].

Um outro grupo diagnóstico algo controverso são as "psicoses esquizoafetivas". Este grupo foi inicialmente descrito por Kasanin em 1933, onde estudou um grupo de doentes com sintomas mistos de esquizofrenia e afetivos [27]. Mais tarde também os estudos de Kendell mostraram que nem sempre era possível distinguir entre as duas psicoses descritas por Kraepelin com base nos sintomas [28,29]. Assim, nem sempre era possível um "ponto de raridade" ou definir exatamente onde uma síndroma tinha início e a outra terminava. Em vez desta separação clara, os sintomas dos doentes diagnosticados com

uma das psicoses de Kraepelin fundiam-se com os doentes diagnosticados com a outra psicose. Mais tarde também Murray e O´Callaghan concordaram, com esta visão de Kendell, na ausência de uma linha clara entre as duas categorias de Kraepelin e defendendo "Assim, a distinção entre a psicose maníaco-depressiva e esquizofrenia em termos de fenomenologia, prognóstico e homotipia familiar é essencialmente imperfeita" [30]. Estes autores preferiram a divisão da esquizofrenia naquela de início congénito e a de início no adulto, sendo a primeira semelhante à descrição original de Kraepelin.

Tem havido também ao longo do tempo defensores da ideia de psicose unitária. Um destes foi Werner Janzarik considerando a psicose como uma força normalmente mantida por mecanismos do corpo e quando esta dinâmica fica fora do controlo das cadeias biológicas a psicose poderá ocorrer [31]. As estruturas através das quais esta dinâmica é quebrada/descarrilada determina o tipo de psicose. Assim Janzarik considerava que este descarrilamento demorava tempo a exercer o seu efeito sendo rara em crianças. Este autor concluiu que seria possível a depressão progredir para mania e depois para esquizofrenia paranoide, desta para esquizofrenia catatónica e finalmente para psicose exógena. Também Klaus Conrad defendeu a visão da psicose unitária [32]. Para Conrad, a observação de que pais ciclotímicos produziam filhos esquizofrénicos era um bom argumento favorável à existência de uma psicose endógena. Para Conrad as perturbações que começavam como mania ou depressão tornavam-se cíclicas ou periódicas e depois desenvolviam ideias delirantes e detioração da personalidade. Conrad acreditava também que aspetos típicos da esquizofrenia como humor delirante, alucinações e catatonia poderiam também ser encontrados na mania ou depressão. Estas evidências colocavam como questionáveis para Conrad a separação entre esquizofrenia e psicose maníaco-depressiva defendida por Kraepelin. Conrad também questionou a dicotomia endógeno-exógeno, defendendo que diferentes agressões como "exaustão física ou elevada emoção atacam a mesma estrutura, mecanismo fisiológico, metabolismo bioquímico", produzindo depressão, depois ideias delirantes e "insanidade".

Em suma, a visão de meados do século XIX das perturbações mentais defendia a psicose unitária como dominante. Griesinger desviou-se desta opinião, defendendo que perturbações do pensamento poderiam ocorrer sem o estádio de depressão. Kraepelin defendeu a divisão entre duas entidades da psicose: *demência praecox* e *insanidade maníaco-depressiva.* Apesar da existência de visões contrárias ao longo do século XX, a sua visão dominou. Schneider, discípulo de Kraepelin, manteve essencialmente aquelas categorias. Outros, como Psiquiatras da Escandinávia, propuseram que as psicoses

atípicas constituíam uma entidade independente das duas categorias de Kraepelin. Wimmer propôs o termo psicose psicogénica e Stroemgren a designada psicose reactiva. Kasanin defendeu a psicose esquizoafetiva, não encontrando um ponto claro de separação entre a esquizofrenia e a perturbação maníaco-depressiva. A visão da psicose cicloide de Kleist foi defendida por Leonhard e também por Perris Cutting. Para alguns autores representam uma ponte entre as psicoses e as neuroses.

Assim se verifica uma evolução significativa ao longo da história do conceito de psicose desde 1845 até ao presente. Originalmente a psicose foi incluída na categoria das deficiências mentais e outras perturbações psiquiátricas. Todavia logo depois, tornou-se sinónimo de "psicopatia" e "psiconeurose", tornando-se mais tarde distinta destas duas entidades. Começou então a ser discutida em termos das dicotomias: endógeno-exógeno, funcional-orgânico, psicose-psicopatia e a psicose unitária-múltipla. Alguns destes conceitos continuam ainda a fazer o seu trajeto e a gerar controvérsia.

Psicose e Sistemas de Classificação

A evolução do conceito de psicose em Psiquiatria está plasmada nos principais sistemas de classificação: Diagnóstico e Estatística das Perturbações Mentais (DSM) e na Classificação Internacional de Doenças (CID). A dicotomia entre a neurose e psicose permaneceu nos sistemas de classificação até à segunda edição do DSM (DSM-II) [33] e à 9ª revisão do CID [34]. Este facto deveu-se sobretudo à influência psicodinâmica na Psiquiatria Americana após a segunda guerra mundial e menos à de Jaspers e Schneider. O conceito de psicose foi amplamente definido no DSM-II. Nestas edições a base classificativa das perturbações psiquiátricas assentava na divisão entre neuroses e psicoses. Será importante aqui citar a contribuição dos conhecidos critérios de Feighner percursores do DSM-III [35]. Em meados do século XX onde o domínio da visão psicanalítica na Psiquiatria Americana era regra, o Departamento de Psiquiatria da Universidade de Washington, contrário a esta visão, desenvolveu uma série de reuniões com o objetivo fundamental de dar uma forte contribuição para a classificação das principais perturbações psiquiátricas, defendendo um modelo médico. A acompanhar o médico John Feighner existiam mais 5 investigadores, cujas reuniões de discussão durante um ano culminaram na publicação dos conhecidos critérios de Feighner em 1972, e que foram amplamente citados em investigação nos anos seguintes [35]. Estes critérios serviram de base para o desenvolvimento do DSM-III. Crê-se que foram três os

contributos centrais deste trabalho para a Psiquiatria: o uso de critérios de diagnóstico operacionalizados; a ênfase no curso e prognóstico das diversas perturbações; a necessidade da base dos critérios de diagnóstico na evidência empírica [36]. Em relação à esquizofrenia estes critérios requeriam a existência de pelo menos 6 meses de sintomas, sem retorno ao nível de ajustamento psicossocial pré-mórbido, requerendo a presença de ideias delirantes, alucinações ou perturbação do pensamento. Para Eli Robins, o coordenador do grupo, estudioso de Schneider, Leonhard e Fish, a esquizofrenia seria uma perturbação deteriorante, defendendo que os sintomas em si não tinham significado prognóstico, sendo também encontrados em perturbações afetivas com sintomas psicóticos. Este Psiquiatra defendia que o curso da doença, com sintomas por um longo período de tempo e deterioração social e ocupacional, era mais importante que as características das ideias delirantes ou alucinações.

A publicação do DSM-III em 1980 procurou validar várias categorias diagnósticas com critérios de diagnóstico mais objetivos [37]. Os conceitos de psicose e neurose foram quase inteiramente abandonados. Também no CID-10 se abandonaram estas designações, referindo o Psiquiatra Cooper a este propósito "a diferenciação entre a psicose e a neurose como princípio organizador fundamental foi abandonado" [38,39]. Nas edições posteriores dos principais sistemas de classificação o termo psicose foi quase inteiramente limitado ao adjetivo "psicótico". Assim no DSM-IV (1994) no capítulo "Esquizofrenia e outras perturbações psicóticas" incluiu um número de perturbações nas quais os sintomas psicóticos dominam o quadro clínico [40], considerando que outras perturbações, como a depressão, podem ser acompanhadas de sintomas psicóticos. O termo psicótico refere-se aos sintomas como ideias delirantes e alucinações. No caso da esquizofrenia, perturbação esquizofreniforme, perturbação esquizoafetiva e perturbação psicótica breve podem incluir outros sintomas como pensamento desorganizado ou comportamento catatónico. O diagnóstico de esquizofrenia passou a ser primariamente efetuado com base nas perturbações da expressão e comportamentos observáveis, aumentando a concordância entre os clínicos e investigadores.

Também no DSM-5 as principais características e descrições das psicoses do DSM-IV são mantidas [41]. Os sistemas de classificação atuais são redutores e conceptualizam a psicose como uma síndroma clínica de sintomas observáveis. Apesar de serem reconhecidos aspetos diversos na etiopatogenia das diversas perturbações psicóticas, como a genética ou a neuroimagiologia, ainda não são determinados a nível individual para um dado caso de psicose.

A 5ª edição do manual Americano DSM faz referência na sua introdução que as perturbações psicóticas são definidas pela presença de alterações de um ou mais de cinco domínios: ideias delirantes, alucinações, pensamento ou discurso desorganizado, comportamento motor anormal ou grandemente desorganizado e sintomas negativos [42]. O CID-11 não apresenta uma definição de psicose [43]. Ambos os sistemas de classificação incluem as perturbações psicóticas nas perturbações do "espectro da esquizofrenia" ou "esquizofrenia e outras perturbações primárias psicóticas". Estas classificações consideram também outras perturbações mentais onde a psicose pode ocorrer como as perturbações de humor. Apesar de uma tentativa de harmonização entre as duas classificações algumas diferenças ainda persistem no campo das perturbações psicóticas: 1)A classificação DSM-5 tem uma categoria especial para as perturbações psicóticas breves; 2)A classificação DSM-5 considera a perturbação esquizotípica como uma perturbação de personalidade; 3)As perturbações psicóticas secundárias, são classificadas na DSM-5 com as perturbações psicóticas primárias ao contrário da CID-11.

Na conceptualização das mais recentes classificações emergiu ainda o designado síndroma psicótico atenuado, que acabou por não ser incluído na versão final de nenhuma das referidas classificações, necessitando de maior investigação. Esta condição clínica é caracterizada por uma síndroma clínica com sintomas "*psychosis-like*" abaixo do limiar para psicose [44]. A operacionalização do limiar a partir do qual se considera sintomas psicóticos é algo controversa, sendo sugerido que esta síndroma seja considerada quando estes sintomas são menos graves e transitórios e em que o *insight* está relativamente conservado.

Conceptualização

Os estudos são relativamente consistentes em considerar 4 dimensões nos sintomas das perturbações psicóticas: os sintomas positivos, negativos, desorganizados e afetivos [45]. Alguns autores consideram ainda os sintomas cognitivos como um *cluster* central da psicose [46]. A psicose é considerada uma síndroma clínica e não uma entidade nosológica. Todavia não existe ainda uma definição de psicose operativa e satisfatória, tendo também em conta o inúmero conhecimento gerado nas últimas décadas sobre os múltiplos fatores que condicionam o seu início e perpetuação.

Diferentes conjuntos de sintomas são encontrados nas perturbações psicóticas, constituindo a nível individual um determinado quadro clínico, perfazendo que os

sintomas como as ideias delirantes, alucinações, pensamento desorganizado, sintomas negativos suplementados por sintomas afetivos (mania ou depressão) são o centro da psicose. Estes sintomas ocorrem em diferentes perturbações, existindo considerável sobreposição entre as apresentações clínicas nas diferentes perturbações psicóticas [47]. Existe ainda elevada variabilidade interindividual e intraindividual ao longo do tempo dos principais sintomas da psicose.

A possibilidade de aparecimento de sintomas psicóticos na sequência do consumo de drogas ou doenças cerebrais indica que qualquer pessoa pode experienciar sintomas de psicose. Entende-se assim que estes sintomas são a via final comum de uma variedade de vias etiopatogénicas, em que todas conduzem a um quadro clínico similar. Este facto evidencia aquilo que já Kraeplin considerou como o "cérebro humano possui um número limitado de reações em resposta a insultos diferentes" [17].

Epidemiologia

A prevalência de todas as perturbações psicóticas na população geral é de aproximadamente 3% [48]. Os estudos apresentam alguma divergência, sobretudo na incidência anual, mas também na prevalência ao longo da vida, na maior parte das perturbações psicóticas. Estes resultados divergentes têm origem em dificuldades que os estudos epidemiológicos apresentam no campo das perturbações psicóticas, sendo as principais: 1) Variabilidade quanto aos critérios de diagnóstico das diferentes perturbações psicóticas; 2) Dificuldade em determinar com exatidão o tempo de início dos sintomas; 3) Adequada seleção da amostra para estudos epidemiológicos. Vários fatores condicionam a variabilidade da incidência das perturbações psicóticas, nomeadamente idade, sexo e residência em área urbana. Vários estudos constataram que a incidência da psicose é mais elevada nos jovens [49], no sexo masculino [50], em grupos raciais/étnicos minoritários [51] e naquelas amostras com maior diagnóstico de psicose não afetiva [52]. Em cerca de 68% dos homens e 51% das mulheres as perturbações psicóticas têm o seu início antes dos 35 anos de idade [53].

Um estudo Finlandês sobre a prevalências das diferentes perturbações psicóticas encontrou taxas de 0,9% para a esquizofrenia, 0,32% para a perturbação esquizoafetiva, 0,1% para a perturbação esquizofreniforme, 0,18% para a perturbação delirante, 0,42% para as perturbações psicóticas induzidas por substâncias, 0,21% para as perturbações psicóticas secundárias a doença médica, 0,24% para a perturbação bipolar tipo I e 0,35%

para a perturbação depressiva *major* com sintomas psicóticos. Do total verifica-se que 71,5% das perturbações psicóticas são do designado espectro esquizofrénico ou psicose não afetiva (esquizofrenia, perturbação delirante, perturbação esquizoafetiva) e 17,2% das psicoses afetivas (perturbação bipolar com sintomas psicóticos e perturbação depressiva *major* com sintomas psicóticos) [48]. Num outro estudo publicado, que incluiu diversos países europeus e o Brasil, a incidência da psicose encontrada foi em geral de 21 novos casos por 100.000 habitantes, com incidência de 17 casos por 100.000 habitantes por ano para a psicose não afetiva (esquizofrenia, perturbação delirante, perturbação psicótica aguda e transitória, perturbação esquizoafetiva) e de 4 casos por 100.000 habitantes por ano na psicose afetiva (perturbação afetiva bipolar com sintomas psicóticos e perturbação depressiva *major* com sintomas psicóticos) [53]. Poucos estudos de incidência têm sido realizados nos países do sul da Europa, contudo os escassos estudos existentes mostram que as taxas de incidência são uniformemente baixas [54–56]. A título de exemplo referimos um estudo italiano que mostrou uma incidência total de perturbações psicóticas na região da Sicília de 15,9 casos por 100.000 habitantes, uma incidência de 9,6 casos por 100.000 habitantes na esquizofrenia, 1,5 por 100.000 habitantes nas psicoses afetivas e 4,8 por 100.000 habitantes no grupo das outras psicoses [54]. Também no já referido estudo multinacional que investigou a incidência das perturbações psicóticas em vários países europeus e Brasil se demonstrou que as taxas de incidência mais baixas foram encontradas em várias áreas de Espanha e Itália [53]. Infelizmente não encontrámos estudos sobre a prevalência e incidência das perturbações psicóticas em Portugal.

O padrão etário da incidência do primeiro episódio psicótico (PEP) difere entre homens e mulheres. No sexo masculino o pico de incidência ocorre entre os 18 e os 24 anos (taxa de incidência de cerca de 61 por 100.000 habitantes/ano), com ligeira e progressiva redução a partir deste escalão etário [53]. No sexo feminino a taxa de incidência também é máxima no escalão etário entre os 18 e os 24 anos (taxa de incidência 27 por 100.000 habitantes/ano). A partir deste escalão etário existe uma redução mais lenta e gradual nas mulheres, com um segundo pequeno pico, inferior ao inicial, para lá dos 45 anos [57,58].

Primeiro Episódio Psicótico

No contexto da investigação em Psiquiatria, tem havido nas últimas décadas um interesse crescente nas fases iniciais da psicose. Assim a designação de "primeiro episódio psicótico" (PEP) tem vindo a ser usada como o termo que representa o estádio em que o limite categorial para a perturbação psicótica é atingido, isto é, quando sintomas psicóticos e declínio funcional são evidentes. Os doentes referidos como tendo sintomas que não ultrapassam o limiar definido para um episódio psicótico referem-se a doentes designados como "risco ultra-elevado de psicose" ou "*ultra-high risk*" (UHR) [59]. Alguns destes doentes vão desenvolver sintomas que ultrapassam em duração e intensidade o limiar para uma perturbação psicótica. Quando um jovem ultrapassa este limiar para um episódio psicótico pela primeira vez é referido como tendo um PEP. O limiar para uma perturbação psicótica é definido como existência de sintomas psicóticos francos, como ideias delirantes, alucinações ou perturbação do pensamento com duração superior a uma semana [60]. A partir deste limiar o doente tem indicação para receber tratamento antipsicótico associado a um conjunto de intervenções psicossociais, referidas como intervenção precoce na psicose [61].

Apesar de amplamente utilizado, não existindo consenso na sua definição, o termo "primeiro episódio psicótico" é usado para designar os doentes que estão a experienciar uma curta duração de doença ou tratamento para uma perturbação psicótica pela primeira vez [62]. Alguns autores advogam o uso do termo "psicose de início recente" que descreve com maior precisão estes doentes uma vez que as perturbações psicóticas nem sempre seguem um curso episódico [63]. Do ponto de vista operacional é aceite que, em contexto clínico e de investigação, a definição de "primeiro episódio psicótico" deve incluir um critério de duração da psicose. Este critério deve ser usado com medidas especificas que permitam a comparação de diferentes populações, como por exemplo data do primeiro contacto com a equipa terapêutica ou a duração do uso de medicação antipsicótica [64].

Vários argumentos conduziram à ampla divulgação e utilização da designação de PEP. Primeiro, a evidência de que a intervenção em estádios precoces da doença (intervenção precoce na psicose) com intervenções biopsicossociais reduz a duração de psicose não tratada (DUP), maximizando a remissão sintomática e recuperação funcional. Os primeiros anos de doença (2 a 5 anos) foram designados como "período crítico" para prevenção do declínio clínico e psicossocial [65]. Segundo, com exceção da terapêutica

psicofarmacológica, as diversas intervenções terapêuticas são comuns às fases iniciais de várias das perturbações psicóticas. Terceiro, os quadros clínicos nas fases iniciais da psicose são frequentemente polimórficos, inespecíficos, dificultando o diagnóstico nosológico. Também a instabilidade diagnóstica, tendo em conta o curso da doença, é frequente [66]. Só em fases posteriores das perturbações psicóticas, tendo em conta a sua evolução, é possível a clarificação diagnóstica e efetuar o seu diagnóstico nosológico definitivo.

O PEP é divido em dois grupos: PEP não afetivo (também designado espectro esquizofrénico) e PEP afetivo. No grupo do PEP não afetivo estão incluídos a esquizofrenia (e perturbação esquizofreniforme), perturbação esquizoafetiva e perturbação delirante. No grupo PEP afetivo incluem-se a perturbação depressiva *major* com sintomas psicóticos e perturbação afetiva bipolar com sintomas psicóticos.

Intervenção Precoce na Psicose

As perturbações psicóticas, nomeadamente a esquizofrenia, são graves doenças psiquiátricas que têm habitualmente o seu início na idade jovem (mais de 80% tem o seu início entre as 16 e 35 anos) [67,68]. Durante muitos anos os cuidados prestados aos doentes psicóticos foram tardios e limitados, muito baseados na ideia errónea do mau prognóstico intimamente associado ao seu diagnóstico. Contrariando este facto, desde a década de 1990, um movimento de intervenção nas fases iniciais das perturbações psicóticas foi constituído, acompanhado de robusta evidência científica e sua ampla disseminação internacional, numa verdadeira reforma dos cuidados clínicos a estes doentes [69,70]. Inicialmente teve a sua origem em Melbourne, na Austrália, e posteriormente um pouco por todo o mundo, nomeadamente em vários países da Europa, Ásia, América do Sul, Estados Unidos da América (EUA), Canadá e Ásia [71]. Existem atualmente centenas de programas e unidades em todo o mundo com cuidados específicos para jovens com perturbações psicóticas em fases iniciais e suas famílias [72–79]. A figura 1 mostra a história natural da psicose e o racional para a intervenção precoce na psicose.

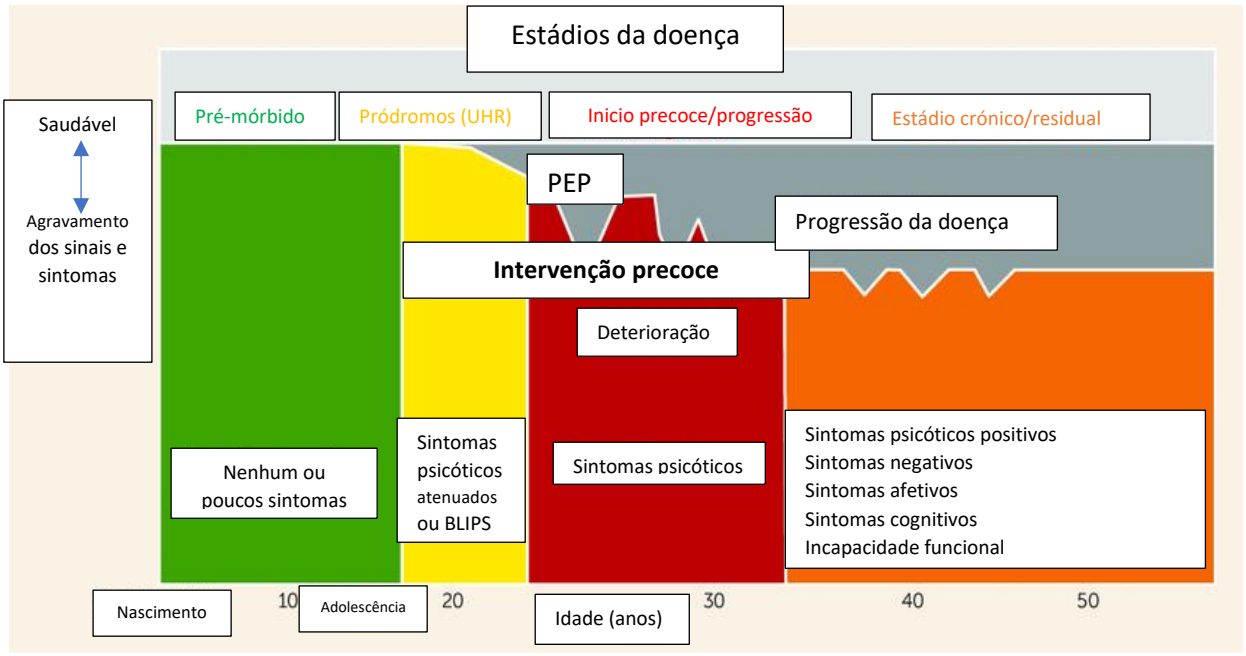

Figura 1. História natural da psicose e racional para a intervenção precoce
Adaptado de Lieberman et al. [80]

A intervenção precoce na psicose refere-se à prevenção secundária precoce nos doentes com manifestações clínicas das perturbações psicóticas, divididas por 3 fases distintas: UHR, PEP e o período crítico ou de recuperação. Esta distinção é feita com base nas intervenções psicofarmacológica e psicossociais especificas para cada um destes estádios [81]. Os benefícios da intervenção precoce na psicose são vários: redução da DUP, redução do tempo de internamento hospitalar, redução das recaídas e recorrências, redução do risco de suicídio, melhor qualidade de vida, melhor integração escolar e laboral, melhor funcionamento social e melhor adesão ao tratamento. O componente central das equipas de intervenção precoce na psicose é a natureza multidisciplinar das mesmas, oferecendo múltiplas intervenções com gestores de caso, com número de casos de cerca de 10 a 20 por cada técnico. Estas equipas incluem diversos técnicos como Psiquiatras, Psicólogos, Terapeutas Ocupacionais, Enfermeiros, Técnicos de Serviço Social etc. [82]. O objetivo é para além da remissão psicopatológica, a abordagem de outras problemáticas que afetam estes doentes como emprego/ocupação, uso de substâncias, comportamento suicida, problemas económicos etc. O local e tempo do contacto das equipas com os doentes é diverso, mas a existência de uma forte componente de assistência na comunidade é a regra. As intervenções oferecidas nas equipas de intervenção precoce na psicose encontram-se indicadas na tabela 1. A psicoeducação,

individual ou de grupo, e a intervenção familiar são consideradas intervenções cruciais nas equipas de intervenção precoce.

Os programas originais, assim como na maioria dos programas e unidades de intervenção precoce no PEP e no período crítico, fazem as suas intervenções a todas as perturbações psicóticas e não apenas nas perturbações do espectro da esquizofrenia (incluindo assim também as psicoses afetivas). Duas justificações têm sido referidas para este facto. Primeiro, como já referido, as fases iniciais da psicose, nomeadamente o PEP, são um tempo de particular dificuldade no diagnóstico nosológico, sendo difícil separar aqueles dois grupos de perturbações. Segundo, a instabilidade diagnóstica, como já foi também referido anteriormente, é frequente nas fases iniciais das perturbações psicóticas [83–85].

Nos últimos anos vários estudos têm sido publicados sobre as poupanças nos serviços de saúde com a instituição de programas de intervenção precoce na psicose, o que tem impulsionado a sua expansão geográfica [86,87].

Tabela 1. Componentes da intervenção precoce na psicose [87,88]

- Baixas doses de antipsicóticos atípicos e outras medicações
- Intervenção familiar
- Emprego protegido
- Terapia cognitivo-comportamental para a psicose
- Psicoeducação (individual e/ou de grupo)
- Terapia ocupacional
- Treino de aptidões sociais
- Remediação cognitiva

Mortalidade nas perturbações psicóticas

Os estudos mostram que as taxas de mortalidade nas perturbações psicóticas por causas naturais e não naturais são elevadas [89–91]. Nas causas naturais incluem-se aquelas em que uma doença é responsável pelo início de eventos que diretamente conduziram à morte (ex. doença cardiovascular). As causas não naturais, também designadas por externas, referem-se às circunstâncias em que acidentes ou violência produzem a fatalidade (ex. suicídio) [92]. Entre os doentes com doença mental grave, incluindo as psicoses afetivas e não afetivas, a mortalidade por todas as causas está aumentada em 2 a

3 vezes em relação à população geral [93]. Este facto é evidenciado pela reduzida esperança média de vida nestes doentes, vivendo os doentes psicóticos entre 10 e 25 anos menos em comparação com a população geral. A investigação evidencia que a razão de taxa de mortalidade padronizada (razão entre a taxa de mortalidade padronizada nos doentes com psicose e a taxa de mortalidade padronizada na população geral) nesta população varia entre 1.5 e 4.2 [89,94,95]. As explicações para esta diferença são diversas, e ainda não totalmente esclarecidas, entre as quais estilos de vida não saudáveis (tabagismo, uso de álcool, sedentarismo), obesidade, limitado acesso a cuidados de saúde, reduzida qualidade dos cuidados de saúde recebidos, efeitos adversos da terapêutica psicofarmacológica e taxa de suicídio elevada [96–100].

Relativamente poucos trabalhos têm investigado os fatores que podem ter impacto no risco aumentado de morte prematura em todas as perturbações psicóticas ou se esta diferença de mortalidade com a população geral está a sofrer alterações ao longo do tempo. Também é equívoco se o excesso de mortalidade nas perturbações psicóticas é predominantemente por causas naturais ou não naturais [98,101–103]. A mortalidade cardiovascular (ex. doença coronária), entre as causas naturais, e o suicídio, entre as causas não naturais, têm sido demonstrados como os principais motivos de morte dos doentes com perturbações psicóticas, nomeadamente perturbação bipolar e esquizofrenia [104–106].

Nas últimas duas décadas ocorreram significativas alterações nos cuidados de saúde aos doentes psiquiátricos. Uma importante alteração ocorreu com a passagem dos cuidados centralizados no hospital para cuidados na comunidade. Outra mudança aconteceu com uma melhoria, mas ainda insuficiente, do reconhecimento do risco cardio-metabólico dos doentes com perturbações psicóticas, tendo sido introduzidos programas de rastreio dos doentes com perturbações psicóticas para encontrar e tratar fatores de risco metabólicos. Não obstante o aumento da esperança média de vida para a população geral ao longo das últimas décadas nos países desenvolvidos [107], e apesar das referidas alterações nos cuidados de saúde aos doentes com psicose, os estudos apontam para um agravamento da diferença da taxa de mortalidade entre os doentes psicóticos e a população geral [92,108]. Assim a investigação nesta área, incluindo o estudo das mortes naturais (ex. doença cardiovasculares) e não naturais (ex. suicídio) em doentes com psicose, é emergente no sentido de inverter as atuais taxas de mortalidade deste grupo de doentes.

Mortalidade no primeiro episódio psicótico

O risco de mortalidade nas perturbações psicóticas é particularmente elevado nas primeiras fases da perturbação [89,93,109,110]. Os estudos publicados sobre a prevalência da mortalidade após o primeiro episódio psicótico variam entre 0,5% (*follow-up* de 12 meses) a 16% (*follow-up* de 11 anos), variando fundamentalmente com o período de *follow-up* considerado [92,93,103,109–114]. Independentemente do período de *follow-up*, todos os estudos mostram que o risco de mortalidade é superior à população geral da mesma idade. Os estudos apontam assim um risco de mortalidade que varia entre 2 a 24 vezes superior à população geral para o mesmo escalão etário [109]. Apesar da magnitude dos números, os estudos sobre a mortalidade após o PEP são escassos e exclusivamente de alguns países da Europa (Reino Unido, Irlanda e Finlândia), Austrália, Canadá e Estados Unidos da América.

As principais causas de excesso de mortalidade nas perturbações psicóticas, e designadamente nas fases iniciais, são, como já referido, as doenças cardiovasculares, nomeadamente doença isquémica coronária, e o suicídio [110,115,116]. Os métodos de suicídio mais frequentemente usados são o enforcamento, estrangulamento e sufocamento [103,111,117]. Alguns estudos sugerem que a morte por manifestação de doenças crónicas, como doenças cardiovasculares, tende a surgir com mais tempo de diagnóstico de perturbação psicótica, onde existe um período suficientemente longo de fatores de risco para a doença cardiovascular ocorrer e se manifestar clinicamente [118].

Os dados disponíveis indicam também que a mortalidade é superior no sexo masculino comparativamente ao sexo feminino, e em todos os escalões etários após o PEP [89,92,109,112,114]. As informações existentes não são conclusivas em relação à idade de diagnóstico do PEP e o risco subsequente de mortalidade. Os estudos mostram que não existem diferenças significativas de mortalidade após o PEP entre o grupo com diagnóstico de psicose não afetiva e grupo com psicose afetiva [112]. O uso de drogas ilícitas parece ser um fator que aumenta o risco de mortalidade após o PEP [89]. Foi assim demonstrado os primeiros anos após o PEP parecem ser um período de risco especialmente elevado para morte, nomeadamente nos primeiros 12 meses, onde ocorre parte significativa dos óbitos [92].

Fatores de Risco para mortalidade na psicose

Dada a evidência de que as doenças cardiovasculares e o suicídio representam os principais motivos do excesso de mortalidade nas perturbações psicóticas, tem-se procurado nos últimos anos investigar a identificação dos doentes em risco e eventuais intervenções, particularmente nas fases iniciais das perturbações psicóticas. Assim tem sido investigada a síndroma metabólica como identificadora de doentes com particular risco para mortalidade cardiovascular. Da mesma forma para o suicídio, tem sido estudado o comportamento suicida, incluindo ideação, plano e tentativa de suicídio, no sentido da identificação de doentes psicóticos com risco aumentado para mortalidade por suicídio.

Comportamento suicida e psicose

O suicídio é um importante problema de Saúde Pública, sendo responsável pela perda de cerca de 800.000 vidas anualmente em todo o mundo. Em 2019 a taxa de suicídio anual mundial foi de 9.0 óbitos por 100.000 habitantes, na Europa de 10.5 por 100.000 habitantes e em Portugal de 7.2 por 100.000 habitantes [119]. Nove entre os dez países com mais elevadas taxas de suicídio encontram-se na Europa. Estes números estão eventualmente subvalorizados pelo estigma associado a cada suicídio. Por cada suicídio muito mais tentativas são efetuadas, sendo este o principal fator de risco individual para suicídio na população em geral. Cada suicídio representa uma tragédia para o próprio, para a família, amigos e comunidade, com efeitos a longo prazo.

Apesar dos números e do impacto do suicídio, este está longe de ser uma prioridade a nível das políticas de cada país, e nesse sentido a Organização Mundial de Saúde (OMS) lançou o *World Mental Health Plan*, onde a identificação precoce e tratamento das perturbações mentais, assim como do comportamento suicida, podem ser efetivos [120]. Este plano faz ainda referencia a estratégias nacionais que os países devem implementar de modo a reduzir o suicídio, nomeadamente em grupos específicos de risco. Mais tarde foi também publicada pela OMS um plano específico para o suicídio designado "*Preventing Suicide—A Global Imperative*". Este também faz referência ao suicídio em doentes com perturbações psiquiátricas, com especial foco nas fases iniciais destas perturbações [121]. Também o Plano Nacional de Saúde Mental faz referência à

estratégia de prevenção do suicídio e depressão, tendo sido também elaborado o Plano Nacional de Prevenção do Suicídio [122].

Os doentes com perturbações mentais constituem um grande grupo de risco para o suicídio, sendo o risco particularmente elevado nas perturbações psicóticas. Numerosos estudos mostram que o risco relativo de suicídio está aumentado em cerca de 20 vezes nestas doenças comparativamente com a população geral [123–125]. Os primeiros estudos apontavam para cerca de 10% na prevalência do suicídio ao longo da vida na esquizofrenia [126]. Assim, verifica-se que a taxa de suicídio nas psicoses é significativa, muito superior à população geral e com impacto elevado para os doentes, suas famílias e médicos que lhes prestam cuidados.

De forma semelhante à população em geral, os doentes do sexo masculino com esquizofrenia morrem mais frequentemente do que o sexo feminino, mas as diferenças entre os dois géneros no que concerne às vítimas de suicídio não são tão díspares como na população em geral (H: 60%; M:40%) [127]. Também em relação às tentativas de suicídio as diferenças não são significativas entre os dois sexos, ao contrário da população geral onde as mulheres efetuam mais atos suicidas não letais [127,128]

Vários fatores de risco para suicídio têm sido apontados em estudos com doentes com psicose: idade precoce, sexo masculino, viver sozinho, estar desempregado, bom ajustamento ou funcionamento pré-mórbido, história familiar de suicídio, elevado nível de psicopatologia, história de comportamento suicida, depressão comórbida, uso de substâncias, má adesão à medicação, elevado *insight* e acesso a meios letais [129–131]. Em relação aos sintomas psicóticos, sejam eles positivos ou negativos os resultados não são uniformes entre todos os estudos. Todavia os resultados parecem indicar que os sintomas psicóticos positivos, nomeadamente alucinações acústico-verbais de comando, são fatores de risco para suicídio. Alguns estudos mostram que a existência de sintomas negativos pode pelo contrário ter um efeito protetor em relação ao suicídio, mas estes resultados não são significativos nas meta-análises [132]. Tal como na população geral, um dos fatores mais associado ao suicídio nas perturbações psicóticas tem sido a existência de história prévia de comportamento suicida, nomeadamente ideação suicida e tentativa de suicídio, especialmente por enforcamento [133,134].

Tal como para a população em geral, alguns estudos sugerem a existência de uma base neurobiológica para o comportamento suicida nas perturbações psicóticas, nomeadamente na esquizofrenia. Alterações no teste de supressão da dexametasona têm sido encontradas nos doentes com esquizofrenia que fizeram tentativas de suicídio,

sugerindo que uma hiperatividade do eixo hipotálamo-hipófise-supra-renal pode constituir um fator no processo do comportamento suicida nos doentes psicóticos [135]. Em relação aos níveis de ácido 5-hidroxi-indoloacético (5-HIAA) no líquido cefalorraquidiano (CSF) de doentes suicidas com esquizofrenia os resultados são divergentes entre os estudos. Assim alguns trabalhos encontraram baixos níveis de 5-HIAA no CSF de doentes com esquizofrenia e comportamento suicida [136], enquanto outros não encontraram esta diferença [137].

Outros dados mais experimentais apontam para uma resposta aplanada da prolactina à administração de D-fenfluramina em doentes com esquizofrenia e comportamento suicida [138]. Também estudos genéticos encontraram um *link* significativo entre polimorfismos do gene ADRA2B para a esquizofrenia e o comportamento suicida [139].

Comportamento suicida e primeiro episódio psicótico

Alguns trabalhos evidenciam também que o risco de suicídio é maior no primeiro ano após o primeiro contacto com os cuidados de saúde mental. Apesar de este facto ser verdadeiro para todas as doenças psiquiátricas, o risco de suicídio nos primeiros meses parece ser especialmente elevado para os indivíduos com perturbações psicóticas, nomeadamente com diagnóstico de perturbação bipolar e perturbações psicóticas do espectro da esquizofrenia [140,141]. Trabalhos efetuados com dados de diversos países nórdicos confirmam um excesso de mortalidade de causas externas (que inclui o suicídio), que é 2 vezes superior, durante o primeiro ano após o primeiro contacto hospitalar em comparação com os 3 anos subsequentes nos doentes com perturbações psicóticas [140]. O risco de suicídio durante os primeiros 12 meses após o PEP é 12 vezes superior à população geral [142]. Os trabalhos publicados indicam que entre 2-5% dos doentes que apresentam um PEP vão morrer de suicídio [143]. Este risco é ainda superior nos doentes que necessitam de internamento para o PEP [144] e particularmente elevado nos primeiros meses após a alta hospitalar [145]. Porque ocorre um pico de risco de suicídio nos primeiros anos das perturbações psicóticas uma atenção particular deve ser dada a estes doentes.

Os fatores de risco de suicídio nesta fase particular da doença parecem ser pelo menos parcialmente diferentes dos encontrados em fases posteriores das perturbações psicóticas. Estudos nesta área ainda decorrem no sentido de confirmar alguns destes

dados. Alguns fatores de risco encontrados são os antecedentes de comportamento suicida, história de depressão, uso de substâncias, idade jovem, e longa DUP [146,147]. A depressão tem sido amplamente estudada e identificada como um fator de risco e preditor *major* para o comportamento suicida nas fases iniciais da psicose, seja no período prodrómico, no PEP ou no período seguinte a este [148]. Trabalhos publicados indicam também que a diátese suicida pode nos doentes nas primeiras fases das perturbações psicóticas, ser particularmente rápida, com pouco tempo na passagem da ideação suicida ao ato suicida [131]. A identificação de fatores preditores de suicídio no PEP, identificando quais os subgrupos de doentes em risco particularmente elevado, permitirá o planeamento de estratégias de intervenção precoce que possam diminuir o substancial risco de suicídio deste grupo de doentes, e consequentemente a sua mortalidade [149]. Apesar de ocorrer redução do risco de suicídio após os primeiros anos de doença, este é sempre elevado, com flutuações ao longo do curso da doença [131].

Um dos aspetos referidos na literatura que justifica em parte o elevado risco suicidário nas primeiras fases das perturbações psicóticas é explicado pelo modelo vulnerabilidade-stress para o comportamento suicida, que não é específico das perturbações psicóticas. Neste contexto o PEP representa a primeira exposição a um stress *major* no contexto da perturbação psicótica [147,150]. Interessante é considerar também particularidades na etiopatogenia do comportamento suicida nos primeiros meses após o PEP. Trabalhos publicados sublinham um peso relativo diferente entre os fatores que poderão estar na origem do comportamento suicida nos meses seguintes ao PEP. Assim alguns autores distinguem a existência de dois períodos diferentes em relação ao comportamento suicida no PEP: período precoce e período tardio. O período precoce é considerado o período de tempo em que existe psicose ativa, sendo este o principal fator implicado na etiopatogénese do comportamento suicida nesta fase. Este período variável decorre antes da admissão hospitalar até à resolução da fase da doença mais ativa, geralmente considerada cerca de 1 mês após a alta hospitalar, caso ocorra internamento. O período tardio de comportamento suicida decorre após aquele período e parece estar mais associado a depressão secundária ao PEP [151]. Esta diferença tem importância em termos de distinção dos correlatos psicopatológicos (figura 2).

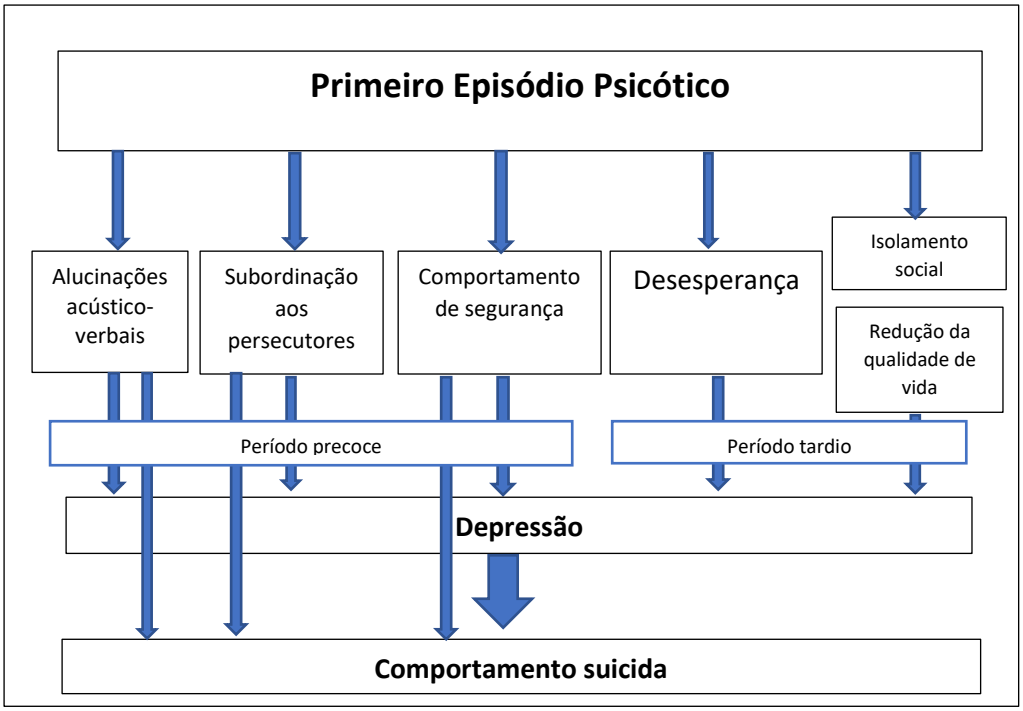

Figura 2. Hipótese de modelo de comportamento suicida no primeiro episódio psicótico

A depressão parece ter um papel central no comportamento suicida no PEP [152–154]. Todavia a depressão tem diferentes manifestações psicopatológicas conforme o tempo considerado. Assim as alucinações acústico-verbais, o uso de um comportamento de segurança e a subordinação aos supostos persecutores estão associados à depressão na fase aguda da psicose, e, portanto, no período exatamente anterior à admissão hospitalar, assim como nos primeiros meses após, enquanto existe psicose ativa [151]. A desesperança, o isolamento social e a redução da qualidade de vida pelo impacto da psicose estão na base da sintomatologia depressiva num período mais tardio, cerca de 3 meses após o PEP e início do seu tratamento [152]. Nesta fase a depressão, associada a *insight* preservado, conduz a uma consciência particularmente dolorosa da doença, das perdas subsequentes, auto-estigmatização e de representação de um fardo para os outros, podendo ser fatores associados ao desenvolvimento de comportamento suicida [147].

Os dados disponíveis indicam também que a maioria dos comportamentos suicidas nas fases iniciais da psicose são efetuados com intoxicações com fármacos, nomeadamente com antipsicóticos (64%). Um número significativo de suicídios ocorre nas unidades de internamento por enforcamento (20%). Os dados disponíveis apontam também para a existência de uma percentagem elevada destes doentes que cometem suicídio terem contacto regular com os serviços de saúde, 49% chegaram mesmo a manifestar a sua intenção e 11% procuraram ajuda especifica [147].

Os dados demonstram que a mortalidade por suicídio nos doentes psicóticos pode ser prevenível com acesso a tratamento adequado e de qualidade, nomeadamente no contexto do modelo compreensivo da intervenção precoce na psicose [155]. As equipas de intervenção precoce que tratam doentes com PEP fazem uma avaliação e tratamento do risco de suicídio. A avaliação do risco de suicídio nos doentes nas fases iniciais da psicose deve ser feita com foco no risco de atos suicidas, designadamente no comportamento suicida. A avaliação clínica na busca de fatores preditores de comportamento suicida nos doentes com PEP é fundamental nas equipas de intervenção precoce. É hoje proposto que estratégias de prevenção do comportamento suicida no PEP não devem ser universais, com necessidade assim de identificação dos doentes em risco particularmente elevado. A implementação de programas de avaliação e prevenção do suicídio tem sido associada a um declínio deste. Na Dinamarca tem-se assistido a uma queda do suicídio nos doentes psicóticos, sendo que se crê que este declínio se deve em parte fundamental à melhoria dos serviços especializados de intervenção precoce na psicose [156,157].

Síndroma metabólica

A síndroma metabólica (MetS) é um complexo conjunto de fatores de risco interrelacionados para doença cardíaca coronária, outras formas de doenças ateroscleróticas cardiovasculares e diabetes tipo 2 [158]. O conceito de MetS foi introduzido de forma a ajudar os clínicos a identificarem e tratarem os doentes em risco aumentado de doença cardiovascular e diabetes. Os seus componentes essenciais incluem alterações do metabolismo da glucose, pressão arterial elevada, níveis de triglicéridos elevados, baixos níveis de *high density lipoprotein* (HDL) e obesidade (particularmente abdominal). A obesidade abdominal e a resistência à insulina têm tido atenção como manifestações centrais da MetS. Nos últimos anos outras alterações como estados proinflamatório e protrombótico, esteatose hepática não-alcoólica e apneia do sono têm sido associados à MetS, tornando a sua definição e fisiopatologia mais complexas. Apesar do reconhecimento da sua importância clínica como marcador de risco cardiovascular ainda não existe uma fisiopatologia universalmente aceite ou critérios de diagnóstico consensuais. Um aspeto que se tem tornado evidente nos últimos anos é o aumento da prevalência da MetS nas crianças e jovens adultos e as implicações futuras que este facto vai acarretar em termos de morbilidade e mortalidade cardiovascular.

Historicamente a primeira conceção da MetS foi de "síndroma X" com o substrato de que era um aspeto central no desenvolvimento de diabetes tipo 2 e doença cardíaca coronária [159]. Posteriormente várias outras organizações internacionais e grupos de peritos procuraram definir a MetS. A primeira tentativa foi feita em 1998 pela OMS, que conceptualizou a MetS como tendo no seu núcleo a disfunção do metabolismo da glucose, evidenciada pela resistência à insulina, intolerância à glucose ou diabetes tipo 2, associada a pelo menos dois outros critérios: hipertensão arterial, aumento dos triglicéridos e/ou baixo HDL, obesidade e microalbuminúria [160,161]. Em 2001 o Americano *National Cholesterol Education Program Adult Treatment Panel III* (NCEP-ATP III) publicou uma série de critérios de MetS que incluíam o perímetro abdominal, perfil lipídico, pressão arterial e glucose em jejum [162,163]. Esta definição diferia da da OMS uma vez que não incluía como critério obrigatório a resistência à insulina. Em 2004, ocorreu uma atualização desta definição com diminuição do limiar para a alteração do valor da glucose em jejum de 110 mg/dL para 100 mg/dL, e a clarificação de que os doentes poderiam já estar em tratamento para dislipidemia ou hipertensão [164]. Esta última definição é designada habitualmente como NCEP-ATP III modificada. A Federação Internacional da Diabetes (IDF) propôs em 2005 uma nova definição de MetS no sentido de uma certa consensualização entre os diferentes grupos e organizações [165]. Nesta definição a IDF tornou central a obesidade como critério obrigatório da MetS, tendo como medida de rastreio simples a medição do perímetro abdominal. Mais recentemente em 2009 ocorreu uma nova tentativa de harmonização de todas as definições propostas numa reunião de peritos de diversas organizações a que designaram de "*harmonizing metabolic syndrome*" [166]. Esta definição similar à NCEP-ATP III modificada, não considera a existência de nenhum critério obrigatório, considerando que quaisquer 3 dos 5 critérios poderão considerar-se para diagnóstico da MetS. Os *cut-offs* utilizados foram definidos para todos os critérios com exceção do perímetro abdominal cujos valores nacionais ou regionais devem ser usados. Esta definição sugere também que a medição do perímetro abdominal é um útil instrumento de rastreio preliminar da MetS. As definições mais usadas são as NCEP-ATP III modificada, IDF e a definição harmonizada, em detrimento da definição da OMS. Este facto sugere que é hoje considerado como aspeto central da MetS a obesidade abdominal. A tabela 2. mostra as principais definições de MetS usadas e suas diferenças.

Tabela 2. Definições mais comuns da síndroma metabólica

	OMS 1999[161] (resistência à insulina mais 2 critérios)	**NCEP-ATP III 2002**[163] (3 de 5 critérios)	**NCEP-ATP III modificada 2005**[164] (3 de 5 critérios)	**IDF 2005**[165] (perímetro abdominal mais 2 critérios)
Perímetro abdominal	Relação perímetro abdominal/anca Homens>0.90 Mulheres>0.8; ou IMC>30Kg/m^2	Homens>102cm; mulheres>88cm	Homens>102cm; mulheres>88cm	Homens≥94cm; mulheres≥80cm
Pressão arterial	≥140/90 mmHg	≥130/85mmHg	≥130/85mmHg (ou tratamento para diagnóstico prévio de hipertensão)	≥130/85mmHg (ou tratamento para diagnóstico prévio de hipertensão)
HDL	HDL homens<40mg/dL; mulheres<50mg/dl ou	Homens<40mg/dl; mulheres<50mg/dl	Homens<40mg/dl; mulheres<50mg/dl (ou tratamento específico para esta alteração lipídica)	Homens<40mg/dl; mulheres<50mg/dl (ou tratamento específico para esta alteração lipídica)
Triglicéridos	TG≥150mg/dl	≥150mg/dl	≥150mg/dl (ou tratamento específico para esta alteração lipídica)	≥150mg/dl (ou tratamento específico para esta alteração lipídica)
Glucose jejum	Resistência à insulina*	≥110mg/dl (ou diagnóstico prévio de diabetes tipo 2)	≥100mg/dl (ou diagnóstico prévio de diabetes tipo 2)	≥100mg/dl (ou diagnóstico prévio de diabetes tipo 2)
Outro critério	Microalbuminuria (excreção taxa de albumina urinária ≥20µg/min. ou relação albumina/creatinina≥30mg/g)			

IDF, Federação Internacional de Diabetes; IMC: Índice de Massa Corporal; NCEP-ATP III, *National Cholesterol Education Program Adult Treatment Panel III*; HDL, *high-density lipoprotein;* TG, triglicéridos;
*Diabetes tipo 2 ou alteração glucose em jejum (>100mg/dl) ou alteração tolerância à glucose

As comparações da prevalência da MetS têm sido dificultadas pela existência de múltiplas definições. A prevalência da MetS varia e depende dos critérios usados nas diferentes definições, mas também das características das populações estudadas (idade, sexo, estatuto socio-económico, etnias etc.). Independentemente das definições usadas, os estudos nos últimos anos têm mostrado uma prevalência elevada da MetS e que a sua prevalência mundial está a aumentar na população geral, o que parece estar relacionada com o aumento da obesidade e estilos de vida sedentários [167].

De acordo com o estudo *National Health and Examination Survey* (NHANES) realizado em 2003-2006, cerca de 34% da população americana cumpria os critérios da definição NCEP-ATP III modificada para MetS [168]. Dois estudos nacionais em Portugal mostraram prevalências de MetS em indivíduos que frequentam os cuidados de saúde primários de acordo com definição NCEP-ATP III de 28.4% e 36.5% [169,170]. Estes valores estão em linha com estudos efetuados noutros países europeus e EUA [167]. Nas últimas décadas uma redução da adesão da população portuguesa à conhecida dieta mediterrânica e a prevalência elevada do estilo de vida sedentário, nomeadamente dos idosos, podem

explicar pelo menos em parte os números referidos [171,172]. Também em Portugal os estudos mostram que a obesidade é elevada e que tem aumentado nos últimos anos [173]. Apesar das diferenças de prevalência na MetS pelo uso de diferentes definições, conclui-se que existe uma vasta proporção da população que se encontra em risco elevado de desenvolvimento de doença coronária e diabetes mellitus tipo 2 [174].

A MetS é um *cluster* de fatores de risco e assim o seu diagnóstico pode ser esperado como preditor de risco cardiovascular. O objetivo fundamental é ter como alvo, de terapêuticas farmacológicas e de mudanças dos estilos de vida, os diferentes componentes da MetS para prevenir as doenças cardiovasculares e diabetes. Estudos prévios concluíram que a definição da NCEP-ATP III, nomeadamente na sua versão modificada, melhor evidencia o risco cardiovascular numa população, com o maior valor preditivo para a identificação dos indivíduos em risco de enfarte agudo do miocárdio [175,176]. A mais recente "*Harmonizing MetS*" é essencialmente sobreponível à definição da NCEP-ATP III, mantendo assim este elevado componente preditivo de doença cardiovascular [177]. Doentes com MetS apresentam um risco de desenvolverem doença cardiovascular nos próximos 5 a 10 anos duplo daqueles que não a têm [177,178]. A MetS confere também um aumento em cinco vezes do risco de diabetes ao longo da vida [178]. Como mencionado anteriormente a MetS está ainda associada a outros problemas graves de saúde, como a esteatose hepática não alcoólica, síndroma de apneia obstrutiva do sono e cancro [179,180].

A etiologia da MetS não está inteiramente estabelecida. A hipótese mais aceite e unificadora para explicar a fisiopatologia da MetS é a resistência à insulina [181]. Existe neste fenómeno complexo a interação entre fatores genéticos e epigenéticos com o meio e dieta, que em conjunto influenciam o aparecimento da MetS.

Um principal contributo para o desenvolvimento da resistência à insulina são os ácidos gordos livres que têm origem no tecido adiposo abdominal [182]. Com a sobrecarga calórica da dieta e o estilo de vida sedentário, o excesso de energia é acumulado no organismo sob a forma de gordura, nomeadamente de tecido adiposo visceral [183]. Em indivíduos suscetíveis, existe uma incapacidade das células beta pancreáticas de compensarem a resistência à insulina resultando numa hipoinsulinemia relativa. A insulina medeia um importante efeito antilipólise. Este facto promove o aumento da atividade da lípase e excesso da lipólise dos triglicéridos acumulados nos adipócitos, especialmente dos depósitos de gordura abdominal, com a excessiva libertação de ácidos

gordos livres. Crê-se que estes ácidos gordos livres são libertados na circulação porta e conduzidos para o fígado onde são armazenados sob a forma de triglicéridos [184]. No fígado os ácidos gordos livres resultam ainda num aumento da produção de glucose e secreção de *very-low-density lipoprotein* (VLDL). Os triglicéridos em excesso são também transferidos para *low-density lipoprotein* (LDL), que se torna num substrato mais atrativo para a lípase hepática, resultando em pequenas partículas densas de LDL. Estas partículas têm capacidade aterogénica muito superior às LDL de maior dimensão e são mais suscetíveis de oxidação e captura pela parede arterial.

O aumento da circulação de ácidos gordos livres para os tecidos periféricos também inibe a sinalização pela insulina. Com a resistência à insulina hepática e abundância de ácidos gordos livres como substrato, ocorre um aumento da gliconeogénese, que contribui para a hiperglicemia [178]. Os ácidos gordos livres também reduzem a sensibilidade à insulina no tecido muscular ao inibirem o *uptake* de glucose mediado pela insulina. A resistência à insulina no músculo predispõe a intolerância à glucose que pode ser agravada pela gliconeogénese hepática. Com o tempo as células beta pancreáticas agravam a sua descompensação pelo aumento da necessidade de insulina na tentativa de compensar a resistência, este facto tem como consequência o surgimento da diabetes tipo 2.

Um outro aspeto relevante na etiopatogénese da MetS é a libertação por parte do tecido adiposo de uma série de produtos, não sendo este um tecido de armazenamento inerte, mas um verdadeiro órgão endócrino com vida [185]. As designadas adipocinas que são secretadas pelo tecido adiposo e que têm efeitos metabólicos robustos, incluindo a leptina, resistina, fator ativador do plasminogénio 1, e adiponectina. Esta última, é uma relevante substância que protege contra o desenvolvimento da diabetes mellitus tipo 2, hipertensão, inflamação e doenças vasculares ateroscleróticas, e que está diminuída nos indivíduos que têm acumulação de gordura visceral e pode estar associada à MetS. Existe também uma ativação de outras células no tecido adiposo, como os macrófagos, que são responsáveis pelo aumento de citocinas (interleucina-6 e fator de necrose tumoral alfa) que aumentam a inflamação e a resistência à insulina, contribuindo para o aumento do risco cardiovascular [186]. A MetS é também reconhecida como um estado protrombótico e proinflamatório. A associação entre a resistência à insulina e a doença cardiovascular é multifatorial, incluindo influência no stress oxidativo, o que produz disfunção endotelial, promove lesão vascular e formação de placas de ateroma [174].

A hipertensão arterial da MetS parece ser multifatorial, resultando de vários mecanismos: 1) disfunção endotelial causada pela formação de espécies reativas de oxigénio mediadas pelos ácidos gordos livres; 2) ativação do sistema nervoso simpático e inibição da sintase do óxido nítrico pela hiperinsulinemia; 3) efeitos das citocinas derivadas do tecido adiposo; 4) hiperatividade do sistema renina-angiotensina-aldosterona que existe na obesidade [187].

Como exposto existe uma enorme complexidade e multiplicidade de fatores envolvidos na relação entre a MetS e doença cardiovascular e diabetes, mas esta é inegável. A chave da implicação clínica no diagnóstico da MetS num doente é a necessidade agressiva da modificação do estilo de vida e eventual tratamento, para redução urgente do risco de morbilidade e mortalidade cardiovascular.

O tratamento da MetS envolve alterações do estilo de vida e hábitos alimentares para redução do peso, tratamento da dislipidemia, tratamento da hipertensão arterial e prevenção da evolução da alteração do metabolismo da glucose para diabetes. A tabela 3. tem indicadas as principais recomendações terapêuticas para cada um dos problemas da MetS e objetivos a atingir.

Tabela 3. Recomendações terapêuticas para a MetS [178,188,189].

Critério da MetS	Objetivo terapêutico	Intervenções
Obesidade	-Reduzir peso abdominal em 7-10% no primeiro ano -Atingir IMC< 25 Kg/m^2 e perímetro abdominal H<102 cm e M<88 cm	-Alteração da dieta Redução do total de gordura para 25% de calorias Redução da gordura saturada para <7% de calorias Escolher gorduras insaturadas Evitar açucares simples -Alteração do exercício físico Atividade aeróbica de moderada intensidade pelo menos 30-60 minutos e pelo menos 5 x por semana Treino de resistência 2xsemana -Considerar medicação anti-obesidade
Dislipidemia Triglicéridos elevados HDL reduzido	Triglicéridos < 100-190 mg/dL em função do risco	-Maximizar estratégias de estilo de vida (dieta e exercício físico) -Intensificar redução de LDL com Estatinas -Se triglicéridos > 500 mg/dL iniciar fibrato -Se colesterol não-HDL permanece elevado após máxima dose tolerada de

		estatina considerar adicionar: -Ezetimibe, fibrato ou inibidor da PCSK9
Pressão arterial elevada	-PA< 140/90 mmHg -Para doentes com diabetes mellitus tipo 2 ou risco elevado PA<130/80 mmHg	-Maximizar estratégias de estilo de vida (dieta e exercício físico) -Iniciar tratamento com medicação anti-hipertensora
Glucose em jejum elevada	-Atrasar progressão para diabetes mellitus tipo 2 -Assegurar bom controlo glicémico com HbA1c<7%	-Maximizar estratégias de estilo de vida (dieta e exercício físico) -Considerar iniciar terapêutica antidiabética

Síndroma metabólica e psicose

Os estudos publicados mostram que doentes com esquizofrenia, perturbação bipolar e outras perturbações crónicas psicóticas têm uma prevalência elevada de MetS, contribuindo esta para um risco elevado de doenças cardiovasculares e elevada mortalidade [190,191]. A evidência mostra que os doentes com perturbações psicóticas apresentam um risco de mortalidade cardiovascular que é 2.5 vezes maior comparativamente à população geral da mesma idade [192]. Os doentes com perturbações psicóticas têm risco aumentado de desenvolvimento de obesidade, hiperglicemia, hipertensão arterial, hiperprolactinemia e MetS [190,193]. As taxas de obesidade são até duas vezes mais frequentes nos doentes com doença mental grave do que na população geral [194]. Em linha com o aumento do risco de mortalidade cardiovascular nos doentes psicóticos, estudos mostram que a prevalência da MetS é 58% superior nos doentes psicóticos do que na população em geral [195]. Este aumento da prevalência da MetS é independente da definição usada e para todos os critérios da MetS. Os dados disponíveis mostram também que este risco de MetS é similar para a psicose afetiva e não afetiva [195].

Doentes com um PEP parecem estar em particular risco de aumento de peso e de desenvolvimento de MetS, mas os estudos ainda são escassos, sobretudo com *design* transversal, e inconsistentes nos seus resultados. Os estudos parecem mostrar que as alterações do metabolismo da glucose ocorrem mesmo antes do início da terapêutica antipsicótica, sugerindo que existem outros fatores para além da medicação que contribuem para a disfunção metabólica no PEP [196]. Achados recentes apontam

claramente que as alterações metabólicas existam devido à psicose em si, nomeadamente no caso da esquizofrenia, na ausência de medicação, e das suas alterações comportamentais crónicas. Alterações da gordura visceral e do metabolismo da glucose estão presentes desde o início das perturbações psicóticas e na ausência da terapêutica antipsicótica [197]. Outros estudos mostram ainda que alterações da MetS ocorrem também em indivíduos UHR e em membros da família de doentes com psicose [198,199].

Os estudos indicam que nas perturbações psicóticas os diversos fatores de risco cardiovasculares e MetS resultam de fatores ligados à própria doença, aos maus estilos de vida (tabaco, sedentarismo, dieta etc.), cuidados de saúde diminutos e de qualidade reduzida e ao tratamento antipsicótico [200–203]. A tabela 4. indica os possíveis fatores implicados na etiopatogenia da síndroma metabólica nos doentes com perturbações psicóticas.

Tabela 4. Possíveis fatores implicados na etiopatogenia da síndroma metabólica na psicose

- Inatividade física
- Padrão nutricional não saudável
- Tabagismo
- Má higiene do sono
- Vulnerabilidade genética partilhada
- Antipsicóticos
- Inflamação
- Alterações eixo hipotálamo-hipofisário-suprarrenal
- Psicopatologia
- Alterações no microbioma intestinal
- Cuidados de saúde de diminuídos e de reduzida qualidade

Um grupo interessante de estudos recentes têm investigado a vulnerabilidade genética partilhada entre as perturbações psicóticas e a MetS. Estes estudos sugerem que existe uma vulnerabilidade genética partilhada para a comorbilidade MetS-psicose, envolvendo os processos fisiopatológicos de ambas as perturbações. Na última década os designados estudos de associação genómica ampla procuraram identificar variantes genéticas que estão em associação com MetS e psicose. Múltiplos estudos evidenciam uma ligação entre genes associados à obesidade e massa gorda, genes da leptina, genes da metiltetrahidrofolato redutase e genes do recetor da serotonina 2C que estão envolvidos simultaneamente na patogénese da esquizofrenia e MetS [204].

Um número significativo de estudos investigou o contributo da terapêutica antipsicótica na etiologia da MetS, que é provavelmente o fator implicado na MetS na

psicose mais bem estudado. Em particular os antipsicóticos de segunda geração têm sido claramente demonstrados na génese de alterações metabólicas como aumento de peso, obesidade abdominal e disfunções do metabolismo da glucose e lípidos [205]. As alterações metabólicas induzidas pelos antipsicóticos têm sido associadas ao aumento de peso, todavia alguns trabalhos mostram também que aquelas ocorrem na ausência deste aumento [206,207]. A clozapina e a olanzapina são os antipsicóticos que têm mostrado maior potencial de aumento de peso através da desregulação do metabolismo do tecido adiposo [208]. Vários mecanismos são apontados para a associação entre os antipsicóticos e a elevada indução da MetS, entre eles: 1)Alterações do equilíbrio da ingestão de alimentos e peso corporal a nível cerebral; 2)Impacto da dopamina na libertação nas células beta pancreáticas produtoras de insulina; 3)Alterações das vias de stress oxidativo; 4)Alteração da libertação da grelina e leptina; 5)Disfunção da atividade do sistema nervoso autónomo; 6)Alterações de diversas vias inflamatórias; 7)Alterações de diversas vias de sinalização celular (envolvendo por exemplo a adiponectina, dopamina, serotonina, histamina, mecanismos muscarínicos etc.).

Entre os fatores que predispõem para a MetS nos doentes psicóticos incluem-se os maus estilos de vida, nomeadamente inatividade física, tabagismo, excessivo consumo de álcool, má higiene do sono e padrões de dieta inadequados [208]. Por outro lado, os doentes com perturbações psicóticas têm também acesso mais limitado a cuidados de saúde de qualidade, o que contribui para uma maior prevalência da MetS nos doentes com esta patologia [209].

Outro grupo importante de alterações que ocorre nas perturbações psicóticas e que têm uma ligação na etiopatogenia da MetS são as desregulações em sistemas de homeostasia, como o eixo hipotálamo-hipófise-suprarrenal e resposta inflamatória [210,211]. Esta interação tem uma bidirecionalidade entre a MetS e as perturbações psicóticas. Em várias doenças psiquiátricas, incluindo nas perturbações psicóticas desde fases iniciais, existe uma hiperatividade do referido eixo que determina um aumento de síntese e acumulação de gordura visceral. Por outro lado, a hipercortisolinemia induz lipólise, com a consequente libertação de ácidos gordos livres e síntese de VLDL e triglicéridos. Como referido anteriormente, o tecido adiposo abdominal é também um órgão endócrino com produção de inúmeras citocinas inflamatórias e hormonas. Estas substâncias produzidas perifericamente podem por um lado atingir o sistema nervoso central, quer através da barreira hematoencefálica, quer indiretamente através da ativação da microglia e exercer alguns efeitos aquele nível, causando perturbações na neurotransmissão e lesão neuronal.

Por outro lado, a ativação da resposta inflamatória e do eixo hipotálamo-hipófise-suprarrenal resulta no aumento da libertação de lípidos na corrente sanguínea, com aumento dos triglicéridos e redução das HDL. Estes dois sistemas atuam também diretamente nas células beta pancreáticas, condicionando a produção de insulina e o metabolismo da glucose.

Para além dos fatores referidos, nos últimos anos tem havido um crescente interesse no microbioma intestinal, isto é, nos triliões de microorganismos que colonizam o nosso intestino, e o impacto que estes podem ter nas doenças psiquiátricas e no metabolismo humano. Uma série de proteínas e neurotrofinas produzidas ou condicionadas pelas bactérias intestinais podem limitar o desenvolvimento e plasticidade cerebral em resultado de um baixo, mas persistente nível de inflamação. Por seu turno esta pode também condicionar o aparecimento da MetS [212]. Esta é uma área do conhecimento muito atual e em que os próximos anos vão ajudar a clarificar.

A identificação precoce dos doentes em risco elevado de doença cardiovascular e diabetes através do diagnóstico da MetS, e tratamento adequado das suas alterações, permitirá abrir um caminho no sentido da redução da elevada morbilidade e mortalidade cardiovascular associadas aos doentes com psicose.

OBJETIVOS DO ESTUDO

OBJETIVOS DO ESTUDO

O objetivo geral do presente trabalho incidiu no estudo dos principais fatores de risco para mortalidade precoce após o primeiro episódio psicótico. Assim investigou-se o comportamento suicida e a síndroma metabólica, numa amostra de doentes nos 12 meses após o PEP, reconhecidos como fatores de risco para mortalidade por suicídio e doença cardiovascular respetivamente.

Assim foram os seguintes os objetivos da presente investigação:

Objetivo 1. Rever a literatura existente em relação ao tema da prevalência do comportamento suicida e fatores associados após o primeiro episódio psicótico.

Objetivo 2. Determinar a prevalência, evolução e fatores preditores do comportamento suicida (ideação suicida, plano suicida e tentativa de suicídio) numa amostra de doentes nos 12 meses após o PEP.

Objetivo 3. Determinar a prevalência, evolução e fatores preditores da síndroma metabólica numa amostra de doentes nos 12 meses após o PEP.

Objetivo secundário 1. Comparar a prevalência do comportamento suicida entre os doentes com diagnósticos de psicoses afetivas e não afetivas numa amostra de doentes nos 12 meses após o PEP.

Objetivo secundário 2. Comparar a prevalência da síndroma metabólica entre os doentes com diagnósticos de psicoses afetivas e não afetivas numa amostra de doentes nos 12 meses após o PEP.

Estes objetivos têm as seguintes hipóteses principais:

Hipótese 1. A prevalência e evolução do comportamento suicida nos 12 meses após o PEP é similar aos estudos de outros países europeus, sendo a primeira superior à população em geral para o mesmo escalão etário.

Hipótese 2. Fatores como o diagnóstico de psicose afetiva, história de comportamento suicida, baixos níveis de colesterol total e sintomas depressivos no PEP são preditores do comportamento suicida após o PEP.

Hipótese 3. A prevalência e evolução da síndroma metabólica nos 12 meses após o PEP é similar aos estudos de outros países europeus, sendo a primeira superior à população em geral para o mesmo escalão etário.

Hipótese 4. A prevalência do comportamento suicida é superior no grupo de doentes com diagnóstico de psicoses afetivas no PEP e 12 meses após o PEP.

Hipótese 5. A prevalência da síndroma metabólica é similar nos grupos com diagnósticos de psicoses afetivas e não afetivas no PEP e nos 12 meses após o PEP.

CAPÍTULO 1. Comportamento suicida após o primeiro episódio psicótico: Revisão sistemática compreensiva

Artigo:

Depressive symptoms and suicidal behavior after first-episode psychosis: A comprehensive systematic review

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Depressive symptoms and suicidal behavior after first-episode psychosis: A comprehensive systematic review

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Abstract

Depressive symptoms and suicidal behavior are common among patients that suffered a first-episode psychosis. We searched Web of Knowledge[SM] and Pubmed® for English and Portuguese original articles investigating prevalence of depressive symptoms and/or suicidal behavior and associated factors after first-episode psychosis. We included 19 studies from 12 countries, 7 studied depressive symptoms and 12 suicidal behavior. The findings confirm that depressive symptoms and suicidal behavior have high rates in the years after first-episode psychosis. Factors identified as being associated with depressive symptoms after first-episode psychosis were anomalies of psychosocial development, poor premorbid childhood adjustment, greater insight, loss, shame, low level of continuing positive symptoms and longer duration of untreated psychosis. Suicidal behavior was associated with previous suicide attempt, sexual abuse, comorbid polysubstance use, lower baseline functioning, longer time in treatment, recent negative events, older patients, longer duration of untreated psychosis, higher positive and negative psychotic symptoms, family history of severe mental disorder, substance use, depressive symptoms and cannabis use. Data also indicates that treatment and early intervention programs reduce depressive symptoms and suicidal behavior after first-episode psychosis. Future research should overcome some methodological discrepancies that exist between studies and limit generalization of current findings.

Keywords: Suicide; schizophrenia; duration of untreated psychosis; suicide attempts;

1. Introduction

Depressive symptoms and suicidal behavior are common among patients that suffered a first-episode psychosis. Published studies revealed that depressive symptoms in patients with first-episode psychosis have prevalence from 17% to 83% [213–215]. Depressive symptoms could occur in different phases of psychosis, including post-psychotic period [216]. Depression is a well-known risk factor for suicidal behavior in psychosis with data showing that occurrence of depression in psychosis have significant correlation with suicide risk [217]. Suicide remains an important cause of premature death in patients with psychotic disorders [218,219]. In long-term follow-up studies suicide accounts for 2-5% of deaths in first-episode psychosis [142,143,220]. The rate of attempted suicide in psychotic patients ranges from 10 to 50% [221,222]. Individuals with first-episode psychosis have a greater risk of suicidal behavior compared with the normal population and chronic disorders [223]. First admissions have three times higher suicide rate than chronic schizophrenia [220]. As suicide risk peaks in the early years of psychotic disorders much attention has been given to this phase of the disorder [220]. Previous studies have been published in order to identify predictors of suicide in patients with psychotic disorders. Identifying factors associated to depressive symptoms and suicidal behavior will permit the development of preventive and treatment interventions. However, despite its prevalence, limited evidence exists regarding factors associated and interventions to reduce suicide risk among young people with first-episode psychosis.

Our aim was to perform a systematic review of the current evidence in this field of knowledge. The main objectives were (1) to assess rate of depressive symptoms and suicidal behavior (including suicidal ideation, suicide plans, suicide attempts and suicide) after first-episode psychosis and (2) to search for the most relevant demographic and clinical factors associated.

2. Methods

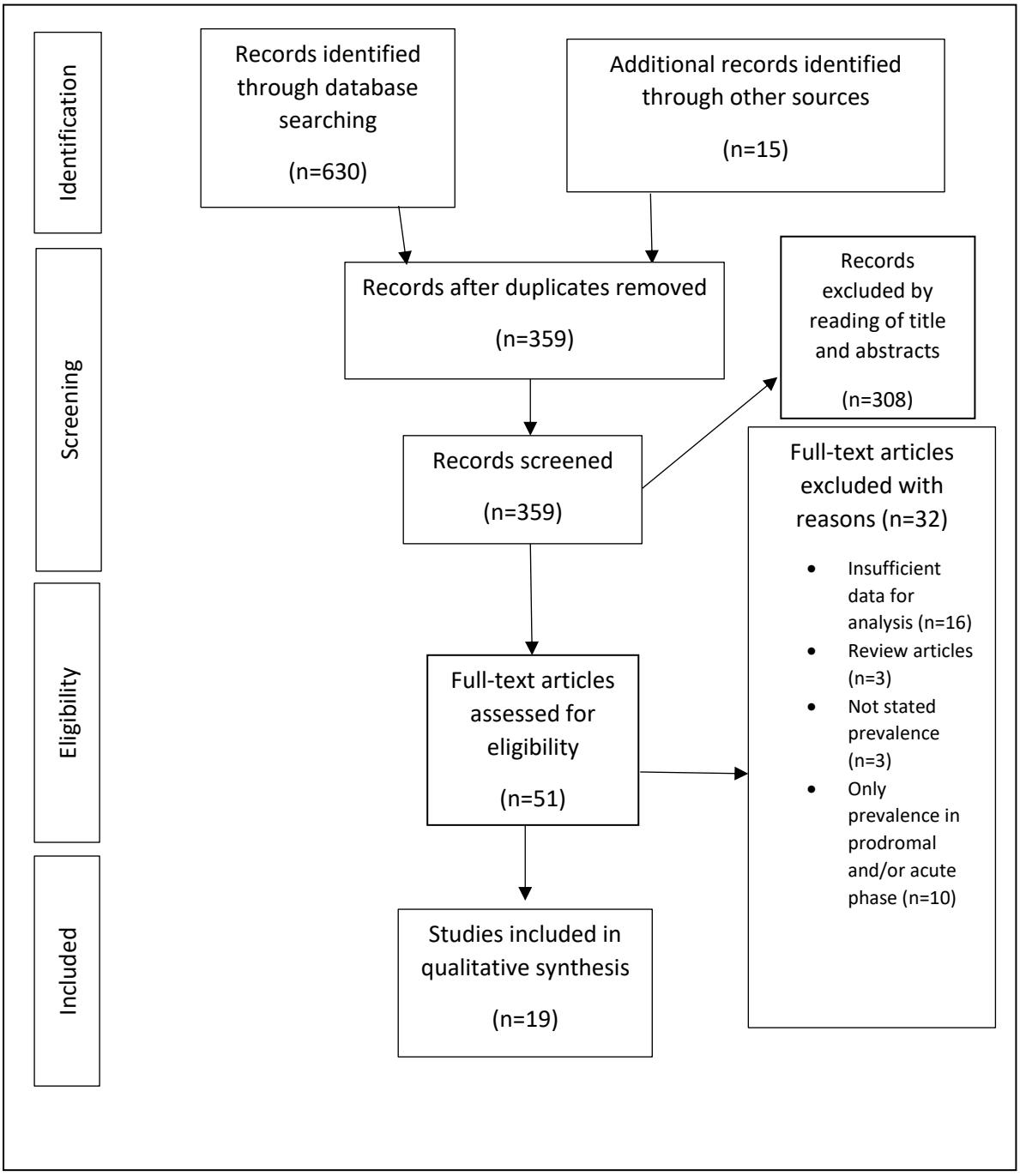
2.1.Selection procedures and data collection

2.1.1. Search strategy

A systematic literature search as described by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was conducted using Web of Knowledge[SM] and Pubmed® databases to find studies that reported the prevalence and associated factors of depressive symptoms and suicidal behavior among patients that

suffered a first-episode psychosis. Articles published until May 2016 and in English and Portuguese languages were considered. Search terms used to find relevant articles were ‘depression’ OR ´depressive´ OR ‘suicidal’ AND ´first-episode psychosis’ OR ´first-episode schizophrenia´. A secondary search was performed by reviewing reference lists of sources identified as relevant in initial search to find additional articles to the review. The articles surviving selection were fully download (PDFs) and evaluated for eligibility after full-text reading.

Fig. 1. Flow Chart of systematic identification of papers following PRISMA Guidance.



2.1.2. Inclusion criteria

Articles were included for the systematic review: (a) included affective and/or non-affective first-episode psychosis patients defined according to international standard definitions (International Classification of diseases, Diagnostic and Statistical Manual of Mental Disorders); (b) clearly stated prevalence of depressive symptoms and/or suicidal behavior in the period after first-episode psychosis; (c) were original articles and written in English or Portuguese language.

2.1.3. Exclusion criteria

We excluded from the review: (a) duplicated reports; (b) report data on non-first episode psychosis patients; (c) did not refer clearly the prevalence of depressive symptoms and/or suicidal behavior; (d) papers with insufficient data for analysis, meta-analysis or reviews; (e) articles that studied depressive symptoms and/or suicidal behavior only in prodromal and/or acute psychosis phases; (f) articles in languages other than English or Portuguese. In case of multiple publications deriving from the same study population, we selected the articles reporting the largest or the most recent data. In case of conflict between these two last criteria, the sample size was the priority.

2.1.4. Recorded variables

We recorded the following variables from each article: authors, year of publication, country, epidemiological data of patient sample (sample size, mean age, proportion of males), clinical variables (instruments used, diagnoses included), type of study, follow-up time, main aim, prevalence of depressive symptoms and/or suicidal behavior and relevant findings.

2.2.Quality assessment

We assessed the internal validity of the included studies using the tool developed by Thomas et al. from the Effective Public Health Practice Project (EPHPP) [224]. The Cochrane Collaboration for non-randomized studies recommends this tool [225]. It includes six components: selection bias, design, confounders, blinding, data collection methods, withdrawals and dropouts. Each component has to be rated as “strong”, “moderate” or “weak” according to a standardized guide and dictionary. All six components made the overall rating of each study. Studies with no “weak” ratings and at least four “strong” ratings are considered strong. Those with less than four “strong” ratings and one “weak”

rating are considered “moderate”. Those with two or more “weak” ratings are considered weak.

3. Results

3.1.Flow of included studies

Search results are summarized in the Prisma Flow Chart in Figure 1. A total of 630 studies were identified through the search strategy from databases. Fifteen additional studies that met the inclusion criteria were found through a manual search of the reference section for relevant additional studies. Three hundred and fifty-nine articles remain after exclusion of duplicate articles. Three hundred and eight articles were excluded by reading of the title and abstracts. Thirty-two articles were excluded with reasons: 16 with insufficient data for analysis, 3 non-systematic review articles, 3 not stated prevalence rate of depression and/or suicidal behavior and 10 articles that only studied prodromal and/or acute psychotic phase. Finally, we included 19 articles in the systematic review (Table 1).

3.2.Quality assessment

The general quality of studies included was “weak” to “moderate”, with only one study “strong” [226] (Table 2). Only BJörkenstam et al. (2014) studied data from a nationwide cohort. The remaining studies selection bias was the rule because information was obtained from samples from clinical centers, mainly single-center and two-center and thus not representative of the target population. Two publications did not report conflicts of interest or statements about funding or grants [227,228].

Table 2

Studies quality assessment according to EPHPP tool for quantitative studies [224]

Study	Selection bias	Design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Total
Koreen et al., 1993	Weak	Moderate	Moderate	Moderate	Strong	Strong	Moderate
Wassink et al., 1999	Weak	Moderate	Moderate	Moderate	Strong	Weak	Weak
Iqbal et al., 2004	Weak	Moderate	Moderate	Moderate	Strong	Weak	Weak
Romm et al., 2010	Weak	Moderate	Moderate	Moderate	Strong	Not applicable	Moderate
Cotton et al., 2012	Weak	Moderate	Moderate	Moderate	Strong	Moderate	Moderate
Upthegrove et al., 2014	Weak	Moderate	Weak	Moderate	Strong	Strong	Weak
Sönmez et al., 2014	Weak	Moderate	Moderate	Moderate	Strong	Weak	Weak
Addington et al., 2004	Weak	Moderate	Weak	Moderate	Strong	Strong	Weak
Clarke et al., 2006	Weak	Moderate	Moderate	Strong	Moderate	Weak	Weak
Bertelsen et al., 2007	Weak	Strong	Moderate	Moderate	Strong	Strong	Moderate
Robinson et al., 2009	Weak	Weak	Moderate	Moderate	Strong	Strong	Weak
Dutta et al., 2010	Weak	Weak	Strong	Moderate	Strong	Strong	Weak
Fedyszyn et al., 2012	Weak	Moderate	Moderate	Moderate	Strong	Strong	Moderate
Mitter et al., 2013	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Björkenstam et al., 2014	Strong	Moderate	Strong	Moderate	Strong	Strong	Strong
Ayesa-Arriola et al., 2015	Weak	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Chang et al., 2015	Weak	Moderate	Strong	Moderate	Strong	Strong	Moderate
Barret et al., 2015	Weak	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Castelein et al., 2015	Weak	Weak	Not applicable	Moderate	Strong	Moderate	Weak

Strong=No weak ratings, Moderate=One weak rating, Weak≥2Weak ratings

3.3.Study characteristics and outcome measures

We included 7 articles that studied depressive symptoms [215,227–232] and 12 articles that studied suicidal behavior [142,151,222,223,226,233–239]. The main outcome measures were prevalence of depressive symptoms and/or suicidal behavior and associated factors during the first years after first-episode psychosis. Main exclusion criteria were the presence of organic brain disorder and intellectual disability.

A total of 11490 patients were included, sample size ranged from 29 to 2819 patients, with mean age from 19.56 to 33.6 years, with male percentage from 50.8% to 77.14%.

Fourteen studies were longitudinal/prospective, 3 retrospectives, 1 retrospective case-control and 1 randomized controlled trial. In longitudinal studies the follow-up was between 12 months and 10 years.

The instruments used to measure depressive symptoms were Calgary Depression Scale for Schizophrenia (CDSS), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI) and Clinical Global Impression for Bipolar Disorder (CGI-BP). Suicidal behavior was mostly assessed by review of medical files. Death certificates confirmed suicide more frequently (Table 3).

Table 3
Major measurement tools for depressive symptoms and suicidal behavior used in the studies

Measure	Population	Items (n)	Scoring	Range	Interpretation	Cut-off
Depressive symptoms						
Beck Depression Inventory (BDI)	Adults and adolescents	21	0-3	0-63	0-13: minimal depression 14-19: mild depression 20-28: moderate depression 29-63: severe depression	≥14
Calgary Depression Scale for Schizophrenia (CDSS)	Adults and adolescents diagnosed with schizophrenia	9	0 to 3	0-27	≥5: depression	≥5
Clinical Global Impression for Bipolar Disorder (CGI-BP)	Adults	6	1 to 7 (items I, II, III)	Not applicable	Depression	>3 (depression item)
Hamilton Depression Rating Scale (HDRS)-17 items	Adults	17	0 to 2 or 3 or 4	0-52	Depression	>17
PANNS (depression item)	Adults and adolescents	30 (Including one of depression in general psychopathology subscale)	1 to 7	Not applicable	Depression	≥4 (depression item)
Suicidal behavior						
Beck Scale for Suicide ideation (BSSI)	Adults and adolescents	21	0 to 2 (items 1-19)	0-38	Higher scores indicate greater severity of	ns

Beck Suicidal Intent Scale (SIS)	Patients who attempt suicide but survive	15 (with more 5 items not included in final score)	1 to 3	15-45	suicidal ideation 15-19: low intent 20-28: medium intent ≥29: high intent	≥20

3.4.Depressive symptoms

3.4.1. Prevalence

The reported prevalence of depressive symptoms after first-episode psychosis among the studies included ranged from 14.15% and 44.8%. All studies found significant rates with prevalence of depressive symptoms on different times of follow-up ranging from 12 months to 10 years. Studies evidenced that depressive symptoms diminished with follow-up time and treatment. However, Sönmez et al. (2016) clearly demonstrated that depressive symptoms progressively decrease with treatment but still significant even 10 years after first-episode psychosis [228]. Using The Positive and Negative Syndrome Scale (PANSS) depression item (g6≥4) at baseline, at 1 year, at 2 years at 5 years and at 10 years authors found prevalence of depressive symptoms respectively 41%, 28%, 20%, 16% and 19%.

3.4.2. Correlates and Risk factors

Many factors were identified as being associated with depressive symptoms after first-episode psychosis: anomalies of psychosocial development [227,228], poor premorbid childhood adjustment [215], greater insight [231], loss [240], shame [240], low level of continuing positive symptoms [240] and longer duration of untreated psychosis (DUP) [240]. Regarding substance use the results were divergent some studies showed that substance abuse was associated with depressive symptoms after first-episode psychosis [215,228] and 1 study found substance use less common in those with depressive symptoms [231].

3.4.3. Treatment

No specific treatment or intervention studies were found regarding depressive symptoms after first-episode psychosis. Some samples studied were included in early intervention programs as treatment for first-episode psychosis [227,231,240]. Also, Koreen et al. (1993) studied prospectively 70 patients with first-episode psychosis with a follow-up to 5 years and received usual treatment. Authors concluded that since depressive

symptoms mostly resolved as the psychosis remitted, antidepressant therapy should be used only in those patients in whom depression persists [229].

3.5.Suicidal behavior

3.5.1. Prevalence

The prevalence of suicide attempts after first-episode psychosis ranged from 2.9% to 18.2% and suicide from 0.4% to 4.29% in studies included. One study that measured suicidal behavior as whole (including suicidal ideation, suicide plan and/or suicide attempt) found a prevalence of 20% [239].

3.5.2. Correlates and risk factors

As in depressive symptoms, a heterogeneity of factors associated with suicidal behavior (including suicide) were studied and found significant: previous suicide attempt [226,235,236,238,239], sexual abuse [235], comorbid polysubstance use [235], lower baseline functioning [235,238], longer time in treatment [235], recent negative events [236], older patients [222,237], longer DUP [237,239], higher positive and negative psychotic symptoms scores [237], family history of severe mental disorder [226], substance use [226,238], depressive symptoms [151,239], cannabis use [151]. Concerning insight the results were divergent with one study revealing that gaining insight during treatment was associated with reduced risk for suicidality [239] and other showing that greater insight was predictor of suicidal behavior after first-episode psychosis [235].

3.5.3. Treatment

Two studies make conclusions about treatment regarding suicidal behavior after first-episode psychosis. Bertelsen et al. (2007) researched treatment intervention in suicidal behavior in first-episode psychosis. It studied suicide rate and predictive factors of suicidal behavior in first-episode psychosis patients comparing treatment as usual and an early intervention program. Results showed lower probability of death by suicide in the specified treatment compared with standard treatment [223]. Also, Addington et al. (2004) studied 290 first-episode psychosis patients in Canada in a longitudinal prospective study with a follow-up of 1-year. Authors concluded that first-episode psychosis programs can reduce suicidal behavior [233].

Table 1
Characteristics of studies included in the systematic review

Authors and publish year	Country	Sample size	Age Mean (SD)	Male percent	Screening tools (depression and/or suicidal behavior)	Diagnosis	Study type/Follow-up time	Main Aim	Prevalence	Relevant findings
<u>Depressive symptoms</u>										
Koreen et al., 1993	USA	70	24.3 (6.0)	56%	HDRS Syndromal definition based on Research Diagnostic Criteria (RDC)	FEP: non-affective psychosis	Prospective, longitudinal/5 years	Prevalence of depressive symptoms In first-episode psychosis	Baseline: depressive symptoms (HRSD (≥15) or RDC): 75% HRSD and RDC: 22%; Follow-up: a)depression: 26%; b)Nonpsychotic ratings:4%	Depressive symptoms may represent a core part of the acute illness or may occur as a subjective reaction;
Wassink et al., 1999	USA	70	24.63 (5.23)	77.14%	CASH	FEP: non-affective psychosis	Prospective, longitudinal/5 years	Prevalence of depressive symptoms early in the course of schizophrenia	Depressive symptoms:> 50% MDD (baseline): 34.3%	Depressive symptoms are common early in the course of schizophrenia and has potential implications in diagnostic and treatment practices.
Iqbal et al., 2004	UK	29	25 (5.2)	72%	BDI	FEP: non-affective psychosis	Prospective longitudinal/ 12 months	Establish whether overgeneral memory is a feature of post-psychotic depression in FEP	PPD: 44.8%	PPD was associated with overgeneral memory and a heightened awareness of the diagnosis.
Romm et al., 2010	Norway	122	28.3 (9.2)	64%	SCID-I CDSS	FEP: non-affective psychosis	Part of ongoing longitudinal	Prevalence of MDE; Demographic and clinical characteristics of patients with MDE	MDE before onset psychosis: 17%; MDE during or after onset of psychosis: 30%	Poor premorbid childhood adjustment, substance abuse and excitative symptoms at start of treatment associated with higher severity of depressive symptoms

Cotton et al., 2012	Australia	405	20.9 (3.7)	68.6%	CGI-BP	FEP: non-affective psychosis	Prospective, longitudinal/18 months	Prevalence of depressive symptoms in patients with FEP and clinical and functional characteristics of those with persistent depressive symptoms	Depression (CGI-BP depression score>3): Baseline: 26.2% Follow-up: 14.2%	Depressive symptoms are common in patients with FES and during the first months of treatment; Greater insight into their illness was associated with depressive symptoms; Substance use was less common in those with depressive symptoms.
Upthegrove et al., 2014	UK	92	22.5 (4.89)	75%	CDSS	FEP: affective and non-affective psychosis	Prospective, longitudinal/12 months	Prevalence of depression in first-episode psychosis, its relationship to other symptom dimensions and recovery in a phase specific manner	Post psychotic depression (CDSS≥7): 37%	Loss, Shame, low level continuing positive symptoms and longer DUP were associated with post psychotic depression
Sönmez et al., 2016	Scandinavia (Norway, Denmark)	299	27.8 (9.66)	58%	PANSS depression item (g6) CDSS	FEP: non-affective psychosis	Prospective, longitudinal/10-year	Patient characteristics at baseline that predict depressive symptoms at 10 years and whether patients prone to depressive symptoms in the first year of treatment had a different prognosis in the following years	Depression (PANSS g6≥4) : Baseline: 41%%; 1 year:28%; 2 years: 20%; 5 years:16%; Depression (PANSS g6≥4 and CDSS≥6): 10 years: 19%	Depressive symptoms are frequent among FEP patients at baseline but decrease after treatment. Patients with poor social functioning in childhood and alcohol use at baseline are more prone to have depressive symptoms at 10 years of follow-up.
Suicidal Behavior										

Addington et al., 2004	Canada	238	24.6 (8.33)	65.7%	Suicidality: regular clinical practice and medical records	FEP: non-affective psychosis	Prospective, longitudinal/12 months	Prevalence of suicidal behavior prior and during 1-year FEP and identify predictors	Suicide attempt during follow-up: 2.9%; Suicide: 0.4%	First-episode programs can reduce the suicidal behavior.
Clarke et al., 2006	Ireland	171	28.5 (11.1)	58%	Clinical interview	FEP: affective and non-affective psychosis	Prospective, longitudinal/4 years	Prevalence of suicide behavior and associated factors	Attempt suicide prior presentation: 10%; Follow-up attempt suicide: 18.2% Follow-up suicide: 3%	Suicide attempts prior to presentation were associated with longer DUP
Bertelsen et al, 2007	Denmark	547	26 (6.3)	59%	Suicide attempts and ideation based on self-reporting; Suicide: Death register and death certificates	FEP: non-affective psychosis	Randomized controlled trial/5 years	Rates of suicide and predictive factors of suicidal behavior	Suicide: 1.3%	Depressive and psychotic symptoms (especially hallucinations) predicted suicidal plans and attempts, and persistent suicidal behavior and ideation were associated with high risk of attempted suicide
Robinson et al., 2009	Australia	661	ns (15-29)	65.65%	Patient medical record	FEP: affective and non-affective psychosis	Retrospective/18 months	Prevalence and predictors of suicide and suicide attempts before and during the first 18 months of treatment	Suicide attempt prior to entry: 14.3%; Suicide attempt during treatment: 8.7%; Suicide: 0.9%	Predictors of suicide attempt were: previous attempt, sexual abuse, comorbid polysubstance, greater insight, lower baseline functioning and longer time in treatment.
Dutta et al., 2010	UK	2723	33.6 (SD ns)	55.2%	Death certificates	FEP: affective and non-affective psychosis	Retrospective /mean follow up: 11.5 years	Rate of deaths by suicide	Suicide: 1.9% Proportionate mortality: 11.9%	The highest risk of suicide occurs soon after presentation but risk is elevated even a decade or longer later.
Fedyszyn et al., 2012	Australia	180 (cases:72; controls:108)	19.56 (2.73)	56.1%	Medical files CAD-SAS	FEP: affective and non-affective psychosis	Case-control study (retrospective)/18 months	1)Determine the relative importance of baseline, past and recent variables to prediction of	Suicidal attempt: 11.9%	Recent negative events and recent non-suicidal self-injurious behavior were strongest predictors of suicide-related behaviors during treatment for FEP

								suicidal behavior; 2)Identify recent characteristics that exert most influence on suicide risk levels		
Mitter et al., 2013	Singapore	1397	27.7 (6.6)	50.8%	Medical records	FEP: affective and non-affective psychosis	Prospective longitudinal/2 years	Prevalence of suicides and associated risk factors	Suicide: 1.9%	Older patients with longer DUPs, higher PANSS positive and negative scores and better functioning appear to be at higher risk of suicide
Björkenstam et al., 2014	Sweden	2819	22.6 (ns)	58%	Death Register	FEP: affective and non-affective psychosis	Longitudinal, prospective study (cohort study)/not applicable	Prevalence of suicide and associated risk factors	Suicide: 4.29%	Impulsive behavior such as self-harm and family history of severe mental disorder or substance use are risk factors for suicide in first-episode psychosis
Ayesa-Arriola et al., 2015	Spain	397	28.94 (9.46)	56.9%	Medical records	FEP: non-affective psychosis	Longitudinal, prospective/3 years	Determine and characterize the highest risk period for suicide	Suicide attempts: 10.83% Suicide: 1.51%	Greatest suicide risk was found during the month before and 2 months after first contact; Severity of depressive symptoms and cannabis use are predominant risk factos across time
Chang et al., 2015	Hong-Kong	700	21.2 (3.4)	51.4%	Medical file review	FEP: affective and non-affective psychosis	Longitudinal, Prospective/3-year	Prevalence and predictors of suicidal behavior	Baseline (Suicide attempt prior treatment): 10.6%; Follow-up: Suicidal behavior: 10%; suicide: 1%	Previous suicide attempt, history of substance abuse and poorer baseline functioning were associated with an increased risk for suicidal behavior after treatment initiation
Barret et al., 2015	Norway	146	Ns (18-65)	62.3%	SCID-I interview (suicide attempts) CDSS item 8 (current suicidality)	FEP: non-affective psychosis	Prospective longitudinal/one year	Predictors of suicidality focusing on the relationship between insight and suicidality	Baseline suicidal behavior: 37% Follow-up suicidal behavior (suicidal CDSS item 8: 1-3): 20%	Gaining insight during treatment was associated with reduced risk for suicidality; More depressive episodes before study entry, longer DUP, more suicide attempts six months prior to follow-up and depression at follow-up are predictors of suicidality at follow-up

Castelein et al., 2015	Netherlands	424	28.5 (9)	71.2%	Patient file search	FEP: affective and non-affective psychosis	Retrospective	Change in suicide risk comparing with a study made two decades ago; Identify predictors of suicide risk	Suicide: 2.4%	Higher age predict suicide Significant reduction in the suicide rate was found for people with psychosis over the past two decades

CAD-SAS: Classification Algorithm for the Determination of Suicide Attempt and Suicide; CASH: Comprehensive Assessment of Symptoms and History; CDSS: Calgary Depression Scale for Schizophrenia; CGI-BP: Clinical Global Impressions Scale – Bipolar Disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FEP: first-episode psychosis; HDRS: Hamilton Rating Scale for Depression; ICD-10: International Classification of diseases, 10th Edition; PPD: Post-psychotic depression; SCID-I: Structured Clinical Interview for DSM-IV; SD: standard deviation.

4. Discussion

This is the first systematic review to summarize the available research of depressive symptoms and suicidal behavior and associated factors in the period after affective and/or non-affective first-episode psychosis. We included articles from 12 countries all over the world with 11490 patients. Seventeen (almost 90%) of the articles included were published in the past 12 years, attesting to the increase interest in depressive symptoms and suicidal behavior following first-episode psychosis in recent years. We found convincing evidence that depressive symptoms and suicidal behavior have high rates in the years after first-episode psychosis. There is a high heterogeneity across individual studies regarding factors associated to depressive symptoms and suicidal behavior which difficult robust evidence. All studies included had a majority of males in first-episode psychosis samples, ranging from 50.8% to 77.14%. This is in line with some studies suggesting higher incidence of psychotic disorders in men [241,242].

Our results should be interpreted with caution as significant methodological limitations condition generalization of the findings. Majority of the studies included only non-affective psychotic patients which is quite artificial in the early phase of psychotic disorders namely because of the diagnostic instability [83,243]. It is quite easy to hypothesize that including also affective psychotic patients the rates of depressive symptoms and suicidal behavior will be different and more approximate to daily clinical practice. Other significant limitation from results of different studies are the instruments used namely to measure depressive symptoms. The use of different instruments certainly affects different prevalence of depressive symptoms found. Also, different cut-offs were used for the same instrument which limits comparisons between studies. For example, to evaluate depression Upthegrove and al. in 2014 [240] used a cut-off of 7 (depression CDSS≥7) in CDSS, with the same instrument Sönmez et al. in 2016 used the cut-off of 6 (depression CDSS≥6) [228]. For evaluation of suicidal behavior, the most used method was the analysis of medical records for suicide attempts and death certificates for suicide which are more reliable. One study evaluated suicidal behavior using item 8 from CDSS [239].

Research indicates that the period of *major* risk to depression and suicidal behavior is the few months after first-episode psychosis [142,151,244] with a reduction with follow-up and treatment but even with long period of follow-up the rates are high. For example, Sönmez et al. (2016) studied 299 first-episode psychosis patients with a follow-up of 10 years. It

was found a prevalence of depressive symptoms of 41% at baseline and 19% at 10-year follow-up [228].

Studies researched different factors regarding correlates and risk factors to depressive symptoms and/or suicidal behavior after first-episode psychosis. Comparison of the findings was not possible because results are limited to few articles. The *major* factors associated with depressive symptoms after first-episode psychosis were anomalies/difficulties in psychosocial and functioning in childhood in 3 studies [215,227,228] and substance and alcohol use in 2 studies [215,228]. The most consistent factors associated with suicidal behavior after first-episode psychosis were previous suicidal attempts found in 7 studies [223,226,234–236,239,245], depressive symptoms in 3 studies [151,223,239] and longer DUP in 3 studies [234,237,239].

Previous studies referred that etiology of depressive symptoms in the period after first-episode psychosis may represent a core part of the acute illness or it is associated with the subjective reaction to psychosis and its deficits impacting in daily life activities [246]. In line with this hypothesis is the included study made by Koreen et al. in 1993 in USA [229]. Independently of the etiology of depressive symptoms, studies demonstrate that depression diminished with antipsychotic treatment [228,229].

The research for treatment of depressive symptoms and/or suicidal behavior after first-episode psychosis is very limited. Some authors conclude that early intervention programs reduced suicidal behavior after first-episode psychosis [223,233]. The only randomized controlled trial published was the included study of Bertelsen et al. (2007) made in Denmark as part of the OPUS Trial [223]. This is a longitudinal, prospective study with 5-year follow-up of 547 patients with first-episode schizophrenia spectrum psychosis in Denmark. Integrated treatment including assertive community treatment model with family involvement and social skills training was compared with standard treatment at a community mental health center. Suicidal behavior and clinical and social status were assessed using validated interviews and rating scales. Authors found a suicide rate of 1.3% during follow-up. Results showed lower probability of death by suicide in the integrated treatment compared with standard treatment. These results underline the importance of dissemination of specific programs on early intervention in first-episode psychosis patients worldwide.

Few limitations of this review exist. We did not perform a meta-analysis of the findings, which may have added additional information. Different methodologies

(sample, study type, instruments used etc.) of studies jeopardizes meta-analysis construction. It also has to be considered that the quality assessment with EPHPP was "weak" for a substantial part of the studies included. Main reasons were selection bias, low evidence level of study design and bias caused by uncontrolled confounding variables. We also compared rates and risk factors for depression and suicidal behavior in studies that used different methodologies that certainly gave different results. Two *major* differences between studies were diagnoses included (affective *versus* non-affective psychosis) and instruments used to measure depressive symptoms. Also, majority of the included studies were from Europe, USA and other developed countries which could restrict the generalization of findings. The exact time when the depressive symptoms found begun are not possible to determine in some papers. We could speculate that in some researches depressive symptoms could have begun not after the first-episode psychosis but in the prodrome or during acute phase of first-episode psychosis and continue in the period after first-episode psychosis. Finally, papers written in other languages than English and Portuguese were not included and therefore some interesting researches may have not been considered.

5. Conclusions

The current systematic review provides convincing evidence that depressive symptoms and suicidal behavior have high rates in the first years after first-episode psychosis. There is a high heterogeneity of factors associated studied between studies. Treatment and early intervention programs can reduce depressive symptoms and suicidal behavior. Some methodological limitations in published studies limit generalization of the findings. Future studies should include more often affective psychosis, more than one center, other countries than Europe and USA/Canada and adequate sample sizes for more meaningful results. Data suggests that there is an opportunity to intervene and reduce depressive symptoms and suicidal behavior after first-episode psychosis.

CAPÍTULO 2. Comportamento suicida após o primeiro episódio psicótico: resultados de um estudo longitudinal a 1 ano

Artigo:

Suicidal behaviour after first-episode psychosis: results from a 1-year longitudinal study in Portugal

Ricardo Coentre, Alexandra Fonseca, Tiago Mendes, Ana Rebelo, Elisabete Fernandes, Pedro Levy, Carlos Góis, Maria Luísa Figueira

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Suicidal behaviour after first-episode psychosis: results from a 1-year longitudinal study in Portugal

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Abstract

Background: Suicide is one of the main causes of excess of premature death in psychotic patients. Published studies found that suicide risk begins in ultra-high risk of psychosis and continues in early years of the disease. Previous studies identifying predictive and risk factors associated with suicidality in first-episode psychosis (FEP) are highly inconsistent. Also, there are relatively few longitudinal studies on suicidal behaviour in FEP. The aim of this study was to examine prevalence, evolution and predictors of suicidal behaviour at baseline and the 12-month follow-up in patients presenting with FEP.

Methods: One hundred and eighteen patients presenting with FEP were recruited from two early psychosis units in Portugal. A comprehensive assessment examining socio-demographic and clinical characteristics was administered at baseline and the 12-month follow-up. Odds ratio were calculated using logistic regression analyses. McNemar test was used to evaluate the evolution of suicidal behaviour and depression prevalences from baseline to 12-months of follow-up.

Results: Follow-up data were available for 60 participants from the 118 recruited. Approximately 25.4% of the patients had suicidal behaviour at the baseline evaluation, with a significant reduction during the follow-up period to 13.3% ($p=0.035$). A multivariate binary logistic regression showed that a history of suicidal behaviour and depression at baseline independently predicted suicidal behaviour at baseline, and a history of suicidal behaviour and low levels of total cholesterol predicted suicidal behaviour at the 12-month follow-up. A significant proportion of patients also had depression at the baseline evaluation (43.3%), with the last month of suicidal behaviour at baseline independently predicting depression at this time.

Conclusions: The findings of our study indicate that suicidal behaviour was prevalent on the year after FEP. Patients with a history of suicidal behaviour, depression at baseline and low levels of cholesterol should undergo close evaluation, monitoring and possible intervention in order to reduce suicide risk in the early phases of psychosis.

Keywords Suicidal behaviour; first-episode psychosis; depression; schizophrenia

Background

Suicide and cardiovascular disorders are the two main causes of excess or premature death in psychotic patients [94]. About 5% of patients with schizophrenia death by suicide, and about 50% have suicidal ideation or attempt suicide [220,247]. Suicide risk differs across the various stages of the disorder, with the highest rates occurring in the early phases [142]. Recent studies found that this suicide risk begins at ultra-high risk of psychosis (UHR) stage and continues in early years of the disease [248,249]. Patients experiencing first-episode psychosis (FEP) have a 60% increased risk of suicide in the first year of treatment compared with those in subsequent phases [250]. The prevalence of suicidal ideation, a consistent antecedent of suicidal behaviour (attempts and completed suicide), ranges from 26.2% to 56.5% during the initial presentation of FEP [251,252]. The prevalence of suicide attempts in the years following FEP ranges from 2.9% to 18.2% and suicide from 0.4% to 4.29% [253].

Therefore, the first years of psychotic disorders represent an important challenge for Public Health and Psychiatry. Consequently, researchers have sought to identify predictive and risk factors associated with suicidality in FEP; however, the findings are highly inconsistent. Younger age of onset of psychosis [223,251,254] and drug and alcohol use [132,255,256] are factors associated with suicidality in FEP. As in the general population, previous suicidal behaviour, e.g. suicide attempts, has been identified as one of the most significant predictors of suicidal risk in FEP [235,257,258]. However, while results are mixed regarding gender [117,234,251,254,259–262], duration of untreated psychosis [234,250,251], positive psychotic symptoms [146,250,263] and insight [132,239,251,262,264,265], treatment compliance has been demonstrated to reduce suicide risk [266].

Current or past significant depressive symptoms are associated with suicide risk in patients after FEP [132,217,267–269]. The prevalence of depressive symptoms after FEP ranges

from 14.15% to 44.80%. Studies evidenced that depressive symptoms diminished with follow-up time and treatment but remained significant even 10 years after FEP [228,253]. Previous studies showed that the most depressive symptoms occur either in prodrome [270] or during FEP [271,272]. Rarely do depressive symptoms occur *de novo* in recovery following FEP [217]. Usually, depressive symptoms follow the course of positive psychotic symptoms and remit with antipsychotic treatment [229], although there are some patients with psychosis who maintain persistent depressive symptoms beyond the acute phase and do not respond to antipsychotic treatment. Co-morbid depression and psychosis increase the risk of suicidality and relapse [273,274]. It has been suggested that early identification and intervention for depression in the early phases of psychosis may constitute an important strategy in the prevention of suicide [142,275].

Published studies suggest that early intervention services – including short treatment delays, maintaining adherence to therapy and specialised programmes – reduce the risk of suicide [276,277], which is an important aim of early intervention teams. Despite the relevance of this theme, there are relatively few longitudinal studies on suicidal behaviour in FEP and early phases of psychosis. Additionally, published studies have some methodological limitations that we tried to overcome. First, many published studies only included first-episode schizophrenia patients [151,223,239]. It is known that a diagnosis of FEP is unstable, with the likelihood of subsequent changes in the first years of the illness [84]. Therefore, it is suggested that studying a broader diagnostic sample of FEP with affective and non-affective psychosis would be more accurate in estimating suicidal behaviour. Second, some studies included heterogeneous samples that mixed patients at different stages of their illness, including chronic and early psychosis patients. Third, many past studies only included hospitalized patients, excluding milder forms of

psychotic disorders. Fourth, most previous studies used retrospective or cross-sectional designs, which are characterised by inherent difficulties in establishing predictive factors.

Greater understanding and knowledge around suicide risk profiles and predictors of suicide in psychotic patients will enable the development of preventive strategies. Appropriate monitoring and managing of suicide risk will be important for services working with early psychosis populations. Prospective studies in patients with FEP are necessary to better identify predictive and risk factors for suicidal behaviour in early psychosis. The prevalence and methods of suicidal behaviour differ between countries and cultures. The literature indicates that socio-cultural factors and healthcare resources may condition the risk of suicide [245,278,279]. Therefore, it is important to have studies from different countries and cultures.

The main aims of this study were: 1) to examine the prevalence and evolution of suicidal behaviour soon after FEP (baseline) and 12 months of follow-up and 2) to determine baseline predictors of suicidal behaviour soon after FEP and at the 12-month follow-up. We also examined the prevalence of depression, its evolution in the 12 months following FEP and the predictors of depression at baseline and follow-up. We hypothesised that affective psychosis, previous suicidal behaviour and depressive symptoms at baseline would predict the occurrence of suicidal behaviour at baseline and the 12-month follow-up.

Methods

Participants and setting

The study was carried out at two specialist psychiatric services within Portuguese hospitals: Hospital Vila Franca de Xira (in Vila Franca de Xira with a catchment area of 245,000 individuals) and Centro Hospitalar Universitário Lisboa Norte (in Lisbon with a

catchment area of 350,000 individuals). The selected patients were from two early intervention teams: the First-Episode Psychosis Program (PPEP) at Hospital Vila Franca de Xira (Vila Franca de Xira) and Programa de Intervenção nas Fases Iniciais da Psicose (PROFIP) at Centro Hospitalar Universitário Lisboa Norte (Lisbon). Both programmes are comprehensive, specialised mental health services for FEP patients originating from geographically defined catchment areas in Vila Franca de Xira and Lisbon, Portugal. Vila Franca de Xira Hospital is a secondary care general hospital in the north metropolitan area of Lisbon. Centro Hospitalar Universitário Lisboa Norte is a tertiary care general university hospital, which interacts closely with the Faculty of Medicine, University of Lisbon. The populations served by the two hospitals live mainly in the suburban and urban areas, respectively, of the metropolitan region of Lisbon. A description of the PROFIP programme was published elsewhere [74].

All FEP patients underwent an assessment by trained personnel as soon as possible after contact with the team. The mean length from service entry to baseline assessment was 5.7 days (SD:1.8). The programmes consisted of low-dose second-generation antipsychotic medication and individual and group psychosocial treatment, namely family intervention.

The participants met the following inclusion criteria at baseline: 1) age between 16 and 40 years; 2) DSM-IV (American Psychiatric Association, 1994) diagnosis of a psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, bipolar psychotic disorder, *major* depressive disorder with psychotic features, brief psychotic disorder, cannabis-induced psychosis and psychosis not otherwise specified); 3) adequate comprehension of Portuguese language; 4) experiencing FEP with less than six months of antipsychotic medication. Exclusion criteria at baseline included:1) head injury, neurological illness, or any other medical

condition presenting with psychiatric symptoms 2) history of past full-blown psychotic episodes, either non-affective or affective, as defined in the Diagnostic and Statistical Manual of Mental Disorders, IV Edition (American Psychiatric Association, 1994); 3) inability to understand and complete the assessments.

The study included all eligible consecutive patients who met the study criteria for the period January 2017 to April 2020. The patients were evaluated at two time points: a baseline evaluation soon after the clinical stabilisation of FEP; 12 months after the baseline assessment. Follow-up data were available for 60 participants from the 118 recruited. The study complied with the ethical principles of good practice embodied in the Declaration of Helsinki. Responsible ethical committees within both hospitals approved the study, and all participants provided informed consent.

Clinical assessments

The clinical assessment included evaluations regarding socio-demographics and clinical data, including age, marital status, education, occupational status, living area (urban or rural), medical history, education, family history of mental illness, presence of stressful life events occurring in the past year before entering the study, mode of onset of FEP, substance use and type and dose of antipsychotic medication. The baseline and 12-month follow-up diagnoses were obtained using all available information, including informant history and medical records. The Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT+) instrument was used to obtain the diagnosis [280,281]. The checklist ratings were entered into the OPCRIT+ software, which generates a diagnosis for the main categories of affective and psychotic disorders, as defined by the DSM-IV, which is the *major* classification system. The duration of untreated psychosis (DUP) was measured using the Nottingham Onset Schedule (NOS) [282]. DUP was defined as the period of time between the onset of psychotic symptoms and the initiation of treatment with

antipsychotic medication. Symptom levels were evaluated using means of the three subscales used to evaluate positive symptoms, negative symptoms and the general psychopathology of the Positive and Negative Syndrome Scale (PANSS) [283]. Suicidal behaviour was assessed at baseline and follow-up evaluations using an instrument developed by Melle [258], which consists in three questions about the last month and lifetime suicidal thoughts, plans or attempts.

The information was cross-checked with the medical records. "Suicidal thoughts" were considered a preoccupation or recurrent thoughts of suicide without a specific plan. "Suicide plans" were considered as the presence of a specific plan to suicide. "Suicide attempts" were defined as a self-non-fatal act with a suicidal intent. The most severe form of suicidal behaviour reported for a lifetime or the past month was registered.

The baseline and 12-month follow-up assessments of depressive symptoms were conducted using the Beck Depression Inventory (BDI). The BDI is a widely used self-report questionnaire designed to measure the severity of depression in individuals between the ages of 13 and 80 years. It contains 21 items, which are rated on a four-point scale according to how the patients felt in the previous two weeks. The scores obtained for the single item are summed to provide a single total score. We used 14 as the global cut-off score to determine patients' depression (depression ≥ 14). We used the Portuguese version, which was translated into Portuguese and adapted to the Portuguese population [284–286].

For the alcohol screening, the Michigan Alcohol Screening Test (MAST) was used. This is a 25-item self-questionnaire requiring yes/no answers, with one point each. A total score of 5 or more indicates hazardous alcohol consumption or alcohol dependence. The Portuguese-translated version, which was adapted to the Portuguese population, has been used before [287,288]. Functioning was measured using the Global

Assessment of Functioning Scale (GAF) [289]. Adherence to medication was evaluated by Medication Adherence Rating Scale (MARS). The MARS is a ten-item self-report measure of medication adherence in psychosis [290]. The total score ranges from 0-10 with a higher score indicating better adherence. We used the translated and validated scale to the Portuguese population [291].

Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Science (SPSS), version 26 (Inc, 2020). Due to non-normality in all the explored statistics, non-parametric tests were used. In the between-group comparisons, categorical variables were examined using Chi-square or Fisher's exact test (if 20% of expected frequency was ≤ 5 or any expected frequency was < 1) and continuous variables with the Mann–Whitney U test. Based on the level of confidence (95%), expected prevalence of suicidal behaviour (30%) and precision (5%) we calculated the sample size needed for our sample.

The primary analysis of this study focused on identifying factors predicting the occurrence of suicidal behaviour at baseline and 12 months after the occurrence of FEP. We also evaluated the predictors of depression in FEP patients (at baseline and 12 months after FEP). Suicidal ideation/behaviour was collapsed into a binary variable suicidal/non-suicidal (i.e., presence/absence of suicidal thoughts, plans or attempts). We also considered depressive/not depressive as well as the above-mentioned cut-off on the BDI scale. First, a univariate binary logistic regression was conducted, with suicidal behaviour as the dependent variable and demographic and clinical variables as the candidate predictors. Second, variables with a significant p value in the preceding analysis were then entered into a multivariate binary regression model to determine which factors independently predicted suicidal behaviour at baseline and the 12-month follow-up. A

stepwise method was used with a forward selection of predictors. The same procedure was conducted, with depression as the dependent variable. Collinearity evaluations were performed by examining correlation matrices for all the variables, tolerance and variance inflation factors.

We used the McNemar test to evaluate the evolution of suicidal behaviour and depression and compare the results at baseline with those at 12 months. The Wilcoxon test for repeated measures was used to evaluate the evolution of depression from the BDI mean score. The level of statistical significance was set at $p < 0.05$.

Results

Characteristics of the sample

The sample comprised 118 patients consecutively admitted to PPEP (n = 39) and PROFIP (n = 79). There were no differences between the two groups in terms of sex and employment. The patients from the PROFIP team were younger (mean years 24.2 vs. 29.61; p = 0.003) and of a higher educational level (mean years of education 11.7 vs. 10.1; p = 0.016) (Mann–Whitney U-Test for both). Of the 118 participants included in the study, 76.3% (n = 90) were male. The mean age of the sample at intake was 26.1 years (SD = 7.1). The majority (49.2%) of the patients were diagnosed with schizophrenia spectrum disorders (schizophrenia: n = 48; delusional disorder: n = 8; schizoaffective disorder: n = 2). Thirty-nine (33%) were diagnosed with four other non-affective disorders, with 8 patients with a brief psychotic disorder, 23 with a non-specified diagnosis of psychosis and 8 with a cannabis-induced psychosis diagnosis. Twenty-one (17.8%) participants had affective psychosis (n = 8 had bipolar affective disorder with psychotic features, and n = 13 had *major* depression with psychotic features). Table 1 shows the socio-demographic and clinical baseline variables of the sample.

Of the initial cohort of 118 patients who completed the baseline assessment, 60 completed the follow-up assessment. We lost contact with 58 patients for the following reasons: 30 moved to other catchment areas in Portugal; 15 moved to other countries and 13 could not be contacted for the follow-up. Non-completers and completers groups had no significant differences regarding socio-demographics and clinical variables, with the exception of more males (p=0.009) and lower affective psychosis diagnoses (p=0.030) on the non-completers group.

Comparisons of socio-demographics and clinical characteristics between the affective psychosis and schizophrenia spectrum disorder diagnoses are shown in a table as supplementary material.

Table 1 Socio-demographic and clinical baseline variables of the sample

Variables	First-episode psychosis patients n=118
Age years - mean (SD)	26.1 (7.10)
Gender - n (%)	
Female	28 (23.7%)
Male	90 (76.3%)
Education years - mean (SD)	11.24 (3.2)
Unemployment - n (%)	51 (43.2%)
Marital status – n (%)	
Living with partner/Married	14 (11.9%)
Single/Divorced	104 (88.1%)
Hospitalization baseline - n (%)	
Yes	101 (85.6%)
No	17 (14.4%)
Cannabis use - n (%)	
Yes	75 (63.6%)
No	43 (36.4%)
Psychiatric family history – n (%)	76 (64.4%)
DUP – days, median (SD)	84 (643.3)
Diagnoses - n (%)	
Schizophrenia spectrum diagnosis	58 (49.2%)
Affective psychosis spectrum diagnosis	21 (17.8%)
Other psychosis diagnosis	39 (33%)
PANSS score - mean (SD)	
PANSS positive subscale	21.24 (8.09)
PANSS negative subscale	15.86 (7.41)
PANSS general subscale	35.97 (8.80)
GAF - mean (SD)	43.40 (18.28)
BDI - mean (SD)	13.18 (10.10)
MARS – mean (SD)	6.08 (2.26)
Total Cholesterol mg/dL – mean (SD)	153.43 (31.72)

SD: standard deviation; DUP: duration of untreated psychosis; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; BDI: Beck Depression Inventory; MARS: Medication Adherence Rating Scale.

Schizophrenia spectrum disorder included schizophrenia, schizophreniform disorder, delusional disorder and schizoaffective disorder. Affective psychosis included bipolar disorder with psychotic symptoms and depressive disorder with psychotic symptoms. Other psychosis included acute and transient psychotic disorders, brief psychotic disorder, cannabis-induced psychosis and psychosis not otherwise specified.

Prevalence of suicidal behaviour

Forty-two (35.6%) participants had a history of suicidal behaviour prior to entering the study, with 34.7% (n = 41) of the cohort having suicidal ideation, 17.80% (n = 21) suicidal plans and 9.32% (n = 11) a suicide attempt. Overdose of medication was the most frequently used attempted suicide method (54.5%), followed by jumping from a height (18.2%), strangulation (18.2%) and phlebotomy (9.1%).

For the total initial FEP group, suicidal behaviour in the last month was found for 25.4% (n = 30) of the cohort, with 15.3% of them experiencing suicidal ideation, 4.2% suicidal plans and 5.9% suicide attempts. The most frequently used methods of attempted suicide in the last month were overdose of medication, jumping from a height and hanging (1.7% in each group). One patient attempted suicide through phlebotomy.

For the participants who completed the 12-month evaluation, 13.3% (n = 8) had suicidal behaviour, 8.3% suicidal ideation, 3.3% suicidal plan and 1.7% a suicide attempt. The only suicide attempt was overdose of medication.

Twelve patients (40%) which reported suicidal behaviour at baseline evaluation had no history of suicidal behaviour. Only one patient that reported suicidal behaviour at follow-up evaluation had no history of suicidal behaviour.

With regard to the longitudinal evolution of suicidal behaviour, a statistically significant decrease at the 12-month follow-up was found (25.4% vs. 13.3%; p = 0.035).

The results regarding comparison of suicidal behaviour between affective psychosis and non-affective psychosis diagnoses revealed significant differences on baseline with higher rate on affective psychosis group (42.9% versus 21.6%; p=0.0043). The results on the 12-month follow-up showed no significant differences between the two

diagnostic groups (affective psychosis 25% versus non-affective psychosis 9.1%; p=0.192).

Univariate associations with suicidal behaviour

The associations of suicidal behaviour at baseline and 12 months of follow-up with the demographic and clinical factors are shown in Table 2. Patients with suicidal behaviour at baseline were significantly more likely to have a history of suicidal behaviour, baseline affective psychosis diagnosis and baseline depression. Suicidal behaviour patients at 12 months of follow-up were found to have a significantly greater history of suicidal behaviour at baseline, baseline suicidal behaviour in the last month and lower total cholesterol at baseline.

Table 2 Demographic, pre-treatment and baseline predictors of suicidal behaviour

	Baseline Suicidal behaviour				12-Months Suicidal Behaviour			
Variables of interest	Patients with suicidal behaviour (n = 30)	Patients without suicidal behaviour (n = 88)	OR (95% CI)	p value	Patients with suicidal behaviour (n = 8)	Patients without suicidal behaviour (n = 52)	OR (95% CI)	p-value
Socio-demographics								
Male/Female sex, n (%)	21(70.0)/9(30.0)	69(78.4)/19(21.6)	1.556 (0.613-3.950)	0.352	4 (50.0)/4 (50.0)	36/16	2.250 (0.499-10.143)	0.291
Age at entry, mean (SD)	26.83 (7.49)	25 (7.01)	0.981 (0.926-1.038)	0.504	30.13 (9.91)	26.63 (7.60)	0.950 (0.869-1.037)	0.252
Years of education, mean (SD)	11.10 (3.60)	11.28 (3.01)	1.018 (0.895-1.159)	0.786	11.88 (3.56)	11.19 (3.33)	0.938 (0.745-1.182)	0.588
Married/With partner, n (%)	5 (16.7)	9 (10.2)	1.756 (0.538-5.725)	0.351	1 (12.5)	7 (13.46)	1.343 (0.136-13.250)	0.801
Living alone, n (%)	1 (3.3)	11 (12.5)	0.241 (0.030-1.954)	0.183	0 (0)	8 (15.38)	0.000	0.999
Employed/Student, n (%)	16 (53.3)	51 (57.9)	0.829 (0.361-1.907)	0.659	6 (75.0)	2 (3.85)	2.200 (0.405-11.949)	0.361
Pre-treatment illness characteristics								
Family history of mental disorder, n (%)	20 (66.67)	56 (63.6)	1.143 (0.477-2.740)	0.765	7 (87.5)	1 (1.92)	3.111 (0.353-27.425)	0.307
History of suicidal behaviour, n (%)	18 (60.0)	24 (27.3)	4.000 (1.679-9.530)	0.002	7 (87.5)	1 (1.92)	13.222 (1.507-116.011)	0.020
History of substance use, n (%)	20 (66.67)	55 (62.5)	1.200 (0.501-2.873)	0.682	6 (75.0)	2 (3.85)	2.032 (0.374-11.052)	0.412
History of alcohol abuse, n (%)	15 (50.0)	37 (42.0)	1.378 (0.600-3.166)	0.449	3 (37.5)	5 (9.62)	0.886 (0.191-4.110)	0.877
Baseline clinical characteristics								
DUP, median (SD) days	28.00 (984.61)	92.00 (473.95)	1.000 (0.999-1.000)	0.204	19 (114.55)	98 (770.42)	1.003 (0.998-1.008)	0.291
Hospitalization, n (%)	27 (90.0)	74 (55.7)	1.703 (0.454-6390)	0.430	0 (0.0)	8 (15.38)	0.000	0.999
Tobacco use, n (%)	18 (60.0)	49 (55.7)	1.194 (0.514-2.773)	0.680	6 (75.0)	2 (3.85)	2.571 (0.474-13.945)	0.274
Last-month baseline suicidal behaviour	-	-	-	-	5 (62.5)	3 (5.77)	5.556 (1.156-26.704)	0.032
Diagnostic categories								
Schizophrenia-spectrum disorder, n (%)	11 (36.67)	47 (53.4)	0.505 (0.215-1.185)	0.116	2 (25.0)	6 (11.54)	0.286 (0.053-1.549)	0.146
Affective psychosis, n (%)	9 (30.0)	12 (12.6)	2.714 (1.008-7.306)	0.048	4 (50.0)	4 (7.69)	3.333 (0.723-15.374)	1.123
Other psychosis, n (%)	8 (26.7)	29 (32.9)	0.740 (0.294-1.862)	0.522	2 (25.0)	6 (11.54)	1.111 (0.198-6.239)	0.905
Symptom severity and functioning								
PANSS positive symptoms, mean (SD)	20.67 (8.05)	21.43 (8.14)	1.012 (0.961-1.065)	0.653	20.63 (7.84)	18.85 (7.29)	0.967 (0.875-1.070)	0.521
PANSS negative symptoms, mean (SD)	17.53 (8.48)	15.30 (6.98)	0.961 (0.910-1.015)	0.155	17.88 (6.643)	17.31 (7.237)	0.989 (0.891-1.098)	0.832
PANSS general symptoms, mean (SD)	39.07 (9.81)	34.91 (8.22)	0.949 (0.905-0.995)	0.031	39.63 (6.02)	35.69 (9.34)	0.959 (0.891-1.032)	0.260
BDI, mean (SD)	18.47 (11.434)	11.42 (8.93)	0.933 (0.894-0.974)	0.002	20.50 (12.11)	12.48 (9.87)	0.933 (0.869-1.001)	0.054
Depression, n (%)	20 (66.7)	32 (36.4)	3.5 (1.460-8.392)	0.005	6 (75.0)	2 (3.85)	4.800 (0.881-26.144)	0.070
GAF, mean (SD)	44.17 (17.52)	43.14 (18,62)	0.997 (0.974-1.020)	0.789	43.75 (15.53)	48.00 (17.60)	1.014 (0.972-1.059)	0.516
MARS, mean (SD)	5.50 (1.78)	6.23 (2.39)	1.154 (0.958-1.390)	0.130	5.75 (2.66)	5.79 (2.30)	0.971 (0.919-1.027)	0.304
Laboratory								
Total Cholesterol	154.50 (32.56)	153.07 (31.62)	0.999 (0.986-1.012)	0.830	170.88 (26.2)	146.17 (30.518)	0.974 (0.949-0.999)	0.045

Abbreviations: DUP = Duration of untreated psychosis; PANSS = Positive and Negative Syndrome Scale; BDI = Beck Depression Inventory; GAF = Global Assessment of Functioning; MARS = Medication Adherence Rating Scale; SD = standard deviation
Schizophrenia-spectrum disorder included schizophrenia, schizophreniform disorder, delusional disorder and schizoaffective disorder
Affective psychosis included bipolar disorder with psychotic symptoms and depressive disorder with psychotic symptoms
Other psychosis included acute and transient psychotic disorders, brief psychotic disorder, cannabis induced psychosis and psychosis not otherwise specified

Predictors of suicidal behaviour in the multivariate model

A multivariate binary logistic regression analysis showed that a history of suicidal behaviour and depression at baseline predicted suicidal behaviour at baseline. A history of suicidal behaviour and low baseline total cholesterol predicted suicidal behaviour at 12-months of follow-up (Table 3).

Table 3 Multivariate logistic regression analysis for predictors of baseline and 12-months suicidal behaviour in first-episode psychosis patients[a,b]

Variables in the Equation	B	SE	Wald	df	p value	OR	95% CI
Baseline							
Depression baseline	1.087	0.463	5.514	1	0.019	2.96	1.20-7.34
History of suicide behaviour	1.237	0.456	7.343	1	0.007	3.44	1.41-8.43
Constant	-0.153	0.367	0.175	1	0.676	0.86	
Final model: Nagelkerke $R^2 = 0.185$, $\chi^2 = 15.850$, $p < 0.0001$							
Hosmer & Lemeshow test supported the goodness of fit of the model ($\chi^2 = 0.006$, df = 2 , p = 0.997)							
12-months follow-up							
History of suicide behaviour	2.849	1.172	5.910	1	0.015	17.27	1.74-171.65
Total Cholesterol baseline	-0.030	0.014	4.411	1	0.036	0.97	0.94-0.99
Constant	5.643	2.369	5.674	1	0.017	282.31	
Final model: Nagelkerke $R^2 = 0.373$, $\chi^2 = 13.600$, p = 0.001							
Hosmer & Lemeshow test supported the goodness of fit of the model ($\chi^2 = 12.657$, df = 8, p = 0.124)							

[a] Affective psychosis diagnosis and PANSS general were entered into stepwise logistic regression model, were excluded as predictors of baseline suicidal behaviour

[b] Last month baseline suicidal behaviour was entered into stepwise logistic regression, was excluded as predictors of 12-month suicidal behaviour

Prevalence and predictors of depression

The longitudinal evolution of depression prevalence showed a significant decrease between baseline and the 12-month follow-up (43.3% vs. 20.0%; p = 0.014).

A univariate analysis of predictors of baseline depression revealed that depressed patients had a significantly higher history of suicidal behavioural (OR: 2.29; p = 0.035). Also, depressed patients at baseline had a higher prevalence of suicidal behaviour in the

last month (OR: 3.50; p = 0.005), which was the only variable that maintained a statistical significance in the multivariate analysis (OR: 2.94; 95% IC: 1.19–7.27; p = 0.020). None of socio-demographic or clinical baseline factors analysed reach statistical significance in the multivariate analysis, with 12 months of depression as the dependent variable.

Discussion

To the best of our knowledge, this is the first study to examine the prevalence and socio-demographic and clinical characteristics of FEP with and without suicidal behaviour in a Portuguese population. The present study examined the evolution of the prevalence of suicidal behaviour in the 12 months after FEP in a cohort of Portuguese young people. We also aimed to identify early predictors of suicide behaviour at 12 months of follow-up (baseline and 12 months). In our present study, the prevalence of suicidal behaviour was 25.4% soon after FEP. This is in line with existing studies which showed that approximately 25% to 50% of FEP patients reported suicidal behaviour at initial presentation [217,250,260,292]. We also confirmed that a history of suicidal behaviour before service entry in FEP patients was a predictor of suicidal behaviour at baseline and follow-up. These results are consistent with previous first-episode studies from other countries [238,293,294].

Comparing with general population our results also show that the prevalence found for suicidal behaviour in our sample of FEP is higher than those found in general population, but these comparisons are difficult because of the scarcity of Portuguese studies. One published study that included University students of four scientific different areas from only one school of the north of Portugal, found prevalence of last week and last year suicidal ideation of 10.7% [295]. Another Portuguese study, evaluated medical school time suicidal ideation, suicidal plan and suicidal attempt on a sample of 456 medical students (4th and 5th years) from one medical school located in Lisbon, Portugal.

This population is well recognized of having high prevalence of suicidal behaviour and completed suicide. The results showed prevalence of suicidal ideation of 3.7%, suicidal plan 1.1% and 0.7% of suicide attempt [296]. A third cross-sectional study researched mental disorders and suicidality of ten European countries participating in the World Mental Health Survey Initiative, including Portugal [297]. The Portuguese sample included 3849 individuals (response rate 57.3%) that completed a Computer-Assisted Personal Interview, that included questions about suicidal behaviour. Any lifetime suicide attempt was found in 0.8–5.4% of women and 0.3–2.4% of men for all countries, with Portugal showing 13.1% for men and 6.7% for women for lifetime suicidal ideation, 4.8% women and 1.4% men for lifetime suicidal plan, and 4.9% for women and 1.8% for men regarding lifetime suicide attempt. A recent published systematic review of prevalence of suicidality in the European general population, included 24 studies of the prevalence and variability in suicidality in the general adult population of Europe between 2008 and 2017. The pooled point prevalence rate was 3.96% (2.37–5.56), pooled 12-month prevalence 2.9% (1.49–4.32), and pooled lifetime prevalence 5.55% (4.31–6.79) [298]. With the caution of comparing different timeframe and instruments used, these results demonstrate that our results show higher rates of suicidal behaviour than general population.

As previous published studies showed, we also confirmed that depression was associated with suicidal behaviour [293,294,299,300]. Our results showed that depression was a predictor of suicidal behaviour at baseline. This result suggests that close evaluation, monitoring and early intervention for depression in FEP are crucial to reducing suicidal behaviour in the early phases of psychosis.

Like our study, a majority of the literature did not find an association between negative symptoms and suicidal behaviour [132,301]. Some studies postulated that patients with significant negative symptoms, namely deficits in emotion expressivity, are impaired

from expressing emotional distress caused by psychosis, consequently reducing the probability of developing depression, hopelessness and suicidal behaviour [302]. In line with this, a few studies found negative symptom severity to be inversely related to the risk of suicidal ideation and suicide attempts [294,300].

Regarding positive symptoms, we failed to demonstrated that these symptoms were predictors of suicidal behaviour, contrary to some prior FEP studies [146,256]. Our results were similar to those found in other published studies where no predictability was found [238].

An interesting finding of our study is that high levels of total cholesterol were a baseline protector of suicidal behaviour at follow-up. This is in concordance with research in this field of knowledge. During the recent decades there has been growing research about the role of lipids and lipoprotein concentrations in suicidal behaviour. Published studies seem to demonstrate an association between low cholesterol and an increased risk of suicide in non-psychotic patients as well as in psychosis [303–307]. These findings seem to be evident to other psychiatric disorders as depression and bipolar disorder [308,309]. Published researches demonstrated that lower total cholesterol and low-density lipoprotein cholesterol (LDL-c) have been found in patients with schizophrenia and a history of suicidal behaviour [310] .There is a dearth of research on the relationship between cholesterol levels and suicidality in FEP. One study found that serum cholesterol concentrations were significantly lower in suicidal than in non-suicidal patients in FEP, suggesting that lower concentrations of serum cholesterol in patients with FEP might be useful as a biological marker of suicidality [303]. Another study in early psychosis demonstrated that lower levels of cholesterol in patients of psychosis were associated with severe suicidal thoughts [305]. More recently, Ayesa-Arriola and colleagues found that lipid profile test may be considered in the assessment of suicidality in FEP and LDL-c an

important biological marker [311]. The exact mechanisms of the relationship between peripheral cholesterol, brain metabolism and suicidal behaviour are not entirely known. Some authors have suggested an existing abnormality in leptin and lipid metabolism in suicidal behaviour [312]. Moreover, post-mortem brain studies have indicated that violent suicide completers have lower grey-matter cholesterol content, specifically in the frontal cortex, particularly in the orbitofrontal cortex and the ventral prefrontal cortex [313]. It is postulated that dysfunctions on orbitofrontal and ventral prefrontal cortex result in impaired impulse inhibition and in violent or suicidal behaviour. Another explanation for the link between lipoprotein concentrations and suicidal behaviour is the diathesis-stress model [314]. On this model the presence of a low lipid profile represents as a trait factor related to aggression, impulsivity and suicidality. These effects of lipids levels on behaviour are through their influences on serotoninergic system and transmission in the brain. Serum lipids play role on myelin sheath and transmembrane transportation, enzyme function, hormone steroid synthesis and neurotransmitter receptor expression [311]. Thus, lipids and cholesterol have a wide-ranging implication in the neurobiology of the central nervous system including neuronal protection, membrane stabilization, lipid metabolism in neurons and as part of the second messenger system. It is indirect linked to norepinephrine and serotonin levels in the brain [315]. Almost all of the previous works on FEP showed that the association of low levels of total cholesterol is also found on antipsychotic naïve patients, underlying that this relationship is independent of medication [316]. We only included total cholesterol because this metabolic parameter is the one with the most robust evidence on previous published researches showing its association with suicidal behaviour.

The present study also showed the high frequency of depression and depressive symptoms in the first year after FEP. Almost half of the patients were depressed at

baseline, while one-fifth had depression at one year of follow-up. As indicated in the BDI score, the depressive symptoms significantly decreased during the first year after FEP. This is also similar to other published studies [217,231,317,318]. Some authors have speculated several pathways to depression in psychosis, namely in schizophrenia. Three possible explanations exist: 1) depression as an intrinsic aspect of the psychotic disorder; 2) depression as a result of the psychotic illness; 3) depression as a result of disturbed developmental pathways [216].

Our findings did not confirm the idea that depressive symptoms in schizophrenia are frequently misdiagnosed with negative symptoms [319]. In this case, high levels of depressive symptoms would exist simultaneously with high levels of negative symptoms, and a significant association between negative and depressive symptoms would have been expected, which did not happen in our study.

The only predictors that we found to be significant to depression at baseline were baseline suicidal behaviour in the last month and a history of suicidal behaviour. Surprisingly, we found no significant baseline predictors of depression at 12 months. Contrary to our findings, other studies found that a long DUP and depressive symptoms at baseline predict depressive symptoms at 12 months of follow-up [320]. Also, some studies found an association between depression scores and positive symptoms and an improvement with successful antipsychotic therapy [229,321]. However, some studies also failed to find this association, indicating that depressive symptoms may also emerge independently of positive symptoms [322,323]. The reasons for our study's failure in finding significant baseline predictors at the 12-month follow-up are not immediately apparent. We could speculate that our baseline evaluation, which was conducted only after a clinical stabilization of FEP, might have been a little late for significant findings.

The inclusion of patients with different subdiagnoses, namely affective and non-affective psychosis, may have partly influenced the results found. On the one hand, this is a reality of clinical practice in patients with first-episode psychosis, in which this nosological division is sometimes difficult and artificial, given the simultaneous symptomatologic multiplicity in the early stages of psychotic disorders and their evolutive instability. On the other hand, the samples of patients included in our study had mostly patients with non-affective psychosis, which is similar to most studies that include patients with first-episode psychosis. Maybe the results obtained reflet mostly the non-affective psychosis patients which diagnosis clearly predominates.

Several clinical implications can be drawn from our results. First, at service entry, a significant proportion of patients had a history of suicidal behaviour and suicidal behaviour in the last month. Thus, at the intake of early intervention teams, all patients should undergo a suicide risk assessment. For those at high risk or experience of previous suicidal behaviour, more intensive monitoring and intervention should be offered. Second, given that baseline depression was found to be a predictor of suicidal behaviour, routine assessments for depression should be offered in early intervention teams, and for those with positive screening, close monitoring of the emergence of suicidal behaviour and adequate treatment should be offered. Third, our results also indicate that an evaluation of total cholesterol should be included in the baseline evaluation of FEP patients, not only for the metabolic evaluation but also as a potential predictor of suicidal behaviour. Therefore, patients with low cholesterol should be screened and closely monitoring for the existence and emergence of suicidal behaviour.

The results of this study should be interpreted with some methodological limitations in mind. First, the evaluation of suicidal behaviour (including suicidal ideation, suicide plan and suicide attempt) was mainly obtained from the participants'

self-reports and, thus, was subject to the problem of under-reporting. Second, standardised classification algorithms for suicidal intent, attempts and completed suicides were not used in this research. These algorithms were found to enhance the reliability of the suicidal behaviour assessment. Third, the relatively high proportion of follow-up losses from 118 participants at baseline to 60 at the 12-month follow-up could have limited the results by reducing in some extension the statistical power of the results. Fourth, we studied the predictors of suicidal behaviour, including suicidal ideation, plans and attempts, as a whole group. It was hypothesised that predictors of suicidal ideation, suicide plans and attempts might differ. Fifth, the low numbers obtained regarding suicidal behaviour during follow-up, namely no completed suicide and only 13.3% of participants reporting suicidal behaviour at the 12-month follow-up evaluation. These numbers compromised the statistical power of the study, which could explain the non-significant associations with sex, age of FEP and DUP in our study. Sixth, other important variables that might be potential predictors of suicidal behaviour were not studied because of the difficulties involved in obtaining them, including childhood abuse or previous trauma. Seventh, the use of self-assessment tools in actively psychotic patients may also be considered limiting, as psychotic symptoms may condition the answers given. Although it was not possible to completely overcome this limitation, we tried to assess the patients when there was some clinical stability, i.e. when the psychotic symptoms, despite existing, interfered less in their behaviour and, therefore, on their answers. However, this period of greater clinical stability may have also reduced the symptoms and, therefore, conditioned the results.

Conclusions

Our results showed that a large proportion of FEP patients had a history of suicidal behaviour or had current baseline suicidal behaviour. We also verified that depression was prevalent in the 12 months after FEP. Our results are in line with those of previous studies, confirming that a history of suicidal behaviour and depression soon after FEP are associated with suicidal behaviour in the early months after FEP. These findings are important for the development of early intervention programmes to lower the risk of suicide and depression in FEP patients. Our finding regarding the predictive role of baseline total cholesterol should be investigated in further prospective research to determine whether our result was predictive of suicidal behaviour.

Supplementary Table Comparison of socio-demographic and clinical baseline characteristics between affective psychosis and schizophrenia spectrum disorders diagnoses

	Affective psychosis (n=21)	Schizophrenia spectrum disorders (n=58)	p-value
Age mean (SD)	31.52 (8.66)	25.50 (6.66)	0.005
Gender female/male n (%)	94(42.9)/12(57.1)	8(13.8)/50(86.2)	0.005
Education mean (SD)	12.00 (3.59)	10.81 (2.98)	0.078
DUP median (SD)	34.00 (138.55)	172.00 (859.13)	0.007
Cannabis use n (%)	12 (57.14)	36 (62.0)	0.692
PANSS positive mean (SD)	19.05 (8.63)	21.55 (7.14)	0.201
PANSS negative mean (SD)	16.29 (7.82)	17.67 (6.95)	0.365
PANSS general mean (SD)	39.62 (11.28)	35.81 (7.47)	0.345
GAF mean (SD)	46.90 (17.50)	40.88 (18.68)	0.194
BDI mean (SD)	14.67 (8.21)	12.24 (10.60)	0.160
Depression n (%)	12 (57.1)	22 (37.9)	0.143
Suicidal behaviour baseline n (%)	9 (42.9)	11 (18.9)	0.031
History suicidal behaviour n (%)	11 (52.4)	18 (31.03)	0.080

Abbreviations: DUP = Duration of untreated psychosis; PANSS = Positive and Negative Syndrome Scale; GAF = Global Assessment of Functioning; BDI = Beck Depression Inventory; SD = standard deviation.
Schizophrenia-spectrum disorder included schizophrenia, schizophreniform disorder, delusional disorder and schizoaffective disorder
Affective psychosis included bipolar disorder with psychotic symptoms and depressive disorder with psychotic symptoms

CAPÍTULO 3. Síndroma metabólica após o primeiro episódio psicótico: resultados de um estudo longitudinal a 1 ano

Artigo:

Metabolic syndrome following a first episode of psychosis: results from a 1-year longitudinal study condicted in metropolitan Lisbon, Portugal

Ricardo Coentre, Pedro Levy, Carlos Góis, Maria Luísa Figueira

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Title:

Metabolic syndrome following a first episode of psychosis: results from a 1-year longitudinal study conducted in metropolitan Lisbon, Portugal

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Abstract

Objective: The key aim of this study is to make an assessment of metabolic syndrome (MetS) prevalence and its course as well as to study metabolic parameters throughout a one-year-long period following the first-episode psychosis.

Methods: This one-year longitudinal study involved 60 patients with first-episode psychosis. It used the MetS defined by the National Cholesterol Education Program Adult Treatment Panel III (modified definition). The study assessed metabolic measures, socio-demographic and psychopathologic data.

Results: The average age of the included patients was 27.1 years, 33.3% of them were female. There was an increase in MetS prevalence from 6.7% to 11.7%, at the baseline and at the 1-year follow-up correspondently. There was also a significant increase from baseline to 1-year of follow-up in the prevalence of abnormal triglycerides levels, abnormal waist circumference, and abnormal HDL. There was considerable worsening of the mean levels of metabolic measures in the course of the follow-up. The study did not reveal any baseline factors which are MetS predictors at the 1-year follow-up.

Conclusions: On the basis of the study findings, it is possible to conclude that the rate of metabolic disturbances in FEP patients is high; moreover, the first year after the disease demonstrates prompt worsening.

Keywords

First-episode psychosis; Metabolic syndrome; Schizophrenia; Cardiometabolic risk;

Introduction

According to the previous studies, life expectancy of patients with psychotic diseases, in particular schizophrenia, is from 13 to 30 years shorter than that of the general population [97,324]. Moreover, as contrasted with the general population, mortality risk in the patients with schizophrenia are two or even three times higher [95,325,326] . The key factors that predetermine this reduction are cardiovascular diseases and suicide [218]. In the course of the last twenty-five years, the risk of suicide has increased 18 times. However, with the exception of natural causes of death and suicide, high rates of morbidity and mortality in the patients with schizophrenia are mostly affected with heart disease [327,328]. The mortality rate from coronary heart disease is significantly higher in schizophrenia patients than in the general population [328]. Metabolic syndrome (MetS) can be defined as a combination of risk factors which can effectively predict cardiovascular diseases and subsequent growth in the risks of cardiovascular mortality and morbidity [329,330]. Clinicians use screening and corresponding treatment of MetS to ensure considerable reduction in the cardiovascular mortality at the early stages. It is essential to ensure adequate and timely screenings in the patients with mental diseases; otherwise, the opportunities to help can be lost. In addition, there are certain barriers to overall metabolic monitoring when it goes about psychotic patients [331,332]. This population faces numerous challenges in obtaining properly integrated healthcare services. Therefore, since metabolic screening requires urgent improvements, it is highly recommended to reorganize the service in its current status, enhance communication, improve the incentives, raise the level of education and corresponding training, boost the accreditation, and encourage the government leadership initiatives. There is no unanimous opinion whether the patients with psychotic disorders are subject to higher risk of cardiovascular diseases because of

the antipsychotic treatment, effects of the inadequate lifestyle, and/or their psychotic disorders [333].

There have hardly been any significant longitudinal studies devoted to the first-episode psychosis and observance of the prevalence of MetS and factors related to it notwithstanding numerous clinical implications. Moreover, the outputs of the conducted studies are rather contradictory. Our goal was to involve the patients in their routine clinical care to resolve the problem of limitations in the already published studies devoted to the present problem. Firstly, most of the studies were cross-sectional; hence, causal associations were specified with specific limitations in design [202,334–337]. Second, the majority of published studies have only examined patients with schizophrenia [200,201,334–336,338]. Taking into consideration the fact of diagnostic instability in first-episode psychosis as well as a diagnostic shift typical for a significant part of the patients, it is a matter of crucial concern to conduct thorough research and study in a wider spectrum of affective and non-affective psychosis to ensure a more accurate evaluation of MetS prevalence in the patients with FEP [339]. Thirdly, the studies conducted previously cannot be trustworthy at the current state as the realities of routine clinical practice have changed. In the majority of studies, in-stay patients were included while those who did not require hospitalization or patients with milder forms of a disease were excluded.

Thus, our longitudinal study was designed to cover real FEP patients and make an assessment of the MetS prevalence and course along with the key metabolic parameters throughout the first year of the psychotic disorders. Furthermore, our study had to cover the development of syndromes and metabolic measures in the first year after the disease. Finally, we aimed to specify potential baseline factors capable of predicting transformations in the metabolic profiles of patients with FEP at the early stages.

Material and methods

Participants

The setting of this prospective observational longitudinal study was health care facilities in hospitals of Portugal with two psychiatric departments. Two teams of early intervention were involved in the study: Centro Hospitalar Universitário Lisboa Norte in the Programa de Intervenção nas Fases Iniciais da Psicose (PROFIP) and Hospital Vila Franca de Xira at the first-episode psychosis program (PPEP). A tertiary care university hospital Centro Hospitalar Universitário Lisboa Norte has a catchment area of approximately 350,000 people. The PROFIP program is presented and explained in a published previous article [74]. A secondary care general hospital Vila Franca de Xira Hospital located in Lisbon in its northern metropolitan area has a catchment area of approximately 245,000 people.

The trained staff assessed patients with FEP. The constituent parts of the programs were group and individual psychosocial treatments, low-dose of atypical antipsychotic medication and family intervention. This study used 60 patients admitted to the hospital with PROFIP (n = 33) and PPEP (n = 27) as a sample.

The baseline criteria for inclusion of the participants were the following: 1) the age range from 16 to 40; 2) diagnosis of a first psychotic disorder DSM-IV (American Psychiatric Association, 1994), in particular delusional disorder, schizophrenia, bipolar psychotic disorder, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, *major* depressive disorder with psychotic features, or psychosis induced with cannabis, and 3) place of residence limited to the catchment of the PROFIP and PPEP services. The study excluded the patients unable to complete or understand the required assessments or those with organic psychosis.

Evaluation of the patients for the study was done twice: at the time of the baseline assessment provided that when there were adequate conditions for completing the assessment and FEP was clinically stabilized and the next time was a year after. The patients were eligible for the study provided that they met the criteria in the period from January 2017 to April 2018. This study got the approval from corresponding ethical committees in each of the hospitals and complied with the Declaration of Helsinki in its ethical principles of good practice. Every study participant wrote and signed an informed consent to take part in the assessments.

Clinical measures

The clinical and sociodemographic information was collected at baseline with a questionnaire completed by the research staff. The required details were age, marital status, employment, education, previous hospitalizations, use of cannabis and tobacco, and family history of psychiatric diseases. The assessments of waist circumference and blood pressure were made twice: at baseline and in the course of a 1-year follow-up. The measurement of waist circumference was done in the standing position at the final stage of normal expiration, midway between the superior border of the iliac crest and inferior costal margin. Recording of blood pressure was done with an automatic manometer in the supine position. The Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT+) instrument was used to obtain the diagnosis [281,282]. The checklist ratings were entered into the OPCRIT+ software, which generates a diagnosis for the main categories of affective and psychotic disorders, as defined by the DSM-IV, which is the *major* classification system. For every patient Global Assessment of Functioning (GAF), and Positive and Negative Syndrome Scale (PANSS), at the two stages of evaluation were completed [283,289]. The patients also completed the self-administered Beck

Depression Inventory (BDI) [284]. We used the Portuguese translated and adaptation version of this scale [285,286].

Metabolic assessments

The study was based on the modified definition of MetS given by the National Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III) [163,340]. The patients receive the diagnosis of MetS only in case they meet three or more out of the following criteria: 1. Waist circumference (>102 cm for male and >88 cm for female). 2. Level of serum triglyceride ≥150 mg/dL or corresponding treatment. 3. Increased blood pressure (≥85 mmHg - diastolic or ≥130 mmHg - systolic) or corresponding treatment. 4. Reduced cholesterol with high-density lipoprotein (HDL) (<40 mg/dL for male and <50 mg/dL for female) or corresponding treatment. 5. Increase in the level of fasting serum glucose (≥100 mg/dL or diabetes mellitus type 2 diagnosed)

An overnight fasting was an obligatory requirement to collecting blood samples. An assigned technician not involved in clinical evaluation took all the measurements of laboratory parameters. Analysis of all results, in particular the level of total cholesterol, blood glucose, triglycerides (TG), low-density lipoprotein cholesterol (LDL), and HDL was done for every study participant. Measuring the levels of TG, HDL and total cholesterol was done in serum via the use of an enzymatic assay. The Friedewald equation was used to calculate the LDL levels [341].

Statistical analysis

Continuous and categorical variables were given as mean values with standard deviations and frequencies correspondently. Evaluating the data distribution for normality was done with the use of Kolmogorov-Smirnov test. Based on the level of confidence

(95%), expected prevalence of metabolic syndrome (15%) and precision (5%) we calculated the sample size needed. Analysis of differences in metabolic parameters was made with the use of Wilcoxon matched pairs signed rank test to compare the patients at baseline and follow-up. Comparison between the MetS prevalence and abnormal metabolic measures was made with the use of McNemar's test at the levels of baseline and follow-up. Stepwise multiple regression analysis was used, in which psychopathology, metabolic measures, and demographic characteristics were used as predictors at baseline and MetS at 1-year follow-up served as a dependent variable. A statistical significance criterion for the study was $p<0.05$. Analysis of all relevant data was made with the IBM SPSS Statistics software (version 24).

Results

Patients

At the baseline level, 33.3% of the patients were female. The average age of the patients was 27.1. The majority of patients (95%) had a hospitalization at baseline. Duration of untreated psychosis (DUP) had a mean duration of approximately 312.87 days. Schizophrenia spectrum disorders were the dominant diagnosis (50% of patients). All clinical and demographic characteristics of the participants at the baseline level are given in Table 1.

Table 1. Socio-demographic and clinical baseline variables of the sample

Variables	First-episode psychosis patients n=60
Age mean (SD)	27.10 (7.93)
Gender n (%)	
Female	20 (33.3%)
Male	40 (66.7%)
Education years - mean (SD)	11.28 (3.34)
Unemployment - n (%)	24 (40%)
Marital status – n (%)	
Living with partner/Married	6 (10%)
Single/Divorced	54 (90%)

Hospitalization baseline - n (%)	
Yes	57 (95%)
No	3 (5%)
Tobacco – n (%)	
Yes	34 (56.7%)
No	26 (43.3%)
Cannabis use - n (%)	
Yes	37 (61.7%)
No	23 (38.3%)
Psychiatric family history – n (%)	43 (71.7%)
DUP – days, mean (SD)	312.87 (722.74)
Diagnoses - n (%)	
Schizophrenia spectrum diagnosis	30 (50%)
Affective psychosis spectrum diagnosis	16 (26.7%)
Other psychosis diagnosis	14 (23.3%)
PANSS score - mean (SD)	
PANSS positive subscale	19.08 (7.321)
PANSS negative subscale	17.38 (7.11)
PANSS general subscale	36.22 (9.031)
GAF - mean (SD)	47.43 (17.272)
BDI - mean (SD)	13.55 (10.453)

SD, standard deviation; DUP, duration of untreated psychosis; PANSS, positive and negative syndrome scale; GAF, global assessment of functioning; BDI, Beck Depression Inventory.
Schizophrenia spectrum disorders included schizophrenia, schizophreniform disorder, delusional disorder, and schizoaffective disorder. Affective psychosis included bipolar disorder with psychotic symptoms and depressive disorders with psychotic symptoms. Other psychosis included acute and transient psychotic disorders, brief psychotic disorders, and psychosis not otherwise specified.

Metabolic profile of patients over the 1-year period

Table 2 presents analysis of the sample with all laboratory measurements at baseline and one-year follow-up. There was an increase in metabolic syndrome prevalence from 6.7% to 11.7% at baseline and follow-up respectively. However, the difference was not significant statistically (p=0.250). Beyond fulfilling all criteria, more than 8.3% at baseline and 15% at follow-up had two MetS criteria. The follow-up stage demonstrated worsening of all metabolic parameter. Still, statistical significance was characteristic only of the parameters of triglycerides (p=0.042), mean waist circumference (p<0.001), and decreased mean levels of HDL cholesterol (p=0.028). There was a significant increase in the prevalence of abnormal values for triglycerides (p=0.040), waist circumference (p=0.039), and HDL (0.019) from the level of baseline to the level of 1-year of follow-up.

In both assessments, the metabolic syndrome prevalence was lower in women; however, there was no statistical significance of these gender results at baseline (p=0.291, 0% female vs. 6.7% male) and at follow-up (p=0.57, 3.3% female vs. 8.3% male).

Comparison of prevalence of MetS both at baseline (affective psychosis 12.5% vs. non-affective psychosis 4.8%; p=0.287) and follow-up (affective psychosis 23% vs. non-affective psychosis 10%; p=0.370) between affective psychosis spectrum disorders and non-affective psychosis diagnostic groups did not show significant statistical differences (Fisher´s exact test for both evaluations).

Table 2. Metabolic parameters on baseline and 12-month follow-up

Parameters	Baseline n=60	12-month n=60	p value
Obesity			
Waist circumference, cm – mean (SD)	83.58 (10.14)	102.50 (99.41)	<0.001*
Abnormal waist circumference (≥102cm M, ≥88cm F) – n (%)	6 (10%)	13(21.7%)	0.039*
Serum triglycerides (mg/dL) – mean (SD)	78.37 (37.27)	96.92 (66.31)	0.042*
Abnormal triglyceride levels (≥150 mg or treatment) – n (%)	4(6.7%)	6 (10%)	0.040*
Serum HDL Cholesterol (mg/dL) – mean (SD)	52.88 (13.11)	50.08 (12.11)	0.028*
Abnormal lower HDL (<40mg M, <50mgF) – n (%)	13(21.7%)	15(25%)	0.019*
Blood pressure (mmHg) – Mean (SD)			
Systolic	122.18 (13.50)	123.17 (13.01)	0.583
Diastolic	66.15 (10.16)	68.02 (9.80)	0.190
Abnormal blood pressure (≥130/85 or treatment) – n (%)	19(31.7%)	21(35.0%)	0.990
Fasting plasma glucose (mg/dL) – mean (SD)	89.42 (13.87)	90.33 (8.07)	0.338
Abnormal fasting blood glucose levels (≥100mg or diabetes) – n (%)	3(5.0%)	8(13.3%)	0.344
MetS – n (%)	4 (6.7%)	7 (11.7%)	0.250
Number of MetS criteria – n (%)			
0	29 (48.3%)	24 (40%)	
1	22 (36.6%)	20 (33.3%)	
2	5 (8.3%)	9 (15.0%)	
3	3 (5.0%)	5 (8.3%)	
4	1 (1.7%)	2 (3.3%)	
5	0 (0%)	0 (0%)	
TG/HDL	1.48	1.94	

SD, standard deviation; HDL, high-density cholesterol; MetS, metabolic syndrome; TG, triglycerides; *p<0.05

Predictors of MetS

We exerted effort to specify the MetS baseline predictors on follow-up. MetS served as a dependent variable with such predictors as age, period of education, gender, marital status, participation in diagnostic groups, family history of psychiatric diseases, use of tobacco and cannabis, BDI and GAF scores, PANSS subscales scores at the baseline, DUP, all MetS metabolic and anthropometric parameters at the baseline. Multivariate analysis included all factors which had $p<0.15$ on univariate analysis. Potential predictors on univariate analysis were DUP ($p=0.119$), period of education ($p=0.126$), baseline waist circumference (0.006), baseline general subscale of PANSS ($p=0.132$), baseline systolic blood pressure ($p=0.055$), and baseline HDL (0.017). No factor was significant on multivariate binary logistic regression as baseline predictor on the MetS on follow-up.

Psychopharmacological treatment

In both assessments, the treatment of all patients was done with atypical antipsychotics, with the domination of oral route (75% and 63.3% at baseline and follow-up respectively). On both evaluations, the patients were prescribed with risperidone as the most atypical antipsychotic alone or with other medicine orally (45% and 26.7% at the baseline and follow-up levels). The injectable antipsychotics were intra-muscular long-acting aripiprazole and paliperidone. Table 3 shows all the prescribed psychopharmacological treatments at baseline and follow-up.

Table 3. Psychopharmacological treatment in the baseline and in the 12-months of follow-up

	Baseline	12-months follow-up
Antipsychotic treatment – n (%)		
Atypical antipsychotic	60 (100%)	60 (100%)
Route of antipsychotic – n (%)		
Only oral	45 (75%)	38 (63.3%)
Only LA IM	1 (1.7%)	11 (18.3%)
Both	14 (23.3%)	11 (18.3%)
Type of atypical antipsychotic – n (%)		
Clozapine oral	2 (3.3%)	5 (8.3%)
Olanzapine oral	14 (23.3%)	11 (18.3%)
Quetiapine oral	1 (1.6%)	9 (15.0%)
Risperidone oral	27 (45.0%)	16 (26.7%)
Paliperidone oral/IM	12 (20.0%)	18 (30%)
Aripiprazole oral/IM	17 (28.3%)	15 (25.0%)
Amissulpride oral	1 (1.7%)	1 (1.7%)
Chlorpromazine equivalents, mean dose (SD) – mg [342,343]	295.42 (220.63)	297.37 (236.02)
Patients with other treatments – n (%)		
Anticholinergics	6 (10%)	17 (28.3%)
Antidepressants	12 (20%)	21 (35%)
Mood Stabilizers	3 (5%)	4 (6.7%)
Benzodiazepines	3 (5%)	3 (5%)

LA: long acting; IM: intra-muscular; SD: standard deviation

Discussion

One of the novelties of this study is that research on the MetS prevalence and metabolic parameters studied in the patients with non-affective and affective FEP longitudinally was done for the first time in Portugal. MetS prevalence in this study was 6.7% at the baseline with a subsequent increase up to 11.7% in the course of the one-year follow-up. This obtained result has no statistical significance, but it shows a tendency of the growing MetS prevalence in almost three-fourths of the involved patients twelve months after FEP. One more output of the research also demonstrated the worsening of mean levels of HDL, triglycerides, and waist circumference from the baseline level to a one-year follow-up along with the prevalence of abnormal measures. The obtained findings emphasize high risks of getting cardiovascular diseases at the early stages of

psychosis and quick decline in the metabolic profile at this phase of the disorder. According to the obtained results, the idea that patients with FEP have predisposition to metabolic dysfunction at the first stages is valid.

The obtained results are in line with the previous publications of longitudinal studies [335,344–347]. There is a 6.6% MetS prevalence reported by Bioque et al. in FEP patients at the baseline level and at the level of two-year follow-up it equals to 14.6% with a corresponding 120% increase according to the criteria of International Diabetes Federation [345]. There is a 2.3% MetS prevalence reported by a Brazilian study in FEP patients at the baseline level and at the level of 6-month follow-up it equals to 9.1% with a corresponding increase of almost three times according to the criteria of NCEP [344]. Both studies reveal worsening of the overall metabolic measures from the baseline level to the level of follow-up, which our study confirmed. Our study demonstrates a 75% increase in MetS prevalence, while the majority of other studies also demonstrated great increases in MetS prevalence at the early stages of psychosis (in the follow-up periods that lasted from half a year to two years). This study had a finding of MetS incidence (5%) which is relevant to that in other studies if the length of the follow-up period was identical (from 3.95% to 5.5%) [348,349]. The studies did not find any significant predictors either at the baseline level or at a 1-year follow-up.

Few studies in Portugal were devoted to the MetS prevalence in comparison with the general population. The research of MetS prevalence in the Valsim cross-sectional multi-center study involved patients from Portuguese primary care facilities (n=16,856); it revealed 6.2 % prevalence in patients at the age range from 18 to 29 [169]. There is similarity of the results we obtained in our study that involves the patients with first-episode psychosis at assessment of the baseline level, but it was almost two times higher at the level of a one-year follow-up. PORMETS (The Portuguese Metabolic Syndrome

Study) cross-sectional study is another recent research devoted to the analysis of MetS prevalence in primary care of all regions in Portugal with 4004 patients involved [170]. The obtained results demonstrated a 5% and 16% MetS prevalence in the patients aged 18-30 and 31-40 respectively. According to our results, in comparison with the general population, the MetS prevalence in these patients is higher; however, this difference becomes evident only in a year. The most commonly criterion of MetS found in PORMETS study was high blood pressure, while in our research the result was different as we found abnormal waist circumference as the most common criterion. PORMETS and Valsim studies covered primary care users in a clinical sample; thus, the level of MetS prevalence is probably higher in comparison with that in general population of Portugal. In addition, there is a significant difference between the MetS definitions. MetS is interpreted according to the ATP-III definition in the Valsim study and the HARM2009 definition in PORMETS study [163,177]. MESYAS research is one more cross-sectional study which is related to general population as it involved 7,256 people from the working population of Spain with the modified ATP-III definition of MetS [163]. The study involved a group of the age range from 20 to 39 and it found a 2.5%–5% MetS prevalence [350]. The results of our study found higher rates of MetS than this study although the definition is the same. All the mentioned studies demonstrate that the MetS prevalence rate we have estimated in the one-year follow-up period after first-episode psychosis raises a lot of concerns.

The publications reveal one more distinct aspect, which is the manner of transformations in the lipid profile components in the course of a follow-up period. It means that it is essential to note decline in HDL cholesterol and evolution of the growth of triglycerides. That leads to an increase in the ratio between triglyceride and HDL. It is crucial to note that HDL and triglyceride ratio is an independent predictor of

cardiovascular problems and mortality[351] as well as an atherogenic marker [352,353]. Our study shows that the TG/HDL ratio had high values (baseline - 1.48; one-year follow-up - 1.94) which are in line with the cardiovascular risk factors in the patients.

According to our results, men showed higher rates of metabolic syndrome prevalence, but they had no statistical significance at the baseline level (p=0.291, 0% female vs. 6.7% male) and follow-up levels (p=0.571, 3.3% female vs. 8.3% male). The obtained findings on early psychosis are in line with those from the previous published studies [354,355]. On the other hand, the early stages demonstrated worse metabolic profile in the male groups in our study and other previous researches [345,356]. Our results are in line with those obtained on the basis of studies on general population [357].

At the early stage, namely in the first days of treatment, the researchers made baseline evaluation; thus, it had little effect of antipsychotic medication. It is possible to assume that the medication could be one of the factors that determine high incidence rate of metabolic syndrome at the stage of follow-up. Still, in both assessments, the treatment of most patients included only medications with medium or low metabolic risk. Because the incident cases were few, there was no further analysis made on antipsychotic medications.

The measures of abnormal glycemic homeostasis, in particular oral glucose tolerance test, was offered as one of the effective ways of evaluating cardiovascular and metabolic risks in patients with FEP in the study of Garcia-Rizo et al.[335]. The results of this cross-sectional study revealed metabolic syndrome prevalence as contrasted with the control group of the study. In a sample of the study with 84 patients with FEP patients, the values of glucose homeostasis had a great difference with them. To some extent, the results we obtained are contradictory, but our study did not include any use of Homeostatic Model Assessment, oral glucose tolerance tests, or any other glycemic

homeostasis measures. We point out that the tool of a metabolic syndrome is valuable in assessing the risks for cardiovascular issues in patients with FEP. One more essential point of our longitudinal study is that performance of parameters related to metabolic syndrome is feasible in clinical practice of psychiatric research unlike the glycemic homeostasis tests.

Limitations

One of the limitations of our study was the sample size that determined the statistical value of predictors and other measures as well as the effect of the antipsychotic treatment. In addition, the comparison between the MetS in psychiatric groups requires the data from control groups. We attempted to compare our study with another one devoted on primary care research in order to overcome the issues related to the current limitation. Finally, we did not monitor potential confounding factors as physical inactivity and diet.

Conclusions

According to our findings, the rates of metabolic disturbances in FEP patients are high. They are also associated with a fast worsening of the mentioned measures at the early stages. It is recommended to conduct more studies to analyze the type of required interventions and their effect on metabolic measures and assess the effects on patients with FEP in terms of morbidity and mortality related to cardiovascular diseases.

DISCUSSÃO

O presente trabalho procurou estudar o comportamento suicida e a síndroma metabólica nos 12 meses seguintes após o PEP. Estudos publicados demonstram que o suicídio e as doenças cardiovasculares são das principais causas de morte nos doentes psicóticos, com particular risco nos primeiros anos de doença. Assim, considerando o comportamento suicida e a síndroma metabólica como importantes fatores de risco para o suicídio e doença cardiovascular respetivamente, o seu estudo e conhecimento mais aprofundado, poderá permitir definir populações de risco e desenhar estratégias para prevenir o suicídio e a doença cardiovascular nos doentes com perturbações psicóticas. Este facto terá potencial impacto positivo na morbilidade e mortalidade destes doentes.

A revisão sistemática da literatura confirmou que o comportamento suicida, assim como os sintomas depressivos, têm elevadas taxas após o PEP. A literatura existente demonstra uma associação entre o comportamento suicida após o primeiro episódio psicótico e tentativas de suicídio prévias, abuso sexual, uso de substâncias, baixo nível de funcionamento pré-mórbido, doentes com idade mais avançada, eventos de vida negativos, longa DUP, mais sintomas positivos e negativos, história familiar de doença mental grave e sintomas depressivos. Apesar da importância do tema, verifica-se a existência de poucos estudos originais longitudinais, e os estudos publicados têm importantes limitações metodológicas já referidas (ex. inclusão de apenas PEP não afetivo, inclusão apenas de doentes hospitalizados etc.) que procurámos ultrapassar no presente trabalho.

Assim, o primeiro ponto estudado foi a prevalência do comportamento suicida e sua evolução nos primeiros 12 meses após o PEP. Procurou-se também identificar fatores preditores do comportamento suicida no PEP (*baseline)* e a 12 meses. O segundo ponto investigado foi a prevalência da síndroma metabólica e sua evolução nos primeiros 12 meses após o PEP. A síndroma metabólica constitui um importante *cluster* de fatores de risco cardiovasculares que é altamente preditiva do desenvolvimento de doenças cardiovasculares. Procurou-se também identificar eventuais fatores preditores da síndroma metabólica.

Quanto ao primeiro ponto da investigação, a prevalência de comportamento suicida, identificada através de um instrumento com três questões sobre ideação, plano e tentativa de suicídio, complementada com a consulta dos processos clínicos dos doentes, encontrou no PEP (*baseline)* o valor de 25,4%. Esta prevalência está em linha com outros estudos publicados internacionalmente [239,254,260,292,320]. No trabalho de Melle *et al.* em 2010, foram estudados 118 doentes com primeiro episódio psicótico não afetivo [260]. Tal como

no nosso trabalho, o comportamento suicida foi avaliado por um questionário com 3 perguntas sobre ideação, plano e tentativa de suicídio, que foram complementadas com informação dos processos clínicos. No grupo de doentes com área geodemográfica com intervenção precoce na psicose, a prevalência de comportamento suicida no PEP foi de 32%.

No nosso estudo fica bem evidente que existe uma elevada prevalência de comportamento suicida nos doentes que sofrem um PEP. Mesmo considerando que alguns eventuais doentes não foram identificados, pelo caracter auto-avaliativo do instrumento utilizado, e que nem todos os processos clínicos façam esta referência, sobretudo em casos menos graves, encontrámos valores que indicam que cerca de 1 em cada 4 doentes com PEP apresenta comportamento suicida na avaliação efetuada logo após a estabilização clínica do PEP. Os métodos usados nas tentativas de suicídio nesta fase são sobreponíveis aos referidos em estudos similares noutros países, tendo sido os mais encontrados a intoxicação medicamentosa, tentativa de enforcamento e a defenestração [320]. Alguns estudos demonstram que o enforcamento, como método de plano e tentativa de suicídio, representa um importante preditor para suicídio consumado em fases posteriores das perturbações psicóticas [124].

O presente trabalho indica também que houve uma redução significativa do comportamento suicida durante os 12 meses de seguimento após o PEP, de 25,4% para 13,3% (p=0,035). Ocorreu assim uma redução para cerca de metade no comportamento suicida durante os 12 meses de seguimento. Esta redução é regra em todos os trabalhos publicados, sendo a sua magnitude diferente entre os estudos, mas quase sempre significativa em termos estatísticos. Os valores da redução do comportamento suicida dos estudos já publicados noutros países são algo heterogéneos, mas existem reduções em dimensão sobreponível à encontrada na nossa investigação [239,250]. Estes resultados parecem corroborar que o comportamento suicida é maior no período imediatamente após o PEP e que com o tempo de doença e seu tratamento ocorre uma redução da sua magnitude. Todavia é importante notar que apesar desta redução com o tempo, os trabalhos com períodos de seguimento longos mostram ainda taxas de comportamento suicida consideráveis [142]. Não foi verificado nenhum suicídio consumado no nosso estudo durante o *follow-up* na amostra de doentes seguidos no período de 12 meses após PEP. Este achado não é único, mesmo em estudos com períodos de seguimento mais longos [269]. A generalidade dos estudos refere taxas de incidência de suicídio a 2 anos que variam entre 0% e 4,3% [118,237]. Uma justificação para estes relativos baixos valores de incidência

de suicídio pode dever-se ao facto de a população estudada ser derivada de uma população clínica, tratada na maioria em equipas de intervenção precoce na psicose. Estas equipas estão particularmente treinadas para a avaliação de doentes com PEP e elevado índice de suspeição de comportamento suicida nestes doentes. Vários estudos demonstram que os números de comportamento suicida são significativamente mais baixos em comunidades onde existem estas equipas de intervenção precoce na psicose [260,276].

Face aos resultados do nosso trabalho confirmámos a hipótese colocada em que a prevalência e evolução do comportamento suicida nos 12 meses após o PEP é similar aos estudos de outros países europeus e superior à população em geral para o mesmo escalão etário.

A história anterior de comportamento suicida e depressão são os mais robustos fatores encontrados associados ao comportamento suicida no PEP [124,235,236,239,245,358]. Similarmente, a presente investigação encontrou a história de comportamento suicida como preditor de comportamento suicida no PEP e a 12 meses. Tendo também a depressão sido encontrada como preditor do comportamento suicida na avaliação no PEP (*baseline)*. A depressão tem sido extensamente demonstrada como fator de risco conhecido para comportamento suicida na psicose, com a sua existência nos doentes psicóticos associada a comportamento suicida. O presente trabalho encontrou prevalência de depressão, considerando a sua existência para cotações do Inventário de depressão de Beck superior a 14, de 43,3% na avaliação no PEP (*baseline)* e de 20% a 12 meses. Estes valores elevados encontrados são sobreponíveis aos resultados de estudos internacionais efetuados com amostras de doentes com PEP e no período após este [228,359]. Na investigação em discussão verificou-se também que o comportamento suicida na *baseline* foi o único fator preditor com relevância estatística encontrado para depressão na avaliação no PEP (*baseline)* e na análise multivariada. Contudo na avaliação univariada também a história de comportamento suicida anterior ao PEP (para além do comportamento suicida na *baseline*) foi considerada como associada a depressão. Estes resultados parecem corroborar a hipótese do modelo de comportamento suicida mostrado na figura 2., pelo menos nos primeiros meses após o PEP, considerando a depressão como um fator chave na interface entre a psicose e o comportamento suicida.

Para além dos fatores preditores em relação ao comportamento suicida, nos últimos anos tem sido estudada a trajetória do comportamento suicida ao longo do tempo, após o PEP. A este propósito é importante referir o estudo de Madsen et *al.*, que analisou as possíveis trajetórias da ideação suicida após o PEP, numa amostra de 547 doentes com

PEP, do conhecido OPUS Trial, na Dinamarca [360]. No recrutamento deste estudo os participantes eram questionados sobre a ideação suicida durante o ano anterior e depois de novo aos 1 e 2 anos. Foi possível identificar 3 grupos de doentes de acordo com a trajetória da ideação suicida. No primeiro grupo, a que os autores designaram "*low-decreasing*", que incluiu 61% dos participantes, os doentes tinham ideação suicida uma vez a poucas vezes no ano anterior à sua inclusão no estudo. Estes doentes apresentaram uma redução quase para inexistência de ideação suicida ao final de 2 anos de *follow-up*. Um segundo grupo (33%), designado "*frequent-stable*", representando uma segunda trajetória, incluiu os doentes que referiam ideação suicida poucas a muitas vezes no ano anterior à inclusão no estudo. Nestes participantes a ideação suicida não mostrou alterações nos dois anos de seguimento. O terceiro grupo (6%), designado de "*frequent-increasing*", incluiu doentes que referiam ideação suicida muitas vezes antes da inclusão no estudo, e com o aumento da frequência da ideação suicida para frequente a muito frequente após os 2 anos de seguimento. Estes grupos poderiam ter assim diferentes associações com o suicídio propriamente dito anos mais tarde, podendo os grupos "*frequent-stable*" e "*frequent-increasing*", ser preditores de suicídio no futuro. Este facto foi verificado, mas sem poder estatisticamente significativo. Por extrapolação desta divisão nestes três grupos de possíveis trajetórias para o comportamento suicida e para o nosso trabalho, verifica-se que 40% dos doentes incluídos no nosso estudo que tinham comportamento suicida na *baseline* não tinham história de comportamento suicídio prévio ao PEP, e assim 60% tinha história prévia de comportamento suicida ao PEP. Por outro lado, em relação aos doentes que apresentavam comportamento suicida na avaliação a 12 meses, apenas 1 doente não tinha história prévia ao PEP de comportamento suicida. Assim, apesar do presente estudo não ter sido efetuado com a finalidade de avaliar a trajetória do comportamento suicida, podemos constatar que a maioria dos doentes da nossa amostra pertencem provavelmente aos 2 grupos considerados de "*frequent-stable*" e "*frequent increasing*". A distinção entre estes dois grupos não é possível na amostra estudada de PEP uma vez que não foi especificada a frequência do comportamento suicida antes da inclusão no estudo. Estudos usando métodos baseados na trajetória já foram usados em amostras clínicas [361], mas ainda foram pouco estudados no desenvolvimento do comportamento suicida nas perturbações psicóticas. Um melhor conhecimento na distinção das trajetórias do comportamento suicida nos doentes com psicose, e especificamente no PEP, pode ter importante implicações, ajudando a identificar os doentes com risco mais elevado e a quem devem ser particularmente dirigidas

intervenções. Assim os autores destes estudos especulam que eventuais intervenções preventivas devem ser dirigidas para os doentes dos grupos com comportamento suicida frequente no início no PEP, uma vez que são estes que apresentam maior probabilidade de persistência ou aumento deste [360].

Os nossos resultados confirmaram a hipótese colocada dos seguintes fatores preditores de comportamento suicida após o PEP: história anterior de comportamento suicida, depressão no PEP e baixos níveis de colesterol total no PEP. Os resultados obtidos não confirmaram o diagnóstico de psicose afetiva como preditor de comportamento suicida. Para este facto pode ter contribuído o baixo número de doentes incluídos com este diagnóstico.

Tendo em conta o grupo heterogéneo de diagnósticos que estão incluídos no PEP, como referido na introdução deste trabalho, procurámos como objetivo secundário estudar potenciais diferenças entre a prevalência do comportamento suicida entre os doentes com diagnósticos de psicose afetiva e não afetiva no PEP e nos 12 meses após o PEP. Os estudos de comportamento suicida na população em geral mostram que as perturbações de humor são os diagnósticos onde a prevalência do comportamento suicida é maior [362]. Os resultados encontrados confirmam só em parte a hipótese colocada de que têm maior prevalência de comportamento suicida o grupo de doentes com o diagnóstico de psicose afetiva, nomeadamente de perturbação depressiva *major* com sintomas psicóticos e perturbação afetiva bipolar com sintomas psicóticos. Assim encontrámos prevalência estatisticamente mais elevada de comportamento suicida apenas na avaliação *baseline* (42,9% versus 21,6%; p=0,0043). Estes resultados parecem ir ao encontro de outros estudos que não encontraram também diferenças estatisticamente significativas entre a morte por suicídio entre doentes com PEP afetivo e não afetivo após o PEP [112].

Em relação ao segundo ponto da investigação, os resultados evidenciam o elevado risco que os doentes em fases precoces das perturbações psicóticas apresentam no desenvolvimento de fatores de risco cardiovasculares, designadamente com critérios para MetS, e o seu rápido agravamento durante os 12 meses seguintes ao PEP.

A prevalência da MetS encontrada no presente estudo na avaliação inicial de 6,7% é sobreponível à identificada noutros estudos europeus [345]. Após os 12 meses de *follow-up* verificou-se um agravamento da prevalência da MetS para 11,7% e de todos os parâmetros metabólicos estudados (perímetro abdominal, triglicéridos, HDL, pressão arterial e glucose em jejum), quer na prevalência de valores não normais, quer no seu valor médio. Contudo apenas obtiveram resultados estatisticamente significativos, nas

diferenças entre a avaliação inicial e os 12 meses, nas prevalências de valores não normais e nas médias dos parâmetros metabólicos estudados, o perímetro abdominal, os triglicéridos e o colesterol HDL. Os resultados na avaliação a 12 meses estão em linha com outros estudos, mostrando que os primeiros meses de doença e tratamento são críticos no agravamento dos principais parâmetros metabólicos [203,345,363]. Apesar da similitude dos resultados da nossa investigação com outros estudos internacionais, nomeadamente europeus, existem outros trabalhos que mostram resultados divergentes. Este facto é patente na prevalência da síndroma metabólica com valores inferiores aos encontrados no nosso estudo. Assim, Srihari *et al*., em 2013, estudaram 76 doentes com psicose não afetiva, que foram avaliados numa equipa de intervenção precoce na psicose numa área urbana nos EUA. A prevalência inicial de síndroma metabólica, usando a definição da NCEP-ATP III, foi de 1,31% e ao fim dos 12 meses de *follow-up* subiu para 5,26% [349]. Outro estudo mais recente, de Saloojee *et al*., incluiu doentes com PEP afetivo e não afetivo, na África do Sul. Dos 36 doentes que completaram 12 meses de seguimento e tratamento verificou-se um aumento da prevalência da síndroma metabólica de 0% para 5,5% [348]. Neste estudo a definição da síndroma metabólica usada foi de *Joint Interim Statement* (JIS) [177], muito semelhante à do nosso trabalho. Estes resultados mostram uma certa heterogeneidade nos estudos publicados, em relação aos valores na primeira avaliação logo após o PEP, mas evidenciam que os resultados obtidos no nosso estudo são preocupantes. Mais consensual entre os trabalhos publicados é o relevante aumento da prevalência da síndroma metabólica nos meses seguintes ao PEP, sendo regra o seu aumento muito significativo, similar aos resultados encontrados na nossa investigação [345,348,349,364]. Os resultados no *follow-up* dos doentes com PEP mostram como os primeiros meses de tratamento são relevantes no aumento da prevalência da síndroma metabólica.

Os resultados desta investigação vão ao encontro da hipótese colocada de que a prevalência e evolução da síndroma metabólica nos 12 meses após o PEP é similar aos estudos de outros países europeus e superior à população em geral portuguesa para o mesmo escalão etário.

Tal como fizemos para o comportamento suicida, também colocámos como objetivo secundário a comparação da prevalência da síndroma metabólica entre os doentes com diagnóstico de psicose afetiva e não afetiva na avaliação *baseline* e após 12 meses do PEP. Colocámos como hipótese a não existência de diferenças significativas, uma vez que os estudos publicados em fases posteriores das perturbações psicóticas mostram prevalências sobreponíveis de MetS entre aqueles grupos diagnósticos,

designadamente entre a esquizofrenia e a perturbação afetiva bipolar [365,366]. Os nossos resultados não mostraram diferenças estatisticamente significativas, confirmando a hipótese formulada. Convém sublinhar, contudo, que os resultados encontrados mostraram prevalências de MetS consistentemente mais elevadas no grupo de PEP afetivo.

Outro resultado importante do nosso estudo foi o aumento do número de doentes com parâmetros metabólicos individuais alterados, para além daqueles que cumprem todos os critérios para MetS. Assim, em adição ao aumento da prevalência da síndroma metabólica de 6,7% para 11,7%, verificámos também um aumento do número de doentes com um ou dois parâmetros metabólicos alterados de 44,9% para 48,3%. Os principais parâmetros metabólicos estudados alterados foram o colesterol HDL e a pressão arterial, quer na avaliação no PEP (*baseline)* (21,7% e 31,7% respetivamente) quer na avaliação a 12 meses (25% e 35% respetivamente). Destes dois parâmetros metabólicos, apenas o aumento do colesterol HDL alterado se mostrou com significado estatístico (p=0,019).

Como referido na introdução deste trabalho, tem-se considerado aspetos nucleares da MetS a obesidade, nomeadamente abdominal, e a alteração do metabolismo da glucose, sendo os restantes fatores secundários a estes. Os mecanismos exatos pela qual a obesidade origina os restantes fatores de risco não são ainda conhecidos integralmente. Neste sentido, existem algumas definições da MetS que consideram obrigatório o critério de obesidade ou alteração do metabolismo da glucose. Assim na definição da IDF a obesidade abdominal é necessária como 1 dos 3 (entre os 5 possíveis) critérios requeridos para o diagnóstico de MetS, com particular ênfase na medição do perímetro abdominal [367]. Também a definição da OMS requer a presença da resistência à insulina, como evidência da alteração do metabolismo da glucose, como critério obrigatório para a MetS. A definição da MetS usada no nosso trabalho (NCEP-ATP III modificada) inclui a obesidade abdominal e alterações da glucose, como critérios entre 3 possíveis de 5, mas não como obrigatórios [340]. Os resultados do presente trabalho parecem ser favoráveis ao papel central da obesidade na etiopatogenia da MetS. Assim, verifica-se que o perímetro abdominal foi um dos três fatores que apresentaram resultados estatisticamente significativos na diferença entre as duas avaliações efetuadas. A prevalência do perímetro abdominal não normal (homens≥102cm; mulheres≥88cm) subiu de 10% na avaliação inicial para 21,7% aos 12 meses (p=0,039), e a média de 83,58±10,14 cm para 102,50±99,42 cm (p<0,001). Sendo a diferença nas médias do perímetro abdominal aquela que apresenta valores mais significativos de todas as diferenças encontradas nos

diversos parâmetros metabólicos avaliados e com significado estatístico. Nesta linha, admite-se que com um *follow-up* mais longo também as diferenças nos valores da pressão arterial e glucose em jejum se tornassem significativas em resultado do efeito da obesidade. Do mesmo modo a dimensão do aumento da prevalência de valores não normais do perímetro abdominal no período de *follow-up* efetuado foi dos mais elevados, com estes valores de prevalência a mais do que duplicarem no período de tempo considerado. Inesperadamente, não observámos uma significativa elevação da glucose em jejum, nem da prevalência de valores não normais da glucose, sugerindo que a disfunção do metabolismo da glucose é uma complicação mais tardia, comparativamente à disfunção lipídica, que mostrou valores para triglicéridos e HDL significativos.

Alguns estudos procuraram também verificar o impacto do efeito da canábis na MetS nos doentes com psicose. Assim um estudo mostrou que o risco da MetS é significativamente inferior nos utilizadores frequentes de canábis comparativamente aos utilizadores ocasionais ou não consumidores [368]. Também Vázquez-Bourgon *et al*., estudaram o efeito da canábis no peso e metabolismo no PEP não afetivo na região de Cantábria, em Espanha [369]. Neste estudo os doentes consumidores de canábis apresentaram na avaliação inicial e na avaliação a três anos valores inferiores de peso, índice de massa corporal e colesterol LDL. Aqueles doentes que descontinuaram o uso de canábis apresentaram um maior aumento no peso, IMC e triglicéridos em comparação com os que nunca consumiram e os que continuaram a consumir. Estes estudos sugerem que o uso de canábis possa produzir um efeito protetor contra o aumento de peso e as alterações metabólicas relacionadas na psicose. No nosso trabalho, todavia, não se encontraram diferenças significativas na prevalência da MetS ou parâmetros metabólicos entre aqueles doentes que usavam e os que não usavam canábis. Talvez por a percentagem de utilizadores de canábis (61,7%) ser muito elevada no nosso estudo, seria necessária uma amostra maior de doentes para se obter uma significância estatística entre o grupo de doentes que usam e os que não usam canábis.

Limitações

As principais limitações que consideramos existirem no trabalho realizado decorrem de quatro ordens. Primeiro, a relativa reduzida dimensão das amostras, poderá ter limitado os resultados encontrados. Segundo, não terem sido incluídas amostras controlo. Pensamos ter ultrapassado esta limitação com o uso de instrumentos e critérios

similares a estudos efetuados noutras populações com as quais comparámos os nossos resultados. Terceiro, as amostras estudadas apenas incluíram doentes com PEP de duas equipas de intervenção precoce da área metropolitana de Lisboa, não sendo esta representativa da realidade nacional, e devendo assim a generalização para a dimensão nacional ser feita com prudência. Quarto, a avaliação do comportamento suicida (ideação, plano e tentativa de suicídio) foi baseada num instrumento de autorrelato, com a inerente possibilidade de *viés* de memória. Para ultrapassar esta limitação procurou-se, por um lado garantir toda a privacidade e confidencialidade do instrumento usado, e por outro complementar a informação do questionário com os dados do processo clínico respetivo.

Implicações para a prática clínica

Os resultados obtidos têm implicações para a prática clínica nos cuidados aos doentes nas fases iniciais da psicose, nomeadamente no PEP e meses seguintes. O objetivo fundamental é a identificação dos doentes com particular risco de suicídio e de doença cardiovascular. Estes doentes devem ser submetidos a estratégias específicas de prevenção e tratamento.

Assim, todos os doentes admitidos com um PEP, nomeadamente em equipas de intervenção precoce na psicose, devem fazer uma completa avaliação do risco para suicídio e doença cardiovascular. Os trabalhos publicados indicam que, designadamente para o comportamento suicida, as estratégias de prevenção não devem ser universais, tornando-se imprescindível identificar cada vez melhor os doentes em risco. Assim, como demonstrado, a avaliação do comportamento suicida e seus preditores, e a MetS permitem identificar o grupo de doentes em particular risco. Esta avaliação deve incluir designadamente história prévia e atual de comportamento suicida (ideação, plano e tentativa de suicídio), avaliação de depressão comórbida no PEP e avaliação metabólica completa (incluindo colesterol total, HDL, triglicéridos, pressão arterial, perímetro abdominal e glucose em jejum).

Os nossos resultados mostram que os doentes com história prévia de comportamento suicida e diagnóstico de depressão no PEP estão em risco particular de suicídio, devendo ter assim uma monitorização intensiva e tratamento adequado. Também os doentes com valor de colesterol total baixo devem ser cuidadosamente monitorizados pela sua possível associação ao comportamento suicida.

Dada a maior prevalência da MetS nos doentes com psicose, incluindo nas fases iniciais destas perturbações, torna-se necessário o diagnóstico, monitorização e tratamento desta síndroma simultaneamente com o tratamento da doença psicótica desde as fases iniciais das mesmas. Esta atitude levará a uma redução das consequências da MetS. Uma questão relevante é qual é a melhor forma de prevenir e tratar a MetS nos doentes nas fases iniciais da psicose. Uma das primeiras atitudes será a adaptação da terapêutica farmacológica, nomeadamente antipsicótica, ao perfil da MetS de cada doente. Este facto é de particular importância naqueles doentes que já apresentam diagnóstico de MetS. Nestes doentes a utilização de fármacos com menor potencial de efeitos metabólicos deve ser uma opção, assim como o uso de doses mais baixas dos mesmos [370]. Aos doentes com critérios para MetS, devem ser implementadas as recomendações terapêuticas para a MetS referidas na tabela 3 na introdução deste trabalho. Todavia são necessários mais estudos de intervenções específicas a este nível nas fases iniciais da psicose para avaliação das particularidades nesta fase da doença psicótica. Múltiplos estudos mostram um subdiagnóstico e subtratamento das comorbilidades metabólicas dos doentes com psicose, daí ser muito importante a generalização destas boas práticas desde as fases iniciais da doença [371]. Deteção precoce, identificando doentes em risco elevado, e tratamento da MetS de acordo com as normas de orientação existentes, e potenciais especificidades de intervenção que estudos futuros demonstrem, deverão ser implementados na prática clínica desde as primeiras fases das perturbações psicóticas.

Cremos que estas medidas podem reduzir de forma significativa a demonstrada elevada mortalidade existente nas doenças psicóticas, com especial foco nas fases iniciais das perturbações psicóticas. A avaliação, monitorização e tratamento permitirá aumentar a esperança média de vida para valores mais próximos aos existentes aos pares da mesma idade e sem diagnóstico psiquiátrico, poupando anos de vida de doentes jovens, assim como o impacto negativo significativo que a morte de um jovem tem na sua família e conviventes.

Implicações para investigação futura

A investigação futura deve desenvolver os achados deste trabalho em vários domínios. Primeiro, será necessário maior número de estudos longitudinais similares, multicêntricos, sobretudo no estudo do comportamento suicida no PEP, cuja escassez de trabalhos com este tipo de *design* é significativa. Mais estudos longitudinais poderão confirmar (ou não) os resultados da presente investigação. Segundo, na sequência da identificação da importância do comportamento suicida e MetS e fatores associados no PEP e meses seguintes, será necessário o estudo de intervenções especificas, tanto para a sua prevenção, como tratamento neste grupo particular de doentes. Estes trabalhos permitirão não só verificar se existe redução da prevalência destes dois fenómenos, mas também se ocorre a tão esperada redução da mortalidade nos doentes psicóticos.

Os estudos com intervenções para a melhoria metabólica (incluindo peso e pressão arterial) para os doentes com perturbações psicóticas crónicas são abundantes e com resultados positivos na prevenção e tratamento da obesidade e na redução de fatores cardio-metabólicos [372,373]. Nos últimos anos foram publicados alguns estudos que procuraram intervir sobre a melhoria metabólica especificamente dos doentes no PEP, que incluíram intervenções na dieta, exercício e intervenção farmacológica para a melhoria da saúde física e metabólica destes [374]. Os resultados não foram consensualmente positivos, tendo alguns dos estudos falhado no seu objetivo (melhoria dos parâmetros antropométricos e das alterações metabólicas) [375,376]. Parece assim ficar evidente a necessidade de mais investigações futuras para uma otimização das intervenções a efetuar no PEP nos doentes com manifesto risco cardiovascular identificado pela presença da síndroma metabólica.

Em relação ao comportamento suicida seria interessante procurar confirmar os nossos resultados, prevalências e preditores. Particularmente, será importante confirmar o nosso resultado do baixo colesterol total como preditor de comportamento suicida. Mais uma vez, as investigações futuras devem confirmar também se as intervenções sobre os doentes com risco de suicídio têm impacto na redução da mortalidade nos doentes psicóticos. Particular atenção deve ser dada à prevenção e tratamento da depressão, aspeto que tem sido demonstrado em trabalhos anteriores, e também no nosso, como importante risco e preditor de comportamento suicida nas fases iniciais das perturbações psicóticas.

CONCLUSÕES

As principais conclusões do presente estudo podem ser resumidas nos seguintes pontos:

1. O comportamento suicida e a MetS são frequentes nos 12 meses seguintes ao PEP. Encontrámos uma prevalência de comportamento suicida na avaliação no PEP de 25,4% e após 12 meses de 13,3%. Em relação à MetS, a prevalência encontrada no PEP foi de 6,7% e de 11,7% na avaliação a 12 meses.

2. Para além das elevadas taxas encontradas e do agravamento da MetS nos 12 meses seguintes ao PEP, existiu um agravamento dos parâmetros metabólicos estudados, com particular significado para a obesidade abdominal.

3. Os valores das prevalências encontradas indicam que são superiores, em todas as avaliações, à população em geral para a mesma idade, quer para o comportamento suicida, quer para a MetS. Os valores encontrados são similares aos resultados obtidos em estudos realizados noutros países europeus.

4. O tratamento nos 12 meses seguintes ao PEP diminuiu a prevalência do comportamento suicida, mantendo-se, todavia, esta sempre considerável.

5. A história prévia de comportamento suicida ao PEP e o diagnóstico de depressão no PEP foram encontrados como fatores preditores de comportamento suicida no PEP. História prévia de comportamento suicida e baixo nível de colesterol total foram encontrados como fatores preditores de comportamento suicida a 12 meses após o PEP. Não foram encontrados preditores para a MetS.

6. Os doentes com PEP com história prévia de comportamento suicida, depressão e baixos níveis de colesterol total no PEP parecem estar em risco particularmente elevado de comportamento suicida, e consequentemente de suicídio, nos 12 meses seguintes ao PEP. Estes doentes poderão beneficiar de cuidadosa monitorização e tratamento adequado no sentido da sua proteção, redução deste risco e mortalidade consequente.

7. Encontrámos apenas diferença significativa na prevalência do comportamento suicida na *baseline* entre o grupo de doentes com diagnóstico de psicose afetiva *versus* psicose não afetiva, com prevalência mais elevada no primeiro grupo. Não se encontraram

diferenças particularmente significativas entre os doentes com PEP afetivo e não afetivo no que concerne à prevalência do comportamento suicida a 12 meses do PEP e na MetS nas avaliações *baseline* e nos 12 meses seguintes ao PEP. Assim os resultados parecem indicar que ambos os grupos diagnósticos devem ser considerados de risco elevado para ambas as variáveis estudadas.

8. Deve existir cuidadosa monitorização dos parâmetros metabólicos nos primeiros 12 meses após o PEP, aqueles doentes que apresentem fatores de risco, nomeadamente critérios de síndroma metabólica, devem ser submetidos a um plano de intervenção sobre os estilos de vida e tratamento quando indicado, para prevenção de doença cardiovascular e mortalidade consequente.

9. A investigação futura deve procurar replicar os achados do nosso trabalho, ampliando também o conhecimento nomeadamente no que concerne ao tipo de intervenções e tratamento nos doentes com PEP e identificados com risco elevado de suicídio e/ou doença cardiovascular. Trabalhos futuros devem ainda confirmar se estas intervenções têm impacto na mortalidade dos doentes psicóticos tal como esperado.

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Depressive symptoms and suicidal behavior after first-episode psychosis: A comprehensive systematic review

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ABSTRACT

Depressive symptoms and suicidal behavior are common among patients that suffered a first-episode psychosis. We searched Web of Knowledge[SM] and Pubmed® for English and Portuguese original articles investigating prevalence of depressive symptoms and/or suicidal behavior and associated factors after first-episode psychosis. We included 19 studies from 12 countries, 7 studied depressive symptoms and 12 suicidal behavior. The findings confirm that depressive symptoms and suicidal behavior have high rates in the years after first-episode psychosis. Factors identified as being associated with depressive symptoms after first-episode psychosis were anomalies of psychosocial development, poor premorbid childhood adjustment, greater insight, loss, shame, low level of continuing positive symptoms and longer duration of untreated psychosis. Suicidal behavior was associated with previous suicide attempt, sexual abuse, comorbid polysubstance use, lower baseline functioning, longer time in treatment, recent negative events, older patients, longer duration of untreated psychosis, higher positive and negative psychotic symptoms, family history of severe mental disorder, substance use, depressive symptoms and cannabis use. Data also indicate that treatment and early intervention programs reduce depressive symptoms and suicidal behavior after first-episode psychosis. Future research should overcome some methodological discrepancies that exist between studies and limit generalization of current findings.

1. Introduction

Depressive symptoms and suicidal behavior are common among patients that suffered a first-episode psychosis. Published studies revealed that depressive symptoms in patients with first-episode psychosis have prevalence from 17% to 83% (Addington et al., 1998; Bottlender et al., 2000; Romm et al., 2010). Depressive symptoms could occur in different phases of psychosis, including post-psychotic period (Birchwood et al., 2005). Depression is a well-known risk factor for suicidal behavior in psychosis with data showing that occurrence of depression in psychosis have significant correlation with suicide risk (Upthegrove et al., 2010). Suicide remains an important cause of premature death in patients with psychotic disorders (Healy et al., 2012; Laursen, 2011). In long-term follow-up studies suicide accounts for 2–5% of deaths in first-episode psychosis (Dutta et al., 2011, 2010; Palmer et al., 2005). The rate of attempted suicide in psychotic patients ranges from op10% to 50% (Aleman and Denys, 2014; Castelein et al., 2015). Individuals with first-episode psychosis have a greater risk of suicidal behavior compared with the normal population and chronic disorders (Bertelsen et al., 2007). First admissions have three times higher suicide rate than chronic schizophrenia (Palmer et al., 2005). As suicide risk peaks in the early years of psychotic disorders much attention has been given to this phase of the disorder (Palmer et al., 2005). Previous studies have been published in order to identify predictors of suicide in patients with psychotic disorders. Identifying factors associated to depressive symptoms and suicidal behavior will permit the development of preventive and treatment interventions. However, despite its prevalence, limited evidence exists regarding factors associated and interventions to reduce suicide risk among young people with first-episode psychosis.

Our aim was to perform a systematic review of the current evidence in this field of knowledge. The main objectives were (1) to assess rate of depressive symptoms and suicidal behavior (including suicidal ideation, suicide plans, suicide attempts and suicide) after first-episode psychosis and (2) to search for the most relevant demographic and clinical factors associated.

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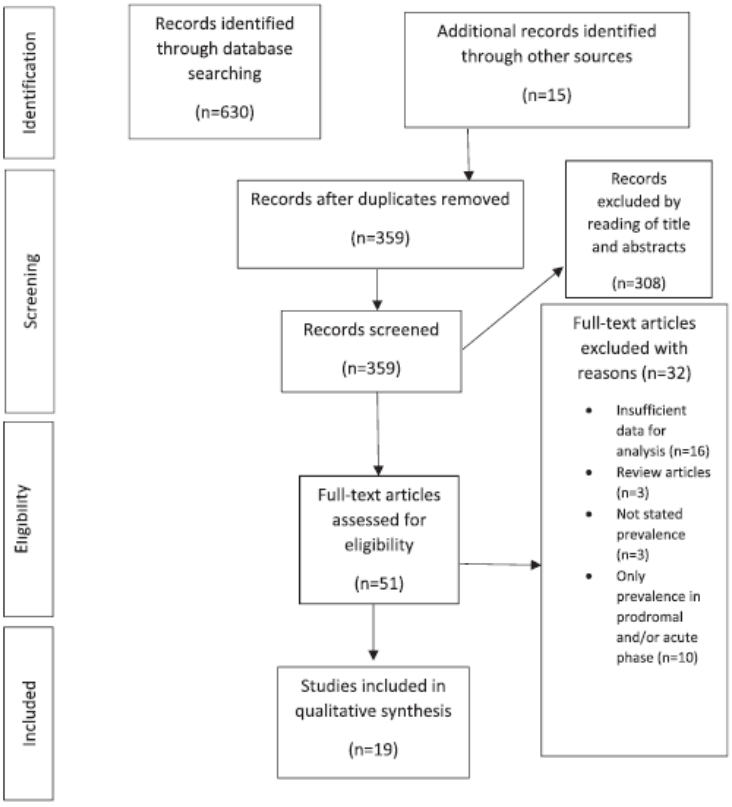

Fig. 1. Flow Chart of systematic identification of papers following PRISMA Guidance.

2. Methods

2.1. Selection procedures and data collection

2.1.1. Search strategy

A systematic literature search as described by the PRISMA statement was conducted using Web of Knowledge℠ and Pubmed® databases to find studies that reported the prevalence and associated factors of depressive symptoms and suicidal behavior among patients that suffered a first-episode psychosis. Articles published until May 2016 and in English and Portuguese languages were considered. Search terms used to find relevant articles were 'depression' OR 'depressive' OR 'suicidal' AND 'first-episode psychosis' OR 'first-episode schizophrenia'. A secondary search was performed by reviewing reference lists of sources identified as relevant in initial search to find additional articles to the review. The articles surviving selection were fully download (PDFs) and evaluated for eligibility after full-text reading.

2.1.2. Inclusion criteria

Articles were included for the systematic rweview: (a) included affective and/or non-affective first-episode psychosis patients defined according to international standard definitions (International Classification of Diseases, Diagnostic and Statistical Manual of Mental Disorders); (b) clearly stated prevalence of depressive symptoms and/or suicidal behavior in the period after first-episode psychosis; (c) were original articles and written in English or Portuguese language.

2.1.3. Exclusion criteria

We excluded from the review: (a) duplicated reports; (b) report data on non-first episode psychosis patients; (c) did not refer clearly the prevalence of depressive symptoms and/or suicidal behavior; (d) papers with insufficient data for analysis, meta-analysis or reviews; (e) articles that studied depressive symptoms and/or suicidal behavior only in prodromal and/or acute psychotic phases; (f) articles in languages other than English or Portuguese. In case of multiple publications deriving from the same study population, we selected the articles reporting the largest or the most recent data. In case of conflict between these two last criteria, the sample size was the priority.

2.1.4. Recorded variables

We recorded the following variables from each article: authors, year of publication, country, epidemiological data of patient sample (sample size, mean age, proportion of males), clinical variables (instruments used, diagnoses included), type of study, follow-up time, main aim, prevalence of depressive symptoms and/or suicidal behavior and relevant findings.

2.2. Quality assessment

We assessed the internal validity of the included studies using the tool developed by Thomas et al. from the Effective Public Health Practice Project (EPHPP) (Thomas et al., 2004). The Cochrane Collaboration for non-randomized studies recommends this tool (Higgins and Green, 2011). It includes six components: selection bias, design,

Table 1
Characteristics of studies included in the systematic review.

Authors and publish year	Country	Sample size	Age Mean (SD)	Male percent	Screening tools (depression and/ or suicidal behavior)	Diagnosis	Study type/Follow-up time	Main Aim	Prevalence	Relevant findings
Depressive symptoms										
Koreen et al., 1993	USA	70	24.3 (6.0)	56%	HDRS Syndromal definition based on Research Diagnostic Criteria (RDC)	FEP: non-affective psychosis	Prospective, longitudinal/5 years	Prevalence of depressive symptoms in first-episode psychosis	Baseline: depressive symptoms (HRSD (≥15) or RDC): 75% HRSD and RDC: 22%; Follow-up: a)depression: 26%; b)Nonpsychotic ratings:4%	Depressive symptoms may represent a core part of the acute illness or may occur as a subjective reaction;
Wassink et al., 1999	USA	70	24.63 (5.23)	77.14%	CASH	FEP: non-affective psychosis	Prospective, longitudinal/5 years	Prevalence of depressive symptoms early in the course of schizophrenia	Depressive symptoms: > 50% MDD (baseline): 34.3%	Depressive symptoms are common early in the course of schizophrenia and has potential implications in diagnostic and treatment practices.
Iqbal et al., 2004	UK	29	25 (5.2)	72%	BDI	FEP: non-affective psychosis	Prospective longitudinal/ 12 months	Establish whether overgeneral memory is a feature of post-psychotic depression in FEP	PPD: 44.8%	PPD was associated with overgeneral memory and a heightened awareness of the diagnosis.
Romm et al., 2010	Norway	122	28.3 (9.2)	64%	SCID-I CDSS	FEP: non-affective psychosis	Part of ongoing longitudinal	Prevalence of MDE Demographic and clinical characteristics of patients with MDE	MDE before onset psychosis: 17%; MDE during or after onset of psychosis: 30%	Poor premorbid childhood adjustment, substance abuse and excitative symptoms at start of treatment associated with higher severity of depressive symptoms
Cotton et al., 2012	Australia	405	20.9 (3.7)	68.6%	CGI-BP	FEP: non-affective psychosis	Prospective, longitudinal/18 months	Prevalence of depressive symptoms in patients with FEP and clinical and functional characteristics of those with persistent depressive symptoms	Depression (CGI-BP depression score > 3): Baseline: 26.2% Follow-up: 14.2%	Depressive symptoms are common in patients with FES and during the first months of treatment; Greater insight into their illness was associated with depressive symptoms; Substance use was less common in those with depressive symptoms.
Upthegrove et al., 2014	UK	92	22.5 (4.89)	75%	CDSS	FEP: affective and non-affective psychosis	Prospective, longitudinal/12 months	Prevalence of depression in first-episode psychosis, its relationship to other symptom dimensions and recovery in a phase specific manner	Post psychotic depression (CDSS ≥ 7): 37%	Loss, Shame, low level continuing positive symptoms and longer DUP were associated with post psychotic depression
Sönmez et al., 2016	Scandinavia (Norway, Denmark)	299	27.8 (9.66)	58%	PANSS depression item (g6) CDSS	FEP: non-affective psychosis	Prospective, longitudinal/10-year	Patient characteristics at baseline that predict depressive symptoms at 10 years and whether patients prone to depressive symptoms in the first year of treatment had a different prognosis in the following years	Depression (PANSS g6 ≥ 4): Baseline: 41%%; 1 year:28%; 2 years: 20%; 5 years:16%; Depression (PANSS g6 ≥ 4 and CDSS ≥ 6): 10 years: 19%	Depressive symptoms are frequent among FEP patients at baseline but decrease after treatment. Patients with poor social functioning in childhood and alcohol use at baseline are more prone to have depressive symptoms at 10 years of follow-up.
Suicidal Behavior										
Addington et al., 2004	Canada	238	24.6 (8.33)	65.7%	Suicidality: regular clinical practice and medical records	FEP: non-affective psychosis	Prospective, longitudinal/12 months	Prevalence of suicidal behavior prior and during 1-year FEP and identify predictors	Suicide attempt during follow-up: 2.9%; Suicide: 0.4%	First-episode programs can reduce the suicidal behavior.
Clarke et al.,	Ireland	171	28.5 (11.1)	58%	Clinical interview	FEP:	Prospective,	Prevalence of suicide behavior	Attempt suicide prior	Suicide attempts prior to

(continued on next page)

Table 1 *(continued)*

Authors and publish year	Country	Sample size	Age Mean (SD)	Male percent	Screening tools (depression and/or suicidal behavior)	Diagnosis	Study type/Follow-up time	Main Aim	Prevalence	Relevant findings
2006						affective and non-affective psychosis	longitudinal/4 years	and associated factors	presentation: 10%; Follow-up attempt suicide: 18.2%	presentation were associated with longer DUP
Follow-up suicide: 3%										
Bertelsen et al., 2007	Denmark	547	26 (6.3)	59%	Suicide attempts and ideation based on self-reporting; Suicide: Death register and death certificates	FEP: non-affective psychosis	Randomized controlled trial/5 years	Rates of suicide and predictive factors of suicidal behavior	Suicide: 1.3%	Depressive and psychotic symptoms (especially hallucinations) predicted suicidal plans and attempts, and persistent suicidal behavior and ideation were associated with high risk of attempted suicide
Robinson et al., 2009	Australia	661	ns (15–29)	65.65%	Patient medical record	FEP: affective and non-affective psychosis	Retrospective/18 months	Prevalence and predictors of suicide and suicide attempts before and during the first 18 months of treatment	Suicide attempt prior to entry: 14.3%; Suicide attempt during treatment: 8.7%; Suicide: 0.9%	Predictors of suicide attempt were: previous attempt, sexual abuse, comorbid polysubstance, greater insight, lower baseline functioning and longer time in treatment.
Dutta et al., 2010	UK	2723	33.6 (SD ns)	55.2%	Death certificates	FEP: affective and non-affective psychosis	Retrospective /mean follow up: 11.5 years	Rate of deaths by suicide	Suicide: 1.9% Proportionate mortality: 11.9%	The highest risk of suicide occurs soon after presentation but risk is elevated even a decade or longer later.
Fedyszyn et al., 2012	Australia	180 (cases:72; controls:108)	19.56 (2.73)	56.1%	Medical files CAD-SAS	FEP: affective and non-affective psychosis	Case-control study (retrospective)/18 months	1)Determine the relative importance of baseline, past and recent variables to prediction of suicidal behavior; 2)Identify recent characteristics that exert most influence on suicide risk levels	Suicidal attempt: 11.9%	Recent negative events and recent non-suicidal self-injurious behavior were strongest predictors of suicide-related behaviors during treatment for FEP
Mitter et al., 2013	Singapore	1397	27.7 (6.6)	50.8%	Medical records	FEP: affective and non-affective psychosis	Prospective longitudinal/2 years	Prevalence of suicides and associated risk factors	Suicide: 1.9%	Older patients with longer DUPs, higher PANSS positive and negative scores and better functioning appear to be at higher risk of suicide
Björkenstam et al., 2014	Sweden	2819	22.6 (ns)	58%	Death Register	FEP: affective and non-affective psychosis	Longitudinal, prospective study (cohort study)/not applicable	Prevalence of suicide and associated risk factors	Suicide: 4.29%	Impulsive behavior such as self-harm and family history of severe mental disorder or substance use are risk factors for suicide in first-episode psychosis
Ayesa-Arriola et al., 2015	Spain	397	28.94 (9.46)	56.9%	Medical records	FEP: non-affective psychosis	Longitudinal, prospective/3 years	Determine and characterize the highest risk period for suicide	Suicide attempts: 10.83% Suicide: 1.51%	Greatest suicide risk was found during the month before and 2 months after first contact; Severity of depressive symptoms and cannabis use are predominant risk factos across time
Chang et al.,	Hong-Kong	700	21.2 (3.4)	51.4%	Medical file review	FEP:	Longitudinal,	Prevalence and predictors of	Baseline (Suicide attempt	Previous suicide attempt,

(continued on next page)

Table 1 *(continued)*

Authors and publish year	Country	Sample size	Age Mean (SD)	Male percent	Screening tools (depression and/or suicidal behavior)	Diagnosis	Study type/Follow-up time	Main Aim	Prevalence	Relevant findings
2015						affective and non-affective psychosis	Prospective/3-year	suicidal behavior	prior treatment): 10.6%; Follow-up: Suicidal behavior: 10%; suicide: 1%	history of substance abuse and poorer baseline functioning were associated with an increased risk for suicidal behavior after treatment initiation
Barret et al., 2015 CDSS item 8 (current suicidality)	Norway Follow-up suicidal behavior (suicidal CDSS item 8: 1–3): 20%	146	Ns (18–65)	62.3%	SCID-I interview (suicide attempts) Gaining insight during treatment was associated with reduced risk for suicidality; More depressive episodes before study entry, longer DUP, more suicide attempts six months prior to follow-up and depression at follow-up are predictors of suicidality at follow-up	FEP: non-affective psychosis	Prospective longitudinal/one year	Predictors of suicidality focusing on the relationship between insight and suicidality		Baseline suicidal behavior: 37%
Castelein et al., 2015	Netherlands	424	28.5 (9)	71.2%	Patient file search	FEP: affective and non-affective psychosis	Retrospective	Change in suicide risk comparing with a study made two decades ago; Identify predictors of suicide risk	Suicide: 2.4%	Higher age predict suicide Significant reduction in the suicide rate was found for people with psychosis over the past two decades

CAD-SAS: Classification Algorithm for the Determination of Suicide Attempt and Suicide; CASH: Comprehensive Assessment of Symptoms and History; CDSS: Calgary Depression Scale for Schizophrenia; CGI-BP: Clinical Global Impressions Scale – Bipolar Disorder; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, 4th Edition; FEP: first-episode psychosis; HDRS: Hamilton Rating Scale for Depression; ICD-10: International Classification of diseases, 10th Edition; PPD: Post-psychotic depression; SCID-I: Structured Clinical Interview for DSM-IV.

Table 2
Studies quality assessment according to EPHPP tool for quantitative studies (Thomas et al., 2004).

Study	Selection bias	Design	Confounders	Blinding	Data collection methods	Withdrawals and drop-outs	Total
Koreen et al. (1993)	Weak	Moderate	Moderate	Moderate	Strong	Strong	Moderate
Wassink et al. (1999)	Weak	Moderate	Moderate	Moderate	Strong	Weak	Weak
Iqbal et al. (2004)	Weak	Moderate	Moderate	Moderate	Strong	Weak	Weak
Romm et al. (2010)	Weak	Moderate	Moderate	Moderate	Strong	Not applicable	Moderate
Cotton et al., 2012	Weak	Moderate	Moderate	Moderate	Strong	Moderate	Moderate
Upthegrove et al. (2014)	Weak	Moderate	Weak	Moderate	Strong	Strong	Weak
Sönmez et al. (2016)	Weak	Moderate	Moderate	Moderate	Strong	Weak	Weak
Addington et al. (2004)	Weak	Moderate	Weak	Moderate	Strong	Strong	Weak
Clarke et al. (2006)	Weak	Moderate	Moderate	Strong	Moderate	Weak	Weak
Bertelsen et al. (2007)	Weak	Strong	Moderate	Moderate	Strong	Strong	Moderate
Robinson et al. (2009)	Weak	Weak	Moderate	Moderate	Strong	Strong	Weak
Dutta et al. (2010)	Weak	Weak	Strong	Moderate	Strong	Strong	Weak
Fedyszyn et al. (2012)	Weak	Moderate	Moderate	Moderate	Strong	Strong	Moderate
Mitter et al. (2013)	Weak	Moderate	Strong	Moderate	Moderate	Strong	Moderate
Björkenstam et al. (2014)	Strong	Moderate	Strong	Moderate	Strong	Strong	Strong
Ayesa-Arriola et al. (2015)	Weak	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Chang et al., 2015	Weak	Moderate	Strong	Moderate	Strong	Strong	Moderate
Barret et al., 2015	Weak	Moderate	Strong	Moderate	Strong	Moderate	Moderate
Castelein et al. (2015)	Weak	Weak	Not applicable	Moderate	Strong	Moderate	Weak

Strong = No weak ratings, Moderate = One weak rating, Weak ≥2Weak ratings.

confounders, blinding, data collection methods, withdrawals and drop-outs. Each component has to be rated as "strong", "moderate" or "weak" according to a standardized guide and dictionary. All six components made the overall rating of each study. Studies with no "weak" ratings and at least four "strong" ratings are considered strong. Those with less than four "strong" ratings and one "weak" rating are considered "moderate". Those with two or more "weak" ratings are considered weak.

3. Results

3.1. Flow of included studies

Search results are summarized in the Prisma Flow Chart in Fig. 1. A total of 630 studies were identified through the search strategy from databases. Fifteen additional studies that met the inclusion criteria were found through a manual search of the reference section for relevant additional studies. Three hundred and fifty-nine articles remain after exclusion of duplicate articles. Three hundred and eight articles were excluded by reading of the title and abstracts. Thirty-two articles were excluded with reasons: 16 with insufficient data for analysis, 3 non-systematic review articles, 3 not stated prevalence rate of depression and/or suicidal behavior and 10 articles that only studied prodromal and/or acute psychotic phase. Finally, we included 19 articles in the systematic review (Table 1).

3.2. Quality assessment

The general quality of studies included was "weak" to "moderate", with only one study "strong" (Björkenstam et al., 2014) (Table 2). Only Björkenstam et al. (2014) studied data from a nationwide cohort. The remaining studies selection bias was the rule because information was obtained from samples from clinical centers, mainly single-center and two-center and thus not representative of the target population. Two publications did not report conflicts of interest or statements about funding or grants (Iqbal et al., 2004; Sönmez et al., 2016).

3.3. Study characteristics and outcome measures

We included 7 articles that studied depressive symptoms (Cotton et al., 2012b; Iqbal et al., 2004; Koreen et al., 1993; Romm et al., 2010; Sönmez et al., 2016; Upthegrove et al., 2014; Wassink et al., 1999) and 12 articles that studied suicidal behavior (Addington et al., 2004; Ayesa-Arriola et al., 2015; Barrett et al., 2015; Bertelsen et al., 2007; Björkenstam et al., 2014; Castelein et al., 2015; Chang et al., 2014; Clarke et al., 2006; Dutta et al., 2010; Fedyszyn et al., 2012; Mitter et al., 2013; Robinson et al., 2009). The main outcome measures were prevalence of depressive symptoms and/or suicidal behavior and associated factors during the first years after first-episode psychosis. Main exclusion criteria were the presence of organic brain disorder and intellectual disability.

A total of 11490 patients were included, sample size ranged from 29 to 2819 patients, with mean age from 19.56 to 33.6 years, with male percentage from 50.8% to 77.14%. Fourteen studies were longitudinal/prospective, 3 retrospectives, 1 retrospective case-control and 1 randomized controlled trial. In longitudinal studies the follow-up time was between 12 months and 10 years.

The instruments used to measure depressive symptoms were Calgary Depression Scale for Schizophrenia (CDSS), Hamilton Depression Rating Scale (HDRS), Beck Depression Inventory (BDI) and Clinical Global Impression for Bipolar Disorder (CGI-BP). Suicidal behavior was mostly assessed by review of medical files. Death certificates confirmed suicide more frequently (Table 3).

3.4. Depressive symptoms

3.4.1. Prevalence

The reported prevalence of depressive symptoms after first-episode psychosis among the studies included ranged from 14.15% and 44.80%. All studies found significant rates with prevalence of depressive symptoms on different times of follow-up ranging from 12 months to 10 years. Studies evidenced that depressive symptoms diminished with follow-up time and treatment. However, Sönmez et al. (2016) clearly demonstrated that depressive symptoms progressively decrease with treatment but still significant even 10 years after first-episode psychosis (Sönmez et al., 2016). Using The Positive and Negative Syndrome Scale (PANSS) depression item (g6 ≥ 4) at baseline, at 1 year, at 2 years at 5 years and at 10 years authors found prevalence of depressive symptoms respectively 41%, 28%, 20%, 16% and 19%.

3.4.2. Correlates and risk factors

Many factors were identified as being associated with depressive symptoms after first-episode psychosis: anomalies of psychosocial development (Iqbal et al., 2004; Sönmez et al., 2016), poor premorbid childhood adjustment (Romm et al., 2010), greater insight (Cotton et al., 2012b), loss (Upthegrove et al., 2014), shame (Upthegrove et al.,

Table 3
Major measurement tools for depressive symptoms and suicidal behavior used in the studies.

Measure	Population	Items (n)	Scoring	Range	Interpretation	Cut-off
Depressive symptoms						
Beck Depression Inventory (BDI)	Adults and adolescents	21	0–3	0–63	0–13: minimal depression 14–19: mild depression 20–28: moderate depression 29–63: severe depression	≥ 14
Calgary Depression Scale for Schizophrenia (CDSS)	Adults and adolescents diagnosed with schizophrenia	9	0 to 3	0–27	≥5: depression	≥ 5
Clinical Global Impression for Bipolar Disorder (CGI-BP)	Adults	6	1 to 7 (items I, II, III)	Not applicable	Depression	> 3 (depression item)
Hamilton Depression Rating Scale (HDRS)-17 items	Adults	17	0 to 2 or 3 or 4	0–52	Depression	> 17
Positive and Negative Syndrome Scale (PANNS) (depression item)	Adults and adolescents	30 (including one of depression in general psychopathology subscale)	1 to 7	Not applicable	Depression	≥ 4 (depression item)
Suicidal behavior						
Beck Scale for Suicide ideation (BSSI)	Adults and adolescents	21	0 to 2 (items 1–19)	0–38	Higher scores indicate greater severity of suicidal ideation	ns
Beck Suicidal Intent Scale (SIS)	Patients who attempt suicide but survive	15 (with more 5 items not included in final score)	1 to 3	15–45	15–19: low intent 20–28: medium intent ≥29: high intent	≥ 20

2014), low level of persistent positive symptoms (Upthegrove et al., 2014) and longer DUP (Upthegrove et al., 2014). Regarding substance use the results were divergent some studies showed that substance abuse was associated with depressive symptoms after first-episode psychosis (Romm et al., 2010; Sönmez et al., 2016) and 1 study found substance use less common in those patients with depressive symptoms (Cotton et al., 2012b).

3.4.3. Treatment

No specific treatment or intervention studies were found regarding depressive symptoms after first-episode psychosis. Some samples studied were included in early intervention programs as treatment for first-episode psychosis (Cotton et al., 2012b; Iqbal et al., 2004; Upthegrove et al., 2014). Also Koreen et al. (1993) studied prospectively 70 patients with first-episode psychosis with a follow-up to 5 years and received usual treatment. Authors concluded that since depressive symptoms mostly resolved as the psychosis remitted, antidepressant therapy should be used only in that patients in whom depression persists (Koreen et al., 1993).

3.5. Suicidal behavior

3.5.1. Prevalence

The prevalence of suicide attempts after first-episode psychosis ranged from 2.9% to 18.2% and suicide from 0.4% to 4.29% in studies included. One study that measured suicidal behavior as whole (including suicidal ideation, suicide plan and/or suicide attempt) found a prevalence of 20% (Barrett et al., 2015).

3.5.2. Correlates and risk factors

As in depressive symptoms, a heterogeneity of factors associated with suicidal behavior (including suicide) were studied and found significant: previous suicide attempt (Barrett et al., 2015; Björkenstam et al., 2014; Chang et al., 2014; Fedyszyn et al., 2012; Robinson et al., 2009), sexual abuse (Robinson et al., 2009), comorbid polysubstance use (Robinson et al., 2009), lower baseline functioning (Chang et al., 2014; Robinson et al., 2009), longer time in treatment (Robinson et al., 2009), recent negative events (Fedyszyn et al., 2012), older patients (Castelein et al., 2015; Mitter et al., 2013), longer DUP (Barrett et al., 2015; Mitter et al., 2013), higher positive and negative psychotic symptoms scores (Mitter et al., 2013), family history of severe mental disorder (Björkenstam et al., 2014), substance use (Björkenstam et al., 2014; Chang et al., 2014), depressive symptoms (Ayesa-Arriola et al., 2015; Barrett et al., 2015), cannabis use (Ayesa-Arriola et al., 2015). Concerning insight the results were divergent with one study revealing that gaining insight during treatment was associated with reduced risk for suicidality (Barrett et al., 2015) and other showing that greater insight was predictor of suicidal behavior after first-episode psychosis (Robinson et al., 2009).

3.5.3. Treatment

Two studies make conclusions about treatment regarding suicidal behavior after first-episode psychosis. Bertelsen et al. (2007) researched treatment intervention in suicidal behavior in first-episode psychosis. It studied suicide rate and predictive factors of suicidal behavior in first-episode psychosis patients comparing treatment as usual and an early intervention program. Results showed lower probability of death by suicide in the specified treatment compared with standard treatment (Bertelsen et al., 2007). Also Addington et al. (2004) studied 290 first-episode psychosis patients in Canada in a longitudinal prospective study with a follow-up of 1-year. Authors concluded that first-episode psychosis programs can reduce suicidal behavior (Addington et al., 2004).

4. Discussion

This is the first systematic review to summarize the available research of depressive symptoms and suicidal behavior and associated factors in the period after affective and/or non-affective first-episode psychosis. We included articles from 12 countries all over the world with 11490 patients. Seventeen (almost 90%) of the articles included were published in the past 12 years, attesting to the increase interest in depressive symptoms and suicidal behavior following first-episode psychosis in recent years. We found convincing evidence that depressive symptoms and suicidal behavior have high rates in the years after first-episode psychosis. There is a high heterogeneity across individual studies regarding factors associated to depressive symptoms and suicidal behavior which difficult robust evidence. All studies included had a majority of males in first-episode psychosis samples, ranging from 50.8% to 77.14%. This is in line with some studies suggesting higher incidence of psychotic disorders in men (Castle et al., 1993; Lewine et al., 1984).

Our results should be interpreted with caution as significant methodological limitations condition generalization of the findings. Majority of the studies included only non-affective psychotic patients which is quite artificial in the early phase of psychotic disorders namely because of the diagnostic instability (Heslin et al., 2015; Tohen et al., 2016). It is quite easy to hypothesize that including also affective psychotic patients the rates of depressive symptoms and suicidal behavior will be different and more approximate to daily clinical practice. Other significant limitation from results of different studies are the instruments used namely to measure depressive symptoms. The use of different instruments certainly affects different prevalence of depressive symptoms found. Also different cut-offs were used for the same instrument which limits comparisons between studies. For example, to evaluate depression Upthegrove and al. in 2014 (Upthegrove et al., 2014) used a cut-off of 7 (depression CDSS $\geq$ 7) in CDSS, with the same instrument Sönmez et al. in 2016 used the cut-off of 6 (depression CDSS $\geq$ 6) (Sönmez et al., 2016). For evaluation of suicidal behavior, the most used method was the analysis of medical records for suicide attempts and death certificates for suicide which are more reliable. One study evaluated suicidal behavior using item 8 from CDSS (Barrett et al., 2015).

Research indicates that the period of major risk to depression and suicidal behavior is the few months after first-episode psychosis (Ayesa-Arriola et al., 2015; Cotton et al., 2012a; Dutta et al., 2010) with a reduction with follow-up and treatment but even with long period of follow-up the rates are high. For example Sönmez et al. (2016) studied 299 first-episode psychosis patients with a follow-up of 10 years. It was found a prevalence of depressive symptoms of 41% at baseline and 19% at 10-year follow-up (Sönmez et al., 2016).

Studies researched different factors regarding correlates and risk factors to depressive symptoms and/or suicidal behavior after first-episode psychosis. Comparison of the findings was not possible because results are limited to few articles. The major factors associated with depressive symptoms after first-episode psychosis were anomalies/difficulties in psychosocial and functioning in childhood in 3 studies (Iqbal et al., 2004; Romm et al., 2010; Sönmez et al., 2016) and substance and alcohol use in 2 studies (Romm et al., 2010; Sönmez et al., 2016). The most consistent factors associated with suicidal behavior after first-episode psychosis were previous suicidal attempts found in 7 studies (Barrett et al., 2015; Bertelsen et al., 2007; Björkenstam et al., 2014; Chang et al., 2014; Clarke et al., 2006; Fedyszyn et al., 2012; Robinson et al., 2009), depressive symptoms in 3 studies (Ayesa-Arriola et al., 2015; Barrett et al., 2015; Bertelsen et al., 2007) and longer DUP in 3 studies (Barrett et al., 2015; Clarke et al., 2006; Mitter et al., 2013).

Previous studies referred that etiology of depressive symptoms in the period after first-episode psychosis may represent a core part of the acute illness or it is associated with the subjective reaction to psychosis and its deficits impacting in daily life activities (Ventriglio et al., 2016). In line with this hypothesis is the included study made by Koreen et al. in 1993 in USA (Koreen et al., 1993). Independently of the etiology of depressive symptoms, studies demonstrate that depression diminished with antipsychotic treatment (Koreen et al., 1993; Sönmez et al., 2016).

The research for treatment of depressive symptoms and/or suicidal behavior after first-episode psychosis is very limited. Some authors conclude that early intervention programs reduced suicidal behavior after first-episode psychosis (Addington et al., 2004; Bertelsen et al., 2007). The only randomized controlled trial published was the included study of Bertelsen et al. (2007) made in Denmark as part of the OPUS Trial (Bertelsen et al., 2007). This is a longitudinal, prospective study with 5-year follow-up of 547 patients with first-episode schizophrenia spectrum psychosis in Denmark. Integrated treatment including assertive community treatment model with family involvement and social skills training was compared with standard treatment at a community mental health center. Suicidal behavior and clinical and social status were assessed using validated interviews and rating scales. Authors found a suicide rate of 1.3% during follow-up. Results showed lower probability of death by suicide in the integrated treatment compared with standard treatment. These results underline the importance of dissemination of specific programs on early intervention in first-episode psychosis patients worldwide.

Few limitations of this review exist. We did not perform a meta-analysis of the findings, which may have added additional information. Different methodologies (sample, study type, instruments used etc.) of studies jeopardizes meta-analysis construction. It also has to be considered that the quality assessment with EPHPP was "weak" for a substantial part of the studies included. Main reasons were selection bias, low evidence level of study design and bias caused by uncontrolled confounding variables. We also compared rates and risk factors for depression and suicidal behavior in studies that used different methodologies that certainly gave different results. Two major differences between studies were diagnoses included (affective *versus* non-affective psychosis) and instruments used to measure depressive symptoms. Also majority of the included studies were from Europe, USA and other developed countries which could restrict the generalization of findings. The exact time when the depressive symptoms found begun are not possible to determine in some papers. We could speculate that in some researches depressive symptoms could have begun not after the first-episode psychosis but in the prodrome or during acute phase of first-episode psychosis and continue in the period after first-episode psychosis. Finally, papers written in other languages than English and Portuguese were not included and therefore some interesting researches may have not been considered.

5. Conclusions

The current systematic review provides convincing evidence that depressive symptoms and suicidal behavior have high rates in the first years after first-episode psychosis. There is a high heterogeneity of factors associated studied between studies. Treatment and early intervention programs can reduce depressive symptoms and suicidal behavior. Some methodological limitations in published studies limit generalization of the findings. Future studies should include more often affective psychosis, more than one center, other countries than Europe and USA/Canada and adequate sample sizes for more meaningful results. Data suggest that there is an opportunity to intervene and reduce depressive symptoms and suicidal behavior after first-episode psychosis.

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Suicidal behaviour after first-episode psychosis: results from a 1-year longitudinal study in Portugal

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Abstract

Background: Suicide is one of the main causes of excess of premature death in psychotic patients. Published studies found that suicide risk begins in ultra-high risk of psychosis and continues in early years of the disease. Previous studies identifying predictive and risk factors associated with suicidality in first-episode psychosis (FEP) are highly inconsistent. Also, there are relatively few longitudinal studies on suicidal behaviour in FEP. The aim of this study was to examine prevalence, evolution and predictors of suicidal behaviour at baseline and the 12-month follow-up in patients presenting with FEP.

Methods: One hundred and eighteen patients presenting with FEP were recruited from two early psychosis units in Portugal. A comprehensive assessment examining socio-demographic and clinical characteristics was administered at baseline and the 12-month follow-up. Odds ratio were calculated using logistic regression analyses. McNemar test was used to evaluate the evolution of suicidal behaviour and depression prevalence from baseline to 12 months of follow-up.

Results: Follow-up data were available for 60 participants from the 118 recruited. Approximately 25.4% of the patients had suicidal behaviour at the baseline evaluation, with a significant reduction during the follow-up period to 13.3% ($p = 0.035$). A multivariate binary logistic regression showed that a history of suicidal behaviour and depression at baseline independently predicted suicidal behaviour at baseline, and a history of suicidal behaviour and low levels of total cholesterol predicted suicidal behaviour at the 12-month follow-up. A significant proportion of patients also had depression at the baseline evaluation (43.3%), with the last month of suicidal behaviour at baseline independently predicting depression at this time.

Conclusions: The findings of our study indicate that suicidal behaviour was prevalent on the year after FEP. Patients with a history of suicidal behaviour, depression at baseline and low levels of cholesterol should undergo close evaluation, monitoring and possible intervention in order to reduce suicide risk in the early phases of psychosis.

Keywords: Suicidal behaviour, First-episode psychosis, Depression, Schizophrenia

Background

Suicide and cardiovascular disorders are the two main causes of excess or premature death in psychotic patients [1]. About 5% of patients with schizophrenia die by suicide, and about 50% have suicidal ideation or attempt suicide [2, 3]. Suicide risk differs across the various

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stages of the disorder, with the highest rates occurring in the early phases [4]. Recent studies found that this suicide risk begins at ultra-high risk of psychosis (UHR) stage and continues in early years of the disease [5, 6]. Patients experiencing first-episode psychosis (FEP) have a 60% increased risk of suicide in the first year of treatment compared with those in subsequent phases [7]. The prevalence of suicidal ideation, a consistent antecedent of suicidal behaviour (attempts and completed suicide), ranges from 26.2% to 56.5% during the initial presentation of FEP [8, 9]. The prevalence of suicide attempts in the years following FEP ranges from 2.9% to 18.2% and suicide from 0.4% to 4.29% [10].

Therefore, the first years of psychotic disorders represent an important challenge for Public Health and Psychiatry. Consequently, researchers have sought to identify predictive and risk factors associated with suicidality in FEP; however, the findings are highly inconsistent. Younger age of onset of psychosis [8, 11, 12] and drug and alcohol use [13–15] are factors associated with suicidality in FEP. As in the general population, previous suicidal behaviour, e.g. suicide attempts, has been identified as one of the most significant predictors of suicidal risk in FEP [16–18]. However, while results are mixed regarding gender [8, 11, 19–24], duration of untreated psychosis [7, 8, 22], positive psychotic symptoms [7, 25, 26] and insight [8, 15, 24, 27–29], treatment compliance has been demonstrated to reduce suicide risk [30].

Current or past significant depressive symptoms are associated with suicide risk in patients after FEP [15, 31–34]. The prevalence of depressive symptoms after FEP ranges from 14.15% to 44.80%. Studies evidenced that depressive symptoms diminished with follow-up time and treatment, but remained significant even 10 years after FEP [10, 35]. Previous studies showed that the most depressive symptoms occur either in prodrome [36] or during FEP [37, 38]. Rarely do depressive symptoms occur de novo in recovery following FEP [31]. Usually, depressive symptoms follow the course of positive psychotic symptoms and remit with antipsychotic treatment [39], although there are some patients with psychosis who maintain persistent depressive symptoms beyond the acute phase and do not respond to antipsychotic treatment. Co-morbid depression and psychosis increase the risk of suicidality and relapse [40, 41]. It has been suggested that early identification and intervention for depression in the early phases of psychosis may constitute an important strategy in the prevention of suicide [4, 42].

Published studies suggest that early intervention services—including short treatment delays, maintaining adherence to therapy and specialised programmes—reduce the risk of suicide [43, 44], which is an important aim of early intervention teams. Despite the relevance of this theme, there are relatively few longitudinal studies on suicidal behaviour in FEP and early phases of psychosis. Additionally, published studies have some methodological limitations that we tried to overcome. First, many published studies only included first-episode schizophrenia patients [12, 29, 45]. It is known that a diagnosis of FEP is unstable, with the likelihood of subsequent changes in the first years of the illness [46]. Therefore, it is suggested that studying a broader diagnostic sample of FEP with affective and non-affective psychosis would be more accurate in estimating suicidal behaviour. Second, some studies included heterogeneous samples that mixed patients at different stages of their illness, including chronic and early psychosis patients. Third, many past studies only included hospitalised patients, excluding milder forms of psychotic disorders. Fourth, most previous studies used retrospective or cross-sectional designs, which are characterised by inherent difficulties in establishing predictive factors.

Greater understanding and knowledge around suicide risk profiles and predictors of suicide in psychotic patients will enable the development of preventive strategies. Appropriate monitoring and managing of suicide risk will be important for services working with early psychosis populations. Prospective studies in patients with FEP are necessary to better identify predictive and risk factors for suicidal behaviour in early psychosis. The prevalence and methods of suicidal behaviour differ between countries and cultures. The literature indicates that socio-cultural factors and healthcare resources may condition the risk of suicide [47–49]. Therefore, it is important to have studies from different countries and cultures.

The main aims of this study were: (1) to examine the prevalence and evolution of suicidal behaviour soon after FEP (baseline) and 12 months of follow-up and (2) to determine baseline predictors of suicidal behaviour soon after FEP and at the 12-month follow-up. We also examined the prevalence of depression, its evolution in the 12 months following FEP and the predictors of depression at baseline and follow-up. We hypothesised that affective psychosis, previous suicidal behaviour and depressive symptoms at baseline would predict the occurrence of suicidal behaviour at baseline and the 12-month follow-up.

Methods

Participants and setting

The study was carried out at two specialist psychiatric services within Portuguese hospitals: Hospital Vila Franca de Xira (in Vila Franca de Xira with a catchment area of 245.000 individuals) and Centro Hospitalar

Universitário Lisboa Norte (in Lisbon with a catchment area of 350.000 individuals). The selected patients were from two early intervention teams: the First-Episode Psychosis Program (PPEP) at Hospital Vila Franca de Xira (Vila Franca de Xira) and Programa de Intervenção nas Fases Iniciais da Psicose (PROFIP) at Centro Hospitalar Universitário Lisboa Norte (Lisbon). Both programmes are comprehensive, specialised mental health services for FEP patients originating from geographically defined catchment areas in Vila Franca de Xira and north region of Lisbon, Portugal. Vila Franca de Xira Hospital is a secondary care general hospital in the north metropolitan area of Lisbon. Centro Hospitalar Universitário Lisboa Norte is a tertiary care general university hospital, which interacts closely with the Faculty of Medicine, University of Lisbon. The populations served by the two hospitals live mainly in the suburban and urban areas, respectively, of the metropolitan region of Lisbon. A description of the PROFIP programme was published elsewhere [50].

All FEP patients underwent an assessment by trained personnel as soon as possible after contact with the team. The mean length from service entry to baseline assessment was 5.7 days (SD: 1.8). The programmes consisted of low-dose second-generation antipsychotic medication and individual and group psychosocial treatment, namely family intervention.

The participants met the following inclusion criteria at baseline: (1) age between 16 and 40 years; (2) DSM-IV (American Psychiatric Association, 1994) diagnosis of a psychotic disorder (schizophrenia, schizophreniform disorder, schizoaffective disorder, delusional disorder, bipolar psychotic disorder, major depressive disorder with psychotic features, brief psychotic disorder, cannabis-induced psychosis and psychosis not otherwise specified); (3) living in the geographical catchment of the PPEP or PROFIP services; (4) adequate comprehension of Portuguese language; (5) experiencing FEP with less than 6 months of antipsychotic medication. Exclusion criteria at baseline included: (1) head injury, neurological illness, or any other medical condition presenting with psychiatric symptoms (2) history of past full-blown psychotic episodes, either non-affective or affective, as defined in the Diagnostic and Statistical Manual of Mental Disorders, IV Edition (American Psychiatric Association, 1994); (3) inability to understand and complete the assessments.

The study included all eligible consecutive patients who met the study criteria for the period January 2017 to April 2020. The patients were evaluated at two time points: a baseline evaluation after the clinical stabilisation of FEP; 12 months after the baseline assessment. Follow-up data were available for 60 participants from the 118 recruited. The study complied with the ethical principles of good practice embodied in the Declaration of Helsinki. Responsible ethical committees within both hospitals approved the study, and all participants provided informed consent.

Clinical assessments

The clinical assessment included evaluations regarding socio-demographics and clinical data, including age, marital status, education, occupational status, living area (urban or rural), medical history, education, family history of mental illness, presence of stressful life events occurring in the past year before entering the study, mode of onset of FEP, substance use and type and dose of antipsychotic medication. The baseline and 12-month follow-up diagnoses were obtained using all available information, including informant history and medical records. The Operational Criteria Checklist for Psychotic Illness and Affective Illness (OPCRIT+) instrument was used to obtain the diagnosis [51, 52]. The checklist ratings were entered into the OPCRIT+ software, which generates a diagnosis for the main categories of affective and psychotic disorders, as defined by the DSM-IV, which is the major classification system. The duration of untreated psychosis (DUP) was measured using the Nottingham Onset Schedule (NOS) [53]. DUP was defined as the period of time between the onset of psychotic symptoms and the initiation of treatment with antipsychotic medication. Symptom levels were evaluated using means of the three subscales used to evaluate positive symptoms, negative symptoms and the general psychopathology of the Positive and Negative Syndrome Scale (PANSS) [54]. Suicidal behaviour was assessed at baseline and follow-up evaluations using an instrument developed by Melle [18], which consists in three questions about the last month and lifetime suicidal thoughts, plans or attempts.

The information was cross-checked with the medical records. "Suicidal thoughts" were considered a preoccupation or recurrent thoughts of suicide without a specific plan. "Suicide plans" were considered as the presence of a specific plan to suicide. "Suicide attempts" were defined as a self-non-fatal act with a suicidal intent. The most severe form of suicidal behaviour reported for a lifetime or the past month was registered.

The baseline and 12-month follow-up assessments of depressive symptoms were conducted using the Beck Depression Inventory (BDI). The BDI is a widely used self-report questionnaire designed to measure the severity of depression in individuals between the ages of 13 and 80 years. It contains 21 items, which are rated on a four-point scale according to how the patients felt in the previous two weeks. The scores obtained for the single item are summed to provide a single total score. We used 14 as the global cut-off score to determine patients' depression (depression $\geq$ 14). We used the Portuguese

version, which was translated into Portuguese and adapted to the Portuguese population [55–57].

For the alcohol screening, the Michigan Alcohol Screening Test (MAST) was used. This is a 22-item self-questionnaire requiring yes/no answers, with one point each. A total score of 6 or more indicates hazardous alcohol consumption or alcohol dependence. The Portuguese-translated version, which was adapted to the Portuguese population, has been used before [58, 59]. Functioning was measured using the Global Assessment of Functioning Scale (GAF) [60]. Adherence to medication was evaluated by Medication Adherence Rating Scale (MARS). The MARS is a ten-item self-report measure of medication adherence in psychosis [61]. The total score ranges from 0 to 10 with a higher score indicating better adherence. We used the translated and validated scale to the Portuguese population [62].

Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Science (SPSS), version 26 (Inc, 2020). Due to non-normality in all the explored statistics, non-parametric tests were used. In the between-group comparisons, categorical variables were examined using Chi-square or Fisher's exact test (if 20% of expected frequency was ≤ 5 or any expected frequency was < 1) and continuous variables with the Mann–Whitney U test.

The primary analysis of this study focused on identifying factors predicting the occurrence of suicidal behaviour at baseline and 12 months after the occurrence of FEP. We also evaluated the predictors of depression in FEP patients (at baseline and 12 months after FEP). Suicidal ideation/behaviour was collapsed into a binary variable suicidal/non-suicidal (i.e. presence/absence of suicidal thoughts, plans or attempts). We also considered depressive/not depressive as well as the above-mentioned cut-off on the BDI scale. First, a univariate binary logistic regression was conducted, with suicidal behaviour as the dependent variable and demographic and clinical variables as the candidate predictors. Second, variables with a significant p value in the preceding analysis were then entered into a multivariate binary regression model to determine which factors independently predicted suicidal behaviour at baseline and the 12-month follow-up. A stepwise method was used with a forward selection of predictors. The same procedure was conducted, with depression as the dependent variable. Collinearity evaluations were performed by examining correlation matrices for all the variables, tolerance and variance inflation factors.

We used the McNemar test to evaluate the evolution of suicidal behaviour and depression and compare the results at baseline with those at 12 months. The Wilcoxon test for repeated measures was used to evaluate the evolution of depression from the BDI mean score. The level of statistical significance was set at $p < 0.05$.

Results

Characteristics of the sample

The sample comprised 118 patients consecutively admitted to PPEP ($n = 39$) and PROFIP ($n = 79$). There were no differences between the two groups in terms of sex and employment. The patients from the PROFIP team were younger (mean years 24.2 vs. 29.61; $p = 0.003$) and of a higher educational level (mean years of education 11.7 vs. 10.1; $p = 0.016$) (Mann–Whitney U-test for both). Of the 118 participants included in the study, 76.3% ($n = 90$) were male. The mean age of the sample at intake was 26.1 years (SD = 7.1). The majority (49.2%) of the patients were diagnosed with schizophrenia spectrum disorders (schizophrenia: $n = 48$; delusional disorder: $n = 8$; schizoaffective disorder: $n = 2$). Thirty-nine (33%) were diagnosed with other psychosis diagnosis, with 8 patients with a brief psychotic disorder, 23 with a non-specified diagnosis of psychosis and 8 with a cannabis-induced psychosis diagnosis. Twenty-one (17.8%) participants had affective psychosis ($n = 8$ had bipolar affective disorder with psychotic features, and $n = 13$ had major depression with psychotic features). Table 1 shows the socio-demographic and clinical baseline variables of the sample.

Of the initial cohort of 118 patients who completed the baseline assessment, 60 completed the follow-up assessment. We lost contact with 58 patients for the following reasons: 30 moved to other catchment areas in Portugal; 15 moved to other countries and 13 could not be contacted for the follow-up. Non-completers and completers groups had no significant differences regarding socio-demographics and clinical variables, with the exception of more males ($p = 0.009$) and lower affective psychosis diagnoses ($p = 0.030$) on the non-completers group.

Comparisons of socio-demographics and clinical characteristics between the affective psychosis and schizophrenia spectrum disorder diagnoses are shown in Additional file 1: Table S1.

Prevalence of suicidal behaviour

Forty-two (35.6%) participants had a history of suicidal behaviour prior to entering the study, with 34.7% ($n = 41$) of the cohort having suicidal ideation, 17.80% ($n = 21$) suicidal plans and 9.32% ($n = 11$) a suicide attempt. Overdose of medication was the most frequently used attempted suicide method (54.5%)), followed by jumping from a height (18.2%), strangulation (18.2%) and phlebotomy (9.1%).

Table 1 Socio-demographic and clinical baseline variables of the sample

Variables	First-episode psychosis patients $n=118$
Age years—mean (SD)	26.1 (7.10)
Gender—n (%)	
Female	28 (23.7%)
Male	90 (76.3%)
Education years—mean (SD)	11.24 (3.2)
Unemployment—n (%)	51 (43.2%)
Marital status—n (%)	
Living with partner/married	14 (11.9%)
Single/divorced	104 (88.1%)
Hospitalisation baseline—n (%)	
Yes	101 (85.6%)
No	17 (14.4%)
Cannabis use—n (%)	
Yes	75 (63.6%)
No	43 (36.4%)
Psychiatric family history—n (%)	76 (64.4%)
DUP – days, median (SD)	84 (643.3)
Diagnoses—n (%)	
Schizophrenia spectrum diagnosis	58 (49.2%)
Affective psychosis spectrum diagnosis	21 (17.8%)
Other psychosis diagnosis	39 (33%)
PANSS score—mean (SD)	
PANSS positive subscale	21.24 (8.09)
PANSS negative subscale	15.86 (7.41)
PANSS general subscale	35.97 (8.80)
GAF—mean (SD)	43.40 (18.28)
BDI—mean (SD)	13.18 (10.10)
MARS—mean (SD)	6.08 (2.26)
Total Cholesterol mg/dL—mean (SD)	153.43 (31.72)

SD standard deviation, *DUP* duration of untreated psychosis, *PANSS* Positive and Negative Syndrome Scale, *GAF* Global Assessment of Functioning, *BDI* Beck Depression Inventory, *MARS* Medication Adherence Rating Scale

Schizophrenia-spectrum disorder included schizophrenia, schizophreniform disorder, delusional disorder and schizoaffective disorder. Affective psychosis included bipolar disorder with psychotic symptoms and depressive disorder with psychotic symptoms. Other psychosis included acute and transient psychotic disorders, brief psychotic disorder, cannabis-induced psychosis and psychosis not otherwise specified

For the total initial FEP group, suicidal behaviour in the last month was found for 25.4% ($n=30$) of the cohort, with 15.3% of them experiencing suicidal ideation, 4.2% suicidal plans and 5.9% suicide attempts. The most frequently used methods of attempted suicide in the last month were overdose of medication, jumping from a height and hanging (1.7% in each group). One patient attempted suicide through phlebotomy.

For the participants who completed the 12-month evaluation, 13.3% ($n=8$) had suicidal behaviour, 8.3% suicidal ideation, 3.3% suicidal plan and 1.7% a suicide attempt. The only suicide attempt was overdose of medication.

Twelve patients (40%) who reported suicidal behaviour at baseline evaluation had no history of suicidal behaviour. Only one patient that reported suicidal behaviour at follow-up evaluation had no history of suicidal behaviour.

With regard to the longitudinal evolution of suicidal behaviour, a statistically significant decrease at the 12-month follow-up was found (25.4% vs. 13.3%; $p=0.035$).

Univariate associations with suicidal behaviour

The associations of suicidal behaviour at baseline and 12 months of follow-up with the demographic and clinical factors are shown in Table 2. Patients with suicidal behaviour at baseline were significantly more likely to have a history of suicidal behaviour, baseline affective psychosis diagnosis and baseline depression. Suicidal behaviour patients at 12 months of follow-up were found to have a significantly greater history of suicidal behaviour at baseline, baseline suicidal behaviour in the last month and lower total cholesterol at baseline.

Predictors of suicidal behaviour in the multivariate model

A multivariate binary logistic regression analysis showed that a history of suicidal behaviour and depression at baseline predicted suicidal behaviour at baseline. A history of suicidal behaviour and low baseline total cholesterol predicted suicidal behaviour at 12 months of follow-up (Table 3).

Prevalence and predictors of depression

The longitudinal evolution of depression prevalence showed a significant decrease between baseline and the 12-month follow-up (43.3% vs. 20.0%; $p=0.014$).

A univariate analysis of predictors of baseline depression revealed that depressed patients had a significantly higher history of suicidal behavioural (OR: 2.29; $p=0.035$). Also, depressed patients at baseline had a higher prevalence of suicidal behaviour in the last month (OR: 3.50; $p=0.005$), which was the only variable that maintained a statistical significance in the multivariate analysis (OR: 2.94; 95% IC: 1.19–7.27; $p=0.020$). None of socio-demographic or clinical baseline factors analysed reach statistical significance in the multivariate analysis, with 12 months of depression as the dependent variable.

Discussion

To the best of our knowledge, this is the first study to examine the prevalence and socio-demographic and clinical characteristics of FEP with and without suicidal

Table 2 Demographic, pre-treatment and baseline predictors of suicidal behaviour

Variables of interest	Baseline suicidal behaviour				12-month suicidal behaviour			
	Patients with suicidal behaviour ($n=30$)	Patients without suicidal behaviour ($n=88$)	OR (95% CI)	*p* value	Patients with suicidal behaviour ($n=8$)	Patients without suicidal behaviour ($n=52$)	OR (95% CI)	*p* value
Socio-demographics								
Male/female sex, n (%)	21(70.0)/9(30.0)	69(78.4)/19(21.6)	1.56 (0.61–3.95)	0.352	4 (50.0)/4 (50.0)	36/16	2.25 (0.50–10.14)	0.291
Age at entry, mean (SD)	26.83 (7.49)	25 (7.01)	0.98 (0.93–1.04)	0.504	30.13 (9.91)	26.63 (7.60)	0.95 (0.87–1.04)	0.252
Years of education, mean (SD)	11.10 (3.60)	11.28 (3.01)	1.02 (0.89–1.16)	0.786	11.88 (3.56)	11.19 (3.33)	0.94 (0.75–1.18)	0.588
Married/with partner, n (%)	5 (16.7)	9 (10.2)	1.76 (0.54–5.73)	0.351	1 (12.5)	7 (13.46)	1.34 (0.14–13.25)	0.801
Living alone, n (%)	1 (3.3)	11 (12.5)	0.24 (0.03–1.95)	0.183	0 (0)	8 (15.38)	0.000	0.999
Employed/student, n (%)	16 (53.3)	51 (57.9)	0.83 (0.36–1.91)	0.659	6 (75.0)	2 (3.85)	2.20 (0.41–11.95)	0.361
Pre-treatment illness characteristics								
Family history of mental disorder, n (%)	20 (66.67)	56 (63.6)	1.14 (0.48–2.74)	0.765	7 (87.5)	1 (1.92)	3.11 (0.35–27.43)	0.307
History of suicidal behaviour, n (%)	18 (60.0)	24 (27.3)	4.00 (1.68–9.53)	0.002	7 (87.5)	1 (1.92)	13.22 (1.51–116.01)	0.020
History of substance use, n (%)	20 (66.67)	55 (62.5)	1.20 (0.50–2.87)	0.682	6 (75.0)	2 (3.85)	2.03 (0.37–11.05)	0.412
History of alcohol abuse, n (%)	15 (50.0)	37 (42.0)	1.38 (0.60–3.17)	0.449	3 (37.5)	5 (9.62)	0.89 (0.19–4.11)	0.877
Baseline clinical characteristics								
DUP, median (SD) days	28.00 (984.61)	92.00 (473.95)	1.00 (0.99–1.00)	0.204	19 (114.55)	98 (770.42)	1.00 (0.99–1.01)	0.291
Hospitalisation, n (%)	27 (90.0)	74 (55.7)	1.70 (0.45–6.40)	0.430	0 (0.0)	8 (15.38)	0.000	0.999
Tobacco use, n (%)	18 (60.0)	49 (55.7)	1.19 (0.51–2.77)	0.680	6 (75.0)	2 (3.85)	2.57 (0.47–13.94)	0.274
Last-month baseline suicidal behaviour	–	–	–	–	5 (62.5)	3 (5.77)	5.56 (1.16–26.70)	0.032
Diagnostic categories								
Schizophrenia-spectrum disorder, n (%)	11 (36.67)	47 (53.4)	0.51 (0.21–1.18)	0.116	2 (25.0)	6 (11.54)	0.29 (0.05–1.55)	0.146
Affective psychosis, n (%)	9 (30.0)	12 (12.6)	2.71 (1.01–7.31)	0.048	4 (50.0)	4 (7.69)	3.33 (0.72–15.37)	1.123
Other psychosis, n (%)	8 (26.7)	29 (32.9)	0.74 (0.29–1.86)	0.522	2 (25.0)	6 (11.54)	1.11 (0.19–6.24)	0.905
Symptom severity and functioning								
PANSS positive symptoms, mean (SD)	20.67 (8.05)	21.43 (8.14)	1.01 (0.96–1.07)	0.653	20.63 (7.84)	18.85 (7.29)	0.97 (0.88–1.07)	0.521

Table 2 (continued)

Variables of interest	Baseline suicidal behaviour				12-month suicidal behaviour			
	Patients with suicidal behaviour (*n* = 30)	Patients without suicidal behaviour (*n* = 88)	OR (95% CI)	*p* value	Patients with suicidal behaviour (*n* = 8)	Patients without suicidal behaviour (*n* = 52)	OR (95% CI)	*p* value
PANSS negative symptoms, mean (SD)	17.53 (8.48)	15.30 (6.98)	0.96 (0.91–1.01)	0.155	17.88 (6.643)	17.31 (7.237)	0.99 (0.89–1.09)	0.832
PANSS general symptoms, mean (SD)	39.07 (9.81)	34.91 (8.22)	0.95 (0.90–0.99)	0.031	39.63 (6.02)	35.69 (9.34)	0.96 (0.89–1.03)	0.260
BDI, mean (SD)	18.47 (11.434)	11.42 (8.93)	0.93 (0.89–0.97)	0.002	20.50 (12.11)	12.48 (9.87)	0.93 (0.87–1.00)	0.054
Depression, n (%)	20 (66.7)	32 (36.4)	3.50 (1.46–8.39)	0.005	6 (75.0)	2 (3.85)	4.80 (0.88–26.14)	0.070
GAF, mean (SD)	44.17 (17.52)	43.14 (18,62)	0.99 (0.97–1.02)	0.789	43.75 (15.53)	48.00 (17.60)	1.01 (0.97–1.06)	0.516
MARS, mean (SD)	5.50 (1.78)	6.23 (2.39)	1.15 (0.96–1.39)	0.130	5.75 (2.66)	5.79 (2.30)	0.97 (0.92–1.03)	0.304
Laboratory								
Total cholesterol	154.50 (32.56)	153.07 (31.62)	0.999 (0.986–1.012)	0.830	170.88 (26.2)	146.17 (30.518)	0.97 (0.95–0.99)	0.045

DUP duration of untreated psychosis, *PANSS* Positive and Negative Syndrome Scale, *BDI* Beck Depression Inventory, *GAF* Global Assessment of Functioning, *MARS* Medication Adherence Rating Scale, *SD* standard deviation

Schizophrenia-spectrum disorder included schizophrenia, schizophreniform disorder, delusional disorder and schizoaffective disorder

Affective psychosis included bipolar disorder with psychotic symptoms and depressive disorder with psychotic symptoms

Other psychosis included acute and transient psychotic disorders, brief psychotic disorder, cannabis-induced psychosis and psychosis not otherwise specified

Table 3 Multivariate logistic regression analysis for predictors of baseline and 12-month suicidal behaviour in first-episode psychosis patients[a,b]

Variables in the equation	B	SE	Wald	df	*p* value	OR	95% CI
Baseline							
Depression baseline	1.087	0.463	5.514	1	0.019	2.96	1.20–7.34
History of suicide behaviour	1.237	0.456	7.343	1	0.007	3.44	1.41–8.43
Constant	− 0.153	0.367	0.175	1	0.676	0.86	
Final model: Nagelkerke $R^2 = 0.185$, $\chi^2 = 15.850$, $p < 0.0001$ Hosmer and Lemeshow test supported the goodness of fit of the model ($\chi^2 = 0.006$, df = 2, p = 0.997)							
12-month follow-up							
History of suicide behaviour	2.849	1.172	5.910	1	0.015	17.27	1.74–171.65
Total cholesterol baseline	− 0.030	0.014	4.411	1	0.036	0.97	0.94–0.99
Constant	5.643	2.369	5.674	1	0.017	282.31	
Final model: Nagelkerke $R^2 = 0.373$, $\chi^2 = 13.600$, $p = 0.001$ Hosmer and Lemeshow test supported the goodness of fit of the model ($\chi^2 = 12.657$, df = 8, p = 0.124)							

[a] Affective psychosis diagnosis and PANSS general were entered into stepwise logistic regression model, were excluded as predictors of baseline suicidal behaviour

[b] Last month baseline suicidal behaviour were entered into stepwise logistic regression, were excluded as predictors of 12-month suicidal behaviour

behaviour in a Portuguese population. The present study examined the evolution of the prevalence of suicidal behaviour in the 12 months after FEP in a cohort of Portuguese young people. We also aimed to identify early predictors of suicide behaviour at 12 months of follow-up (baseline and 12 months). In our present study, the prevalence of suicidal behaviour was 25.4% soon after FEP. This is in line with existing studies which showed that approximately 25% to 50% of FEP patients reported suicidal behaviour at initial presentation [7, 20, 31, 63]. We also confirmed that a history of suicidal behaviour before service entry in FEP patients was a predictor of suicidal behaviour at baseline and follow-up. These results are

consistent with previous first-episode studies from other countries [47, 64, 65].

As previous published studies showed, we also confirmed that depression was associated with suicidal behaviour [64–67]. Our results showed that depression was a predictor of suicidal behaviour at baseline. Using the univariate analysis, baseline depression was also almost significant as predictor of suicidal behaviour at follow-up ($p = 0.07$). This result suggests that close evaluation, monitoring and early intervention for depression in FEP are crucial to reducing suicidal behaviour in the early phases of psychosis.

Like our study, a majority of the literature did not find an association between negative symptoms and suicidal behaviour [15, 68]. Some studies postulated that patients with significant negative symptoms, namely deficits in emotion expressivity, are impaired from expressing emotional distress caused by psychosis, consequently reducing the probability of developing depression, hopelessness and suicidal behaviour [69]. In line with this, a few studies found negative symptom severity to be inversely related to the risk of suicidal ideation and suicide attempts [65, 67].

Regarding positive symptoms, we failed to demonstrate that these symptoms were predictors of suicidal behaviour, contrary to some prior FEP studies [14, 26]. Our results were similar to those found in other published studies where no predictability was found [47].

An interesting finding of our study is that high levels of total cholesterol were a baseline protector of suicidal behaviour at follow-up. This is in concordance with research in this field of knowledge. Published studies seem to demonstrate an association between low cholesterol and an increased risk of suicide in non-psychotic patients as well as in psychosis [70–74]. There is a dearth of research on the relationship between cholesterol levels and suicidality in FEP. One study found that serum cholesterol concentrations were significantly lower in suicidal than in non-suicidal patients in FEP, suggesting that lower concentrations of serum cholesterol in patients with FEP might be useful as a biological marker of suicidality [70]. Another study in early psychosis demonstrated that lower levels of cholesterol in patients of psychosis were associated with severe suicidal thoughts [72]. The exact mechanisms of the relationship between peripheral cholesterol, brain metabolism and suicidal behaviour are not entirely known. Some authors have suggested an existing abnormality in leptin and lipid metabolism in suicidal behaviour [75]. Moreover, post-mortem brain studies have indicated that violent suicide completers have lower grey-matter cholesterol content, specifically in the frontal cortex [76]. We only included total cholesterol because this metabolic parameter is the only one with previous studies showing association with suicidal behaviour.

Our findings also indicate that a baseline affective psychosis diagnosis and a high score on the PANSS general subscale were potential predictors of baseline suicidal behaviour; however, these results did not reach significant statistical significance in the multivariate analysis. Affective psychosis, which includes major depressive disorder with psychotic symptoms, is a diagnosis associated with suicidal behaviour. The low proportion of patients included with affective psychosis (17.8%) could explain the non-statistical significance of this diagnosis in the multivariate analysis. The PANSS general subscale was composed of 16 items evaluating other symptoms, including depressive symptoms. We argue that these items conditioned the result obtained.

The present study also showed the high frequency of depression and depressive symptoms in the first year after FEP. Almost half of the patients were depressed at baseline, while one-fifth had depression at one year of follow-up. As indicated in the BDI score, the depressive symptoms significantly decreased during the first year after FEP. This is also similar to other published studies [31, 77–79]. Some authors have speculated several pathways to depression in psychosis, namely in schizophrenia. Three possible explanations exist: (1) depression as an intrinsic aspect of the psychotic disorder; (2) depression as a result of the psychotic illness; (3) depression as a result of disturbed developmental pathways [80].

Our findings did not confirm the idea that depressive symptoms in schizophrenia are frequently misdiagnosed with negative symptoms [81]. In this case, high levels of depressive symptoms would exist simultaneously with high levels of negative symptoms, and a significant association between negative and depressive symptoms would have been expected, which did not happen in our study.

The only predictors that we found to be significant to depression at baseline were baseline suicidal behaviour in the last month and a history of suicidal behaviour. Surprisingly, we found no significant baseline predictors of depression at 12 months. Contrary to our findings, other studies found that a long DUP and depressive symptoms at baseline predict depressive symptoms at 12 months of follow-up [77, 82]. Also, some studies found an association between depression scores and positive symptoms and an improvement with successful antipsychotic therapy [39, 83]. However, some studies also failed to find this association, indicating that depressive symptoms may also emerge independently of positive symptoms [84, 85]. The reasons for our study's failure in finding significant baseline predictors at the 12-month follow-up are

not immediately apparent. We could speculate that our baseline evaluation, which was conducted only after a clinical stabilisation of FEP, might have been a little late for significant findings.

Several clinical implications can be drawn from our results. First, at service entry, a significant proportion of patients had a history of suicidal behaviour and suicidal behaviour in the last month. Thus, at the intake of early intervention teams, all patients should undergo a suicide risk assessment. For those at high risk or experience of previous suicidal behaviour, more intensive monitoring and intervention should be offered. Second, given that baseline depression was found to be a predictor of suicidal behaviour, routine assessments for depression should be offered in early intervention teams, and for those with positive screening, close monitoring of the emergence of suicidal behaviour and adequate treatment should be offered. Third, our results also indicate that an evaluation of total cholesterol should be included in the baseline evaluation of FEP patients, not only for the metabolic evaluation but also as a potential predictor of suicidal behaviour. Therefore, patients with low cholesterol should be screened and closely monitoring for the existence and emergence of suicidal behaviour.

The results of this study should be interpreted with some methodological limitations in mind. First, the evaluation of suicidal behaviour (including suicidal ideation, suicide plan and suicide attempt) was mainly obtained from the participants' self-reports and, thus, was subject to the problem of under-reporting. Second, standardised classification algorithms for suicidal intent, attempts and completed suicides were not used in this research. These algorithms were found to enhance the reliability of the suicidal behaviour assessment. Third, the relatively high proportion of follow-up losses from 118 participants at baseline to 60 at the 12-month follow-up could have limited the results by reducing in some extension the statistical power of the results. Fourth, we studied the predictors of suicidal behaviour, including suicidal ideation, plans and attempts, as a whole group. It was hypothesised that predictors of suicidal ideation, suicide plans and attempts might differ. Fifth, the low numbers obtained regarding suicidal behaviour during follow-up, namely no completed suicide and only 13.3% of participants reporting suicidal behaviour at the 12-month follow-up evaluation. These numbers compromised the statistical power of the study, which could explain the non-significant associations with sex, age of FEP and DUP in our study. Sixth, other important variables that might be potential predictors of suicidal behaviour were not studied because of the difficulties involved in obtaining them, including childhood abuse or previous trauma.

Conclusions

Our results showed that a large proportion of FEP patients had a history of suicidal behaviour or had current baseline suicidal behaviour. We also verified that depression was prevalent in the 12 months after FEP. Our results are in line with those of previous studies, confirming that a history of suicidal behaviour and depression soon after FEP are associated with suicidal behaviour in the early months after FEP. These findings are important for the development of early intervention programmes to lower the risk of suicide and depression in FEP patients. Our finding regarding the predictive role of baseline total cholesterol should be investigated in further prospective research to determine whether our result was predictive of suicidal behaviour.

Abbreviations

BDI: Beck Depression Inventory; CI: Confidence interval; DUP: Duration of untreated psychosis; FEP: First-episode psychosis; OR: Odds ratio; PANSS: Positive and Negative Syndrome Scale; GAF: Global Assessment of Functioning; MARS: Medication Adherence Rating Scale; SD: Standard deviation.

Supplementary Information

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Additional file1: Table S1. Comparison of socio-demographic and clinical characteristics between affective psychosis and schizophrenia spectrum disorders diagnoses.

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Authors' contributions

RC: conceptualisation, methodology, formal analysis, writing. AF, TM, AR: resources, data curation. PL, CG, MLF: conceptualisation, supervision. EF: methodology, formal analysis. All authors have read and approved the manuscript.

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Availability of data and materials

Research data can be requested from ricardomcoentre@gmail.com.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki and was approved by both ethical committees of Hospital Vila Franca de Xira and Centro Hospitalar Universitário Lisboa Norte. All individual-level data were anonymous. All patients gave their written informed consent.

Consent for publication

This manuscript is approved by all authors for publication.

Competing interests

The authors have declared that no competing interests exist.

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Metabolic syndrome following a first episode of psychosis: results of a 1-year longitudinal study conducted in metropolitan Lisbon, Portugal

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Abstract

Objective: We aimed to assess the prevalence and course of metabolic syndrome (MetS) and the associated metabolic parameters during the year following a first episode pf psychosis (FEP).
Methods: We performed a 1-year longitudinal observation of 60 patients who experienced FEP. MetS was defined using the modified definition of the National Cholesterol Education Program Adult Treatment Panel III. We assessed the metabolic parameters and socio-demographic and psychopathological data for the participants.
Results: The mean age of the participants was 27.1 years, and 33.3% of them were women. There was an increase in the prevalence of MetS from 6.7% to 11.7% during the year following the baseline assessment during the year following the baseline assessment ($p = 0.250$). There were also significant increases in the prevalences of abnormal triglyceride concentration, waist circumference, and high-density lipoprotein (HDL)-cholesterol concentration during this period. In addition, there was a considerable worsening of the metabolic profile of the participants. No baseline parameters were identified to be predictors of MetS over the 1-year follow-up period.
Conclusions: We can conclude that metabolic abnormalities are common in patients with FEP and that these rapidly worsen during the first year following the diagnosis of FEP. Studies on interventions are needed to reduce metabolic risk to cardiovascular diseases following the FEP.

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Keywords
First episode of psychosis, metabolic syndrome, schizophrenia, cardiometabolic risk, triglyceride, high-density lipoprotein cholesterol, waist circumference

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Introduction

According to the results of previous studies, the life expectancy of patients with psychotic diseases, and particularly schizophrenia, is 13 to 30 years shorter than that of the general population.[1,2] Moreover, the risk of mortality in patients with schizophrenia is two or even three times higher than in the general population.[3–5] The key factors that explain this difference are cardiovascular diseases and suicide.[6] During the last 25 years, the risk of suicide has increased 18-fold. However, the high incidences of morbidity and mortality in patients with schizophrenia are principally associated with the presence of coronary heart disease.[7,8] The mortality rate associated with coronary heart disease is significantly higher in patients with schizophrenia than in the general population.[8]

Metabolic syndrome (MetS) can be defined as a combination of risk factors for cardiovascular disease and is associated with higher risks of cardiovascular mortality and morbidity.[9,10] MetS is also associated with other diseases, such as benign prostatic hyperplasia and obstructive sleep apnea syndrome.[11–13] Therefore, clinicians should screen for and treat MetS as early as possible to minimize cardiovascular mortality. Furthermore, it is essential to ensure adequate and timely screening of patients with mental disorders; otherwise, opportunities to help can be lost. In addition, there are certain barriers to the monitoring of metabolic status in patients with psychosis.[14,15] In particular, this population faces numerous challenges in obtaining properly integrated healthcare services. Therefore, the metabolic screening of such patients requires urgent improvement, involving a reorganization of the service in its current form, better communication, incentives for improvements, better education and training, more robust accreditation, and government leadership initiatives. There is no unanimous opinion regarding whether patients with psychotic disorders are subject to higher risks of cardiovascular diseases because of antipsychotic treatment, poor lifestyle, or the presence of a psychotic disorder.[16]

The most studied factor associated with obesity in patients with psychosis is antipsychotic medication. Weight gain occurs in patients taking such medication, is most rapid in the early stage of treatment, and is accompanied by central obesity.[17] Antipsychotic treatment is associated with a greater appetite, an unhealthy diet, disordered eating behavior, and sedentary behavior with lower energy expenditure.[18–21] The exact mechanisms whereby antipsychotics induce weight gain are not completely understood. Antipsychotics with high affinity for 5-HT2C or muscarinic receptors are associated with the greatest risk of weight gain, but other serotonin, histamine, and dopamine receptors may also be involved.[22] In addition, the eating habits of patients experiencing psychosis are impaired because of impaired executive function, which limits the restraints to food consumption and facilitates disinhibition.[23] This is associated with insensitivity of reward systems, which changes the preferences of

patients toward less nutritious foods, containing high levels of sugar, salt, and fat, in patients with psychosis from the early stages of the disorder.[24]

Indications of predispositions toward both psychotic and metabolic disorders have been identified in the same individuals. In addition, the existence of several pathophysiological mechanisms that underpin metabolic disturbances are well recognized in patients with psychosis, including adipokine dysregulation, inflammation, smoking, poor lifestyle, and obesity.[25]

Obesity in patients with psychosis is present even before antipsychotic treatment is commenced. Candidate obesity gene variants have been shown to be present in patients who experience a first episode of psychosis (FEP).[26] Moreover, unhealthy dietary habits and low levels of physical activity contribute to the obesity and metabolic disturbances present in patients with psychosis.[21,27] Specifically, they consume diets that lack fruit and fiber and are rich in simple sugars. In addition, they undertake less physical activity, especially moderate and vigorous physical activity, and show more sedentary behavior, with more time spent lying down and sleeping each day.[20,28,29]

One of the most challenging areas of research with respect to FEP is immune dysfunction, which is largely associated with adipocyte dysfunction. Numerous proteins and cytokines that are secreted by adipose tissue have been shown to play physiological roles in the human body, including in inflammation, coagulation, vascular remodeling, regulation of blood pressure, lipid metabolism, glucose metabolism, energy balance, and appetite.[30,31] These include the adipokines interleukin (IL)-6, tumor necrosis factor (TNF)-α, insulin-like growth factor-1, leptin, resistin, nesfatin 1, apelin, visfatin, and C-reactive protein; and sex hormones.[32] Several previous studies have demonstrated that high circulating concentrations of these substances are present in patients with psychotic disorders, both during the early and later phases.[30,31,33] Several types of adipokine receptors have been identified in components of the central nervous system and have been demonstrated to affect brain function.[34] This provides an important link between obesity/MetS and psychotic disorders, namely greater monocyte/macrophage activation and inflammation.

There have been few substantial longitudinal studies of patients who experience FEP that have aimed to determine the prevalence of MetS and related factors, despite the numerous clinical implications. Moreover, the results of the studies that have been conducted to date have been contradictory. We wished to involve patients in their routine clinical care and to overcome the limitations of previously published studies of this relationship. First, most of the studies were cross-sectional; therefore, causal relationships could not be identified.[35–39] Second, the majority of the published studies only included patients with schizophrenia.[35–37,40–42] Considering the diagnostic instability associated with FEP and that the diagnosis is typically adjusted in a significant proportion of the patients, it is important to study patients with a broader spectrum of affective and non-affective psychoses, to ensure a more accurate evaluation of the prevalence of MetS in patients with FEP.[43] Third, the results of studies conducted previously cannot be relied on when making decisions in modern clinical practice, because procedures have changed. For example, in the majority of these studies, inpatients were recruited, whereas patients who did not require hospitalization and those with milder forms of the disease were excluded.

We aimed to perform a longitudinal study of patients with FEP in which we would measure the prevalence of MetS,

characterize its course, and assess metabolic parameters throughout the first year following the diagnosis of the disease. Furthermore, we aimed to identify baseline parameters that might represent predictors of changes in the metabolic profiles of patients with early-stage psychosis.

Material and methods

Participants

The setting of this prospective observational longitudinal study was a healthcare facility in two Portuguese hospitals with psychiatric departments. Two early-intervention teams were involved in the study: Centro Hospitalar Universitário Lisboa Norte in the Programa de Intervenção nas Fases Iniciais da Psicose (PROFIP) and Hospital Vila Franca de Xira in the first-episode psychosis program (PPEP). Centro Hospitalar Universitário Lisboa Norte, a tertiary care university hospital, has a catchment area that includes approximately 350,000 people. The PROFIP program has been described previously.[44] The secondary care general hospital Vila Franca de Xira Hospital, located in the northern metropolitan area of Lisbon, has a catchment area that includes approximately 245,000 people. Trained staff assessed all the patients that were consecutively diagnosed with FEP. The therapeutic program consisted of group and individual psychosocial treatments, low-dose atypical antipsychotic medication, and family interventions.

The baseline criteria for the inclusion of patients were as follows: 1) age 16 to 40 years; 2) first diagnosis of a psychotic disorder made according to DSM-IV (American Psychiatric Association, 1994); in particular, delusional disorder, schizophrenia, bipolar psychotic disorder, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, major depressive disorder with psychotic features, or cannabis-induced psychosis; and 3) place of residence within the catchment areas of the PROFIP and PPEP services. Patients who could not complete or understand the required assessments and those with organic psychosis were excluded. The participants were evaluated twice: at baseline, provided that the conditions were appropriate for the assessment and the FEP had been clinically stabilized, and 1 year later. Patients were eligible for inclusion in the study if they met the criteria during the period between January 2017 and April 2018.

The study was approved by the ethics committee of each hospital (Centro Hospitalar Universitário Lisboa Norte: January 2017; Hospital Vila Franca de Xira: June 2016) and complied with the principles of the Declaration of Helsinki. The participants also provided their written informed consent. We de-identified all of the data during the study to guarantee the anonymity of the participants. The reporting of the study conforms to the STROBE guidelines.[45]

Clinical measures

Clinical and sociodemographic information was collected at baseline using a questionnaire that was completed by the research staff. The required details were age, marital status, employment, education, details of previous hospitalizations, details of the use of cannabis and tobacco, and any family history of psychiatric disease. The waist circumference and blood pressure of the participants were measured twice: at baseline and 1 year later. Waist circumference was measured in the standing position at the end of normal expiration, midway between the superior border of the iliac crest and the inferior costal margin. Blood pressure was measured using an automatic sphygmomanometer in the supine position. The Global

Assessment of Functioning (GAF) and Positive and Negative Syndrome Scale (PANSS) were completed for each participant during both evaluations, and the patients also completed the Beck Depression Inventory (BDI) themselves.[46–48]

Metabolic assessments

We used the modified definition of MetS published by the National Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP-ATP-III).[49,50] Participants were diagnosed with MetS if they met three or more of the following criteria: 1. Waist circumference >102 cm in men and >88 cm in women; 2. Serum triglyceride (TG) concentration >1.7 mmol/L or the use of an antihyperlipidemic drug; 3. High blood pressure (≥85 mmHg diastolic or ≥130 mmHg systolic) or the use of an antihypertensive drug; 4. Low high-density lipoprotein (HDL)-cholesterol concentration (<1.04 mmol/L for men and <1.3 mmol/L for women); and 5. High fasting serum glucose concentration (≥5.6 mmol/L) or a diagnosis of type 2 diabetes mellitus.

Overnight fasting was obligatory for the collection of blood samples. An assigned technician who was not involved in the clinical evaluation made the measurements of the laboratory parameters for each participant (total cholesterol, glucose, TG, low-density lipoprotein (LDL)-cholesterol, and HDL-cholesterol concentrations). The serum concentrations of TG, HDL-cholesterol, and total cholesterol were measured using enzymatic assays, and the Friedewald equation was used to calculate the LDL-cholesterol concentration.[51]

Statistical analysis

Continuous and categorical variables are presented as means with standard deviations and frequencies, respectively. Normality was evaluated using the Kolmogorov–Smirnov test. Comparisons of the baseline characteristics of the participants between the hospital teams were made using the Mann–Whitney U-test. The metabolic data at baseline and 1 year later were compared using the Wilcoxon matched pairs signed rank test. The prevalences of MetS and metabolic abnormalities were compared between the time points using McNemar's test. Stepwise multiple regression analysis was used to identify potential predictors of MetS after 1 year of follow-up (the dependent variable), using the psychopathology, metabolic parameters, and demographic characteristics at baseline as independent variables. Statistical significance was accepted when $p < 0.05$. Data were analyzed using SPSS version 24 (IBM Corp., Armonk, NY, USA).

Results

Participants

We studied 60 patients admitted to PROFIP (n = 33) or PPEP (n = 27). The mean age of the PPEP patients was higher (mean years 29.6 *vs.* 24.2; $p = 0.003$), but their educational level was lower (mean number of years of education 10.1 *vs.* 11.7; $p = 0.016$). However, the employment and sex distribution of the participants did not differ between the teams.

At baseline, 33.3% of the participants were women and the mean age of the entire group was 27.1 years. The majority of the participants (95%) were hospitalized at baseline. The mean duration of untreated psychosis (DUP) was approximately 313 days. Schizophrenia spectrum disorders was the most common diagnosis (50% of the participants). The clinical and demographic characteristics of the participants at baseline are presented in Table 1.

Table 1. Socio-demographic and clinical baseline parameters of the participants.

Parameter	Value in patients with first-episode psychosis, n = 60
Mean age (SD)	27.10 (7.93)
Sex, n (%)	
Women	20 (33.3%)
Men	40 (66.7%)
Duration of education, years, mean (SD)	11.28 (3.34)
Unemployment, n (%)	24 (40%)
Marital status, n (%)	
Living with partner/Married	6 (10%)
Single/Divorced	54 (90%)
Hospitalization at baseline, n (%)	
Yes	57 (95%)
No	3 (5%)
Tobacco user, n (%)	
Yes	34 (56.7%)
No	26 (43.3%)
Cannabis user, n (%)	
Yes	37 (61.7%)
No	23 (38.3%)
Family history of psychiatric disease, n (%)	43 (71.7%)
DUP, days, mean (SD)	312.87 (722.74)
Diagnosis, n (%)	
Schizophrenia spectrum	30 (50%)
Affective psychosis spectrum	16 (26.7%)
Other psychosis	14 (23.3%)
PANSS score, mean (SD)	
PANSS positive subscale	19.08 (7.32)
PANSS negative subscale	17.38 (7.11)
PANSS general subscale	36.22 (9.03)
GAF, mean (SD)	47.43 (17.27)
BDI, mean (SD)	13.55 (10.45)

SD, standard deviation; DUP, duration of untreated psychosis; PANSS, positive and negative syndrome scale; GAF, global assessment of functioning; BDI, Beck Depression Inventory.
"Schizophrenia spectrum disorders" included schizophrenia, schizophreniform disorder, delusional disorder, and schizoaffective disorder. "Affective psychosis" included bipolar disorder with psychotic symptoms and depressive disorders with psychotic symptoms. "Other psychosis" included acute and transient psychotic disorders, brief psychotic disorders, and psychosis not otherwise specified.

Metabolic profiles of the participants

Table 2 presents the laboratory measurements for the participants obtained at baseline and 1 year later. There was an apparent increase in the prevalence of metabolic syndrome, from 6.7% to 11.7%, between baseline and follow-up, but the difference was not statistically significant ($p = 0.250$). Of the entire cohort, 8.3% at baseline and 15% at follow-up had two criteria for MetS. At the follow-up examination, all of the metabolic parameters had deteriorated. There were significant increases in mean triglyceride concentration ($p = 0.042$) and mean waist circumference ($p < 0.001$), and a significant decrease in mean HDL-cholesterol ($p = 0.028$). There were also significant increases in the prevalences of abnormal triglyceride concentration ($p = 0.040$), waist circumference ($p = 0.039$), and HDL-cholesterol concentration ($p = 0.019$) between baseline and the 1-year follow-up examinations.

At both time points, the prevalence of MetS appeared to be lower in women, but there were no significant differences at baseline ($p = 0.291$, 0% women *vs.* 6.7% men) or follow-up ($p = 0.57$, 3.3% women *vs.* 8.3% men).

Predictors of MetS

We next attempted to identify baseline parameters that were predictors of MetS at follow-up. MetS served as the dependent variable, and age, duration of education, sex, marital status, diagnostic group, a family history of psychiatric diseases, the use of tobacco or cannabis, the BDI and GAF scores, PANSS subscale scores, DUP, and all the metabolic and anthropometric components of MetS at baseline were interrogated as potential predictors. All the parameters with $p < 0.15$ on univariate analysis were included in the multivariate analysis. These were DUP ($p = 0.119$), the duration of education ($p = 0.126$),

Table 2. Metabolic parameters at baseline and 12 months later.

Parameter	Baseline	12 months later	*p*-value
Waist circumference, cm, mean (SD)	83.58 (10.14)	102.50 (99.41)	<0.001*
Abnormal waist circumference (≥102 cm in men, ≥88 cm in women), n (%)	6 (10%)	13 (21.7%)	0.039*
Serum triglycerides, mmol/L, mean (SD)	0.886 (0.42)	1.095 (0.75)	0.042*
Abnormal triglyceride concentration (>1.7 mmol/L) or treatment, n (%)	4 (6.7%)	6 (10%)	0.040*
Serum HDL-cholesterol (mmol/L), mean (SD)	1.368 (0.34)	1.295 (0.31)	0.028*
Abnormally low HDL-cholesterol (<1.04 mmol/L in men, <1.3 mmol/L in women), n (%)	13 (21.7%)	15 (25%)	0.019*
Blood pressure (mmHg), mean (SD)			
Systolic	122.18 (13.50)	123.17 (13.01)	0.583
Diastolic	66.15 (10.16)	68.02 (9.80)	0.190
Abnormal blood pressure (≥130/85 mmHg) or treatment, n (%)	19 (31.7%)	21 (35.0%)	0.990
Fasting plasma glucose concentration (mmol/L), mean (SD)	4.963 (0.77)	5.014 (0.45)	0.338
Abnormal fasting blood glucose (≥5.6 mmol/L) or diabetes, n (%)	3 (5.0%)	8 (13.3%)	0.344
MetS, n (%)	4 (6.7%)	7 (11.7%)	0.250
Number of MetS criteria, n (%)			
0	29 (48.3%)	24 (40%)	
1	22 (36.6%)	20 (33.3%)	
2	5 (8.3%)	9 (15.0%)	
3	3 (5.0%)	5 (8.3%)	
4	1 (1.7%)	2 (3.3%)	
5	0 (0%)	0 (0%)	
TG/HDL ratio	1.48	1.94	

SD, standard deviation; HDL, high-density lipoprotein; MetS, metabolic syndrome; TG, triglyceride. *$p < 0.05$.
Comparisons of the prevalences of abnormal values of metabolic parameters and MetS were performed using McNemar's test, and comparisons of mean metabolic and anthropometric values were performed using the Wilcoxon matched-pairs signed rank test.

baseline waist circumference ($p = 0.006$), the baseline general subscale of PANSS ($p = 0.132$), baseline systolic blood pressure ($p = 0.055$), and baseline HDL-cholesterol concentration ($p = 0.017$). However, none of these was found to be significant on multivariate binary logistic regression, and therefore to be a predictor of MetS at 12-months of follow-up.

Psychopharmacological treatment

At both assessments, all of the participants were being treated with atypical antipsychotics, predominantly *via* the oral route (75% and 63.3% at baseline and follow-up, respectively). At both evaluations, the participants were being prescribed risperidone as the most atypical antipsychotic alone or in combination with other medicines, orally (45% and 26.7% at baseline and follow-up, respectively). The injectable antipsychotics used were long-acting aripiprazole and paliperidone, which were administered intramuscularly. Table 3 lists the prescribed psychopharmacological treatments at the two time points.

Table 3. Psychopharmacological drugs being used at baseline and 12 months later.

	Baseline	12 months later
Antipsychotic treatment, n (%)		
Atypical antipsychotic	60 (100%)	60 (100%)
Route of antipsychotic, n (%)		
Only oral	45 (75%)	38 (63.3%)
Only LA IM	1 (1.7%)	11 (18.3%)
Both	14 (23.3%)	11 (18.3%)
Type of atypical antipsychotic, n (%)		
Clozapine, oral	2 (3.3%)	5 (8.3%)
Olanzapine, oral	14 (23.3%)	11 (18.3%)
Quetiapine, oral	1 (1.6%)	9 (15.0%)
Risperidone, oral	27 (45.0%)	16 (26.7%)
Paliperidone, oral/IM	12 (20.0%)	18 (30%)
Aripiprazole, oral/IM	17 (28.3%)	15 (25.0%)
Amissulpride, oral	1 (1.7%)	1 (1.7%)
Chlorpromazine equivalents, mean (SD) dose, mg[52,53]	295.4 (220.6)	297.4 (236.0)
Other drugs, n (%)		
Anticholinergics	6 (10%)	17 (28.3%)
Antidepressants	12 (20%)	21 (35%)
Mood stabilizers	3 (5%)	4 (6.7%)
Benzodiazepines	3 (5%)	3 (5%)

LA: long-acting; IM: intramuscular; SD: standard deviation.

Discussion

The present study is the first to assess the prevalences of MetS and metabolic parameters in patients diagnosed with non-affective or affective FEP longitudinally in Portugal. The prevalence of MetS was found to be 6.7% at baseline and 11.7% 1 year later, with the prevalence having increased in almost three-fourths of the participants over this period. We have also identified a worsening of the HDL-cholesterol and triglyceride concentrations and the waist circumference of the participants over this period, and increases in the prevalences of abnormalities of these parameters. These findings emphasize that there is a high likelihood of developing cardiovascular risk factors during the early stages of psychosis and a rapid deterioration in the metabolic profile at the same time. Thus, we have provided additional evidence that patients with FEP are predisposed toward metabolic dysfunction in the relatively short term.

The present findings are consistent with the those of previous longitudinal studies.[36,54–57] A prevalence of MetS of 6.6% was reported by Bioque *et al*. in patients with FEP, according to the criteria of the International Diabetes Federation, with a prevalence of 14.6% 2 years later, corresponding to a 120% increase.[55] A prevalence of 2.3% was identified in a study of Brazilian patients with FEP at baseline, according to the NCEP criteria, and 6 months later it was 9.1%, representing an almost three-fold increase.[54] Thus, both previous studies and the present study have demonstrated worsening of the metabolic profiles of patients with FEP. We have shown an apparent 75% increase in the prevalence of MetS, and the majority of

previous studies have also demonstrated significant increases in the prevalence of MetS during the early stages of psychosis (6 months to 2 years). The incidence of MetS during the first year identified in the present study (5%) is similar to those identified previously over the same time period (from 3.95% to 5.5%).[58,59] However, none of these studies identified significant predictors of MetS at baseline or 1 year later, as in the present study.

There have been few studies of the prevalence of MetS in the general population in Portugal. The prevalence of MetS in the Valsim cross-sectional multi-center study of 18- to 29 year-old patients attending Portuguese primary care facilities was 6.2%.[60] This is a similar prevalence to that obtained for patients with FEP at baseline in the present study, but the prevalence in these patients 1 year later was almost twice as high. The prevalences identified in the PORMETS cross-sectional study of 4004 patients attending primary care facilities throughout Portugal[61] were 5% and 16% in 18- to 30-year-olds and 31- to 40-year-olds, respectively. Thus, the MetS prevalence identified in the present study is higher than that in the general population, but this difference only became evident after one year. The most common criterion for MetS in the PORMETS study was high blood pressure, whereas in the present study it was abnormal waist circumference. It should be noted that the PORMETS and Valsim studies were of primary care users, and therefore the level of prevalence of MetS would probably be lower in the real general population of Portugal. In addition, there were differences in the definitions of MetS that were used. MetS was defined using the ATP-III criteria in the Valsim study and using the HARM2009 criteria in the PORMETS study.[49,62] The MESYAS cross-sectional study of 7256 members of the working population of Spain defined MetS using the modified ATP-III criteria,[49] and showed a 2.5% to 5% prevalence in 20- to 39-year-olds,[63] which was lower than in the present study, in which we used the same definition of MetS. However, the results of all the studies discussed imply that the prevalence of MetS is high 1 year following a diagnosis of FEP.

Some other previous cross-sectional studies have shown a high prevalence of MetS in patients with psychoses, such as schizophrenia. As expected, the prevalence of MetS in patients with chronic schizophrenia seems to be higher than that in patients with FEP. For example, Sahpolat *et al*. stated that the prevalence of MetS in Turkish patients with schizophrenia was 40%,[38] Grover *et al*. calculated the same prevalence in Indian patients with schizophrenia,[64] and other studies have calculated prevalences of 51% and 67.6% in Australian and British patients with schizophrenia, respectively.[65,66]

A number of factors that are associated with MetS, including body mass, lifestyle, obesity, adipokine dysregulation, and inflammation, have been shown to be associated with psychosis.[25]

Diet, smoking, and physical activity affect the prevalence of MetS in patients with psychosis.[67] The importance of these variables have not been thoroughly investigated, but patients with FEP have more unhealthy lifestyles than healthy individuals of similar ages. This is evident in terms of higher prevalences of cigarette smoking and alcohol abuse; poor dietary habits, with the consumption of large amounts of saturated fatty acids, carbohydrates, and salt; and small amounts of fruit and vegetables; and low levels of physical activity.[29,67,68] A recent study showed that the majority of patients with FEP have unhealthy dietary habits, as defined by a lack of consumption of a Mediterranean-style diet, and that this poor diet was associated with a low educational level.[67] However,

we did not evaluate or control for the diet or physical activity of the participants in the present study.

In our research, waist circumference was the parameter that most significantly changed during the 12-month follow-up period ($p < 0.001$). This is consistent with the important role of adipocytes in both psychotic disorders and MetS, and suggests that excess weight may have a deleterious effect on the immune system, manifesting in a pro-inflammatory effect on the central nervous system.[31,69,70] Previous studies have revealed an association of chronic inflammation and adipokines with psychosis and evidence of immune dysfunction.[71] These immunological changes include high concentrations of pro-inflammatory cytokines and chemokines in the circulation and cerebrospinal fluid, as well as changes in immune cell function in the central nervous system.[72,73] Adipose tissue directly or indirectly secretes pro-inflammatory cytokines and proteins (IL-6, TNF-α, insulin-like growth factor-1, leptin, resistin, apelin, visfatin, CCL22, and nesfatin-1),[30,31,33,74] and patients with schizophrenia also show activation of microglia, which contributes to the high serum concentrations of pro-inflammatory cytokines.[73,75] Some of these substances are present and/or have receptors in parts of the central nervous system, but their exact roles in the pathophysiology of psychosis are still being studied. It is interesting to note that recent studies revealed that baseline metabolic and inflammatory parameters may be diagnostic, associated with the severity of the symptoms, and/or be predictors of the treatment response in FEP.[76,77]

The previous studies also characterized the changes in the lipid profiles of patients following a diagnosis of FEP, which include a decrease in HDL-cholesterol concentration and an increase in triglyceride concentration, resulting in an increase in the triglyceride-to-HDL ratio. It is important to note that this ratio is an independent predictor of cardiovascular disease and mortality[77] and a marker of atherogenesis.[79,80] The TG/HDL ratios of the participants in the present study were high (baseline, 1.48; 1-year follow-up, 1.94), consistent with the presence of cardiovascular risk factors.

The male participants in the present study tended to have higher prevalences of MetS at baseline ($p = 0.291$, 0% women *vs.* 6.7% men) and follow-up ($p = 0.571$, 3.3% women *vs.* 8.3% men), consistent with the results of previous studies of patients with FEP.[81,82] However, the male participants in the present study had worse metabolic profiles in the early stages of psychosis than those in previous studies,[55,83] and these findings are consistent with those obtained in studies of the general population.[84]

The baseline evaluation was made soon after the diagnosis of FEP, during the first few days of treatment. Therefore, the medication is likely to have had a minor effect on the findings at baseline. However, the medication used may have affected the incidence of MetS during the follow-up period. Nevertheless, at both time points, medications with moderate or low metabolic impacts were used, and because few participants developed MetS during the study, no further analysis was performed regarding the antipsychotic medication.

Assessments of glucose homeostasis, and in particular oral glucose tolerance testing, were suggested to be an effective way of evaluating cardiovascular and metabolic risk in patients with FEP in the report by Garcia-Rizo et al.[36] The cross-sectional study reported therein aimed to calculate the prevalence of MetS in patients with FEP and controls. The glucose homeostasis of the 84 patients with FEP varied greatly. To some extent, the results we have obtained in the present study are not consistent with this, but we did not perform

homeostatic model assessment, oral glucose tolerance testing, or any other assessment of glucose homeostasis. However, we contend that the assessment of MetS is a useful means of judging the risk of cardiovascular disease in patients with FEP, and the measurement of parameters related to MetS is more feasible in clinical psychiatric research than other assessments of glucose homeostasis.

One limitation of the present study was the small sample size, which could have reduced the likelihood of identifying predictors of MetS and prevented an assessment of the effect of antipsychotic treatment. In addition, it would have been desirable to compare the prevalence of MetS in the psychiatric patients with that of a control group. However, we have compared our findings with those of a study of primary care data, in an attempt to overcome this limitation. Furthermore, we did not analyze the effects of each of the second-generation antipsychotics used by the participants on their metabolism. Finally, we did not account for potential confounding factors, such as physical activity and diet.

In conclusion, the present findings suggest that the prevalence of metabolic abnormalities in patients with FEP is high, and that these rapidly worsen during the early stages of the disorder. Further studies should be conducted to analyze the effects of specific interventions on these metabolic parameters and on the morbidity and mortality associated with cardiovascular disease in patients with FEP. In addition, the effects of each of the second-generation antipsychotics on the metabolism and inflammation of patients with FEP should be assessed.

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Author contributions

RC, PL, CG, and MLF participated in the clinical work. RC and PL performed the literature review. CG and MLF supervised the project and contributed to the manuscript content and editing. All the authors contributed to the manuscript revision and read and approved the submitted version.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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