CHILDREN'S MENTAL HEALTH RESEARCH

Quarterly

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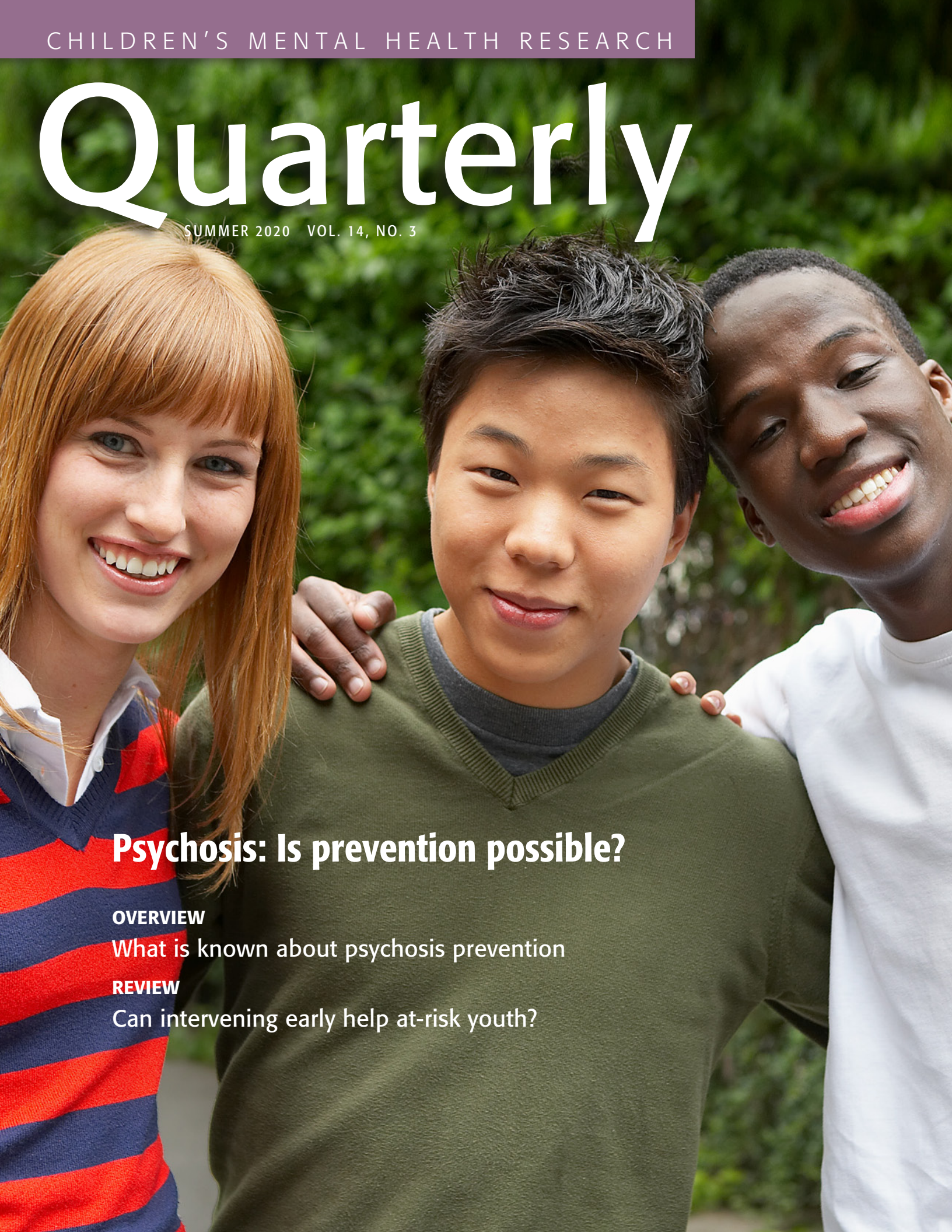

Psychosis: Is prevention possible?

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What is known about psychosis prevention

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Can intervening early help at-risk youth?

Summer

Quarterly

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Children's Health Policy Centre

About the *Quarterly*

We summarize the best available research evidence on a variety of children's mental health topics, using systematic review and synthesis methods adapted from the Cochrane Collaboration and Evidence-Based Mental Health. We aim to connect research and policy to improve children's mental health. The BC Ministry of Children and Family Development funds the *Quarterly.*

About the Children's Health Policy Centre

We are an interdisciplinary research group in the Faculty of Health Sciences at Simon Fraser University. We focus on improving social and emotional well-being for all children, and on the public policies needed to reach these goals. To learn more about our work, please see childhealthpolicy.ca.

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This Issue

NEXT ISSUE

Treating psychosis in young people

Young people with psychosis need ready access to effective treatments. We present research on both medications and psychosocial approaches for this population.

How to Cite the *Quarterly*

We encourage you to share the *Quarterly* with others and we welcome its use as a reference (for example, in preparing educational materials for parents or community groups). Please cite this issue as follows:

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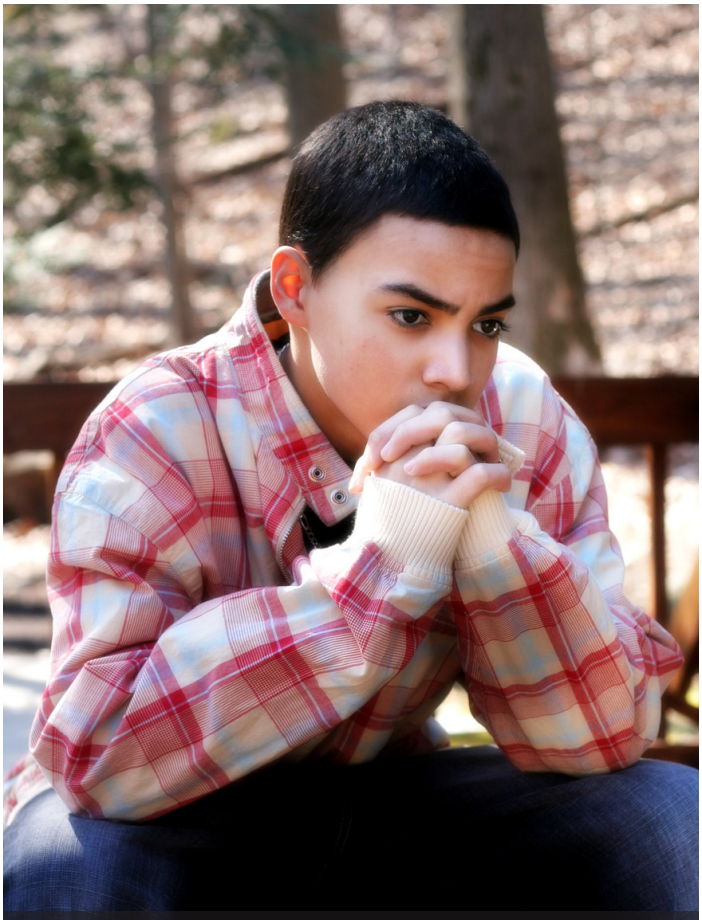
OVERVIEW

What is known about psychosis prevention

Psychotic disorders typically involve delusions and hallucinations, among other symptoms.[1] Delusions are strongly held false beliefs that persist despite evidence to the contrary and that cannot be explained by the individual's cultural or religious background. Hallucinations are sensations, such as hearing voices, in the absence of external causes. Psychosis may also include disorganized thinking, atypical motor behaviour and "negative" symptoms, such as loss of motivation and lack of social engagement. As with many mental disorders, potentially reversible causes such as infection or intoxication must be ruled out when diagnosing psychosis. Schizophrenia, schizoaffective disorder and delusional disorder are among the psychotic disorders recognized in the *Diagnostic and Statistical Manual of Mental Disorders*.[1]



Substance-induced psychotic disorders are preventable.

When primary prevention is possible

Controversy persists about whether it is possible to prevent all forms of psychosis. But one form — namely substance-induced psychotic disorders — is clearly preventable. Youth can develop these disorders due to substance intoxication or withdrawal, including from alcohol and cannabis. And many young Canadians require medical care for this problem. In fact, among 10- to 24-year-olds, 15% of hospital stays for harms caused by substance use involved this form of psychosis, leading to 3,537 hospitalizations between 2017 and 2018.[2]

Reducing the number of youth who experience substance-induced psychosis is a viable goal. Mainly, this can be achieved by providing effective substance use prevention programs and by offering effective treatments to youth who are struggling with problematic substance use. (Please see previous *Quarterly* issues for more information on primary and targeted prevention programs as well as effective treatments for problematic substance use.)

Controversy persists about whether it is possible to prevent all forms of psychosis.

Determining who is at greatest risk

Researchers are now examining whether it is possible to prevent other psychotic disorders, beyond substance-induced psychosis. The first step in developing prevention interventions for any health problem is usually to understand the underlying causes. However, understanding these causes can be challenging for disorders like schizophrenia that appear to arise from complex interactions when multiple environmental exposures influence gene expression over time. These interactions also play out across dynamic stages of brain development throughout childhood and adolescence, making it difficult to pinpoint targets for prevention

programming.[3] Environmental factors, such as prenatal and perinatal exposures to infections and stress, may be the best candidates for prevention efforts. Yet even these environmental factors are not understood sufficiently to inform the development of interventions.[3]

In the interim, another approach involves identifying young people most at risk for psychosis, and then developing interventions to reduce their risk. To this end, consensus has emerged around using a precisely defined "clinical high-risk" threshold to identify those who are most likely to develop psychosis. To meet this threshold, youth must experience at least one of the following:

- subthreshold psychotic symptoms such as intermittent, brief periods of disorganized speech
- psychotic symptoms that are brief, self-limiting and resolve without treatment
- significantly decreased functioning coupled with having a first-degree relative with a psychotic disorder[4]

These clinical high-risk criteria are now widely used in research, including in the three intervention studies accepted for the Review article that follows.

Balancing benefits and harms of early identification

Considerable potential benefits come with correctly predicting who may be at high risk for psychosis. The most important benefit is that early identification may facilitate more youth receiving effective early interventions.[5] Early identification and intervention in turn may lead to other benefits, such as better engagement with mental health services and with practitioners.[5] Compounding these benefits, youth receiving early mental health services may be less likely to need hospital care for psychosis, compared with those who receive services only after psychosis develops.[6]

Youth receiving early mental health services may be less likely to need hospital care for psychosis.

Yet the clinical high-risk criteria have also garnered criticism. A systematic review examining 27 studies on this topic found that most individuals who met the clinical high-risk threshold did *not* go on to develop psychotic disorders.[7] Specifically, 18% developed a psychotic disorder at six-month follow-up, 22% at one year, 29% at two years and 32% at three years.[7] In other words, nearly two-thirds of those deemed high risk did not develop a psychotic disorder during the ensuing three years. Importantly, being older increased the risk of developing a psychotic disorder, suggesting that the designation may have less utility for youth. As well, being treated with antipsychotics reduced the risk of developing a psychotic disorder. Among those prescribed antipsychotics, 22.9% developed a psychotic disorder, compared with 36.5% of those who were not prescribed these medications.[7]

There is also considerable potential for harm in incorrectly labelling a young person as being at high risk for psychosis — including unnecessary treatment and stigma.[8] Plus, this designation could cause considerable fear and distress for youth and their families. Consequently, the clinical high-risk criteria are not recommended for screening purposes, even though they remain useful for research.[5]

Next steps

Researchers have made considerable progress in evaluating interventions that aim to prevent psychosis, based on identifying high-risk youth. In the Review article that follows, we examine three such interventions.

REVIEW

Can intervening early help at-risk youth?

Early effective treatments can lead to better outcomes for youth.

It is well established that young people with psychosis have better outcomes when they receive effective treatment early in the course of the disorder.[9] This knowledge has spurred efforts to try to prevent the onset of psychosis in at-risk young people. But how well are these efforts working? To answer this question, we conducted a systematic review of interventions designed to prevent psychosis in at-risk youth.

To identify the best available research evidence, we built quality assessment into our inclusion criteria. In particular, we required all studies to use randomized controlled trials (RCTs). We then searched for RCTs evaluating relevant interventions published between 2009 and 2020. (Please see the Methods section for more details on our search strategy and inclusion criteria.)

We retrieved and assessed 41 studies. Three RCTs evaluating three interventions met our inclusion criteria. The interventions were Omega-3 Polyunsaturated Fatty Acids (PUFAs),[10–11] Auditory Cognitive Training[12] and Family-Focused Treatment.[13] The sidebar provides information on two medication studies that failed to meet our inclusion criteria.

Diverse efforts to prevent psychosis

Participants in all three studies were assessed as being at high risk for psychosis based on the clinical high-risk threshold. But the interventions diverged considerably. The first study set out to determine whether PUFAs could prevent psychosis, based on reports that the supplement showed some evidence of beneficial effects for adults with schizophrenia.[10] This double-blinded RCT randomly assigned participants to receive either PUFA or placebo capsules four times daily for three months. (Researchers did not receive any funding from the makers of this dietary supplement.) Both intervention and control youth also received case management services, including education and support.[10] As well, all youth were offered nine counselling sessions to address symptoms, social relationships and family issues, plus crisis management sessions if needed. Case management and counselling were offered for 40 weeks and were accessed by youth in both groups at similar rates. However, youth were not permitted to use antipsychotics during the three-month trial period. Although the authors did not explain this restriction, they may have wanted to ensure that medications did not confound the outcomes.[10]

What about medications?

In our search for prevention interventions, we found randomized controlled trials evaluating the antipsychotic medications olanzapine and risperidone.[15–16] However, both studies failed to meet inclusion criteria because they did not enroll enough youth to adequately test for differences between medications and placebos. Since medications may show promise for prevention of psychosis, it would be helpful to address this serious limitation in future trials.

In contrast, Auditory Cognitive Training aimed to improve cognitive functioning for at-risk young people — given that deficits in memory, attention and verbal fluency can be common in this group.[12] Training involved computerized exercises designed to improve the speed and accuracy of auditory information processing, as well as improve working memory.[14] Tasks included distinguishing between two similar sounds and carrying out verbal instructions from memory.[14] Participants were randomly assigned to receive Auditory Cognitive Training or video games, the active control condition, for 40 hours over eight weeks. Youth in both groups could also receive treatments not provided through the study, including psychotherapy and medications.[12]

Even though prevention research is still emerging, practitioners can play a crucial role by providing services for youth at risk of psychosis.

The third intervention, Family-Focused Treatment, aimed to reduce psychotic symptoms and improve overall functioning. This intervention focused on assisting parents to help youth engage and encouraged positive family interactions.[13] Participating families were randomly assigned to either the intervention or a one-month family educational program. Family-Focused Treatment consisted of 18 family therapy sessions. These sessions included identifying stressors associated with psychotic symptoms and providing participants with ways of coping with them. They also encouraged positive family communications and worked on building problem-solving and conflict resolution skills. Both intervention and control families could also receive study-based crisis management sessions as needed. Study psychiatrists managed psychiatric medications, unless youth preferred to continue with their community practitioners. Study psychiatrists could start antipsychotic medications during the trial if needed.[13] Table 1 gives more information about the three studies.

Table 1: Psychosis Prevention Studies

Intervention	**Approach**	**Sample size**	**Ages*** (years) (countries)
Omega-3 Polyunsaturated Fatty Acids (PUFAs)[10]	PUFA capsules 4 times daily over 3 months	81	13–25 (Austria)
Auditory Cognitive Training[12]	40 hours of computerized training in auditory information processing over 2 months	83	12–30 (United States)
Family-Focused Treatment[13]	18 hours of family therapy over 6 months	129	12–32 (United States + Canada)

* Although these studies included individuals older than 18, the average age of participants was 18 or younger for all studies.

Dietary supplement outcomes

PUFA supplements led to substantial benefits for young people at long-term follow-up of nearly seven years, with a high retention rate (87.7% of participants). At this follow-up, 9.8% of intervention youth had developed a psychotic disorder, compared with 40.0% of controls.[11] This benefit was found despite fewer intervention youth than controls being prescribed antipsychotic medications by follow-up (29.4% vs. 54.3%, respectively). As well, intervention youth reported fewer psychotic symptoms and better overall functioning than controls. They were also less likely to meet diagnostic criteria for other mental disorders, including mood, anxiety and substance use disorders (52.9% vs. 82.9%, respectively). How might PUFAs work? The study authors admitted uncertainty, but speculated that PUFAs may prevent brain changes that could contribute to psychosis.[11]

Psychosocial intervention outcomes

Auditory Cognitive Training did not produce significant benefits.[12] At the end of the intervention, there was no difference between the intervention and control groups regarding psychotic symptoms, overall functioning or any cognitive outcomes, including learning, memory, problem-solving and processing speed. These poor outcomes may be related to high attrition, as 42% of youth left the study before its completion.[12] (The trial still met our inclusion criteria because the authors used a statistical technique to account for attrition.)

Family-Focused Treatment also failed to produce significant benefits.[13] At the end of treatment, no statistically significant difference was found between intervention and control groups regarding psychotic symptoms or overall functioning. Poor attendance may have played a role in these poor outcomes; approximately 25% of families participated in less than half of the sessions.

Notably, both psychosocial intervention studies lacked long-term follow-up, which may have contributed to the poor findings. Only about 18% of youth who meet clinical high-risk criteria go on to develop psychotic disorders within six months of receiving the designation.[7] So assessing outcomes only at the end of treatment was likely insufficient to identify long-term gains. Table 2 summarizes the outcomes for these three studies.

Table 2: Psychosis Prevention Study Outcomes

Intervention	Follow-up	Outcomes
Omega-3 Polyunsaturated Fatty Acids (PUFAs)[11]	6¾ years	↓ Psychotic disorder diagnoses ↓ Psychotic symptoms ↓ Antipsychotic medication use ↑ Overall functioning
Auditory Cognitive Training[12]	None	NS Psychotic symptoms NS Overall functioning NS Learning, memory, problem-solving + processing speed
Family-Focused Treatment[13]	None	NS Psychotic symptoms NS Overall functioning

↓ or ↑ Statistically significant improvements for intervention over control participants.
NS No statistically significant difference between treatment and control participants.

Implications for research, practice and policy

The results of these three studies suggest three recommendations to guide research, practice and policy.

- *Build on what has been discovered so far.* Although the one RCT examining PUFA supplements had promising outcomes, more studies are needed because these results have yet to be replicated. More research is particularly important given that the other RCT evaluating PUFAs with high-risk individuals found no benefits in preventing psychosis.[17] (This study did not meet our inclusion criteria because the average age of participants was 19.) Future studies could also make psychosocial interventions such as cognitive training and family therapy more appealing — with the goal that improved attendance might lead to better outcomes. Psychosocial studies could also ensure long-term follow-up.
- *Learn from effective adult interventions.* Rigorous evidence from studies involving high-risk adults indicates that psychosocial interventions can prevent psychosis in this population. For example, one RCT found that cognitive training reduced the likelihood of developing psychosis.[18] Another RCT found that an integrated psychological intervention, which included cognitive-behavioural therapy, skills training, cognitive training and family education, effectively

Further research is needed, particularly on possible environmental causes of psychotic disorders.

prevented psychosis in young adults.[19] Evaluating these two interventions in high-risk youth could result in new — and earlier — prevention options. Policy-makers may want to consider supporting such evaluations.

- *Provide comprehensive care for high-risk young people.* Even though prevention research is still emerging, practitioners can play a crucial role by providing services for youth at risk of psychosis. Such services include monitoring, providing education and supports, and prescribing antipsychotics if these medications become warranted.

Given that psychosis profoundly influences developmental trajectories starting in adolescence, and given the high associated burdens and costs for individuals and for society,[3, 20] preventing psychosis is an important goal. Positive youth results for PUFA supplements and positive adult results for psychological interventions suggest that prevention may be achievable for some young people. Further research is needed, particularly on possible environmental causes of psychotic disorders. Such causes have the potential to guide new prevention interventions.[3] Meanwhile, it is imperative to support youth at high risk for psychosis as well as their families.

Ample support from family members enables youth to flourish.

METHODS

We use systematic review methods adapted from the *Cochrane Collaboration* and *Evidence-Based Mental Health*. We build quality assessment into our inclusion criteria to ensure that we report on the best available research evidence — requiring that intervention studies use randomized controlled trials (RCTs) and meet additional quality indicators. For this review, we searched for RCTs on effective interventions for preventing psychosis. Table 3 outlines our database search strategy.

Table 3: Search Strategy

Sources	• CINAHL, ERIC, Medline and PsycINFO
Search Terms	• Schizophrenia or psychosis *and* prevention, intervention or treatment
Limits	• Peer-reviewed articles published in English between 2009 and 2020 • Pertaining to children aged 18 years or younger • RCT methods used

To identify additional RCTs, we also hand-searched the Web of Science database, reference lists from relevant published systematic reviews and previous issues of the *Quarterly*. Using this approach, we identified 41 RCTs. Two team members then independently assessed each RCT, applying the inclusion criteria outlined in Table 4.

Table 4: Inclusion Criteria for RCTs

- Participants were randomly assigned at study outset to intervention and comparison groups (i.e., no intervention or minimal intervention)
- Participants had mean age of 18 years or younger
- Studies provided clear descriptions of participant characteristics, settings and interventions
- Interventions were evaluated in settings that were applicable to Canadian policy and practice
- Interventions aimed to prevent psychosis
- At study outset, most participants did not meet diagnostic criteria for a psychotic disorder
- Attrition rates were 20% or less at final assessment and/or intention-to-treat analysis was used
- Youth outcome indicators included psychotic symptom and/or diagnostic outcomes
- Studies reported levels of statistical significance for primary outcome measures
- Psychosocial studies had at least one outcome rater blinded to participants' group assignment
- Medication and supplement studies used double-blinding procedures and placebo controls
- Studies were excluded when there was insufficient statistical power or inappropriate analyses*

* We defined inappropriate analyses as those that did not control for multiple comparisons and/or variables that might influence the outcome of interest.

Three RCTs met all the inclusion criteria. Figure 1 depicts our search process, adapted from Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Data from these studies were then extracted, summarized and verified by two or more team members. Throughout our process, any differences between team members were resolved by consensus.

For more information on our research methods, please contact
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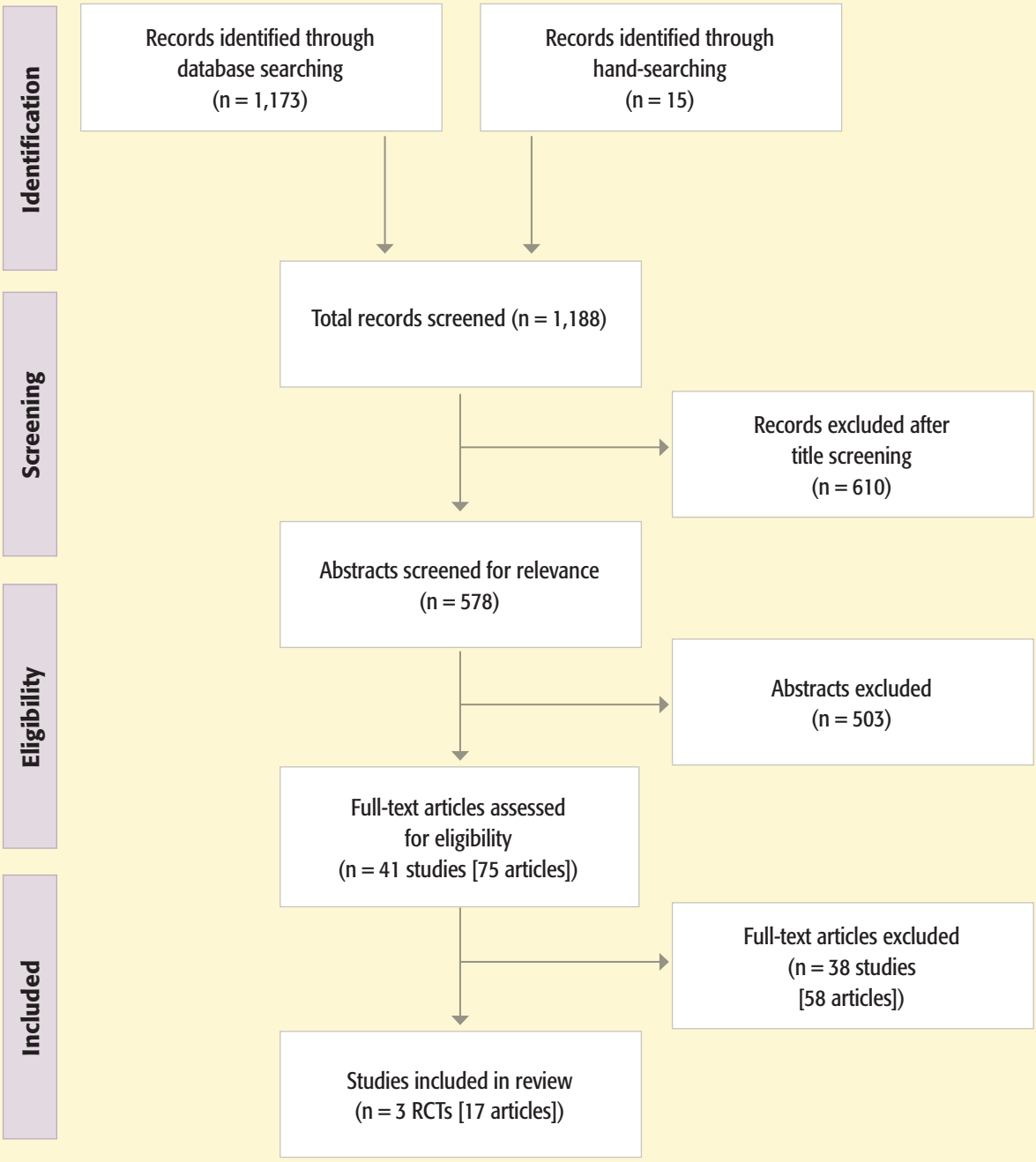
Figure 1: Search Process for RCTs



RESEARCH TERMS EXPLAINED

Practitioners and policy-makers need good evidence about whether a given intervention works to help children. **Randomized controlled trials** (RCTs) are the gold standard for assessing whether an intervention is effective. In RCTs, children, youth or families are randomly assigned to the intervention group or to a comparison or control group. By randomizing participants — that is, by giving every young person an equal likelihood of being assigned to a given group — researchers can help ensure the only difference between the groups is the intervention. This process provides confidence that benefits are due to the intervention rather than to chance or other factors. As well, the RCT assessing PUFAs was **double-blinded** so neither youth nor researchers knew who was in the intervention and control groups. This approach is typical for dietary supplement and medication studies. It helps to ensure that beliefs about the potential effectiveness of the intervention do not influence outcomes.

Then, to determine whether the intervention actually provides benefits, researchers analyze relevant outcomes. If an outcome is found to be **statistically significant,** it helps provide certainty the intervention was effective rather than results appearing that way due to chance. In the studies we reviewed, researchers set a value enabling at least 95% confidence that the observed results actually reflected the program's real impact.

When researchers and youth are unaware of who is receiving the intervention, it helps to ensure that beliefs about effectiveness do not influence outcomes.

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BC government staff can access original articles from BC's Health and Human Services Library. Articles marked with an asterisk (*) include randomized controlled trial data that was featured in our Review article.

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LINKS TO PAST ISSUES

The *Children's Mental Health Research Quarterly* Subject Index provides a detailed listing of topics covered in past issues, including links to information on specific programs.

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