

## REVIEW ARTICLE OPEN

## Predictors of outcome in early-onset psychosis: a systematic review

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Given the global burden of psychotic disorders, the identification of patients with early-onset psychosis (EOP; that is, onset before the age of 18) at higher risk of adverse outcome should be a priority. A systematic search of Pubmed, Embase, and PsycInfo (1980 through August 2014) was performed to identify longitudinal observational studies assessing correlates and/or predictors of clinical, functional, cognitive, and biological outcomes in EOP. Seventy-five studies were included in the review. Using multivariate models, the most replicated predictors of worse clinical, functional, cognitive, and biological outcomes in EOP were premorbid difficulties and symptom severity (especially of negative symptoms) at baseline. Longer duration of untreated psychosis (DUP) predicted worse clinical, functional, and cognitive outcomes. Higher risk of attempting suicide was predicted by greater severity of psychotic illness and of depressive symptoms at the first episode of psychosis. Age at onset and sex were not found to be relevant predictors of outcome in most multivariate models, whereas studies using bivariate analyses yielded inconsistent results. Lower intelligence quotient at baseline predicted lower insight at follow-up, worse functional outcomes, and a diagnostic outcome of schizophrenia. Biological predictors of outcome in EOP have been little studied and have not been replicated. Lower levels of antioxidants at baseline predicted greater brain volume changes and worse cognitive functioning at follow-up, whereas neuroimaging markers such as regional cortical thickness and gray matter volume at baseline predicted remission and better insight at follow-up, respectively. EOP patients with poorer premorbid adjustment and prominent negative symptoms at initial presentation are at risk of poor outcome. They should therefore be the target of careful monitoring and more intensive interventions to address whether the disease course can be modified in this especially severely affected group. Early intervention strategies to reduce DUP may also improve outcome in EOP.

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## INTRODUCTION

Neuropsychiatric disorders are the greatest contributor to global burden of disease in adolescents and young adults worldwide.<sup>1</sup> There has been growing interest in prevention and early intervention in psychiatry in recent years,<sup>2,3</sup> as it has become increasingly evident that effective management of child and adolescent psychiatric disorders can help prevent the development of persistent mental health concerns in adulthood<sup>4,5</sup> and that early intervention strategies can positively impact long-term outcome of severe mental disorders, especially in young people.<sup>6–9</sup>

As neurodevelopmental disorders, schizophrenia and other psychoses usually show their first manifestations during childhood and adolescence, and 11–18% of patients present with their first episode of psychosis before age 18 (early-onset psychosis; EOP).<sup>10,11</sup> Outcome in EOP is negatively affected by the impact of illness onset on individuals whose neurobiological and psychosocial development is not yet complete,<sup>12</sup> leading to 50–60% of EOP patients with poor outcome.<sup>13</sup> Although almost 40% of patients with schizophrenia will achieve social or functional recovery,<sup>14</sup> and some will have a positive outcome even if medication is discontinued,<sup>15</sup> there is still a large group of patients at risk of poor outcome. This group may constitute an even larger proportion in the population with an early-onset form of the illness, which makes identification of the risk factors

associated with a poor outcome in this population especially valuable. This would facilitate more intensive and tailored interventions in those patients deemed to be at higher risk of having poor outcome, facilitating a rationalization of resources' use and expectations.

Despite the interest of identifying predictors of outcome in this population, studies are still scarce and have shown contradictory results. One previous systematic review of predictors of outcome in adolescent first episode psychosis in papers published in 1989–1999 did not find any variable significantly predictive of diagnostic or overall outcome, except for (i) presence of abnormal premorbid personality traits, which was suggestive of a diagnostic outcome of schizophrenia, and (ii) lower functioning before and after the first episode of psychosis, which was associated both with a diagnostic outcome of schizophrenia and poorer overall outcome.<sup>16</sup> Similarly, a more recent non-systematic review reported the following predictors of chronic long-term course in early-onset schizophrenia: younger age at illness onset, insidious onset, positive family history of non-affective psychosis, developmental delays, poor premorbid adjustment, longer duration of the first episode of psychosis, greater symptom severity and poorer psychosocial functioning at discharge, and higher number of relapses through follow-up.<sup>17</sup>

Given the potential clinical relevance of identifying predictors of outcome in children and adolescents with psychosis, we aimed to

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perform a comprehensive systematic review of the literature to date on predictors and correlates of clinical, functional, cognitive, and biological outcomes in EOP. We hypothesized that there would be a set of main predictors that overlap with those reported for adult-onset psychoses, and that those related to premorbid difficulties and developmental delays would play an especially important role in this population.

## MATERIALS AND METHODS

### Search strategy

A systematic two-step literature search was performed following the guidelines of the PRISMA statement.<sup>18</sup> A Pubmed, Embase, and PsycInfo search (1980 through August 2014) was performed using the following search terms: (early-onset, childhood-onset, adolescent-onset, child\*, adolescent\*) combined with (psychosis, psychotic, schizophrenia, first-episode psychosis, first-episode psychotic, bipolar psychotic). In a second step, we manually reviewed the reference lists of the selected studies and previous reviews to identify any potentially relevant studies not identified by the computerized search.

The initial literature search yielded 3,750 studies and the manual search identified 47 additional studies. After removing duplicates, 2,293 potential studies were identified.

### Selection criteria

The abstracts of the 2,293 resulting studies were assessed for eligibility using the following hierarchical criteria:

1. Studies were peer-reviewed original articles published in English.
2. Studies had a longitudinal and observational design. As the main objective of this review was to assess predictors and correlates of the course of EOP and not specific therapeutic interventions, studies assessing predictive and outcome variables in the context of a clinical trial were not included.
3. Participants had a diagnosis of schizophrenia or other psychotic disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria - DSM-III, DSM-III-R, DSM-IV, DSM-IV-TR, or to the International Classification of Diseases (ICD) criteria - ICD-9 or ICD-10. This limitation was applied since, before the DSM-III, the definition of categories such as childhood-onset schizophrenia included clinical pictures that would currently be classified under the diagnostic category of autism spectrum disorders.<sup>19</sup>
4. Onset of psychotic illness in childhood or adolescence (that is, either the upper limit of the range of age at onset was < 18 years or the onset was defined by the authors as a 'childhood onset', 'adolescence onset', and/or 'early-onset'). In four studies, the upper limit of the range of the age at onset was > 18, but mean age at onset or at baseline was < 18 and the authors referred to these as participants with EOP.<sup>20-23</sup> In two studies, the range of the age at onset or at baseline was not provided, but mean age at baseline was < 18 and the authors referred to the sample as adolescent onset.<sup>24,25</sup>
5. Studies assessed clinical, functional, cognitive, and/or biological (that is, neuroimaging, biochemical) outcome measures or suicide risk. This broad definition of outcome was used to provide a more comprehensive perspective on the issue and to increase the clinical applicability of the results.
6. Studies assessed the association between demographic, clinical, functional, cognitive, and/or biological baseline variables and follow-up outcome measures using bivariate (for example, Student's *t*-tests, analysis of variance,  $\chi^2$ -tests, correlations) or multivariate (for example, linear/logistic regression models or novel multivariate machine-learning methods) techniques.

When the Abstract did not provide sufficient information to assess study eligibility, the full text was consulted. In instances where the full text was not available, the authors were contacted by e-mail. Of the 2,293 assessed studies, 214 full-text articles were selected and further assessed for eligibility. Of those, 75 studies fulfilled all the inclusion criteria and were ultimately included in the review. Figure 1 shows the flowchart of the literature review process.

### Data extraction

Data were extracted by two reviewers (CMD-C, AR-Q) and supervised by an external reviewer (LP-C). For each study, the following data were retrieved: author names, year of publication, name or acronym of the cohort, design (retrospective, prospective, or mixed), number of subjects, demographic variables (age at baseline, proportion of male subjects), clinical variables (age at onset, diagnosis distribution), length of follow-up, outcome measures, and predictors/correlates of outcome. Papers reporting on the same cohort were included as long as they provided additional information on any of the relevant outcome measures. Discrepancies were resolved by discussion.

### Data synthesis and analysis

Studies were classified according to the type of outcome measures assessed (clinical, functional, cognitive, biological, or suicide risk), length of follow-up, and study cohort. For reporting purposes, findings are displayed (i) separately for studies using multivariate/regression models and those using bivariate analyses and (ii) only if associations/predictions reach a significance threshold of  $P < 0.05$ .

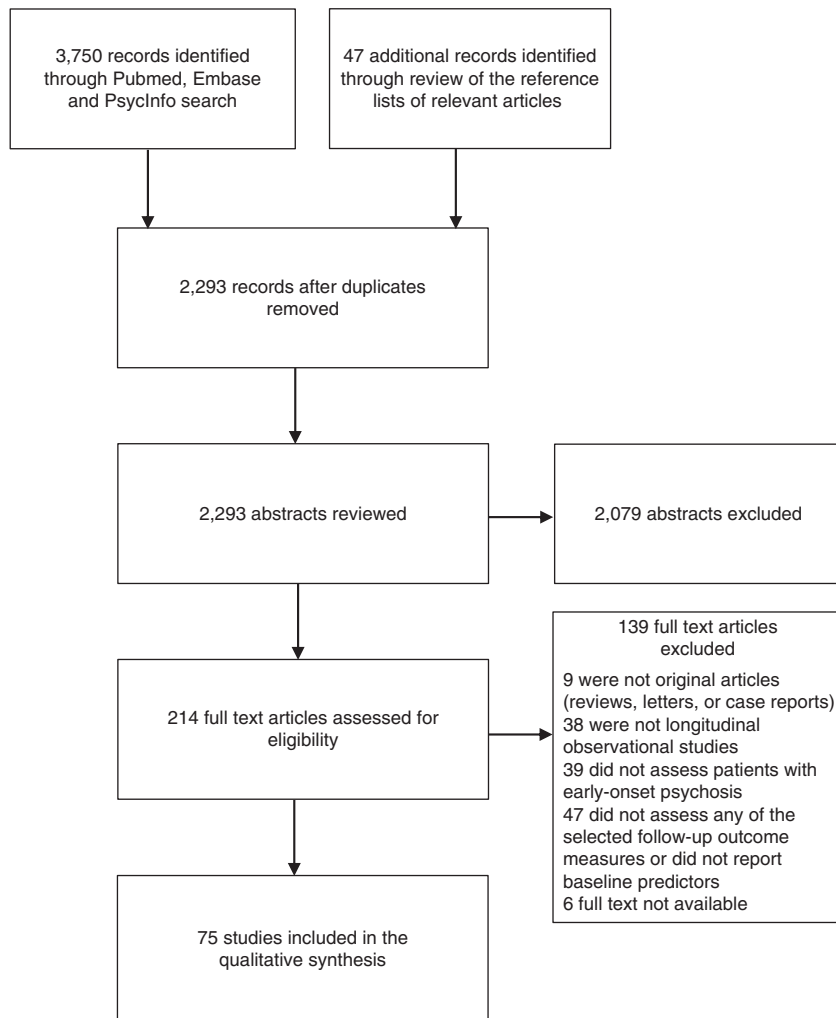
## RESULTS

Table 1 provides a summary of the reported significant predictors (in studies using multivariate/regression models) or correlates (in studies using bivariate approaches) for each outcome category. For further description of the characteristics and main findings of the reviewed articles (for example, sample size, design, statistical methods, outcomes assessed), see Supplementary Table 1.

Using multivariate models, premorbid difficulties (that is, poorer premorbid adjustment, history of developmental disorder) and greater symptom severity (especially negative symptoms) at baseline were consistently found to be significant predictors of worse outcome across all areas (clinical, functional, cognitive, and neuroimaging). This is also true for studies using bivariate analyses (Table 1). A diagnosis of schizophrenia was a significant predictor of greater disability, lower global functioning, and poorer quality of life at follow-up. Longer duration of untreated psychosis (DUP) was a significant predictor of worse clinical, functional, and cognitive outcomes in multivariate models (Table 1). However, the association between DUP and clinical or functional outcomes was not replicated in an EOP sample with longer DUP using a bivariate approach.<sup>26</sup>

Although sex has not been found to be a relevant predictor in most studies using regression models,<sup>27-30</sup> being female has been found to predict better insight and higher number of readmissions (see Table 1). In studies using bivariate approaches, being female has also been found to be associated with better global functioning, less likelihood of a chronic course and receiving clozapine, more likelihood of being in remission at follow-up, and less regional gray matter (GM) loss through follow-up (see Table 1). However, other studies have not found significant associations between sex and outcome.<sup>31,32</sup>

Lower age at onset has been found to predict worse quality of psychiatric care and poorer social, educational, and occupational functioning in multivariate models, but is not a consistently reported predictor of these and other outcomes in studies using regression models<sup>27,28,33</sup> (Table 1). In bivariate studies, lower age at onset has



**Figure 1.** Flowchart of study selection.

been found to be associated with less likelihood of remission, worse global functioning, and greater disability, although there are also studies that do not find this association.<sup>31,34</sup>

Cognitive variables such as lower intelligence quotient (IQ) at baseline have been found to predict worse functional outcome, a diagnostic outcome of schizophrenia, or poorer insight at follow-up in multivariate models (Table 1).

Using multivariate models, biological predictors such as lower antioxidant levels at baseline have been found to predict greater brain volume changes and worse cognitive functioning at follow-up. Among neuroimaging markers, cortical thickness and GM volume at baseline in different brain regions have been found to predict remission and insight at follow-up, respectively (Table 1). However, other studies using multivariate techniques have not found significant associations/predictions between biological variables and outcomes such as diagnosis at follow-up in first-episode patients.<sup>35</sup>

## DISCUSSION

In this systematic review, we found that the most replicated predictors of worse clinical, functional, cognitive, and/or biological outcomes in EOP are a positive history of premorbid difficulties (developmental delays and poor premorbid adjustment), greater symptom severity (especially of negative symptoms) at baseline and longer DUP. Greater initial symptom severity is also a good

predictor of attempting suicide during follow-up, together with greater severity of depressive symptoms at baseline or at discharge after the first episode. Cognitive variables such as lower IQ at baseline predict poorer insight at follow-up, worse functional outcomes, and a diagnostic outcome of schizophrenia. Biochemical variables such as lower blood antioxidant levels at baseline predict greater brain volume changes and worse cognitive functioning at follow-up, whereas regional brain thickness and volume measures of different brain regions at baseline predict remission status and insight at follow-up, respectively. Age at psychosis onset and sex do not seem to be consistent predictors of any outcome in EOP samples.

It has been proposed that developmental continuity may exist from premorbid difficulties to primary negative symptoms in EOP.<sup>36</sup> The coexistence of severe premorbid impairments and negative symptoms delineate a large subgroup of EOP individuals with higher neurodevelopmental load who are eventually at risk of a deleterious course.<sup>37</sup> This would be consistent with our finding that poorer premorbid adjustment and more prominent negative symptoms at illness onset are core predictors of functional and clinical outcomes in EOP and would further support the neurodevelopmental nature of psychotic disorders,<sup>38</sup> with early-onset forms at one extreme of the continuum of disease severity and genetic liability.<sup>39</sup> Indeed, both negative symptoms and premorbid adjustment have also been found to be good predictors of outcome in adult-onset psychosis,<sup>40–42</sup> which would

**Table 1.** Summary of the predictors and variables associated with outcome in early-onset psychosis

	Multivariate analyses	Bivariate analyses
<b>Clinical outcomes</b>		
Diagnosis	<p>A follow-up diagnosis of SSD predicted by:</p> <ul style="list-style-type: none"> <li>• More severe positive and negative symptoms and less severe affective and somatic symptoms at baseline<sup>35</sup></li> <li>• Poorer insight<sup>35</sup></li> <li>• More frequent history of obstetric complications<sup>35</sup></li> <li>• Lower IQ, lower scores in attention and global cognition, and greater motor impairment at baseline<sup>35</sup></li> <li>• Use of risperidone and aripiprazole and higher dose of antipsychotic treatment during FEP<sup>35</sup></li> </ul>	<p>A follow-up diagnosis of SSD associated with:</p> <ul style="list-style-type: none"> <li>• More severe positive symptoms at baseline<sup>22</sup></li> <li>• More severe negative symptoms at baseline<sup>84</sup> and at discharge after an admission for FEP<sup>22</sup></li> <li>• More severe cognitive symptoms at baseline<sup>84</sup></li> <li>• Longer duration of the acute index episode<sup>22</sup></li> <li>• Regional GM volume deficits at baseline in left medial frontal and left middle frontal gyrus as compared with controls (versus left medial frontal cortex in BD I and bilateral insular and right occipital cortex in other psychotic disorders)<sup>85</sup></li> <li>• Increased temporal, parietal, and occipital sulcal width at baseline compared with controls (not found in BD I)<sup>53</sup></li> </ul>
Symptom type and severity	<ul style="list-style-type: none"> <li>• Positive symptoms: More severe positive symptoms at follow-up predicted by more severe positive symptoms during acute episodes in childhood<sup>86</sup></li> <li>• Negative symptoms: More severe negative symptoms at follow-up predicted by more severe negative symptoms at baseline,<sup>28</sup> more severe positive and negative symptoms during acute episodes in childhood,<sup>86</sup> insidious onset,<sup>62</sup> poorer premorbid functioning,<sup>86</sup> and worse baseline social functioning<sup>28</sup></li> <li>• PANSS total: Higher scores at follow-up predicted by being female,<sup>28</sup> more severe baseline negative symptoms,<sup>28</sup> insidious onset,<sup>62</sup> poorer premorbid adjustment,<sup>62</sup> and worse baseline social functioning<sup>28,62</sup></li> <li>• Illness severity (CGI): Greater severity at follow-up predicted by insidious onset<sup>62</sup></li> </ul>	<p>Positive symptoms:</p> <ul style="list-style-type: none"> <li>• More severe symptoms at follow-up associated with a diagnosis of schizophrenia,<sup>48,87</sup> greater premorbid emotional withdrawal,<sup>88</sup> and positive family history of non-affective psychosis<sup>64</sup></li> <li>• Less severe symptoms at follow-up in baseline cannabis users versus cannabis non-users<sup>89</sup></li> <li>• Less improvement through follow-up in cannabis non-users versus cannabis users<sup>89</sup></li> </ul> <p>Negative symptoms:</p> <ul style="list-style-type: none"> <li>• More severe symptoms at follow-up associated with a diagnosis of schizophrenia,<sup>39,48,87</sup> positive family history of non-affective psychosis,<sup>64</sup> and lower baseline IQ<sup>90</sup></li> <li>• Less severe symptoms at follow-up in cannabis users versus non cannabis users<sup>89</sup></li> </ul> <p>Cognitive symptoms: More severe symptoms at follow-up associated with a diagnosis of schizophrenia<sup>84</sup></p> <p>Depressive symptoms: More severe symptoms at follow-up associated with a diagnosis of schizophrenia<sup>87</sup></p> <p>PANSS general:</p> <ul style="list-style-type: none"> <li>• More severe symptoms in patients with a diagnosis of schizophrenia<sup>87</sup></li> <li>• Less severe symptoms at follow-up in cannabis users versus cannabis non-users<sup>89</sup></li> </ul> <p>PANSS total:</p> <ul style="list-style-type: none"> <li>• Higher scores at follow-up associated with worse executive functioning, learning and memory, and global cognition at baseline<sup>91</sup></li> <li>• Less severe symptoms at follow-up in cannabis users versus cannabis non-users<sup>89</sup></li> </ul> <p>Chronic course associated with a diagnosis of schizophrenia<sup>39,55,92</sup> and being male<sup>31</sup></p>
Course		
Remission	<p>Short-term remission (12 weeks) predicted by:</p> <ul style="list-style-type: none"> <li>• Greater baseline cortical thickness in left prefrontal cortex, left superior and middle temporal gyri, and left and right postcentral and angular gyri<sup>81</sup></li> </ul> <p>Remission status at follow-up (18 months to 42 years) predicted by:</p> <ul style="list-style-type: none"> <li>• Acute onset<sup>93</sup> or shorter DUP<sup>50</sup></li> <li>• Higher baseline functioning (C-GAS)<sup>50</sup></li> <li>• No use of cannabis at baseline<sup>94</sup> (although the effect disappeared after controlling for treatment adherence)</li> </ul>	<p>Short-term remission (8 weeks) associated with:</p> <ul style="list-style-type: none"> <li>• Being female<sup>95</sup></li> <li>• Better premorbid adjustment<sup>95</sup></li> </ul> <p>Remission status at follow-up (2 years) associated with:</p> <ul style="list-style-type: none"> <li>• Older age at onset<sup>26</sup></li> <li>• Acute onset<sup>26</sup></li> <li>• Less developmental and educational delays<sup>26</sup></li> <li>• Better premorbid adjustment<sup>26</sup></li> <li>• Less severe negative symptoms and behavioral problems at baseline<sup>26</sup></li> <li>• Higher IQ at baseline<sup>26</sup></li> </ul>
Relapse/readmission	<p>A higher risk of relapse/readmission throughout follow-up predicted by:</p> <ul style="list-style-type: none"> <li>• Being female<sup>96</sup></li> <li>• Decline in social support before first admission<sup>96</sup></li> </ul>	<p>A diagnosis of SSD (versus acute transient psychotic disorders) associated with higher number and longer duration of admissions<sup>24</sup></p> <p>A higher risk for relapse/readmission throughout follow-up associated with:</p> <ul style="list-style-type: none"> <li>• More severe disorganization symptoms at discharge<sup>22</sup></li> <li>• Higher expressed emotion at discharge<sup>97</sup></li> </ul>
Treatment	<p>Treatment adherence predicted by prescription of psychotropic treatment for affective symptoms (mood stabilizer or antidepressant) at baseline<sup>98</sup></p> <p>Quality of psychiatric care: In EOS, lower quality of psychiatric care predicted by delusions at baseline and lower age at onset,<sup>56</sup> in EO-BD predicted by older age at onset<sup>56</sup></p>	<p>Treatment discontinuation for all causes associated with being male<sup>99</sup></p> <p>Higher likelihood of prescription of clozapine associated with longer duration of index hospitalization<sup>21</sup> and being male<sup>21</sup></p>
Insight	<p>In SSD, better insight predicted by shorter DUP, IQ at baseline (different direction of association depending on insight subdomain), and greater left frontal and parietal GM volume at baseline<sup>82</sup></p>	<p>Better insight associated with:</p> <ul style="list-style-type: none"> <li>• Non-SSD diagnosis<sup>82</sup></li> <li>• Better premorbid adjustment<sup>100</sup></li> </ul>

**Table 1.** (Continued)

	Multivariate analyses	Bivariate analyses
Suicidality	In non-SSD, predicted by sex and lower baseline severity of psychotic symptoms <sup>82</sup> Suicide attempt predicted by: <ul style="list-style-type: none"> <li>Greater illness severity at baseline<sup>101</sup></li> <li>More depressive symptoms<sup>87,101</sup> and less severe negative symptoms<sup>102</sup> at FEP</li> </ul>	Completed suicide associated with: <ul style="list-style-type: none"> <li>Diagnosis of schizophrenia (versus BD)<sup>102</sup></li> </ul>
<i>Functional outcomes</i>		
Global functioning	Better global functioning at follow-up predicted by: <ul style="list-style-type: none"> <li>Non-schizophrenia diagnosis<sup>39,103</sup></li> <li>Acute onset<sup>62</sup> and shorter DUP<sup>50</sup></li> <li>Negative family history of non-affective psychosis in EO-SSD<sup>103</sup></li> <li>Absence of abnormal premorbid personality traits<sup>56,73,104</sup></li> <li>Better premorbid adjustment<sup>50</sup> and functioning<sup>27,55,56</sup></li> <li>Better baseline functioning<sup>22,105</sup></li> <li>Lower number of previous hospital admissions<sup>22</sup></li> <li>Less severity of positive symptoms during acute episodes in childhood<sup>86</sup></li> <li>Less severity of negative symptoms at baseline<sup>22,33,55,106</sup> or during acute episodes in childhood<sup>86</sup></li> <li>Less severe behavioral problems at baseline<sup>106</sup></li> <li>Higher IQ in EOP<sup>103</sup> and in EO-BD<sup>56,73</sup></li> <li>Less impairment at discharge from the index hospitalization in EO-SSD<sup>104</sup></li> <li>Better insight at baseline<sup>100</sup></li> </ul>	Better global functioning at follow-up associated with: <ul style="list-style-type: none"> <li>Non-schizophrenia diagnosis<sup>24,47,55,84,87</sup></li> <li>Being female<sup>64</sup></li> <li>Older age at onset in EO-SSD<sup>63,64</sup></li> <li>Acute onset<sup>63,64</sup></li> <li>Negative family history of non-affective psychosis in EO-SSD<sup>64</sup></li> <li>Absence of developmental disorder<sup>64,107</sup></li> <li>Better premorbid adjustment<sup>108</sup> and functioning<sup>63</sup></li> <li>In EOS, more affective symptoms and paranoid subtype<sup>63</sup> (versus worse functioning associated with disorganized subtype)<sup>63</sup></li> <li>Better executive functioning<sup>109</sup> and visual memory<sup>109</sup> at baseline</li> </ul>
Social functioning	Better social functioning predicted by: <ul style="list-style-type: none"> <li>Older age at onset in EOS<sup>104</sup></li> <li>Negative family history of non-affective psychosis in EO-BD<sup>56</sup></li> <li>Lack of abnormal premorbid personality traits<sup>56,104</sup></li> <li>Better social functioning at baseline<sup>28</sup></li> <li>Less severity of negative symptoms at baseline<sup>28</sup></li> <li>Higher baseline processing speed<sup>23</sup></li> <li>Less impairment at discharge from the index hospitalization<sup>56,104</sup></li> </ul>	Better social functioning associated with: <ul style="list-style-type: none"> <li>Non-schizophrenia diagnosis<sup>39,87,92,103</sup></li> <li>Better premorbid adjustment<sup>108,110</sup></li> <li>Lack of abnormal premorbid personality traits<sup>108</sup></li> <li>Better baseline executive functioning<sup>109</sup> visuomotor processing,<sup>109</sup> motor coordination,<sup>109</sup> working memory,<sup>109</sup> and verbal learning<sup>110</sup></li> <li>Being in a romantic relationship negatively associated with a schizophrenia diagnosis (versus acute psychosis) and discharge against medical advice from index hospitalization<sup>21</sup></li> </ul>
Occupational/educational functioning	Better occupational/educational functioning predicted by: <ul style="list-style-type: none"> <li>Older age at onset in EO-SSD<sup>104</sup></li> <li>Negative family history of non-affective psychosis for EO-BD<sup>56</sup></li> <li>Better premorbid functioning<sup>56</sup></li> <li>Absence of abnormal premorbid personality traits in EO-SSD<sup>56,104</sup></li> <li>Shorter length of first admission<sup>30</sup></li> <li>Less impairment at discharge for EO-SSD<sup>56,104,111</sup></li> <li>No use of cannabis at baseline<sup>25</sup></li> </ul>	Better occupational/educational functioning associated with: <ul style="list-style-type: none"> <li>Non-schizophrenia diagnosis<sup>39,48,87,92,103</sup></li> <li>Being female<sup>21</sup></li> <li>Better verbal memory, visuomotor processing, and visual attention at baseline<sup>109</sup></li> <li>Shorter duration of FEP<sup>111</sup></li> <li>Less severe residual symptoms<sup>111</sup> and less impairment<sup>111</sup> at discharge from the index episode</li> </ul>
Disability/dependency	Greater disability or dependency at follow-up predicted by: <ul style="list-style-type: none"> <li>Schizophrenia diagnosis<sup>56</sup></li> <li>Positive family history of non-affective psychosis<sup>56</sup></li> <li>Abnormal premorbid personality traits<sup>56,104</sup></li> <li>Poorer premorbid social adjustment<sup>93</sup></li> <li>More severe positive symptoms,<sup>30</sup> greater impairment,<sup>104</sup> and poorer social competence<sup>30</sup> at discharge from the index hospitalization</li> </ul>	Greater disability or dependency at follow-up associated with: <ul style="list-style-type: none"> <li>More premorbid emotional withdrawal<sup>88</sup></li> <li>Lower age at onset<sup>72</sup></li> <li>Schizophrenia diagnosis,<sup>21,48,103</sup> A diagnosis of schizophrenia has also been associated with lower likelihood of living independently<sup>39,103</sup></li> <li>Premorbid developmental disorder<sup>107</sup></li> <li>Poorer verbal learning, working memory, and attention at baseline<sup>110</sup></li> <li>More severe negative<sup>111</sup> and total<sup>111</sup> symptoms and greater impairment<sup>111</sup> at discharge</li> <li>Longer duration of FEP<sup>111</sup> and of index hospitalization<sup>21</sup></li> </ul>
Quality of life		Better quality of life associated with a non-schizophrenia diagnosis <sup>87</sup>
Composite clinical +functional outcomes		Better outcome (defined as CGAS > 70 and clinical remission) associated with better premorbid adjustment, lower baseline negative and general PANSS, and higher baseline IQ <sup>26</sup>
<i>Cognitive outcomes</i>		
Attention	Better attention at follow-up predicted by: <ul style="list-style-type: none"> <li>Cognitive reserve at baseline<sup>112</sup></li> <li>Higher total antioxidant status at baseline<sup>78</sup></li> </ul>	
Working memory	Better working memory at follow-up predicted by: <ul style="list-style-type: none"> <li>Higher premorbid IQ and cognitive reserve at baseline<sup>112</sup></li> </ul>	
Learning and memory	Better learning and memory at follow-up predicted by: <ul style="list-style-type: none"> <li>Higher total antioxidant status at baseline<sup>78</sup></li> </ul>	Better learning and memory at follow-up associated with: <ul style="list-style-type: none"> <li>Non-schizophrenia diagnosis (although association mediated by higher scores on PANSS)<sup>91</sup></li> </ul>
Executive function	Better executive functioning at follow-up predicted by: <ul style="list-style-type: none"> <li>Better premorbid adjustment<sup>29</sup></li> </ul>	

**Table 1.** (Continued)

	Multivariate analyses	Bivariate analyses
Global cognition	<ul style="list-style-type: none"> <li>• Lower scores in negative symptoms at baseline<sup>29</sup></li> <li>• In SSD, higher total antioxidant status at baseline<sup>78</sup></li> </ul> Improvement in executive functioning throughout follow-up predicted by: <ul style="list-style-type: none"> <li>• Lower negative symptoms at baseline<sup>29</sup></li> <li>• Shorter DUP<sup>29</sup></li> </ul> Better global cognition at follow-up predicted by: <ul style="list-style-type: none"> <li>• Higher total antioxidant status at baseline<sup>78</sup></li> </ul>	
IQ		In SSD, follow-up IQ associated with GM volume at baseline <sup>113</sup>
Neuroimaging outcomes		
Volume change	Greater frontal GM loss and CSF increase as compared with controls in EOS or psychosis NOS but not EO-BD <sup>114</sup> Greater rate of GM loss throughout follow-up predicted by: <ul style="list-style-type: none"> <li>• Baseline symptom severity<sup>115</sup></li> <li>• More premorbid developmental dysfunction<sup>115</sup></li> </ul> Greater frontal, parietal, and temporal GM loss and total CSF volume increase throughout follow-up predicted by lower baseline GSH levels <sup>77</sup>	Greater GM loss throughout follow-up associated with: <ul style="list-style-type: none"> <li>• Being male<sup>116</sup></li> <li>• Baseline symptom severity<sup>116</sup></li> <li>• A diagnosis of COS but not psychosis NOS associated with frontal, temporal, and parietal GM loss<sup>117</sup></li> <li>• Temporal GM loss associated with baseline positive symptom severity<sup>118</sup></li> <li>• Hippocampal volume loss associated with baseline negative and positive symptom severity<sup>118</sup></li> </ul>

Abbreviations: BD, bipolar disorder; C-GAS, Child Global Assessment of Functioning; COS, childhood-onset schizophrenia; CSF, cerebrospinal fluid; DUP, duration of untreated psychosis; EO-BD, early-onset psychotic bipolar disorder; EO-SSD, early-onset schizophrenia spectrum disorders; EOP, early-onset psychosis; EOS, early-onset schizophrenia; FEP, first episode of psychosis; GM, gray matter; GSH, glutathione; IQ, intelligence quotient; NOS, not otherwise specified; PANSS, Positive and Negative Syndrome Scale; SSD, schizophrenia spectrum disorders.

support the continuity between EOP and adult-onset psychosis.<sup>39</sup> However, as children and adolescents seem to present more frequently with poor premorbid adjustment and greater initial negative symptom severity than adults,<sup>43–45</sup> patients with EOP would be at increased risk of poor outcome and should be subject to close monitoring and to early and intensive interventions when required.

The fact that patients with early-onset schizophrenia spectrum disorders usually present with more severe premorbid impairments and initial negative symptoms than other types of EOP<sup>8,11–13</sup> could underlie our finding that a diagnosis of schizophrenia predicts greater disability, worse global functioning, and poorer quality of life at follow-up. That being said, it should also be considered that numerous studies have failed to find a significant association between psychosis diagnostic subgroup and functional<sup>20,33,47,48</sup> or cognitive<sup>49–51</sup> outcomes. In addition to potential methodological issues that could underlie these inconsistent findings, it has been proposed that presenting with psychotic symptoms at a young age may be a common phenotypic manifestation of similar deviant neurodevelopmental trajectories in early-onset schizophrenia spectrum disorders and early-onset psychotic bipolar disorder and that differences between the two disorders may be quantitative rather than qualitative in nature.<sup>52,53</sup> On the basis of shared genetic vulnerability, having additional neurodevelopmental impairments would shift the phenotypic expression toward more severe presentations that would be associated with worse outcome.<sup>54</sup> In keeping with this, poorer outcome would more likely be associated with presence of premorbid impairments or negative symptoms transdiagnostically rather than with a categorical diagnosis of early-onset psychotic bipolar disorder or early-onset schizophrenia spectrum disorders. In fact, when diagnosis, premorbid adjustment and negative symptoms are introduced as independent variables in regression models, premorbid adjustment and baseline negative symptoms are the strongest predictors of functional outcome, accounting together for 55% of the explained variance at 1-year follow-up and for 44% at 2-year follow-up.<sup>55</sup> Along those lines, negative symptoms were found to be stronger predictors of functional outcome and of improvement in executive functioning than diagnosis in a

prospective cohort of first-episode EOP,<sup>29,33</sup> whereas premorbid adjustment was found to be a stronger predictor of functional outcome than diagnosis in a retrospective cohort of EOP.<sup>56</sup> These data would further support the relevance of poorer premorbid adjustment and more prominent negative symptoms as markers of more severe outcome in EOP.

Moreover, the association of a diagnosis of schizophrenia with worse outcome should also be appraised in light of the fact that most EOP studies use a follow-up diagnosis to categorize patients into diagnostic subgroups. This strategy can help more accurately define patient diagnosis as it minimizes the impact of diagnostic instability inherent in first episodes of EOP.<sup>57</sup> However, if a follow-up diagnosis of schizophrenia is used as a predictor of outcome, there is a risk that those patients showing poorer outcome are also those more likely to receive this diagnosis during follow-up.

Insidious onset and longer DUP are well-replicated predictive factors of worse outcome in EOP in keeping with what has been found in adult-onset psychosis samples.<sup>58–61</sup> Indeed, insidious onset is a good predictor of greater illness severity<sup>62</sup> and poorer global functioning<sup>62–64</sup> at follow-up, whereas longer DUP predicts worse clinical, functional, and cognitive outcomes.<sup>29,50</sup> The association between insidious onset and worse outcome may be confounded by the fact that this presentation is also more common in more developmentally impaired patients<sup>65</sup> who present poorer outcomes as mentioned above. This may also be the case for DUP, as longer DUP has also been associated with poorer premorbid adjustment.<sup>66,67</sup> However, premorbid adjustment and DUP have both been found to be independent predictors of 2-year improvement in functioning in patients with a DUP shorter than 6 months.<sup>50</sup> Given that DUP is reported to be longer in EOP than in adult-onset psychosis cases<sup>43,44,68</sup> and that it is a potentially modifiable factor, worldwide mental health policies should give priority to early intervention services for children and adolescents, which have proven to be cost effective in this population.<sup>69</sup> Such interventions should be considered for numerous psychiatric disorders starting in childhood and adolescence, since reducing the duration of episodes at these developmental stages can positively impact mental health in adulthood.<sup>4</sup>

Sex and age at onset have yielded inconsistent associations with outcome in EOP, which contrasts with the classical assumption

tion, based on adult-onset studies, that male sex and earlier age at onset are associated with poorer outcomes.<sup>70,71</sup> The finding of a worse outcome in adult male patients is frequently contaminated by the fact that males usually have an earlier age at onset and insidious onset.<sup>71</sup> In this review, being female was found to be a good predictor of better insight at follow-up and a higher number of readmissions, as well as a significant correlate (by bivariate analyses) of less regional GM loss through follow-up. The lack of a consistent association between sex and outcome in EOP could be due to the fact that females who develop a psychotic disorder during childhood or adolescence probably have a higher load of genetic, neurodevelopmental, or environmental factors leading to significantly earlier onset of the disease in spite of potential protective factors (for example, estrogens). In these individuals, outcome may already be impoverished by the presence of a more severe form of the disorder from the outset. Furthermore, it has also been proposed that prepubertal onset may preclude the protective effect of estrogens on development of the disorder, leading to a more severe course.<sup>71</sup> In this review, lower age at onset was found to predict worse quality of psychiatric care and poorer social, educational, and occupational functioning in some multivariate models. However, it was not consistently reported as a significant predictor of functional and other outcomes in other studies using regression models, nor was it a good correlate in studies using bivariate approaches. A narrow age range in studies exclusively including adolescent-onset cases decreases the capability of detecting a significant effect of age at onset. The effect of age at onset (at least in studies using bivariate comparison) seems to be more marked in schizophrenia samples.<sup>63,64,72</sup> This may be due to the fact that these are more homogeneous samples in which the contribution of age at onset would be more easily detected than in mixed samples with stronger differences in other relevant predictors (negative symptoms, premorbid functioning), which may obscure the predictive value of age at onset.

Among cognitive predictors of clinical outcomes, lower IQ at baseline was found to predict worse functional outcomes, a diagnostic outcome of schizophrenia, and poorer insight at follow-up in multivariate models, whereas its association with other outcomes such as disability was more inconsistent. Interestingly, higher baseline IQ was found to be a good predictor of functional outcome only for early-onset psychotic bipolar disorder patients in one cohort.<sup>56,73</sup> This could be due to a specific effect of IQ in this diagnostic subgroup or to the fact that a higher developmental load in early-onset schizophrenia spectrum disorders may obscure the predictive value of this variable. Other cognitive variables (for example, baseline speed of processing) have been described as good predictors of functional outcomes, but more inconsistently, which highlights the complexity of the interaction between global cognition measures and outcome in EOP and the need to specifically assess the relationship between specific neurocognitive domains and specific dimensions of outcome<sup>17,74</sup> or to develop complex predictive models by combining multiple clinical and neuropsychological variables.<sup>35</sup> Furthermore, the finding of a strong association between cognition and functional outcome in this review is consistent with results in first episodes of adult-onset schizophrenia, in which cognitive variables and negative symptoms have been found to be the main predictors of long-term functional outcome,<sup>74</sup> and points to the potential usefulness of cognitive remediation strategies for improving functional outcome in EOP.<sup>75</sup>

Although biomarker discovery efforts in psychiatry have gained priority in recent years,<sup>76</sup> this review found few studies that focused on the predictive value of biological variables for outcomes in EOP. Lower baseline antioxidant status was found to predict greater loss of GM volume and worse cognitive functioning at follow-up in one cohort.<sup>77,78</sup> These findings provide some support for the role of oxidative stress in EOP<sup>79</sup> warranting further replication. These findings may also point to the potential applicability of antioxidant strategies to the treatment of EOP

patients, as suggested by the promising results of a developmental animal model of schizophrenia indicating that the use of *N*-acetylcysteine can prevent the later expression of schizophrenia-like traits in adulthood.<sup>80</sup> Among neuroimaging markers, cortical thickness and GM volume at baseline in different brain regions were reported to significantly predict remission<sup>81</sup> and insight<sup>82</sup> at follow-up, respectively, in studies using multivariate models. These are also findings with high potential for translational applicability warranting further replication. Even if implementation of biological predictors in psychiatric settings is still a way off, assessment of their predictive value is warranted by complex predictive models in combination with other relevant clinical, functional, and cognitive variables on a subject-by-subject basis using novel multivariate machine-learning methods. This could help design personalized medicine models by stratifying patients according to their risk of poor outcome or treatment response. These models would help determine whether more intensive interventions (for example, earlier initiation of clozapine treatment or more intensive psychosocial support) would be justified for a defined subset of EOP patients, an issue of great clinical and economic importance as this could improve quality of life in patients with EOP and reduce the burden of disease and cost to national health systems.

This work is subject to several caveats. First, differing outcome measures, length of follow-up, outcome measures, and designs make it difficult to compare studies. Many studies used a retrospective design, with retrospective identification of cases and use of clinical records for assessment of baseline variables. The lack of standardized data-recording methods may have led to inaccuracy or inconsistent reporting of different predictors. Furthermore, attrition rates were high in most of the studies, which may have affected the results to some extent, since it is usually difficult to establish whether discontinuation is due to factors such as lack of compliance or more severe course. Although many studies used appropriate statistical methods to identify predictors, most of the older studies provided only descriptive data and bivariate comparisons between potentially relevant variables, which precluded assessing the impact of potential covariates in the results. This is illustrated by studies finding significant results in bivariate comparisons that do not survive regression analyses.<sup>26</sup> That being said, given the scarcity of studies on EOP and relevant outcomes, studies using traditional bivariate comparisons were ultimately included in this review so as to acquire a broader view of the issue. It should also be considered that our findings from multivariate models may have been influenced by the covariates introduced into the models, which differed among studies and were rarely selected systematically. Furthermore, the inclusion of studies using different diagnostic criteria (see Methods) may have also affected our findings to some extent. However, all patients included in this review were diagnosed or re-diagnosed with at least the DSM-III-R, whose diagnostic criteria for psychotic disorders are similar to those of current classification systems. Second, since findings on neurobiological predictors are mostly based on single studies, further replication would be needed to support their predictive value. Third, the exclusion of results based on clinical trials from this review may have prevented us from detecting some significant predictors of treatment response or short-term adherence. For example, data from a 6-month clinical trial found that a better attitude toward antipsychotic medication at a first lifetime psychiatric admission for a first early-onset psychotic episode was significantly related to lower all-cause antipsychotic treatment discontinuation.<sup>46</sup> However, we decided not to include results from clinical trials to ascertain predictors of outcome over the course of EOP not related to specific therapeutic interventions.

These limitations notwithstanding, this is to the best of our knowledge the first systematic review to provide a comprehensive overview of recent studies on predictors of clinical, functional, cognitive, and neurobiological outcomes in EOP. Accurate research

with potential for replication based on long-term longitudinal studies targeting the search for such predictors is needed.<sup>83</sup> This could help identify subjects with EOP at higher risk of poor outcome in whom more intensive and earlier interventions would be warranted. Early intervention services in EOP should aim at shortening DUP and at carefully monitoring patients with poorer adjustment and more severe negative symptoms at first presentation. Novel therapeutic approaches targeting negative and cognitive symptoms are needed to improve the outcome of EOP.

## CONTRIBUTIONS

All authors contributed to the protocol for this work. CMD-C, LP-C, and AR-Q performed the literature review and the selection of references. CMD-C and AR-Q extracted the data. CMD-C and LP-C wrote the first draft of the manuscript, which was subsequently edited by all authors, who contributed to the interpretation of the findings and approved the final version. All authors had full access to the data and take responsibility for their integrity and accuracy.

## COMPETING INTERESTS

The authors declare no conflict of interest.

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