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META-ANALYSIS OPEN ACCESS

Impact of Early Intervention for Early Psychosis on Suicidal Behavior—A Meta-Analysis

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ABSTRACT

Introduction: Early-onset psychotic disorders include the prodromal phase and the first-episode psychosis (FEP). They constitute a high-risk period for suicidal behavior. Early intervention for psychosis (EIP) consists of intervening as early as possible. The effectiveness of early intervention on overall prognosis has been reported in numerous studies, and EIP services are emerging worldwide. Several authors report an improvement in suicidal behavior, but no study has looked at all the data.

Aims of the Study: The aim of work is to study whether early intervention for psychosis has an impact on deaths by suicide and suicide attempts, and study which intervention methods have an impact on suicidal behavior.

Methodology: By respecting the PRISMA criteria, previously declared on PROSPERO, by exploring 5 medical databases (PubMed, Cochrane, PsycINFO, Scopus, Embase), from their creation dates, published until 20/02/2023, in English, we carried out a meta-analysis. The articles selected had to deal with the EIP and deaths by suicide or suicide attempts. Our primary outcome is the deaths by suicide and the secondary outcome the suicide attempt.

Results: The exhaustive search identified a total of 2310 references. Nine articles were included. Their intervention modalities were pharmacotherapy, psychotherapy, case-management, or related services, and psycho-social therapies. Our meta-analysis shows that early intervention for early-onset psychotic disorders is associated with a statistically significant reduction by a third in deaths by suicide (ORa = 0.66 (0.49–0.88), $p = 0.005$) and by a third in suicide attempts (ORa = 0.66 (0.50–0.86), $p = 0.002$), with non-significant heterogeneity. Sensitivity analyses excluding the study with statistical difficulties due to the absence of an event and studies with a high risk of bias point in the same direction, that is a statistically significant reduction and non-significant heterogeneity.

Conclusion: The literature shows that early intervention programs are associated with positive impact on deaths by suicide and suicide attempt. This is the first meta-analysis of early intervention in early psychotic disorders and its impact on suicidal risk. The deployment of EIP should be supported worldwide in order to intervene as early as possible and prevent the risk of suicide.

Trial Registration: PROSPERO CRD42022366976

These results are based on only 9 studies, and there are many biases. Biases related to the absence of randomization, retrospective cohorts, and geographic location (few countries and not all continents are represented).

Summary

- Significant Outcomes
  - Early intervention is associated with a one-third reduction in deaths by suicide and with a one-third reduction in suicide attempts. These associations are statistically significant, with non-significant heterogeneity.
  - All the intervention programs associated with a reduction in suicidal behaviour were composed in this way: pharmacotherapy, psychotherapy, psychosocial therapies, as well as case-management or related device.
- Limitationss
  - These results are based on only 9 studies, and there are many biases. Biases related to the absence of randomization, retrospective cohorts, and geographic location (few countries and not all continents are represented).

1 | Introduction

The lifetime prevalence of all psychotic disorders is 3%. These are disorders involving impaired contact with reality and disorganization, with repercussions on family and socio-professional functioning [1]. The development of psychotic disorders is a dynamic process with different phases [1]. A premorbid phase or vulnerability phase corresponding to the phase without psychotic symptoms, with, for example, a greater likelihood of presenting minor psychomotor and cognitive difficulties. This can then lead to a prodromal phase when psychotic symptoms are subclinical or transitory. The psychotic transition leads to the emergence of the first-episode psychosis (FEP) when psychotic symptoms exceed the clinical threshold. The length of time between the appearance of the first psychotic symptoms and the first contact with care is known as the duration of untreated psychosis (DUP).

It should be noted that there is some debate about the delimitations of the DUP.

This can lead to a chronic phase such as schizophrenia, other chronic psychotic disorders, or mood disorders. In this evolutionary process, the notion of incipient psychotic disorder covers the prodromal phase and the FEP.

Worldwide, 700,000 people die by suicide every year [2] making it a major public health problem with a significant human and economic impact [3].

Regardless of age, gender, or geographical location, psychiatric pathology appears to be the leading risk factor for deaths by suicide and attempted suicides [4]. A psychological autopsy is a post-mortem examination of the psychological state of the deceased patient, documenting the existence of psychiatric disorders and the type of care the patient had received [5]. The data collected by psychological autopsy show that the majority of patients who died by suicide had a psychiatric history [6].

People with schizophrenia have a decreased life expectancy of 13 to 15 years [7]. The most common causes are cardiovascular disease [8] or suicide [9], which is the most important cause of potential years of life lost in schizophrenia [9].

Psychotic disorders lead to suicidal thinking and behavior, with significant treatment implications. Schizophrenia affects 0.7% of the population. Contemporary research studies, on American cohorts for example, indicate that a lifetime modal rate of suicide in individuals with schizophrenia is about 10%. The reported rates of suicide attempts in patients with schizophrenia vary between from 18% to 55% [10]. By comparison, in the general American population, the death by suicide rate is 0.013% per year [11].

In schizophrenia, suicide frequently occurs in the early stages of the illness [12] with an annual incidence 12 times higher than in the general population [13].

This trend is particularly noticeable in the first 2 years after diagnosis [14]. In the first year, there is a 60% increase in the risk of suicide compared to the other phases [15].

Suicidality is also marked in early psychotic disorders: the prevalence of suicidal ideation is 40% [16], of suicide attempt from 8.5% to 31% [17], and of deaths by suicide from 0.4% to 4.29% [18]. It should also be noted that early-onset psychotic disorders affect a young population, most often aged between 15 and 35, and suicide is the second leading cause of death among young people aged between 10 and 34, after road accident trauma [19]. Numerous risk factors have been identified in patients with early psychosis [20].

The systematic review by Coentre et al. on suicidal behavior in FEP [21] identified several risk factors, the most consistent of which were a history of suicidal ideation, depressive symptoms, and a prolongation of the DUP [22]. Early intervention makes it possible to act at the earliest possible stage [23]. The effectiveness of early intervention on the overall prognosis of the condition has been demonstrated in numerous studies. With regard to suicidal behavior in particular, several authors have discussed the effectiveness of early intervention [24–26].

These authors state that the findings in the literature show that when people are educated about psychosis, they are more likely to seek treatment when symptoms occur. This finding underscores the potential utility of psychoeducational approaches leading to decreased morbidity and mortality. The findings also demonstrate that individuals who are less symptomatic and have a better quality of life are less likely to be victims of suicidal behavior. These studies highlight the need for early interventions in psychosis.

2 | Aims of the Study

The aims of this study are to examine whether early intervention for early-onset psychotic disorders has an impact on rates of death by suicide and suicide attempts, and to determine which intervention methods have an impact on suicidal behavior.

3 | Methodology

We carried out a meta-analysis according to the PRISMA criteria [27].

This study was submitted to the PROSPERO international prospective registry, identifier CRD42022366976.

3.1 | Eligibility Criteria

Controlled studies (with a control group without early intervention) dealing with early intervention in early psychotic disorders studying deaths by suicide and suicide attempts were selected.

Early intervention refers to all types of intervention (pharmacotherapy, psychotherapy, case-management) carried out on subjects with early-onset psychotic disorders.

Early psychosis refers to any person in the prodromal phase or presenting a FEP.

Uncontrolled trials, those dealing with suicidal behavior in psychotic disorders outside the early phase, studies of early intervention in early psychotic disorders but not dealing with suicidal behavior, and studies with other intervention modalities as a control group were not included.

The data relating to these results will be subjected to meta-analysis. As recommended in the literature [28, 29], Figure 1 shows the logic model for the review.

3.2 | Research Strategy

We searched the scientific databases PubMed, Cochrane, PsycINFO, Scopus, Embase, without restriction of publication date, from their creation dates until 20/02/2023, in English. The keywords were chosen on the basis of terms that could designate early psychotic disorders, whether in the prodromal phase or the FEP. The following bibliographic search terms were used ((early psychosis) OR (prodromal schizophrenia) OR (at-risk for psychosis) OR (at-risk mental state) OR (high risk state for psychosis) OR (clinical high risk for psychosis) OR (CHR) OR (ultra-high risk for psychosis) OR (UHR) OR (first episode psychosis) OR (FEP)) AND (early intervention) AND (suicid*).

The Endnote bibliographic management software for bibliography management was used.

3.3 | Data Extraction and Selection

The data was extracted by two independent operators, ET and AB. Any discrepancies were resolved by discussion until a consensus was reached with a third evaluator.

All the references found were imported into Endnote.

Duplicates have not been included.

As regards the search strategy, an initial selection was made after reading the titles and abstracts. This initial selection led to the retrieval of full texts, with articles without full text (such as conference abstracts, for example) not included.

The database searches were supplemented by bibliographical references of interest in the texts studied.

Data extraction was carried out in a standardized manner by two examiners and included:

_publication details (study authors, year of publication).

_the characteristics of the study (design, country, sample size).

_the characteristics of the intervention (method of implementation, duration of the program, content, and components, suicidal behaviors targeted).

_criteria for assessing interest (death by suicide, suicide attempt).

_the measurement tools used (objective measurements).

_details of the control group.

_data to assess the risk of bias in each study were extracted.

If necessary, the corresponding author of the included studies was contacted by e-mail to obtain any required data not included in the published article.

The data were entered into Review Manager (RevMan) Web 2022 software [30].

3.4 | Judging Criteria

The primary outcome was the impact of the EIP on deaths by suicide. The secondary outcome was the impact of the EIP on suicide attempt.

Data on outcomes at any point during follow-up were extracted and summarized for all eligible studies.

3.5 | Risk of Bias

Two reviewers, JB and ET, independently assessed the risk of bias of the included studies. Any discrepancies were resolved until a consensus was reached by a third reviewer.

For randomized controlled trials we used the Cochrane risk-of-bias tool for randomized trials (RoB 2) [31], for non-randomized controlled studies we used Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) [32].

The results of the bias analysis were entered into Review Manager (RevMan) Web 2022 [30] and presented in the form of a risk of bias summary and a forest plot.

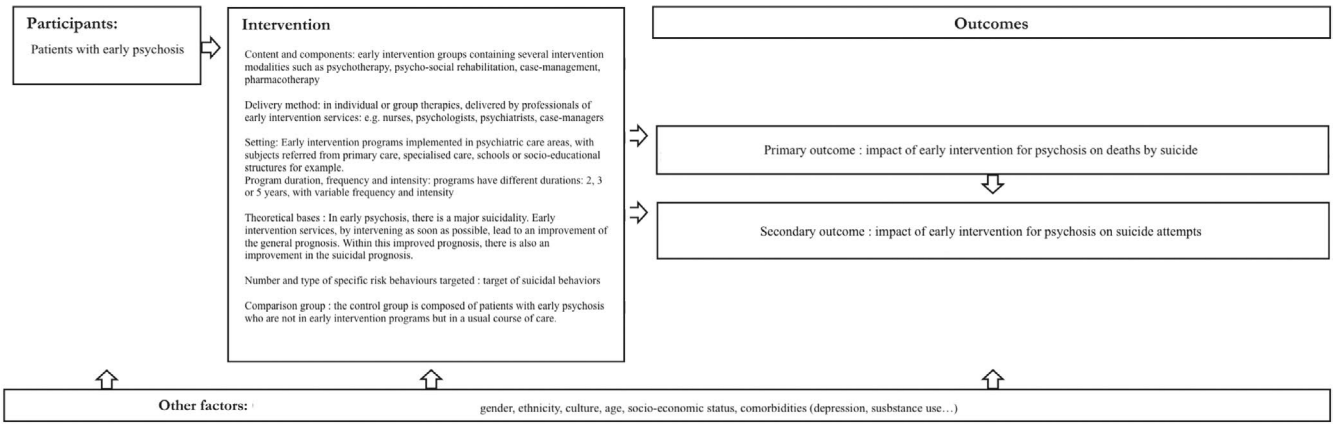

FIGURE 1 | Logic model: Impact of early intervention in early psychotic disorders on deaths by suicide and suicide attempts.

3.6 | Statistics

For each study, we recorded the number of deaths by suicide and suicide attempts in each group (EIP group and control group), and subject these data to statistical analysis.

The effect of EIP on the incidence of deaths by suicide and suicide attempts was the subject of a meta-analysis. This therapeutic effect was summarized by an odds ratio (OR), adjusted for the different studies (each study constituted a group), estimated by a fixed-effects model, and presented with a 95% confidence interval. Statistical significance was achieved if the p-value of the Mantel–Haenszel test was less than 5%.

For each individual study, an OR was estimated with a 95% confidence interval.

Statistical heterogeneity was summarized by the I2 statistic, considered moderate if close to 50%. This heterogeneity was statistically significant if the Chi2 test produced a *p* value of less than 5%.

The meta-analysis was carried out using Review Manager Web 2022 software [30].

A sensitivity analysis was performed for the problematic values (event values equal to 0), and another sensitivity analysis was performed excluding studies with a high risk of bias.

4 | Results

The results of the search are summarized in the Figure 2. The exhaustive search identified a total of 2310 references.

The search for duplicates (automated by endnote and then manually to complete the search) resulted in the non-inclusion of 740 references.

After reading the 1570 titles and abstracts, 97 references were selected.

Of these 97 references, 24 references that did not contain a full text but only an abstract (such as conference abstracts) and 1 article in a language other than English were not selected.

Of the 72 remaining references, we excluded 65 and retained 7.

The bibliographic references were used and 18 articles were selected. After reading the full texts of these 18 articles, 2 were included and 16 excluded.

For clarification, in the study by Anderson et al. 2018, the evolution of deaths by suicide and suicide attempts was specified with a survival analysis, but their exact numbers were not specified. After writing to the author, she informed us that in Ontario when the rate was less than 6, it was not legally communicable. This study was excluded due to the absence of the number of deaths by suicide and suicide attempts.

In the article by Chan et al. 2015, we contacted the author who was able to provide us with the missing event rates.

The studies of Nordentoft et al. 2002, Petersen et al. 2005, and Bertelsen et al. 2007, were based on the same sample. The methodology being comparable but the first study being at 1 year, the second at 2 years, and the last at 5 years, we have therefore kept only the data from Bertelsen et al. 2007.

We initially included 9 studies. They include 3 randomized controlled trials and 6 non-randomized controlled trials; the studies come from six countries: Hong Kong [3], Denmark [2], United Kingdom [1], Norway [1], Canada [1], Australia [1].

The 9 trials had an intervention group with an early intervention program, and a control group. In the control group, subjects received standard treatment usually at a community mental health center. The control group was carried out prospectively in the three randomized studies (Petersen et al. 2005, Grawe et al. 2006, Bertelsen et al. 2007) and in two other studies (Harris et al. 2008, Agius et al. 2007). The other four studies (Chen et al. 2011, Chan et al. 2015, Randall et al. 2016, Chan et al. 2018) used a historical control cohort, in the years immediately prior to the start of the program.

The characteristics of the studies are presented in the Table 1.

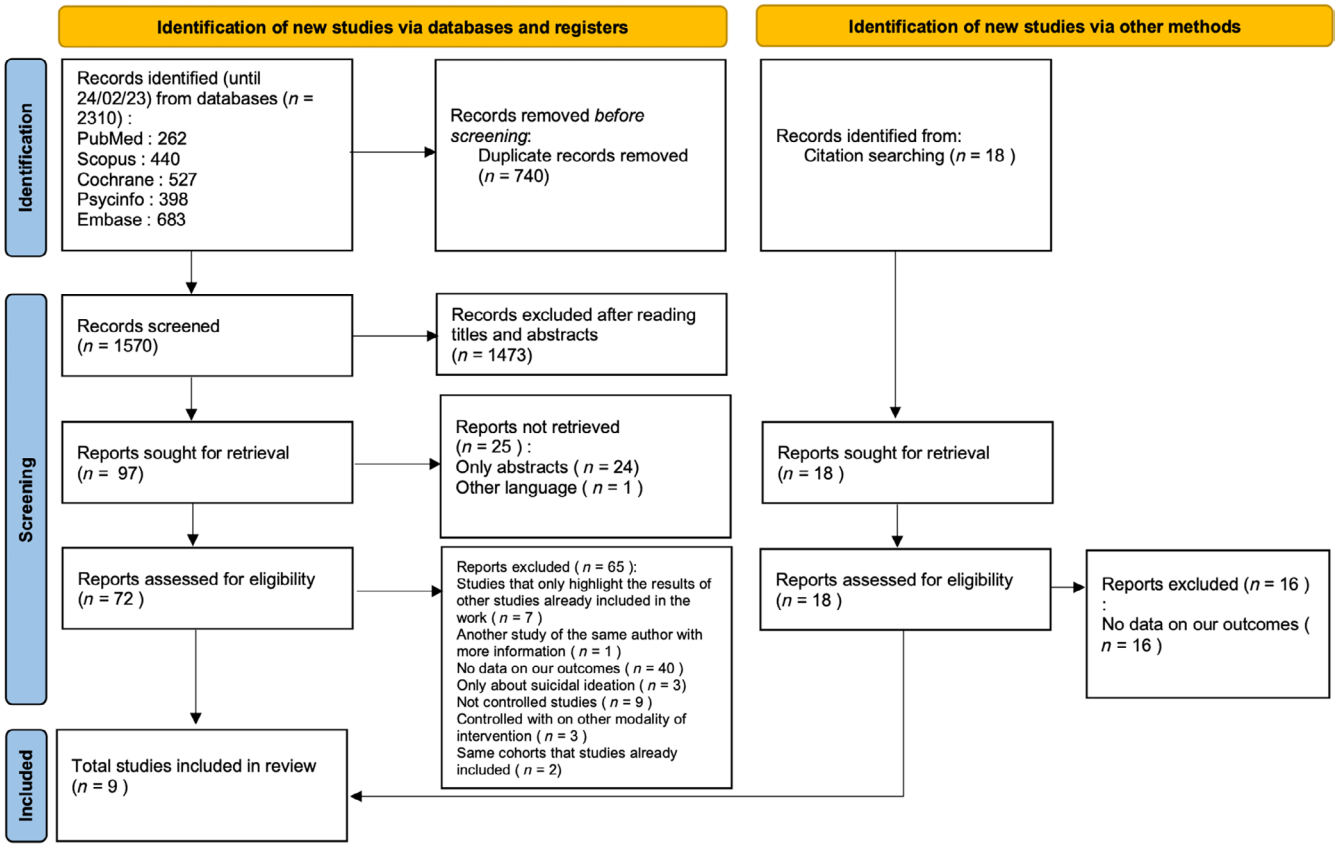

FIGURE 2 | Flow chart.

Of the nine studies included, five refer to deaths by suicide. The results for the primary outcome of death by suicide are summarized in the Figure 3.

In these five studies, there were a total of 68 deaths by suicide out of 2881 patients in the intervention group, compared with 218 deaths by suicide out of 8356 patients in the control group.

We thus see that the EIP was associated with a reduction in deaths by suicide with an ORa = 0.66 (0.49–0.88), or a one-third reduction, with a $p = 0.005$. The heterogeneity of the therapeutic effect between studies was $I^2 = 51\%$, not significant ($p = 0.09$).

In the study by Harris et al. 2008, at 8.5 years follow-up, 21 deaths occurred out of 1141 patients in the intervention group. Of these 21, only 8 (38%) were last seen as part of the program, suggesting that suicide tends to occur beyond the period of specialized treatment [33].

Take-home messages: Early intervention is associated with a one-third reduction in deaths by suicide. This association is statistically significant, with non-significant heterogeneity.

Of the nine studies included, six refer to suicide attempts. The results for the secondary outcome of suicide attempt are summarized in the Figure 4.

In six studies, a total of 102 suicide attempts were made by 1459 patients in the intervention group, compared with 150 suicide attempts by 1651 patients in the control group.

We thus see that the EIP was associated with a reduction of suicide attempts with an ORa = 0.66 (0.50–0.86), or a one-third reduction, with a $p = 0.002$. The heterogeneity of the therapeutic effect between studies was low with an $I^2 = 28\%$, not significant ($p = 0.23$).

In the study by Randall et al. the reduction in the suicide attempts rate remained significant post-program over several years, with a hazard ratio of 0.39 [41].

Take-home messages: Early intervention is associated with a one-third reduction in suicide attempts. This association is statistically significant, with non-significant heterogeneity.

4.1 | Bias

For our 3 randomized controlled trials (Bertelsen et al. 2007, Petersen et al. 2005, Grawe et al. 2006) we used the Cochrane risk-of-bias tool for randomized trials (RoB 2) [31], for our 6 non-randomized controlled studies we used Risk Of Bias In Non-randomized Studies—of Interventions (ROBINS-I) [32]. The bias are summarized in the Figure 5. Two studies have a global low risk of bias, five studies have a global moderate risk of bias, and two studies have a global high risk of bias.

TABLE 1 | Studies included and their characteristics.

Authors and year of publication	Study	Country	Sample size	Affection	Type of study	Control group	Duration of study (years)	Risk of bias	Data extracted on our primary endpoints
Harris et al. 2008 [33]	EPPIC	Australia	7760	FEP	Retrospective cohort	Yes	8.5	Moderate (ROBINS-I)	During follow-up, 154 suicides, 21 in IG (/1141), versus 133 in CG (/6619). 10 occurred before 3 years of admission; versus 97 5 between 3 and 4.5 years; versus 20 6 after 4.5 years; versus 16 **On analysis (Cox model) adjusted, nearly half as many of suicides in IG within 3 years of admission (secondary endpoint), HR = 0.51 (95% CI 0.27 to 0.99), p = 0.048.** However, no decrease in suicides over the 8.5 years of follow-up (primary endpoint) The cumulative suicide rate is At the end of the 1st year: 0.6% in the IG versus 0.7%. After 3 years: 0.9% versus 1.6%. After 5 years: 2.2% versus 2.3%. During the follow-up period: 3.8% versus 4.2%. Over the duration of follow-up, no significant difference between the 2 groups (logrank c2 = 0.04, d.f. = 1, $p = 0.84$).
Bertelsen et al. 2007 [34]	OPUS	Denmark	547	FEP	RCT	Yes	5	Low (RoB 2)	SA decrease at 1 and 2 years. At 5 years, there were 7 suicides in the IG, compared with 4 in the CG. In the 5-year follow-up survival analysis, regarding being in the CG with usual care, the OR was 1.02 (0.2–5) for suicide.
Petersen et al. 2005 [35]	OPUS	Denmark	547	FEP	RCT	Yes	2	High (RoB 2)	SA: At 2 years, 8 (IG) versus 10 (CG), OR = 0.8 (0.4 to 1.7), $p = 0.5$. Suicides: At 2 years, 1 (IG) versus 4 (CG)

(Continues)

TABLE 1 | (Continued)

Authors and year of publication	Study	Country	Sample size	Affection	Type of study	Control group	Duration of study (years)	Risk of bias	Data extracted on our primary endpoints
Chen et al. 2011 [36]	EASY	Hong-Kong	1400	FEP	Controlled historical study	Yes	3	Moderate (ROBINS-I)	**SA at 3 years 65 subjects (9.3%) (IG) versus 80 (11.4%) (CG), $\chi 2/t = 1.73$, $p = 0.19$. Suicides: At 3 years, 7 (IG) versus 20 (CG), HR 95% CI = 0.32 (0.13–0.75) (Cox regression), p = 0AUTHOR: Please note that leading zeroes have been added for decimal values in accordance with journal style. Please check and approve..009. By Kaplan–Meier method, lower estimate suicides in IG 1.1% (95% CI 0.27%–1.95%) versus 3.4% (95% CI 1.9%–4.9%), $\chi 2 = 7.64$, p = 0.006, by log-rank. Secondary analysis incorporating 2nd-generation antipsychotic drug use as a covariate, performed only in patients who were taking it, significance maintained.**
Chan et al. 2015 [37]	EASY	Hong-Kong	296	FEP	Controlled historical study	Yes	10	Moderate (ROBINS-I)	**Decrease in SA at 10 years, $\chi 2 = 11.47$, df = 1, $p = 0.001$** Suicides: 6 patients (4.1%)(IG) vs. 15 (10.3%)(CG)
Chan et al. 2018 [38]	EASY	Hong-Kong	1234	FEP	Controlled historical study	Yes	12	Moderate (ROBINS-I)	**At 12 years, lower suicides in IG: 27 (4.4%), versus 46 (7.5%) (McNemar's $\chi 2 = 5.55$, $p = 0.02$)** Lower standardized mortality index for suicide in the IG: 28.01 (95% CI, 18.84–40.19), versus 44.66 (95% CI, 33.08–59.06) **Better suicide survival rate in the IG (HR, 0.57; 95% CI, 0.36–0.91; $p = 0.02$)**
Grawe et al. 2006 [39]	*	Norway	50	Schizophrenic disorders < 2 years	RCT	Yes	2	Low (RoB 2)	**Decrease in a composite clinical score of good prognosis at 2 years including: occurrence of SA or suicide, but also hospital admissions, a minor or major psychotic episode, persistence of psychotic symptoms, poor compliance with treatment. 53% of patients in the intervention group had a good prognosis compared with 25% in the standard group, $\chi 2 = 4.96$, $p < 0.05$.**
Agius et al. 2007 [40]	*	United Kingdom	144	FEP	Controlled trial	Yes	3	Serious (ROBINS-I)	SA at 3 years, 4 in the IG versus 8 in the CG.

(Continues)

TABLE 1 | (Continued)

Authors and year of publication	Study	Country	Sample size	Affection	Type of study	Control group	Duration of study (years)	Risk of bias	Data extracted on our primary endpoints
Randall et al. 2016 [41]	EPPIS	Canada	693	FEP	Controlled trial	Yes	≥ 2	Moderate (ROBINS-I)	SA: There was no SA during the program in the intervention group, and 2.7% (12 subjects) in the control group. At 2 years post-program 1.4% (exact number of subjects censored) of SA in the intervention group versus 1.8% (8 subjects). In total post-program (average of 3.1 years for the intervention group and 10.2 years for the control group), there were 1.4% of SA in the intervention group (exact number of subjects censored) versus 8% (36 subjects). In the post-program period, suicidal events were lower in the EPPIS program (HR = 0.39, 95% CI = 0.17 to 0.94). Suicides: No suicide in the IG during the program, number of deaths in the CG not specified. In the post-program period, there were no suicide in the intervention group, less than 5 suicides in the CG (exact number of subjects censored). **Statistically significant difference during the program (Pearson Chi2, $p < 0.0001$) in favor of the intervention group for suicidal events (statistical test performed on the SA + suicide criterion)**.

Note: Statistically significant data in bold. *No data.
Abbreviations: CG: control group, EI: early intervention, FEP: first episode psychosis, IG: intervention group, NA: not applicable, RCT: randomized controlled trial, SA: suicide attempt, SI: suicidal ideation.

4.2 | Sensitivity Analysis

Considering a meta-analysis of x studies, when the judgement criterion is dichotomous (binary) the results of each study can be presented by a 2*2 table giving the number of participants who had or did not have the event in the two groups. In the intervention group, a is the number of events and b the number of non-events, and in the control group c the number of events and d the number of non-events.

The OR for each study is thus given by the calculation OR = (a*d)/(b*c), with the calculation for the standard deviation (from its logarithm) as specified in the Formula (1) [42].

$$SE\{\ln(OR_i)\} = \sqrt{\frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}} \quad (1)$$

4.2.1 | Formula 1 Calculation of the Standard Deviation

The latter calculation is impossible in the event of an event equal to 0 (regardless of the group concerned). In the study of suicide attempt, the Randall et al. 2016 study did not show any events in the intervention group. In this case, the RevMan software uses a formula to produce an OR by adding 0.5 to all cells (a,b,c,d) [30]. Given this unjustified methodological aspect, we performed a sensitivity analysis excluding this study. The purpose of this sensitivity analysis was to test the robustness of the study's conclusions to the statistical choices made.

The sensitivity analysis results for the secondary outcome of suicide attempt are summarized in the Figure 6.

In five studies, there were a total of 102 suicide attempts out of 1215 patients in the intervention group, compared with 138 suicide attempts out of 1202 patients in the control group.

We thus see that the EIP was associated to a reduction in suicide attempts with an ORa = 0.70 (0.53–0.92) with a $p = 0.02$. The heterogeneity of the therapeutic effect between studies was low with an $I^2 = 9\%$, non-significant ($p = 0.35$).

We included six studies in the main analysis (Figure 4), of which the studies of Agius et al. 2007 and Petersen et al. 2005 had a high risk of bias. We therefore performed a second sensitivity analysis, excluding these two studies with a high risk of bias, as shown in the Figure 7.

In four studies, there were a total of 90 suicide attempts out of 1122 patients in the intervention group, compared with 132 suicide attempts out of 1317 patients in the control group.

We can see that the EIP was associated to a reduction in suicide attempts with an ORa = 0.66 (0.50–0.88), with a $p = 0.005$. The heterogeneity of the therapeutic effect between studies was $I^2 = 54\%$, non-significant ($p = 0.09$).

4.3 | Methods of Intervention

We studied the intervention modalities of our 10 studies, that is the EPPIC, EASY, OPUS, EPPIS programs (Randall et al., 2016), as well as those delivered in the studies by Agius et al. 2007 and Grawe et al. 2006.

Our finding is that all the programs consisted of the following means: pharmacotherapy, psychotherapy, psycho-social therapies, as well as case-management or related device (care coordinator, keyworker, team member in charge of coordination...).

However, within these similar approaches, there are naturally differences, for example in the nature of the psychosocial therapies, or of the case-management. Indeed, the case-load is a maximum of 12 patients in the OPUS program [34, 35], but 80 patients in the EASY program [37]. Nonetheless, these differences do not compromise the comparability of the studies for the

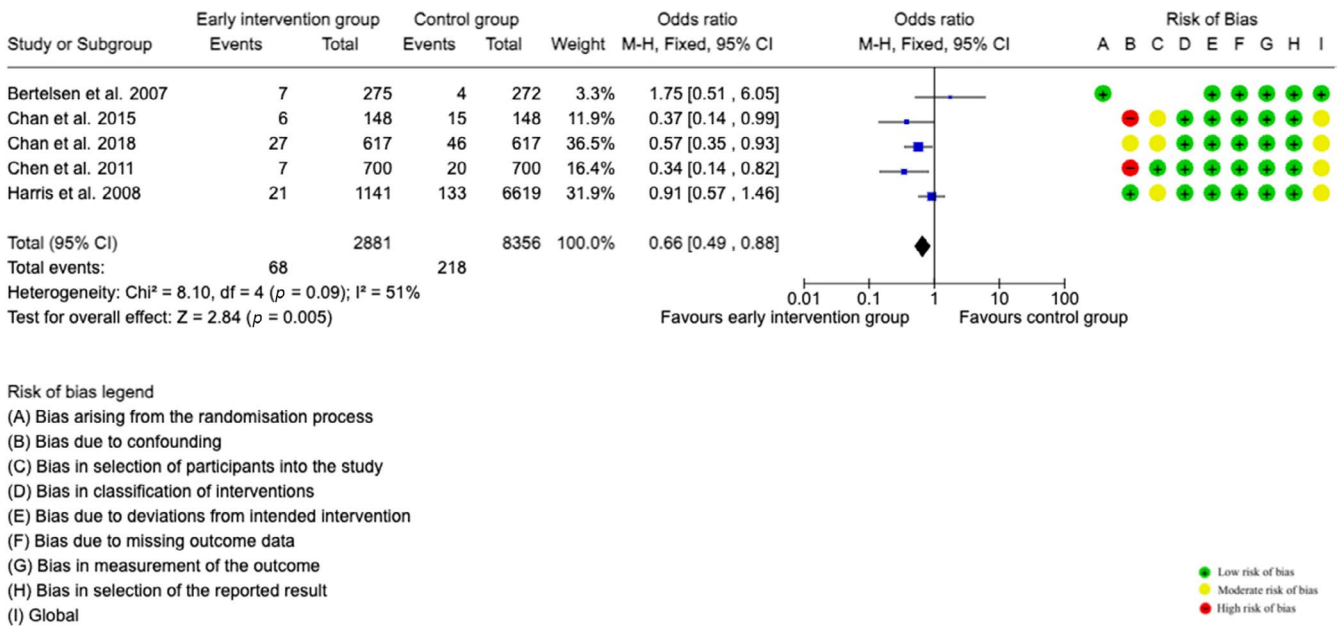

FIGURE 3 | Early intervention in early psychotic disorders and deaths by suicide.

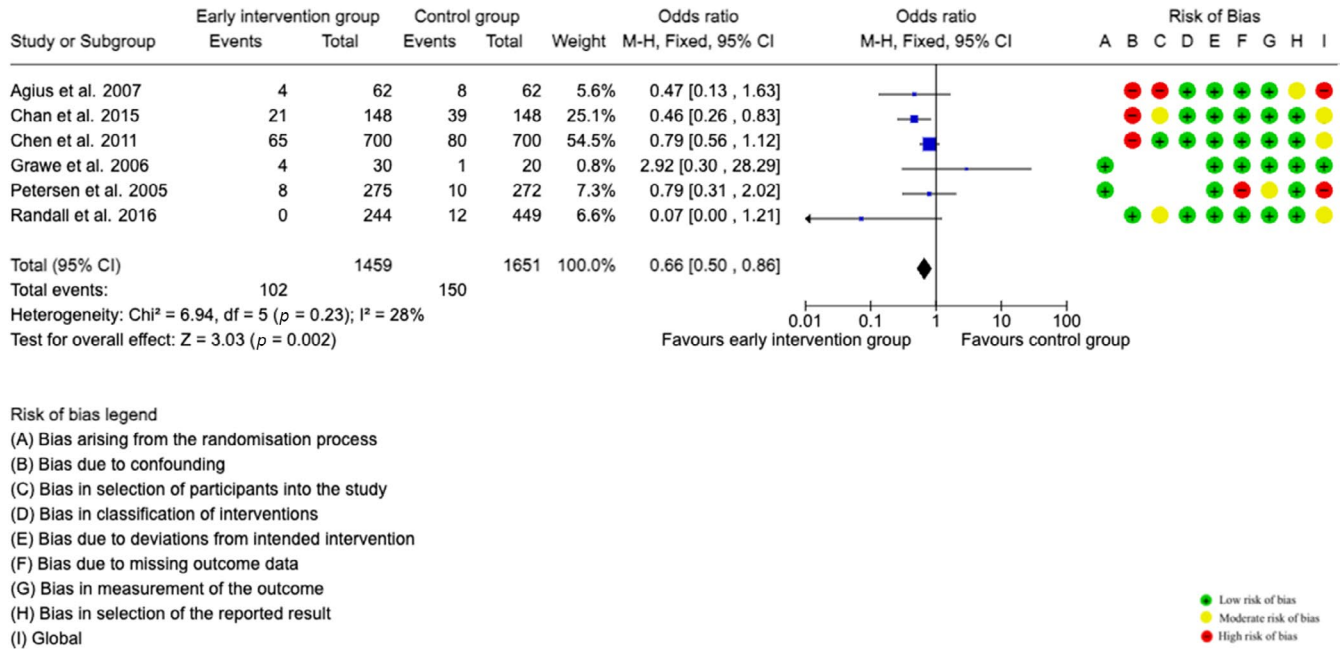

FIGURE 4 | Early intervention in early psychotic disorders and suicide attempts.

statistical analysis, our I^2 heterogeneity is non-significant in all our analyses.

> Take-home messages: All the intervention programs associated with a reduction in suicidal behavior were composed in this way: pharmacotherapy, psychotherapy, psycho-social therapies, as well as case-management or related device.

5 | Discussion

Our findings are major. We have shown statistically that in a disorder as frequent as early-onset psychotic disorder, marked by such a high prevalence of suicidal behavior, a dramatic consequence of mortality, that early intervention is associated with a statistically significant reduction by a third in deaths by suicide and by a third in suicide attempts.

Our study is the first meta-analysis on this subject. It highlights the importance of developing early intervention services.

For statistical reasons, we have only included controlled studies in our analysis. In uncontrolled studies, that is with only one group of subjects receiving early intervention, we observed a reduction in suicidal behavior too.

In Portugal, Coentre et al. 2021 [18] observed a statistically significant decrease in the number of SA at 1 year from 5.9% to 1.7% in their intervention program.

Numerous other studies in which there was no statistical analysis, show a reduction in SA over time in the intervention group (as in the study by Power et al. 2003 [43], with a reduction of SA at 10 weeks) or lower SA rates than expected from the literature (as in the study by Addington et al. 2004, where the SA rate was 2.9%).

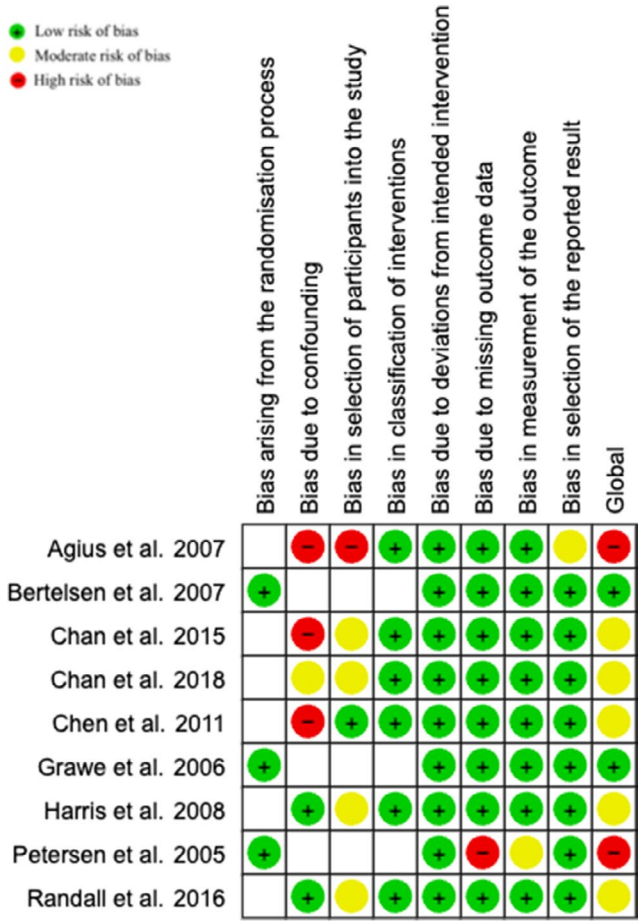

FIGURE 5 | Bias.

This is also the case for deaths by suicide: although there was no statistical analysis in these studies, rates were lower than expected in the literature, with, for example, no suicides during

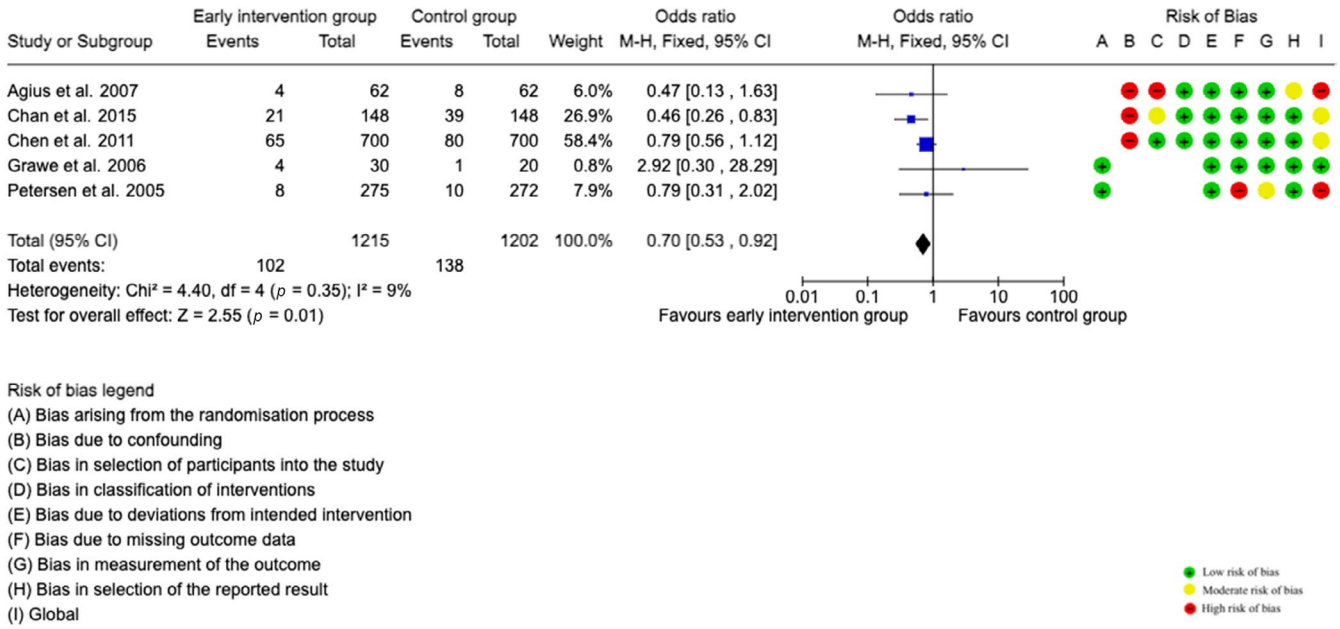

FIGURE 6 | Early intervention in early psychotic disorders and suicide attempts, sensitivity analysis.

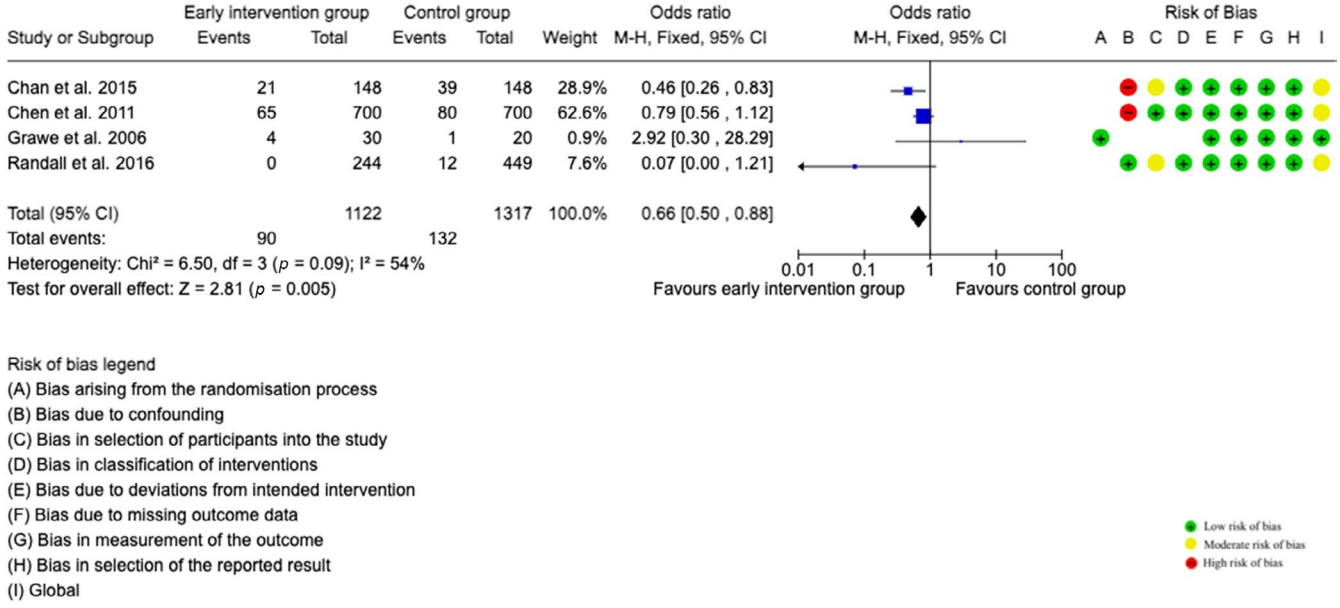

FIGURE 7 | Early intervention in early psychotic disorders and suicide attempts, sensitivity analysis 2.

5 years of follow-up in the study by Iyer et al. 2021, or a rate of 0.4% in the study by Addington et al. 2004 [44].

Our meta-analysis as outcomes deaths by suicide or suicide attempts.

It's interesting to note that the literature also shows a positive effect on suicidal ideation (SI).

In the Nordentoft et al. 2002 study [45], for example, we observed a reduction in SI with method in the last week: 7% in the intervention group and 9.6% in the control group at 1-year follow-up. Nevertheless, measurement instruments differed in studies: BPRS (Brief Psychiatric Rating Scale), BDI-II (Beck Depression Inventory) or SIQ (Suicidal Ideation Questionnaire), for example. On the other hand, other variations were encountered such as whether or not suicidal ideation have a method, and temporality (during the study period, or the last week, for example). The diversity of SI measures and scales used, compromises the homogeneity of these results, and means that this criterion cannot be meta-analyzed at present. It would be appropriate to universalize the measures used in different studies, so as to be able to carry out a meta-analysis on this subject in the future.

5.1 | Strengths and Limitations

We processed 5 major databases with over 2000 articles searched, using key search words covering the entire spectrum of the prodromal phase or FEP, with studies published

up to 20/02/2023, and searched the bibliographic references of the articles studied.

The methodology was rigorous, in line with that of systematic literature reviews, and followed the PRISMA recommendations. It was previously registered with PROSPERO, the international prospective register.

Although randomized controlled trials provide the highest level of scientific evidence, the low incidence of suicidal events explains the difficulty of carrying out this type of study, where large samples would be required. In fact, in the articles included, there are a large number of retrospective cohorts. This does, however, give rise to the selection biases inherent in retrospective cohorts, such as the allocation of control groups in different geographical areas, as developed by Harris et al. [33]. It is notable that some of the historical cohort data used in the Hong Kong studies use control data from the late 1990s, when an economic collapse occurred in Southeast Asia [15]. Nevertheless, to minimize the potential cohort effects, samples were chosen with close temporal proximity in the four studies with historical cohorts [36–38, 41].

It is important to note that two studies results were unfavorable in the intervention group, one for deaths by suicide [34] and one for suicide attempt [39]. In the two cases, no statistical tests had been carried out in the studies, so the meta-analysis shows that despite these unfavorable events, the efficacy is in favor of the intervention.

In the case of suicide attempt, it is important to take account of the reporting bias likely to affect non-medicalized suicide attempts.

Another measurement bias is that of differentiating between deaths by suicide and deaths from any cause, which can sometimes be complicated. The differences between states in the rates of suicide and violent death of undetermined intent can be explained, in part, by the different procedures and practices for investigating, recording, and coding these deaths [46].

Another important factor to take into account is that a certain number of suicides are not known from national death statistics. In particular, some are recorded as unknown causes of death or violent deaths whose intention is not determined. The underestimation of the number of deaths by suicide [47] is a measurement bias in our review.

As mentioned in the introduction, there is disagreement about the end of DUP. Some authors stop it at the first contact with psychiatric care, others at the first prescription of antipsychotics, which can also be made by the general practitioner, still others at the start of EIP or antipsychotics at adequate doses for an adequate period of time. There are many different methods for assessing DUP, and their reliability remains difficult to determine [48].

These different means of measuring DUP thus constitute an element of heterogeneity between studies.

We can also assume that the different lengths of intervention and intervention methods will have a different influence on suicidal behavior, and thus constitute a bias.

Despite the extension of our key words to the prodromal phase, almost all the studies deal with a FEP population. The data should therefore be treated with caution when extrapolating to the prodromal phase and thus to the entire phase of onset of psychotic disorders. In the prodromal phase, the symptomatology is sub-clinical and these samples tend to have many comorbid diagnoses and a high false positive rate that make comparability with FEP challenging [49]. Further studies are needed to examine this population in the field of suicidology in early intervention.

Another selection bias is the failure in the vast majority of studies to differentiate between affective and non-affective psychoses. It should be remembered that there is diagnostic instability and that a FEP may lead to the onset of a schizophrenic disorder, but also to that of a mood disorder. In addition, the affective nature of psychosis may constitute an exclusion criterion in certain studies. This non-differentiation may therefore be problematic and have repercussions on the homogeneity of the results [19].

The relationship between the EIP and the outcome measures is subject to performance bias, as none of the studies were blinded. Nevertheless, we can emphasize the difficulty of conducting this type of blind program.

Our methodology includes several selection biases:

We explored 5 databases: PubMed, Cochrane, PsycINFO, Scopus, Embase, and did not process all the other medical databases, so relevant articles may not have been selected.

On the other hand, publication bias must be taken into account: studies on the subject may have been carried out but not published by the authors, which may overestimate the effect of the EIP on suicidal behavior.

The fact that we have limited the articles to the English language is also a limitation, however only one article in Dutch has been excluded for this reason.

The 9 studies included in the first review come from just six countries.

America is only represented by Canada, Asia by Hong Kong, Oceania by Australia, and no studies have been carried out in Africa.

Europe is the most represented continent, but only the northern countries are represented, with Denmark, Norway and the United Kingdom.

In fact, the data in this review must take account of their origin and the ethnopsychiatric dimension must be taken into account in the field of suicidology, therefore, this study cannot be extrapolated to the world entire population.

5.2 | Methods of Intervention

Case management is defined by McGorry as the centerpiece of early intervention programs for early psychotic disorders [50].

The quality of the relationship between the clinician and the patient is crucial for treatment. For this, the work of the case manager is essential and indispensable since he/she is in close contact with the patient and the professionals, guarantees the organization and the good articulation of the care, ensures that the care is carried out in an adapted manner and listens to the patient and his/her family. The case manager is proactive, supports the demand, has a function of organization and coordination of care [51]. The case manager must be able to create a genuine contact with the patient, respect the patient's experiences and concerns, and support the patient in his or her attempts to come to terms with reality. The relationship is facilitated if the case manager is introduced very early in the treatment, or even during the initial assessment. The case manager should play a central role and should remain involved with the patient and the family.

In the literature, almost all early intervention programs include pharmacotherapy, psychotherapy, and psycho-social therapies. Case-management or related services are not always found. Nevertheless, it is interesting and extremely important to point out that study with data and statistics that could be used in our meta-analysis included case-management or a related device. The association observed between EIP and a reduction in suicidal behavior is present in the case of the following interventions: pharmacotherapy, psychotherapy, psycho-social therapies, case-management or related services; this aspect could be an orientation for the constitution of future programs to have an impact on suicidal behavior.

5.3 | Impact on Public Health

Suicidal behavior is associated with serious consequences, the most notable being premature death by suicide, but there is also a high risk of premature death from other causes such as homicide, accidental death, cardiovascular or respiratory diseases [23]. They are also associated with a socio-professional impact, since they lead to a lower rate of employment, and have repercussions on the social, friendly, and family environment [23]. Thus, if early intervention has an impact on the patient's suicidal behavior, but also on all the other consequences it can have [23] the impact would therefore be broader.

Beyond death by suicide, there is a "continuum" [52] in which the author identifies those at risk (defined as anyone who knows or identifies someone who has committed suicide), those affected and those in mourning. In the United States, for every death by suicide, 135 people are said to be exposed [52]. They are more likely to have suicidal thoughts (9% compared with 5% of those not exposed to suicide) and are twice as likely to have scores suggestive of depression or anxiety disorder [53].

A number of programs includes the family in early intervention, either individually or in multi-family group workshops. The OPUS program for example, offers multi-family groups with a problem-solving approach in which suicidal ideation and behavior are also addressed.

6 | Conclusion

Our meta-analysis shows that early intervention for psychosis is associated with a statistically significant reduction by a third in deaths by suicide and by a third in suicide attempts, with non-significant heterogeneity. Sensitivity analyses excluding statistical difficulties due to the absence of an event and studies with a high risk of bias point in the same direction, that is a statistically significant reduction and non-significant heterogeneity.

The reduction is present in the case of interventions with pharmacotherapy, psychotherapy, psycho-social therapies, case-management or related services; this aspect could be an orientation for the constitution of future programs to have an impact on suicidal behavior.

Our work provides an additional argument for the deployment of early intervention systems: the impact on suicidal behavior and thus on the mortality of our young patients.

Author Contributions

E.T. conceptualized the systematic review design and completed the PROSPERO registration. E.T. developed the search strategy. E.T., A.B. extracted data independently. E.T., B.G. carried out the statistical analyses. J.B., E.T. analyzed bias independently. E.T., J.B., B.G., P.N., M.G., A.B., M.W., C.L. contributed to the review methodology and manuscript preparation. All authors read and approved the final manuscript.

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Ethics Statement

The data to be collected and synthesized in this study are data processed in previous studies, in this context, we have not requested ethical approval.

Consent

All authors consent for publication.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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