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Risk Stratification for Treatment Decisions in People at Ultra-High Risk for Psychosis: A Cost-Effectiveness Analysis

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Abstract

People with psychotic disorders have long-term negative health outcomes and contribute large health system costs. Intervening among those at ultra-high risk (UHR) for psychosis may prevent or mitigate risk for psychotic disorder; however, it is unclear if we should treat all UHR individuals or only those above a certain risk threshold. The objectives were to systematically review the literature on the cost-effectiveness of UHR programs, and to conduct an economic evaluation of a risk stratification strategy, where treatment decisions are based on the probability of transitioning to psychotic disorder. Our systematic review found that UHR programs are potentially cost-effective. The economic evaluation found that only treating those at ≥20% risk to transition is cost saving to the Canadian health system, but returns worse health outcomes ($15,466 per quality-adjusted life-year), relative to treating all UHR individuals. Future research requires better valuation of cost and outcomes and trials examining risk stratification.

Keywords

Cost-Benefit Analysis; Costs and Cost Analysis; Early Medical Intervention; Models, Economic; Prodromal Symptoms; Psychotic Disorders; Schizophrenia

Summary for Lay Audience

Psychotic disorders are mental illnesses that have long-term negative consequences for a person's functioning and quality of life, and are often expensive to treat and manage. Some studies have found that treating people at high risk for psychosis in specialized programs may be effective for slowing down progression to psychosis or preventing it entirely. Little is known about the cost-effectiveness of high risk programs compared to alternative treatment plans. Therefore, it is important to examine the cost-effectiveness of treating people in high risk programs to help inform future health policy decisions related to this population. The aim of this thesis was to review all available studies on the cost-effectiveness of high risk programs, and to then use this knowledge to inform the creation of an economic model to evaluate the potential benefit of prioritizing treatment to those at a much higher risk for psychosis (≥20% risk). In our review of prior economic studies comparing high risk programs to standard care, we found that high risk programs may provide value for money, but no conclusions can be drawn on what aspects of the treatment plan are cost-effective. Next, an economic evaluation was done to assess the Canadian health care system costs of only treating those at a very high risk for converting to psychosis (≥20% risk) based on a risk calculator compared to a standard 'treat all' strategy. Risk stratification has incremental costs of $15,466 to the health system per quality-adjusted life-year, compared to the other strategy. More specifically, our results show that risk stratification has potential to provide cost savings, but returns worse outcomes. This means that cost savings can occur only if health system decision-makers are willing to accept losses in health. Future economic evaluations would benefit from more rigorous methods of examining health care outcomes and costs associated with high risk programs. Future clinical trials that compare the effectiveness of personalized treatment plans to the standard of care may also help inform future economic models.

Co-Authorship Statement

This submitted thesis contains two integrated articles. **Chapter 2** contains a systematic review that has been published.[1] **Chapter 3** is the economic model and is an extended version of what is expected to be submitted.

Chapter 2: This is the peer reviewed version of the following article: [Ologundudu OM, Lau T, Palaniyappan L, Ali S, and Anderson KK. Interventions for people at ultra-high risk for psychosis: A systematic review of economic evaluations. Early Interv Psychiatry. 2020. doi:10.1111/eip.13061], which has been published in final form at [https://onlinelibrary.wiley.com/doi/10.1111/eip.13061].[1] This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Use of Self-Archived Versions. We have also applied for copyright permission. See Appendix D for copyright details.

Olajumoke M. Ologundudu helped conceptualize the research question, designed and ran all the analyses, and wrote the manuscript. Tammy Lau served as a second reviewer (screening, data extraction, and risk of bias). Dr. Kelly K. Anderson participated in the conception and design of the study and resolved reviewer conflicts. Dr. Shehzad Ali and Dr. Lena Palaniyappan provided insight on economic concepts and clinical concepts, respectively. All members revised the manuscript.

Chapter 3: Ologundudu OM, Palaniyappan L, Cipriano LE, Wijnen, BFM, Anderson KK, and Ali S. Risk Stratification for Treatment Decisions in People at Ultra-High Risk for Psychosis: A Cost-Effectiveness Analysis. Being prepared for journal submission.

Olajumoke M. Ologundudu helped conceptualize the research question, designed and ran all the analyses, and wrote the manuscript. Dr. Lena Palaniyappan provided estimated service use data and clinical advice. Dr. Ben F.M. Wijnen provided the original model (PsyMod) and technical advice. Dr. Shehzad Ali and Dr. Kelly K. Anderson conceptualized the research question and provided technical advice. Dr. Lauren E. Cipriano provided technical advice. All members revised the manuscript.

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Abbreviations

ABC	Adversity Belief Consequence
ARMS/ CHR/ UHR	At Risk Mental State/ Clinical High Risk/ Ultra-High Risk
AUC	Area Under the Curve
APS	Attenuated Psychotic Symptoms
BLIPS	Brief Limited Intermittent Psychotic Symptoms
CAARMS	Comprehensive Assessment of At-Risk Mental States
CAMHS	Child and Adolescent Mental Health Services
CAU	Care as Usual
CBT	Cognitive Behavioral Therapy
CAYR	The Clinic for Assessment of Youth at Risk
CEA	Cost-Effectiveness Analysis
CHEC	Consensus on Health Economic Criteria
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence Interval
CUA	Cost-Utility Analysis
DSA	Deterministic Sensitivity Analyses
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
DUP	Duration of Untreated Psychosis
EI	Early Intervention
ED	Emergency Department
EDIE-NL	Dutch Early Detection and Intervention Evaluation
FEP	First Episode Psychosis
FFS	Fee-for-Service
GP	General Practitioner
GRD	Genetic Risk and Deterioration
ICER	Incremental Cost-Effectiveness Ratio

ISPOR	International Society of Pharmacoeconomics and Outcomes Research
LEGs	Liaison and Education in General Practice
NAPLS	North American Prodrome Longitudinal Study
N/A	Not Applicable
NBI	Needs-Based Intervention
NICE	National Institute for Health and Care Excellence
OASIS	Outreach and Support in South London
PAU	Practice as Usual
PEPP	Prevention and Early Intervention Program for Psychoses
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PROSPECT	PROdromal Symptoms of Psychosis: Early Clinical identification and Treatment
PSA	Probabilistic Sensitivity Analyses
RC	Routine Care
RCT	Randomized Controlled Trial
ROB	Risk of Bias
RPN	Registered Practical Nurse
RR	Relative Risk
SC	Standard Care
SD	Standard Deviation
SIPS	Structured Interview of Psychosis-risk Syndromes
SMR	Standardized Mortality Ratio
SOB	Schedule of Benefits
SPI	Specific Preventive Intervention
WTA	Willingness-to-Accept
WTP	Willingness-to-Pay
QALY	Quality-Adjusted Life-Year

Chapter 1

1 Introduction

1.1 Overview

An episode of psychosis occurs when a person cannot adequately distinguish between what is and is not reality.[2] It is characterized by the presence of positive symptoms – such as delusions, hallucinations, and disorganized thought and behavior patterns – but may also include negative symptoms, such as diminished facial expressions, loss of motivation, and minimized speech.[2] Psychotic episodes may occur in the context of a number of mental disorders diagnosed using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5),[3] but most commonly occur in schizophrenia spectrum disorders.[4,5] Observational studies indicate that psychotic disorders are often comorbid with other mental illnesses, such as substance use disorders and depression.[6]

Psychotic disorders contribute to the global burden of disease by increasing the risk of long-term disability, negative health outcomes, and premature mortality.[6–9] Psychotic disorders are also responsible for substantial economic costs. The most recent meta-analysis found the pooled worldwide incidence of psychotic disorders to be approximately 26.6 cases per 100 000 person-years (95% CI 22.0–31.7).[10] Psychotic disorders like schizophrenia – which alone affect 25 million people worldwide– have poor long-term outcomes, such as higher rates of unemployment, hospitalizations, and suicide.[6–8] There are also physiological outcomes associated with these disorders. For example, schizophrenia is associated with increased cardiovascular disease[11] and higher rates of premature mortality.[9] Similarly, the economic impact of psychotic disorders is substantial and can be partially attributed to its emergence during adolescence and young adulthood, as well as the fact that the mentioned symptoms and their corresponding impact on health outcomes may persist throughout the lifespan.[12] A 2016 systematic review of studies examining the economic burden of schizophrenia determined that the annual cost of this illness, in U.S dollars, ranged from $94 million to $102 billion (0.02% to 5.46% of the gross domestic product).[12] Lower estimates were partially explained by some countries having tax-funded healthcare, but more general reasons for the wide

range in costs included differences in: health care systems, resource use, types of costs evaluated, and populations studied.[12] In Canada, the financial burden of schizophrenia in 2004 was estimated to be approximately $6.85 billion, with nearly 70% of these costs attributable to productivity losses – largely due to morbidity – whereas the remaining 30% was due to direct healthcare and non-healthcare costs.[13] More locally, Ontario estimates for 2012 direct health care costs of chronic psychotic disorders to the ministry of health was about $10,398 per patient.[14] Overall, psychotic disorders are associated with negative long-term health outcomes, which contribute to large economic burdens on a national and global level.

There is evidence to suggest that the longer one waits to diagnose and treat the first episode of psychosis (FEP), the poorer the prognosis.[15,16] Knowing that poorer outcomes may further contribute to the health burden and subsequent economic costs associated with psychotic disorders, early research in the field sought to examine the course of illness and clinical stages in which intervention may be appropriate. Eventually, researchers were able to observe a prodromal phase that often preceded the first psychotic episode, characterized by increasing psychotic symptoms and a decline in functioning.[6,17] This prodromal stage was often only identifiable retrospectively – once symptoms of psychosis emerged – since prodromal features can be fairly non-specific.[6] Nevertheless, there are subthreshold symptoms and observable declines in functioning that can be identified using systematic assessments prospectively.[6,17] This clinical stage is known as the ultra-high risk (UHR) state for psychosis, though other terms exist, such as the clinical high risk state (CHR) or the at risk mental state (ARMS).[6,18] These terms indicate that though transition to psychosis is possible, it is not inevitable.[6] Programs now exist to treat those at UHR for psychosis,[19] and trials have since been published to attest to their clinical effectiveness.[20] Unlike the clear clinical symptoms of the FEP diagnosis, the UHR state is more challenging to identify due to the previously mentioned fact that only some may go on to transition to psychosis.[6,21] As a result, there are now assessment tools in development – such as individualized risk calculators – which compute a probability for the risk of transitioning to psychosis among people identified as UHR.[22] Individualized risk scores may then allow future treatment plans to offer more personalized and intensive intervention to those with higher transition probabilities. With

limited funds available for mental health treatment, there is value in modeling assessment tools that allow prioritized allocation of scarce resources in order to estimate their potential cost-effectiveness in the context of UHR clinics.

1.1.1 Summary of Thesis Layout

The purpose of this thesis is to identify and address gaps in the literature regarding the economic value of UHR programs. We aim to investigate the economic value of allocating treatment for UHR patients based on an individualized risk calculator that computes the probability of transitioning to psychosis – those with higher risk scores would be enrolled in more vigorous case management strategies compared to those with lower scores. We first systematically reviewed the literature on economic evaluations of UHR programs. We then created an economic model examining the cost-effectiveness of providing annual risk assessments to UHR patients at low risk of transitioning and UHR treatment (active case management) to those at high risk, compared to treating all UHR patients with UHR treatment irrespective of risk. This thesis follows an integrated format, which includes published and unpublished manuscripts. Chapter 1 will provide background information and will detail concepts pertinent to the UHR state, current evidence regarding the effectiveness of early psychosis intervention programs, and describe assessment tools available for the UHR state. Chapter 2 will present a published systematic review manuscript of available health economic evaluations completed on the UHR population, and identify the current gaps in the literature on this topic in order to inform the analyses in later chapters. Chapter 3 will present the unpublished manuscript of the economic evaluation, detailing the results of the base case analysis and sensitivity analysis. Chapter 4 will contain an extended discussion of the results and integration of findings across the two manuscripts, including future directions.

1.2 First Episode Psychosis Programs and Treatment

An episode of psychosis occurs when a person is unable to determine what is or is not reality.[2,3] In recent decades, there has been an emphasis on early intervention for the first psychotic episode[2,3] and for those identified as being at UHR of transitioning to psychosis.[17] The main goal of early psychosis intervention is to provide comprehensive treatments to those experiencing symptoms indicative of psychosis (FEP stage) or

impending psychosis (UHR stage),[6] with the latter aimed at preventing transition to full psychotic disorder. The types of treatments may vary depending on the stage, but are ultimately aimed at preventing poor long-term outcomes, and potentially avoiding the FEP stage completely if administered during the UHR stage.[6]

1.2.1 First Episode Psychosis and Duration of Untreated Psychosis

Psychotic episodes are characterized by positive and negative symptoms.[2,3] Positive symptoms include delusions, hallucinations, and disorganized speech, thoughts or behavior.[2,3] Negative symptoms include alogia (restricted speech), avolition (reduced motivation), and affective flattening (limited facial expression).[2,3] In addition to the distress and confusion one may feel from the onset of their first psychotic episode, there may also be a delay in receiving prompt treatment. Although specific definitions vary, the period between the onset of the first psychotic symptom and the commencement of antipsychotic treatment is termed the duration of untreated psychosis (DUP).[23] A long DUP is associated with unfavorable clinical outcomes, some of which may include an increase in the severity of positive and negative symptoms and a lower likelihood of remission.[24]

1.2.2 First Episode Psychosis Programs

In an effort to reduce the DUP and improve outcomes, FEP programs have been developed to provide intensive treatment during the early phases of psychosis. They use personalized treatment plans involving both medication and therapy – which may include family intervention and social skills training – overseen by a multidisciplinary team of mental health professionals.[5,8,25] FEP programs are usually provided in the first two years after the onset of psychosis, though it has been suggested that an extension of the program for up to five years may be needed to improve patient outcomes.[26,27] Quality treatment during this ‘critical period’ is essential in order to improve long-term outcomes, especially given that patient disengagement from services may occur at this time.[6]

Worldwide, the effectiveness of FEP programs has been established.[5] A 2018 systematic review and meta-analysis by Correll et al[5] showed that programs for early-phase psychosis were more effective in treating FEP compared to standard care across all

outcome indicators examined – this includes all-cause treatment discontinuation and psychiatric hospitalization. More locally, in a cohort of incident cases of nonaffective psychosis in the London catchment area, all-cause mortality rates were four times lower among people who used the FEP service, compared to non-users.[16]

Independent economic evaluations have also found FEP programs to be cost-effective in a variety of settings.[28–30] A 2019 systematic review found FEP programs to be potentially cost-effective, though the heterogeneity in the methodology, health contexts, and treatment plans between FEP programs – among other limitations – contribute to the uncertainty in the conclusions.[31]

1.3 The Ultra-High Risk Concept

Due to the poor outcomes and increased costs associated with treatment delay following the first psychotic episode, there has been an increased interest in examining an earlier clinical stage – the UHR stage – to pre-emptively treat early symptoms of psychosis.[17] Those in the UHR stage may experience changes in normal constitution, such as anxiety, a reduced motivation to attend school or work, and the emergence of subthreshold positive symptoms.[2,17,32] Much like those who have transitioned to FEP, people identified as UHR may also experience comorbid non-psychotic disorders, such as depression and anxiety.[33] Because some of these symptoms may be indicative of other mental illnesses, people must meet at least one of the following criteria to be considered UHR: (i) attenuated psychotic symptoms (APS); (ii) brief limited intermittent psychotic symptoms (BLIPS); or (iii) genetic risk and deterioration (GRD).[17,34] APS describes subthreshold or mild symptoms experienced in the past year that do not meet the diagnostic criteria for a psychotic disorder.[17] BLIPS refers to short periods of frank psychotic symptoms that disappear without treatment within a week.[17] GRD may refer to either the presence of a psychotic disorder within a first-degree family member or evidence of declining functioning and a diagnosis of schizotypal personality disorder in the person being examined.[17] Usually, identification of the UHR state is restricted to adolescents and young adults between the ages of 14 and 30.[17] Different psychometric instruments may be used to determine if someone is UHR, though some popular assessment tools include the Comprehensive Assessment of At-Risk Mental States (CAARMS)[35] interview and the

Structured Interview of Prodromal Syndromes (SIPS).[36] CAARMS and SIPS have previously been shown to be acceptable assessment tools to identify the UHR state.[37,38]

1.3.1 The Risk for Transition from the Ultra-High Risk State to First Episode Psychosis

An early proof of concept study by Yung et al[39] in 2003 found that approximately 40% of people at UHR for psychosis transitioned to psychosis within a year, though more recent estimates from a 2015 meta-analysis have determined that this number may be as low as about 10% at six months to 37% over four years.[40] These transition probabilities are still reasonable, given that other risk states exist with comparable values.[18] The pre-diabetic classification with a 5% to 10% chance of transitioning to diabetes,[18,41] and the 12% chance of conversion to dementia from mild cognitive impairment,[42–44] are two examples.

Some theories exist as to why there have been recent declines in transitions to psychosis. One theory suggests that transition rates may be declining because treatment is being appropriately and swiftly provided to those early in the course of illness.[45] Another reason was provided by a meta-analysis of recruitment strategies to UHR clinics.[46] This study found that the declining transition risk may be explained by a high proportion of self-referrals from the general public, rather than referrals from mental health care providers.[46] Specifically, it was argued that intensive outreach campaigns – especially ones that capture a high number of self-referrals – may draw potential patients from a population that may exhibit UHR symptoms that would be considered to be benign or not clinically significant.[42,46] Patients exhibiting these milder UHR symptoms may never transition to psychosis, resulting in risk dilution.[42,46] Another potential reason for the recent declines in transitions was suggested by Simon et al,[42] who stated that some non-psychotic disorders may have psychotic-like symptoms, such as anxiety and depression. People presenting to UHR programs with psychotic-like symptoms attributable to other disorders may then meet the criteria for APS, but not actually transition.[42] Finally, given that most studies examine transitions to psychosis within two years, there is the possibility that additional transitions that occur after this time may not be captured.[42]

1.3.2 Ultra-High Risk Programs

Programs targeting people identified as being in an UHR state have been developed with an aim of encouraging early engagement with essential treatments and services for distressed youth, to potentially delay or prevent the transition to psychosis.[47] In addition, these programs may provide an opportunity to improve clinical outcomes by lowering the chances of being admitted to the hospital during a crisis and by also reducing the DUP.[47,48] UHR programs tend to be a mixture of active case management, pharmacological treatments, psychosocial therapies, and additional therapies.[19] It is important to note that Canadian guidelines – which are derived from the European Psychiatric Association and National Institute for Health and Care Excellence guidelines – recommend that antipsychotics should not be used in preventative treatments plans for mild cases.[49] Similar to FEP programs, UHR programs provide support to patients for a duration of about two years, and may be extended depending on need.[19,50]

There are numerous UHR programs world-wide. For example, the Outreach and support in South London (OASIS) program is one of the largest and most well-established UHR programs in the UK.[50–52] In Canada, the Montreal Clinic for Assessment of Youth at Risk (CAYR) program has been active for over ten years,[19] and more locally, the PROSPECT (PROdromal Symptoms of Psychosis: Early Clinical identification and Treatment) clinic has been operating since 2018.

Several prior systematic reviews and meta-analyses examining the clinical effectiveness of UHR programs have yielded inconclusive findings.[53] A review of seven meta-analyses on interventions targeting people identified as UHR found that the results did not adequately determine whether one intervention was favored over another or favored over a control condition.[53] Similarly, a 2019 Cochrane systematic review reported individual studies that did not find evidence in favor of one intervention over the alternative.[54] For example, there was no significant difference in outcomes when comparing a cognitive behavioral therapy (CBT) and risperidone combination treatment to CBT with a placebo.[54] It must be noted that the studies included in the review were of low quality and affected the ability to draw firm conclusions on the effectiveness of any of the treatment combinations over an alternative.[54] It should also be noted that control groups are not

completely untreated due to the ethical concerns in denying treatment to help-seeking and distressed individuals.[45] Therefore, when comparing interventions to these treated controls, the lack of a significant difference in outcomes could suggest equal effectiveness between groups instead of neither intervention being effective.[45] Despite these limitations, there are still studies supporting the clinical effectiveness of UHR programs. For example, in the same 2019 Cochrane review, researchers found that a combination of supportive therapy and CBT yielded fewer transitions to psychosis (8% in the intervention group), with twice as many transitions in the control group who were engaged in supportive therapy alone.[54] Similarly, omega-3 fatty acids have also shown some promising results.[54] As UHR programs continue to operate and expand world-wide, so too must efforts increase in establishing the true clinical effectiveness of UHR interventions and the corresponding economic impacts of these treatment strategies.

1.3.3 Limitations to the Ultra-High Risk Concept

The UHR concept itself is not without limitations. Firstly, prior research suggests that there is stigma associated with the UHR state,[7,17,55] which may contribute to reduced well-being.[55] However, when one study examined how stigma was perceived by UHR patients, compared to health professionals, the patients thought that the 'UHR' and 'APS' labels were both less stigmatizing and less likely to be a cause of fear or shame, compared to the opinions of mental health professionals.[56] In fact, UHR patients have previously expressed that the symptoms are more stigmatizing than the label itself.[57] Rather, it is the patients who had transitioned to FEP or had family members with psychosis who were more likely to find the term 'UHR' stigmatizing.[56] Interviews with UHR patients following treatment have shown that they find value in the care given by staff.[58]

Another limitation of the UHR concept is that high-quality studies on the effectiveness of UHR programs are still lacking.[54] As mentioned previously, it is challenging to examine the true clinical effectiveness of intervention on UHR populations when control groups cannot be completely untreated due to ethical concerns associated with denying treatment to help-seeking and distressed individuals.[45] Regardless, there is some promise in

improving outcomes among those at UHR for psychosis with certain interventions, such as omega-3 fatty acids and CBT with supportive therapy.[54]

A final limitation of the UHR concept is that there has been a global decline in the risk of conversion to FEP over time,[46] which may lead to concerns regarding whether treatment from UHR programs is necessary or being appropriately provided to patients. As mentioned previously, transition risks may be lower because of effective early treatment.[45] In addition, the ability of the UHR concept to predict transition to FEP is still reasonable given that other prodromal states – such as the 12% chance of transitioning to dementia from mild cognitive impairment – have comparable values.[42–44] The decline in transitions to FEP helped influence novel research concerning the creation of assessment tools that can better predict transitions and provide more personalized transition risk scores to better inform treatment plans for UHR symptoms that differ in severity.

1.4 Assessment Tools for the UHR State

Treating schizophrenia is costly to the health system, with productivity losses amounting to about $4.83 billion in 2004 in Canada alone.[13] UHR programs are beneficial in that they aim to treat patients exhibiting symptoms that precede a psychotic episode to potentially avoid the costs associated with the long-term course of psychotic illness and future negative outcomes. Of equal importance are the assessment tools used to determine who meets the UHR criteria and who will then have access to the scarce resources for treatment provided by the UHR programs.

UHR clinics may use a myriad of assessment tools to determine whether an individual meets the UHR criteria. Unfortunately, one of the limitations of the UHR concept is the low risk of transitioning to psychosis, which may impart additional costs from treating those who are unlikely to transition, despite being identified as UHR by these assessment tools.[42,46] Research in the field has sought to address this concern through the use of individualized risk calculators that distinguish between those among the UHR population who are more likely to transition to psychosis compared to less severe UHR cases.[22] Individualized risk calculators for psychosis provide a score that estimates the likelihood for a person to transition to psychosis based on several risk factors, which are usually

incorporated into a multivariable model.[59] Established UHR clinics could benefit from using risk scores to help inform the best way to allocate resources to maximize treatment effectiveness. Current practice in UHR clinics usually involves an initial assessment of help-seeking individuals using well-established instruments to identify the UHR state, such as CAARMS and SIPS, before a treatment plan is determined based on presumed need.

1.4.1 Current Assessment Tools to Identify the UHR State

Typically, in order to receive treatment at an UHR clinic, a help-seeking individual needs to meets the criteria for the UHR state. In North America, CAARMS and SIPS are commonly used in UHR clinics to determine whether a person meets said criteria.[17,49] In Montreal, the CAYR clinic uses CAARMS,[19] whereas the more local London PROSPECT clinic uses SIPS. A meta-analysis of the prognostic accuracy of these tools to predict transition to psychosis found the sensitivity of these prognostic tools – specifically, the proportion of people who transition to psychosis and test positive on the tool – to be very high [SIPS: 0.96 (95%CI = 0.88, 0.99) and CAARMS: 0.96 (95%CI = 0.82, 0.99)].[60] Unfortunately, the specificity – specifically, the proportion of people who do not transition to psychosis and test negative – was low for both tools [SIPS: 0.39 (95%CI = 0.32, 0.46) and CAARMS: 0.56 (95%CI = 0.38, 0.73)].[60] Although an ideal test would have both high sensitivity and specificity, these tools are considered to have excellent prognostic accuracy for conversion to psychosis if they are used by appropriately trained staff on a help-seeking population.[60]

1.4.2 The North American Prodrome Longitudinal Study (NAPLS) Individualized Risk Calculator

Though CAARMS and SIPS are highly sensitive tests, their low specificity could result in a high false positive rate, which means that there could be unnecessary treatment given to individuals who may not actually transition to psychosis. As a result, current research in early psychosis seeks to identify potential variables that may improve the prediction accuracy of transitioning to psychosis among people identified as UHR. Variables may include: index diagnosis, age, sex, and ethnicity.[51,61] Unfortunately, a previous systematic review examining risk prediction tools for transition to FEP found that many depended

on small sample sizes for model development and lacked external validation.[59] Yet, there are some risk prediction tools that show promise.

One risk prediction tool of interest is the North American Prodrome Longitudinal Study (NAPLS) individualized risk calculator, which is a tool that offers an individualized score between zero and one that corresponds with the probability of transitioning to psychosis.[22] This calculator is one of several research products derived from the NAPLS research study, which involves a cohort of 764 UHR participants and 280 healthy controls located in eight sites in North America – University of California Los Angeles (UCLA), Emory, Beth Israel Deaconess Medical Center, Zucker Hillside Hospital, University of North Carolina (UNC), University of California San Diego (UCSD), Calgary, and Yale.[22,62] This study follows the largest cohort of UHR participants to date.[62]

The risk predictions from the individualized calculator are modelled from a sample of the NAPLS cohort, consisting of 596 UHR patients followed over two years.[22] Participants were recruited between 2008 and 2013 and were followed up until they transitioned to psychosis or up to two years.[22] The NAPLS risk calculator is based on a cox proportional hazards regression model[22] and has since been externally validated in different populations.[63–65] In order to use the risk calculator, participants need to be identified as UHR by SIPS.[22] The NAPLS calculator determines transition risk based on the following eight variables that describe demographic, cognitive, and clinical characteristics: age, unusual thought content and suspiciousness, processing speed, verbal learning and memory functioning, social functioning, stressful life events, childhood traumas, and family history of psychotic disorder.[22]

The NAPLS risk calculator is currently being used for research purposes and shows excellent predictive capability.[22] Specifically, the Harrell C index score was used to determine how well each variable could distinguish between converters to psychosis and non-converters.[22] The index score ranges between 0.5 to 1, with higher values indicating better discrimination between converters and non-converters.[22] The NAPLS risk calculator (cox model) achieved an acceptable score of 0.714.[22] Similar to the results of

the internal performance assessment, external validation in an independent sample from the United States (U.S) found that this risk calculator continued to display acceptable predictive capability (Harrell C index score = .790).[64] Additional external validation in another U.S sample, published by Osborne et al,[63] determined that the calculator showed moderate discrimination ability based on the Area Under the Curve (AUC) score, which provides the same information as Harrell C (AUC = 0.71). One assumption that must be made when administering the NAPLS risk scores is that the sample must be inherently similar to the NAPLS (North American) cohort in which the original cox model was developed from.[22] Yet, even when used on a Chinese (Shanghai) population, the AUC score of the risk calculator was still fair (AUC = 0.631).[65] Overall, the individualized risk calculator shows potential to be used worldwide as long as future external validation studies both inside and outside of North America continue to show favorable results.

In the NAPLS cohort, more non-converters to psychosis were observed compared to converters among those with a risk score below 0.20.[22] In contrast, at a risk level of 0.20 or higher, there were more converters relative to non-converters in their respective risk categories.[22] These findings suggest that we could consider providing more intensive treatment plans to those in the higher risk categories (≥0.20 or ≥20% risk to transition), as they have more people transitioning to psychosis compared to lower risk categories (<0.20 or <20% risk to transition). Overall, there is potential to make future decisions on treatment allocation in UHR clinics based on the level of risk determined by the NAPLS calculator.[22] In fact, the NAPLS tool has been used in local settings at the London PROSPECT clinic to record NAPLS risk scores at baseline, but has not yet been used to guide clinical decision-making.

1.5 Thesis Rationale and Objectives

A recent 2019 review by Yung et al[18] suggested that there is value in UHR programs because they provide a service for people who are distressed and will likely develop negative outcomes during the course of the illness. With the appearance of UHR programs worldwide, and with limited budgets allocated to mental health research, it is of great importance to identify and address gaps in the literature regarding the economic value of these programs. Though literature is available examining the cost[66] and cost-

effectiveness[31] of early psychosis intervention programs (both FEP programs and UHR programs together), these are predominantly focused on FEP rather than UHR.[31] At this time, there is no recent systematic review examining UHR programs exclusively. Therefore, a comprehensive review of all current economic evaluations of UHR programs is required. Understanding the state of the literature on the economic value of UHR programs will inform future economic evaluations.

A further exploration of available tools to allocate care to those in need and minimize costs in UHR programs may benefit already established Canadian clinics, such as the Montreal CAYR clinic and the more local London PROSPECT clinic. Previous work by Cannon et al[22] has shown that those who score <0.20 on the NAPLS risk calculator (in the risk classes: 0.01-0.04, 0.05-0.09, 0.10-0.14, and 0.15-0.19) had more non-converters to psychosis compared to converters in their respective risk classes, while those who score values that are ≥0.20 (from risk classes: 0.20-0.24 to 0.60-0.64) show the opposite trend. Therefore, severe UHR cases may be categorized by scores that are ≥0.20 and less severe cases may be seen as scores that are <0.20. The NAPLS calculator may help maximize efficiency by allocating already scarce resources to severe cases at risk for transitioning to psychosis, while providing less severe cases with yearly risk assessments to monitor risk levels. The London PROSPECT clinic already uses the NAPLS calculator for research purposes, so understanding the cost-effectiveness of priority-based treatment based on NAPLS scores in a Canadian context may help inform the potential utility of these scores in a clinical setting.

1.5.1 Thesis Objectives

This thesis uses an integrated style format and is divided into two manuscripts, which are aligned with the thesis objectives:

1. The first objective was to conduct a systematic review of prior literature on economic evaluations of the UHR population.

2. The second objective was to create an economic model examining two different strategies to intervene on those at UHR for psychosis. We determine whether cost-effectiveness is impacted by either the use of a risk stratification strategy or a

‘treat all’ treatment strategy in the context of a UHR clinic. Specifically, the risk stratification treatment strategy will provide UHR treatment (active case management) to those who receive high risk scores through the NAPLS calculator (predicted risk to transition ≥20%), while less severe cases (predicted risk to transition <20%) are provided an annual risk assessment using the NAPLS calculator to monitor risk levels. The alternative treatment strategy provides UHR treatment to all patients, regardless of their risk level.

Chapter 2

2 Interventions for People at Ultra-High Risk for Psychosis: A Systematic Review of Economic Evaluations

2.1 Abstract

Aim: Psychotic disorders have long-term negative consequences for functioning and quality of life. Ultra-high risk (UHR) programs aim to identify and treat people during the prodromal period before their first psychotic episode. Though studies on the clinical effectiveness of treating prodromal symptoms in people at UHR for psychosis exist, no review has exclusively and comprehensively evaluated the economic impact of UHR programs. Our objective was to systematically review the literature on economic evaluations of UHR programs. **Methods:** We searched the Cochrane, EMBASE, MEDLINE, and PsycInfo electronic databases, in addition to grey literature, from inception to March 2020 to identify economic evaluations of UHR programs. We included all cost and cost-effectiveness studies of interventions for people at UHR. The data were synthesized qualitatively, and a risk of bias assessment was performed. **Results:** Of the 1,916 articles retrieved, six studies met our inclusion criteria. These included three cost analysis studies and three cost-effectiveness studies. Five studies were conducted from the health system perspective and the time horizon varied between six months and ten years. Only two reported quality-adjusted life-years (QALYs) as their outcome. Overall, all cost-effectiveness studies and one cost analysis suggested that UHR programs were cost-effective and cost saving, respectively. The risk of bias assessment suggested moderate levels of bias across all studies. **Conclusion:** Economic evaluations of UHR programs varied in terms of outcomes and length of follow-up; however, most studies found them to be cost-effective. Future studies would benefit from long-term evaluations of UHR programs and consistent valuation of outcomes.

Keywords

Cost-Benefit Analysis, Costs and Cost Analysis, Prodromal Symptoms, Psychotic Disorders, Schizophrenia

2.2 Introduction

Psychotic disorders are debilitating mental illnesses that are associated with negative effects on quality of life and functioning, especially when the course of illness is characterized by cycles of relapse and remission.[17,67] The pooled worldwide incidence of psychotic disorders is estimated to be about 26.6 cases per 100,000 person-years (95% CI 22.0–31.7).[10] Psychosis, a symptom of psychotic disorder, is often associated with comorbid disorders that further contribute to future negative health outcomes.[6,33] Examples of comorbid disorders include: substance use disorders, depression, and anxiety.[33] Given the fact that episodes of psychosis can have negative consequences not only for the affected person, but also for their family and society, treatment strategies have been devised to intervene early in the course of illness. These early psychosis intervention programs have been shown to be effective in treating people experiencing their first episode of psychosis in a variety of settings.[5,16,68] One systematic review concluded that early psychosis intervention programs are superior to treatment as usual for improving global functioning, symptom severity, and quality of life, while also lowering rates of relapse and all-cause treatment discontinuation.[5]

Given the effectiveness of early psychosis intervention programs, there has been increasing interest in intervening at an earlier stage, with an aim of preventing the first episode of psychosis, known as the ultra-high risk (UHR) paradigm. Those at UHR for psychosis have not yet experienced a first episode of psychosis, but are at an increased risk to do so based on genetic and psychometric evaluations[69] – these include the Comprehensive Assessment of At-Risk Mental States[35] and the Structured Interview of Prodromal Syndromes.[36] People at UHR for psychosis may experience depression and anxiety[33] and have substantial functional impairments.[69] As well, the young age at presentation – between 14 and 30 years – means there could be significant implications for social, educational, and professional development.[17] A systematic review on UHR programs suggests that treatment during this phase of illness may delay or prevent transition to first-episode psychosis, but limitations, such as the high attrition in this population, affect the strength of this effect.[7] Although there is evidence that UHR programs may be effective in reducing transition rates to psychosis, long-term

effectiveness may diminish once the program ends.[70] Furthermore, intervention among people at UHR for psychosis is especially challenging, given that only a small percentage will ultimately transition to a first episode of psychosis.[17,22] For instance, an estimated 10% and 37% of people identified as UHR will go on to transition to psychosis within six months and four years, respectively, though this number may vary depending on the study population and other methodological considerations.[40]

Despite these challenges, interventions for people identified as UHR for psychosis have been incorporated into clinical practice guidelines. For example, the European Psychiatric Association compared seven randomized controlled trials (RCT) examining UHR programs and found that the risk of conversion to psychosis was reduced by 56% at 12 months – these results have contributed to the recommendations for care in the UK and countries like Canada.[49,71] There has been a growing number of UHR programs worldwide, and with this proliferation comes debate regarding the cost-effectiveness of this prevention strategy. A systematic review from 2012 was inconclusive regarding whether UHR programs are cost-saving in different health care settings, and this review included both recent-onset psychosis and UHR populations.[66] A 2019 systematic review on early intervention for psychosis – also including both UHR and first-episode psychosis populations – found that these programs may be cost-effective during the program's duration. However, this review only included cost-effectiveness analyses, and did not focus exclusively on the UHR population.[31] An update to this evidence base that focuses exclusively on UHR populations and includes both partial and full economic evaluations is warranted in order to provide a comprehensive assessment of the potential economic impact of UHR programs.

The objective of this study was to conduct a systematic review of economic evaluation studies examining the cost and cost-effectiveness of interventions for people identified as UHR for psychosis.

2.3 Methods

We used the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines for this review, and the completed checklist can be found in the Supporting Information document (**Appendix A**).[72]

2.3.1 Information Sources and Search Strategy

We searched the Cochrane, EMBASE, MEDLINE, and PsycInfo databases from inception to September 2019 for economic evaluations of interventions targeted to the UHR population, and updated the search in March 2020. The types of studies examined included partial (cost analyses) and full (cost-effectiveness, cost-utility, and cost-benefit) economic evaluations.[73] We used a combination of keywords and controlled vocabulary adapted to each database using their unique syntax. These keywords included: (at risk mental state* OR ARMS* OR psychosis risk* OR psychosis prediction* OR psychosis onset* OR prodrom* OR prodromal psychosis* OR high risk* OR ultra-high risk* OR ultra high risk* OR UHR OR CHR OR clinical high risk* OR clinical-high risk* OR high clinical risk* OR referr* OR help seeking* OR progression to first-episode psychosis*) AND (economic evaluation* OR health economic* OR cost-effectiveness* OR cost-benefit* OR cost analysis) AND (Psychosis OR psychotic OR schizophreni* OR sever* mental ill* OR sever* mental disorder* OR psychiatric crisis* OR crises*). We also searched the grey literature, including the ProQuest database for dissertations and theses and the Scopus database. Forward and backward citation tracing of included studies was used to identify any articles missed by our electronic search strategy. Complete details on the keywords and controlled vocabulary used for all databases and grey literature sources can be found in Online Supplement 2 (**Appendix B**).

2.3.2 Eligibility Criteria and Study Screening

To be included in our systematic review, studies had to meet the following inclusion criteria: 1) The sample included people identified as “ultra-high risk (UHR)”, “clinical high risk (CHR)”, or “at risk mental state (ARMS)” for psychosis, with no restrictions on age, country of origin, or comorbidities at baseline; 2) The study conducted an economic evaluation relating to intervention in the UHR group using randomized trials, observational studies, simulated data, or a model; and 3) The study used an outcome

examining cost, quality-adjusted life years (QALY), incremental cost-effectiveness ratio (ICER), or a cost/effectiveness measure. There were no limits on follow-up time, but we restricted studies to the English language.

We excluded studies where the main focus of the economic evaluation was not on intervention in an UHR sample, studies that only briefly mentioned economic costs or outcomes, studies examining only clinical effectiveness, as well as reviews, abstracts, and other non-peer reviewed publications.

Level one screening (title and abstract) was conducted by one reviewer (O.M.O), and level two screening (full text) was conducted independently by two reviewers (O.M.O & T.L). Any disagreements concerning the inclusion of studies in the systematic review were resolved by discussion with a third reviewer (K.K.A).

2.3.3 Data Extraction and Risk of Bias Assessment

A standardized form was created and pilot tested to extract information from included articles. We extracted information on key variables, including: authors, year, country, type of economic evaluation, intervention and comparator details, sample size, cost measure, effectiveness measure, major model assumptions, time horizon, perspective, transition probabilities, results, and noteworthy limitations. Where data were missing, previous publications from the same study were accessed to fill in missing information. We used two risk of bias tools recommended by the Cochrane Collaboration: the Consensus on Health Economic Criteria (CHEC) checklist,[74] and the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) checklist, with the latter used specifically for the model-based evaluations, given that it provides additional criteria relevant to this type of study.[75] Risk of bias assessments were based only on the included article and supplementary documents, and did not incorporate information available from other referenced articles or protocols. For the CHEC checklist, studies were given numerical scores out of 19 (cost-effectiveness studies) or 15 (cost analyses). Model-based evaluations were similarly scored on the ISPOR checklist (out of 15). Assessments of the risk of bias were based on CHEC scores for trial-based evaluations, and both CHEC and ISPOR scores for model-based evaluations.

The data were extracted by one reviewer (O.M.O.) and verified by a second reviewer (T.L.). Two reviewers (O.M.O. & T.L.) completed the risk of bias assessments independently. Discrepancies in either the data extraction form or the risk of bias assessments were resolved between the reviewers, with a third reviewer (K.K.A.) involved where a consensus could not be reached.

2.3.4 Synthesis of Results

We synthesized the findings qualitatively. We were unable to conduct a meta-analysis due to heterogeneity in the context or setting of the economic evaluations, such as currency used and mental health care structure in the country, as well as inconsistent outcome measures across the studies.

2.4 Results

2.4.1 Study Selection

Our search strategy retrieved 1,438 articles from the electronic databases and 378 articles from grey literature. A total of 1,316 articles remained after the removal of duplicates. From this initial search, 20 articles were eligible for full-text screening. An updated search from September 2019 to March 2020 returned an additional 100 articles, one of which was also eligible for full-text screening. Of the 21 articles screened, 14 articles were excluded for the following reasons: duplicate populations (n=5); not UHR sample (n=3); review article (n=2); abstract only (n=2); only examines comorbidity (n=1); and inappropriate outcome (n=1). In total, six studies met our inclusion criteria for qualitative synthesis, with one unique study published across two reports.[20,76–81] Figure 2.1 provides a flowchart that outlines the selection process.

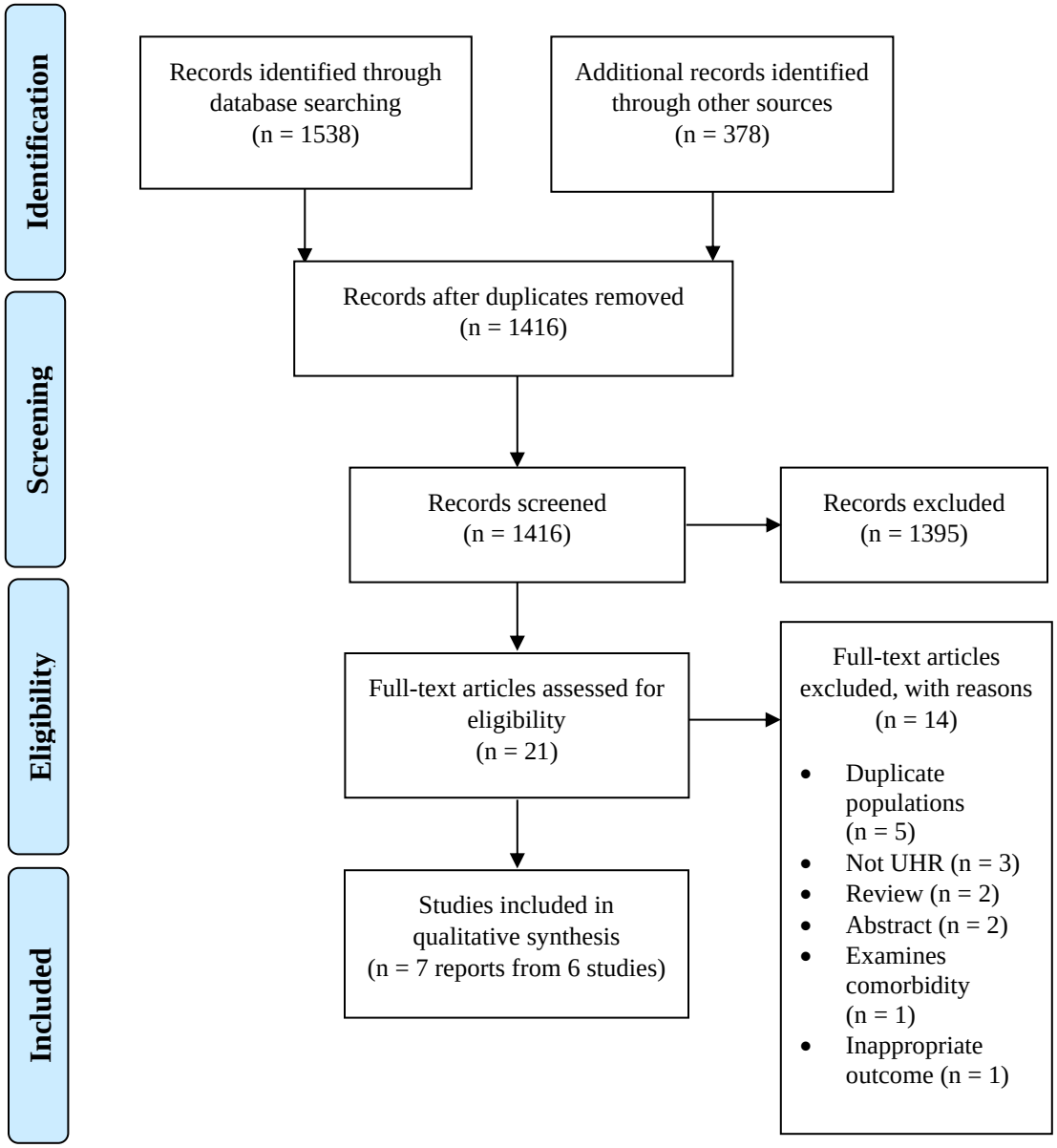

Figure 2.1 Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flowchart of included and excluded studies in the selection process[72]

2.4.2 Characteristics of the Studies and UHR Programs

The characteristics of included studies are summarized in Table 2.1. Four of the included studies were model-based economic evaluations, and the remainder were trial-based (n=2). Five studies compared UHR programs to routine care. The one exception examined whether a high- or low-intensity liaison between general practitioners and mental health services could improve referrals of people at UHR for psychosis to mental health services, relative to standard practice.[80]

The UHR programs were similar in that they often consisted of a combination of pharmacological, psychosocial, and other therapies. Cognitive behavioral therapy (CBT) was the most frequently used psychosocial intervention and was part of the UHR program in three of the included studies.[20,77,79,81] Cognitively oriented psychotherapy[76] – which was part of a specific preventive intervention program – and an unspecified psychosocial intervention[78] were also mentioned. Often, the UHR program would be comprised of routine care supplemented with CBT[20,79,81] or a specific preventive intervention program.[76] If pharmacological treatment plans were included in the UHR program, they typically involved a low-dose antipsychotic or an antidepressant.[77] Specific drugs mentioned included: risperidone (mean dose range: 0.5–2 mg)[76,78] or quetiapine (25–75 mg).[78] Additional supplementary therapies included supportive counselling and regular case management.[76] Routine care involved typical treatment plans common for non-psychotic Axis 1 or Axis 2 disorders,[20,79,81] no treatment specific to the UHR state,[77] needs-based treatment (supportive counselling, regular case management, and occasional medication),[76] or unspecified care at a Child and Adolescent Mental Health Service.[78]

2.4.3 Types of Economic Evaluations

Of the trial-based studies (n=2), one was a cost analysis and one conducted both a cost-effectiveness analysis and a cost-utility analysis. Of the model-based studies (n=4), two were cost analyses and two were cost-effectiveness analyses. Different cost perspectives were used, including a health system perspective (n=4), a societal perspective (n=1), and both a health system and societal perspective (n=1). The time horizon ranged from six months to ten years. Two of the studies were based on participants from the Dutch Early

Detection and Intervention Evaluation Trial in the Netherlands (EDIE-NL), and the remaining studies originated in either Australia (n=1) or the UK (n=3).

2.4.4 Cost and Effectiveness Measures

Cost measures varied between the studies. Costs examined from a health system perspective included: outpatient costs, inpatient costs, and medication costs.[76–78] The study by Perez et al[80] included liaison service costs, diagnostic costs, and costs for the referrals. The two studies that examined costs from a societal perspective included lost productivity costs in addition to the associated health system costs.[20,77] The authors of included studies used various strategies to deal with cost uncertainty, such as using a gamma distribution for cost values,[80,81] considering a societal perspective in addition to the health system perspective,[20] varying the cost values,[77,79,80] or using a bootstrap method to estimate a 95% confidence interval of the mean cost difference between the services.[76] In one case, no explicit strategy for dealing with cost uncertainty was described.[78]

Effectiveness measures varied greatly across the studies, with only two using QALYs (EQ-5D three-level version). However, it is important to note that these two studies were based on the same Dutch population – one unique study published across two reports compared short and long-term outcomes,[20,79] and the other modelled the population using a Markov model.[81] In instances where QALYs were not used, the number of true-positive cases identified[80] or averted transitions to psychosis[20,79] were the alternative effectiveness measures used.

Table 2.1 Summary of study characteristics

Author, Year	City/Country	Analysis Type	Study Design	Trial Design	Intervention	Control	Sample Size (Int., Ctrl)	Perspective	Time Horizon (Years)
Phillips et al,[76] 2009	Melbourne, Australia	Cost analysis	Trial	RCT	SPI	NBI	31, 28	Health system	0.5, 1, & 3
Valmaggia et al,[77] 2009	South London, UK	Cost analysis	Model	N/A	OASIS	CAU	N/A	Societal†	1 & 2
McCrone et al,[78] 2013	Teesside, England	Cost analysis	Model	N/A	EI	CAMHS	N/A	Health system	0.5
Ising et al,[20,79] (2015, 2017)	Netherlands	CEA & CUA	Trial	RCT	EDIE-NL	RC	95, 101	Health system‡	1.5
	Netherlands	CEA & CUA	Trial	RCT	EDIE-NL	RC	56, 57	Health system & societal	4
Perez et al,[80] 2015	Cambridgeshire & Peterborough, UK	CEA	Model	N/A	LEGs (high- and low-intensity)	PAU	N/A	Health system§	2
Wijnen et al,[81] 2019	Netherlands	CEA	Model	N/A	CBT	CAU	N/A	Health system	10

Abbreviations: CAMHS, Child and Adolescent Mental Health Services; CAU, Care as Usual; CBT, Cognitive Behavioral Therapy; CEA, Cost-effectiveness analysis; CUA, Cost utility analysis; EDIE-NL, Dutch Early Detection and Intervention Evaluation; EI, Early Intervention; LEGs, Liaison and Education in General Practice; NBI, Needs-Based Intervention; N/A, Not Applicable; OASIS, Outreach and Support in South London; PAU, Practice as Usual; RC, Routine Care; RCT, Randomized controlled trial; SPI, Specific Preventive Intervention.

†Analysis includes costs with and without lost production, but did not include social care costs, criminal justice costs, or unpaid care and time off work associated with families and friends.

‡Analysis included costs with and without productivity losses, but the authors explicitly stated that the perspective was a healthcare perspective.

§The perspective was not explicitly stated, but the health system perspective was assumed because productivity losses and criminal activity were not included.

2.4.5 Findings of Economic Evaluations of UHR Programs

A summary of the results of the economic evaluations are provided in Table 2.2. Three of the studies conducted cost analyses.[76–78] The UHR programs were not found to be cost saving in the studies by Phillips et al[76] and Valmaggia et al[77] over six and 12 months, respectively. However, Phillips et al[76] found the outpatient costs of the UHR program to be cost saving between 12 and 36 months, with a mean cost of AU$4,101.60 (SD: 8,334.00) compared to AU$10,423.10 (SD: 25,277.30) in a needs-based intervention. Despite this, the UHR program was not significantly different from a needs-based intervention in terms of inpatient, outpatient, or total costs over the entire study period (zero to 36 months). In contrast to these findings, McCrone et al[78] found the UHR programs to be associated with a cost savings of £4,814 per patient at six months, and Valmaggia et al[77] found a cost savings of £961 per patient at 24 months, compared to the comparison intervention. Overall, cost results were heterogeneous across the three studies.

Two of the included cost studies had a corresponding sensitivity analysis, which were generally robust to changes in parameter inputs. Valmaggia et al[77] conducted a one-way sensitivity analysis and determined that the cost savings of UHR programs over routine care were robust, but would revert if there was a large increase in the cost of care for the UHR program or a reduction in costs to treat those who had experienced a long duration of untreated psychosis. McCrone et al[78] conducted a sensitivity analysis by changing parameter values in their model by 50% in both directions and found that the preference for UHR programs would remain unless there were substantial changes in the number of admissions, length of stay, or cases of psychosis.

Three studies conducted cost-effectiveness analyses;[20,79–81] however, one study did not compare a UHR program to routine care.[80] Ising et al[20,79] conducted a cost-utility analysis using QALYs, whereas Wijnen et al[81] constructed a Markov model using the same UHR program and population used by Ising et al.[20,79] In terms of incremental costs, Ising et al[20,79] found that the UHR program was cost saving compared to routine care by about US$844 and US$5,777 over 18 months and four years, respectively. Wijnen et al[81] found

that the cost of the UHR program at a projected ten-year follow-up still resulted in savings of about €654 per patient. The QALYS were consistently larger in the UHR program compared to the alternative at 18 months, four years, and ten years. Finally, the bootstrap analyses of 2500 simulated ICERs found that CBT had a 26.2% probability of being more cost-effective than routine care at 18 months at a willingness to pay (WTP) of US$20,000, and a 92% probability at four years (WTP=US$24,560). One cost-effectiveness study did not examine a UHR program, but was included in the qualitative synthesis because it examined health care costs in the UHR population. Perez et al[80] found that within two years, a high-intensity liaison service between general practitioners and mental health services was more cost-effective compared to routine care – more true positive cases were referred, resulting in greater cost savings.

All cost-effectiveness studies conducted a sensitivity analysis. Ising et al[20,79] used last observation carried forward imputation, Perez et al[80] used a one-way sensitivity analysis, and Wijnen et al[81] used probabilistic sensitivity analysis. In all the analyses, the conclusions in the main analyses were found to be robust to changes in the parameters.

Table 2.2 Summary of study findings

Author, Year	Cost (currency)	Outcome (value)	Main Results	Sensitivity Analysis
Phillips et al,[76] 2009	1997 Australian dollar	N/A	The SPI group had higher mean outpatient costs compared to NBI during the 6 months of treatment [AU$2,584.8 (SD: 2,522.4) vs AU$1,084.0 (SD: 940.0)]. Over the second follow-up from 12-36 months, SPI had lower mean outpatient costs [AU$4,101.6 (SD: 8,334.0) vs AU$10,423.1 (SD: 25,277.3)]. Over 6 months and the 12-36 month follow-up, there were no differences in inpatient, pharmacological, and total costs.	N/A†
Valmaggia et al,[77] 2009	UK pound	N/A	Over 12 months, the OASIS intervention was £1,872 more expensive than CAU in terms of expected costs (£2,596 vs £724). When comparing total costs at 24 months, OASIS was cost saving by £961 (£4,396 for OASIS vs £5,357 for CAU).	One-way sensitivity analysis: The model loses favor of OASIS over CAU if there is a large change in costs of DUP (if below £3841) or if 12-month care costs rises in OASIS (above £3439).
McCrone et al,[78] 2013	UK pound	N/A	Over 6 months, EI had cost savings of £4,814 per patient compared to generic CAMHS (£13,186 for EI vs £18,000 for SC).	Changing parameter values by 50% in both directions: The model is robust, unless there are changes in admission (changing EI from 0.58 to 0.86 or SC from 0.58 to between 0.29 and 0.4 would make EI more expensive), length of stay (changing EI from 66% to excess of 97% to that of SC makes EI more expensive), or percentage of psychosis cases (over 67% for EI and less than 36% for SC makes EI more expensive).
Ising et al,[20,79] (2015, 2017)	2009 Euro, converted to US dollars	Averted transitions to psychosis & QALY	CEA: The incremental costs was US$844 in savings and the incremental effect (risk difference) was 0.13 over 18 months. With bootstrap analysis (2500 simulated ICERs), CBT had a 63.7% chance of being the dominant strategy compared to RC (i.e. less costly	Sensitivity analysis using Last Observation Carried Forward imputation: Both CEA and CUA sensitivity analyses were robust to the previous conclusions.

			and more effective). About 9.3% of simulated ICERs fell below a WTP of US$20,000. CUA: Incremental costs were unchanged (US$844 in savings). The incremental QALY was 0.03. Bootstrap analysis showed that CBT had a 52.3% chance of being the dominant strategy compared to RC. About 26.2% of simulated ICERs fell below a WTP of US$20,000.	
	2014 Euro, converted to US dollars	Averted transitions to psychosis & QALY	CEA: The incremental costs were US$5,777 in savings per participant. In the 4-year follow-up, the incremental effect (risk difference) was 0.122 in favor of CBT. With bootstrap analysis (2500 simulated ICERs), they found an 82.9% probability that CBT is dominant due to more averted transitions for less costs. The intervention had a 92% probability of being cost-effective at a WTP of US$20,000. CUA: More QALY gains occurred in CBT, though this is not significant (QALY difference = 0.164, $P = 0.28$). With bootstrap analysis, they found a 74.8% probability of CBT being dominant due to more QALY gains at a lower cost. The intervention had a 92% probability of being cost-effective at a WTP of US$24,560.	Sensitivity analysis using Last Observation Carried Forward imputation: Both the CEA and CUA sensitivity analyses were robust to the previous conclusions.
Perez et al,[80] 2015	UK pound	True-positive cases identified	The high-intensity intervention was more cost-effective. This practice referred the greatest number of true positives, where the mean number of true-positive cases identified per practice (SD) was 2.2 [1.7], followed by low-intensity at 1.1 [1.7], then PAU at 0.6 [0.85]. The total 2-year cost per practice found high-intensity practice to be the least costly (£26,785), followed by the more expensive low-intensity practice (£27,840), then PAU (£30,007).	One-way sensitivity analyses: The model was robust and rankings remained unchanged (high-intensity was dominant). Probabilistic sensitivity analysis: This analysis had similar results.
Wijnen et al,[81] 2019	2018 Euro	QALY	CBT is dominant over CAU with a per-patient increase of 0.06 QALYs and cost reduction of €654 per patient over 10 years.	Probabilistic sensitivity analysis: CBT is dominant.

Abbreviations: CAMHS, Child and Adolescent Mental Health Services; CAU, Care as Usual; CBT, Cognitive Behavioral Therapy; CEA, Cost-effectiveness analysis; CUA, Cost utility analysis; DUP, Duration of Untreated Psychosis; EI, Early Intervention; ICER, Incremental Cost-Effectiveness Ratio; NBI, Needs-Based Intervention; N/A, Not Applicable, OASIS, Outreach and Support in South London; PAU, Practice as Usual; QALY, Quality-Adjusted Life-Year; RC, Routine Care; SC, Standard Care; SD, Standard Deviation; SPI, Specific Preventive Intervention; WTP, Willingness-to-Pay.

†Bootstrapped 95% CI of mean difference between treatment groups.

2.4.6 Risk of Bias Assessment

The risk of bias scores from the CHEC checklist (**Table 2.3**) and ISPOR checklist (**Appendix C**) varied across all six studies. The methodological quality of the included economic evaluations was generally fair – four of the six included studies met at least 70% of the criteria in the CHEC checklist. The cost-effectiveness analyses performed better on the CHEC checklist compared to the cost analyses, and this trend was similarly seen in the trial-based studies compared to the model-based studies. Consistent limitations across all assessments were the lack of studies examining costs at the societal perspective, as well as a paucity of incremental analyses using ICERs. Discounting was completed in three of the studies, though the rationale provided in the studies that did not employ discounting (n=3) stated that the time horizon was too short. In terms of the ISPOR checklist for model-based evaluations, three of the four studies met at least 70% of the criteria. Nevertheless, it should be noted that the only study with a clear, formal process for developing the model was the Markov model by Wijnen et al,[81] as they had an expert panel to assess model validity and additional supporting documentation. Though there were moderate levels of bias across the model-based studies, a consistent trend was the lack of transparent internal verification and external validation. Overall, the risk of bias scores were similar between the CHEC and ISPOR checklists.

Table 2.3 Summary of the Consensus on Health Economic Criteria (CHEC) risk of bias assessment[74]

No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Author, Year	Is the study population clearly described?	Are competing alternatives clearly described?	Is a well-defined research question posed in answerable form?	Is the economic study design appropriate to the stated objective?	Is the chosen time horizon appropriate to include relevant costs and consequences?	Is the actual perspective chosen appropriate?	Are all important and relevant costs for each alternative identified?	Are all costs measured appropriately in physical units?	Are costs valued appropriately?	Are all important and relevant outcomes for each alternative identified?	Are all outcomes measured appropriately?	Are outcomes valued appropriately?	Is an incremental analysis of costs and outcomes of alternatives performed?	Are all future costs and outcomes discounted appropriately?	Are all important variables, whose values are uncertain, appropriately subjected to sensitivity analysis?	Do the conclusions follow from the data reported?	Does the study discuss the generalizability of the results to other settings and patient/ client groups?	Does the article indicate that there is no potential conflict of interest of study researcher(s) and funder(s)?	Are ethical and distributional issues discussed appropriately?
Phillips et al,[76] 2009	+	+	–	+	+	–	–	+	+	N/A	N/A	N/A	N/A	+	–	+	+	+	+
Valmaggia et al,[77] 2009	+	+	+	–	+	–	–	+	+	N/A	N/A	N/A	N/A	–	+	+	+	+	–
McCrone et al,[78] 2013	+	+	–	+	–	+	–	+	–	N/A	N/A	N/A	N/A	–	+	+	+	+	–
Ising et al,[79] 2015	+	+	–	+	–	+	–	+	+	+	+	+	+	+	+	+	+	+	+
Ising et al,[20] 2017	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Perez et al,[80] 2015	+	+	+	+	+	–	–	+	+	+	+	+	+	–	+	+	+	+	+
Wijnen et al,[81] 2019	–	+	–	+	+	+	–	+	+	+	+	+	+	+	+	+	+	+	+

Abbreviations: **+**, Yes; –, No; N/A, Not Applicable.

2.5 Discussion

In this systematic review of the literature on economic evaluations of interventions for people identified as UHR for psychosis, we found evidence to suggest that, from a health system perspective, UHR programs may be cost-effective compared to routine care. Although sensitivity analyses suggested that the cost-effectiveness findings were robust to changes in the parameters, evidence for cost savings were more equivocal. The cost analysis conducted by Valmaggia et al[77] showed evidence of cost savings over 24 months. However, Phillips et al[76] found that over 36 months, the total costs of the UHR program were not significantly different from the comparison intervention – though it was noted that the study was not suitably powered to make definitive conclusions. The short-term costs at six months returned similarly conflicting results. Phillips et al[76] found the outpatient costs for their UHR program to be more expensive than the alternative, whereas McCrone et al[78] found UHR programs to be superior in cost savings, and was the only cost study to support UHR programs completely. However, McCrone et al[78] only examined one reported time point (six months), and sensitivity analyses in both cost studies conducted by McCrone et al[78] and Valmaggia et al[77] revealed instances where UHR programs were not cost saving. Overall, all the above observations were derived from a small number of cost analyses (n=3) and cost-effectiveness analyses (n=2) from different health systems – the UK, the Netherlands, and Australia – and may not be generalizable across settings. More specifically, data used in the cost-effectiveness analyses originated from the same Dutch trial (EDIE-NL), which may explain the similar results across the studies. Although the cost-effectiveness studies generally adhered to best practices for economic evaluations, the risk of bias assessments found moderate levels of bias across the cost studies. Finally, though there is value in cost analyses, it is preferable that studies be conducted as full economic evaluations (cost-effectiveness, cost-benefit, or cost-utility analyses) comparing UHR programs to routine care to better inform decision-making.[82]

Overall, caution must be exercised when interpreting these findings due to several limitations of the included studies. First, future economic evaluations would benefit from consistent valuation of outcomes and long-term assessments of UHR programs. The

current review found that there were only two studies that used QALYs, which is the preferred outcome measure in health economic evaluations.[82] Only one study, a cost-effectiveness study by Wijnen et al,[81] examined a ten-year time horizon. The short time horizons, equivocal results on cost savings, and prior research suggesting UHR programs are effective only during the program's duration,[70] warrant the need for more economic evaluations examining long-term cost-effectiveness. Although, the risk for transition to psychosis is the most prominent within two years of entry into an UHR clinic, there is still a risk of transition for up to ten years,[83] further highlighting the need for longer time horizons. Another limitation is the small sample size of most included studies, which varied among trial-based evaluations (n=59 to 196). Smaller studies may have large standard deviations and results can be influenced by outliers. Although we could not assess outliers based on published results, Phillips et al[76] (n=59) mentioned that one or two participants in the comparison intervention had higher than expected outpatient costs during the 12 to 36 month follow-up. Another limitation to consider is that the costing perspective across all studies was generally a health system perspective. This means that additional costs associated with psychosis that are relevant to the societal perspective, such as encounters with the criminal justice system,[84] are not included. In addition, UHR programs and routine care are not standardized across different countries and contexts, thereby limiting our ability to comment on which interventions are more cost-effective within the umbrella of UHR programs. One of the included studies did not conduct a sensitivity analysis, and in instances where sensitivity analyses were done, they varied among the individual studies. Therefore, in order to generalize these findings, economic evaluations need to be done using consistent and robust methodology, and generalizability across health care jurisdictions should be explicitly assessed.

A similar systematic review by Aceituno et al[31] assessed the cost-effectiveness of early intervention programs for psychosis, but was limited to cost-effectiveness studies, and did not exclusively examine UHR programs. As a result, their review identified only two of our included studies.[20,79,80] Similar to our findings, their review found early psychosis intervention services to be potentially cost-effective, though firm conclusions could not be drawn due to the high degree of heterogeneity and variations in methodology across the economic evaluations. The previously stated methodological limitations contributed

to this heterogeneity, in addition to differences in outcome valuation, and differences in the countries and study populations. They note that it was unclear whether these differences were due to methodological or reporting errors. An older systematic review by Amos et al[66] examined recent-onset psychosis and UHR populations, including both partial and full economic evaluations. They only identified two out of six studies in the current review.[76,77] Though the study by Valmaggia et al[77] was praised for a thorough sensitivity analysis and Phillips et al[76] was similarly acknowledged for sourcing costs from RCT data believed to have low evidence of bias, final conclusions echoed sentiments similar to Aceituno et al[31] and the current review. In line with the current review, Aceituno et al[31] and Amos et al[66] call for future studies to adhere to consistent, transparent guidelines available for economic evaluations.

2.5.1 Limitations

There are a number of limitations to this systematic review. It was not possible to conduct a meta-analysis due to several key differences across the studies. Examples included the types of economic evaluations conducted and the types of effectiveness measures used. These differences affected our ability to draw firm conclusions on identified trends. We limited our search to English language publications, and as a result, there may be publication bias, as negative studies are more frequently published in non-English language journals.[85] We made efforts to retrieve data from grey literature sources to mitigate the effects of publication bias, whereby economic evaluations supporting the cost-effectiveness of UHR programs are more likely to be published. However, there is still a possibility that the trends we observed in this review may be due to this phenomenon.

2.5.2 Implications for Future Research

UHR programs provide an essential service to people who may be distressed and symptomatic[18] and there is some evidence to suggest the cost-effectiveness of these programs. There are a number of steps that may be taken to strengthen future research. For instance, increasing the number of economic evaluations conducted alongside prospective trials examining the long-term health outcomes of people at UHR for psychosis would result in more comprehensive assessments of the economic value of

UHR programs. In addition, incorporating information from other sectors, such as social services or criminal justice, could enrich cost data so that it may better reflect the societal costs. Finally, health outcomes that can be valued consistently and compared easily across evaluations of different interventions may help inform decision making.

2.5.3 Conclusions

Our qualitative synthesis of economic evaluations of UHR programs suggests that intervening in this population may offer value for money. Specifically, all included cost-effectiveness studies supported the UHR programs, but only one cost analysis study supported the cost savings of this program. Yet, caution must be taken when drawing firm conclusions given that different health care systems were examined, QALYs were used sparingly, and there was a limited number of cost-effectiveness studies based on RCTs. Although the review suggests that UHR programs may be cost-effective, this evidence should be interpreted in light of the heterogeneity of populations across studies and the lack of consensus on what interventions should be offered through UHR programs. Future economic evaluations of UHR programs would benefit from long-term assessments of these services, consistent valuation of outcomes, standardization of UHR programs across jurisdictions and contexts, and the inclusion of costs from the societal perspective to better inform public decision-making.

2.6 Acknowledgements

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2.7 Conflicts of Interest

K.K.A, O.M.O, T.L, and S.A have no conflicts of interest to disclose. L.P reports personal fees from Otsuka Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Sunovion and Otsuka Canada outside the submitted work.

Chapter 3

3 Risk Stratification for Treatment Decisions in People at Ultra-High Risk for Psychosis: A Cost-Effectiveness Analysis

3.1 Abstract

Aim: Current clinical practice at ultra-high risk (UHR) for psychosis clinics is to treat all patients at risk of converting to first-episode psychosis (FEP), regardless of their level of risk. Our objective was to evaluate the cost-effectiveness of using risk stratification for treatment decisions in an UHR program, based on the probability of converting to FEP, compared to the standard 'treat all' strategy. **Methods:** We developed a decision tree followed by a Markov model to evaluate risk stratification for treatment decisions compared to the standard 'treat all' practice in an UHR program. Health states included: Not UHR, UHR (<20% risk and ≥20% risk of developing FEP based on the North American Prodrome Longitudinal Study risk calculator), FEP, Remission, Post-FEP, and Death. A Canadian health system perspective and 15-year time horizon was used. Transition probabilities were informed predominantly by the published literature and cost data were based on a Canadian UHR clinic. Robustness of the results were tested using scenario and sensitivity analyses. **Results:** The incremental cost-effectiveness ratio (ICER) for risk stratification, compared to treating all, was $15,466 per quality-adjusted life-year (QALY) and lies in the southwest quadrant of a cost-effectiveness plane. This implies that risk stratification is a cost-saving strategy (saving $1,193 per person) and has a health opportunity cost of 0.077 QALYs. The decision to adopt or reject risk stratification depends on the willingness-to-accept (WTA) threshold. Sensitivity analyses suggest trends were generally consistent with the main results. **Conclusions:** Treatment decisions based on risk stratification offers lower costs and lower QALYs relative to the standard practice of treating all UHR patients. The ICER estimate suggests that the standard 'treat all' strategy is likely to be cost-effective. Future studies could consider how different treatment intensities based on conversion risk may impact outcomes and cost-effectiveness.

Keywords

Cost-Benefit Analysis, Costs and Cost Analysis, Health Care Costs, Prodromal Symptoms, Psychotic Disorders, Schizophrenia, Quality-Adjusted Life Years

3.2 Introduction

Despite the relatively low prevalence of psychotic disorders, the global economic burden of schizophrenia ranges between $94 million to $102 billion annually.[12] Though cost varies depending on the type of health care system, resource use, and other factors, Canadian estimates approach the billions as well – a 2004 study estimated $4.83 billion in productivity losses alone.[12,13] In Canada, the high cost of psychotic disorders such as schizophrenia can be partially explained by the higher rates of service use – particularly high cost services such as the emergency department (ED), inpatient unit, and long-term prescription medications – relative to mood, anxiety, and substance use disorders.[86]

Psychotic disorders typically emerge in adolescence and early adulthood, and manifest symptoms that contribute to long-lasting negative outcomes, such as ongoing disability and functional impairment, repeated hospitalizations, and unemployment.[8,12,86] Thus, there is a great need to attempt treatment strategies that aim to mitigate symptoms or prevent the disorder entirely. An ideal clinical stage to target for such interventions is the ultra-high risk (UHR) for psychosis state, which precedes the first episode of psychosis (FEP), and is characterized by increasing subthreshold psychotic symptoms and a decline in functioning.[6,17] Early psychosis programs have aimed to provide treatment at the UHR stage and have seen some success.[7] One challenge to intervention in the UHR state is that only a fraction of people will convert to full psychotic disorder,[21] with estimates ranging from 10% at six months to 37% over four years.[40] Assessment tools, such as the Structured Interview of Prodromal Syndromes (SIPS),[36] are commonly used to identify people who meet the UHR criteria.[17,49] However, these tools may also identify people with a very low probability of conversion, which may lead to treatment of people whose symptoms are mild and transient or not clinically significant,[42,46] and therefore limit the resources available to treat more severe cases. In particular, although SIPS has a high

sensitivity (96%), the low specificity (39%) will identify many who will not convert, despite screening positive.[60] With clinicians facing constant pressure to make treatment decisions that minimize resource use and maximize health care benefits,[87] and with finite resources available, strategies are now being proposed that consider these factors in the development of clinical practice guidelines.[87,88]

Psychosis prediction tools aim to quantify the level of risk for conversion to psychosis within the UHR population.[59] One such tool is the North American Prodrome Longitudinal Study (NAPLS) risk calculator, which estimates the probability of conversion to psychosis for people identified as UHR by SIPS.[22] Published work exists examining the conversion outcomes of people with different NAPLS risk scores[22] and the calculator has shown acceptable results in external validation studies.[63–65] The NAPLS calculator may help to optimize resource allocation through the adoption of a treatment strategy based on risk stratification, whereby treatment of prodromal symptoms with an aim of preventing conversion to FEP is limited to people at a sufficiently high risk to convert to psychotic disorder. In the original NAPLS study, those with less than 20% risk for conversion had a larger proportion of non-converters compared to converters, whereas those above this risk class had far more converters compared to non-converters.[22] Prioritizing UHR treatment to those more likely to convert to psychosis (≥20% risk) may be potentially more cost-effective. To our knowledge, the NAPLS scores are currently only being used for research purposes in Canada, but modeling the economic impact of using these risk scores for treatment decisions may inform the potential utility of risk stratification in this population.

3.2.1 Study Objectives

We sought to estimate the cost-effectiveness of using a risk stratification approach for treatment decisions in a UHR program, based on the probability of conversion to psychosis, compared to the standard ‘treat all’ strategy. The analysis was completed from the Canadian health system perspective and assessed over a 15-year time horizon.

3.3 Methods

This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines.[89] The completed checklist can be found in Appendix E.

3.3.1 Model Structure

A decision analytical model was created in Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) examining the 15-year cost-effectiveness of a risk stratification for UHR treatment strategy based on the NAPLS calculator (risk stratification), compared to treating all people identified as UHR for psychosis (standard 'treat all' practice). We used the Canadian health system perspective.

We developed a decision tree model and modified an existing Markov model (**Figure 3.1**). The cohort began in the decision tree (one-year time horizon) before entering the Markov model (14-year time horizon with an annual cycle) and consisted of 1000 UHR patients identified using the SIPS interview. We used a 15-year time horizon because recent estimates suggest that conversion to psychosis can occur up to 15 years after baseline assessments.[90] The time horizon was also sufficient enough to ensure that most people in the model had left the UHR states at the end of the 15 years – less than 2% of the cohort remained in both UHR states (<20% UHR and >20% UHR combined) and in both treatment arms. We assumed that people in the cohort were 19 years of age based on the mean age of the sample in the original NAPLS calculator study.[22] For the risk stratification arm of our model, people who scored <20% on the NAPLS calculator received an annual follow-up with a psychiatrist (i.e. annual risk assessment), but no further treatment for two years, whereas those who scored ≥20% on the calculator received two years of treatment through the UHR program (i.e. UHR treatment). In the standard 'treat all' practice arm of our model, two years of UHR treatment was provided to everyone, regardless of their NAPLS risk score. Those who were treated followed a two-year treatment plan because it is the standard of care in Canadian UHR programs.[19] We assumed that people transitioned to general mental health services after two-years of UHR treatment; however, if conversion to psychosis occurred during the first two years

of UHR treatment or at any point in the long-term follow-up, these people would receive treatment for psychosis from an early psychosis intervention program.

After one year in the decision tree (where people either converted to FEP or stayed UHR), the cohort entered the Markov model. The Markov model was based on PsyMod – a 2019 model created by Wijnen and colleagues[81] that was used to evaluate the cost-effectiveness of cognitive behavioral therapy (CBT) compared to treatment as usual in a Dutch UHR population. PsyMod did not evaluate risk stratification for treatment decisions, but instead assumed that everyone in the UHR state would be treated.[20,81] We modified PsyMod to evaluate the longer-term cost and health consequences of the risk stratification treatment approach. The PsyMod model was obtained from the authors, who also provided advice on model parameters. The original model structure and parameter values are publicly available and described elsewhere.[81] The novel aspects of our analysis included: the addition of a decision tree model that stratified UHR patients by risk, the use of Canadian costs and probabilities (where available), and the shift in focus from the evaluation of treatment effectiveness for the UHR population to treatment allocation strategies.

To evaluate longer-term costs and outcomes, participants entered the Markov model in one of the three states from the decision tree: FEP, <20% UHR (those assessed as <20% risk for psychosis but did not convert to FEP) and ≥20% UHR (those assessed as ≥20% risk for psychosis but did not convert to FEP). In subsequent cycles, participants would either stay in the same state or transition to one of the following Markov states: 'Not UHR' (those who no longer meet the criteria for the UHR state), Remission (total remission from FEP based on consensus criteria from Andreason and colleagues),[91] Post-FEP (incomplete remission following FEP), or Death. Transition to post-FEP or remission was only possible after having experienced FEP. Transition to 'Not UHR' was only possible after being either <20% UHR or ≥20% UHR. Figure 3.1 shows the decision tree with the modified Markov model and the state-transition diagram for the Markov model.

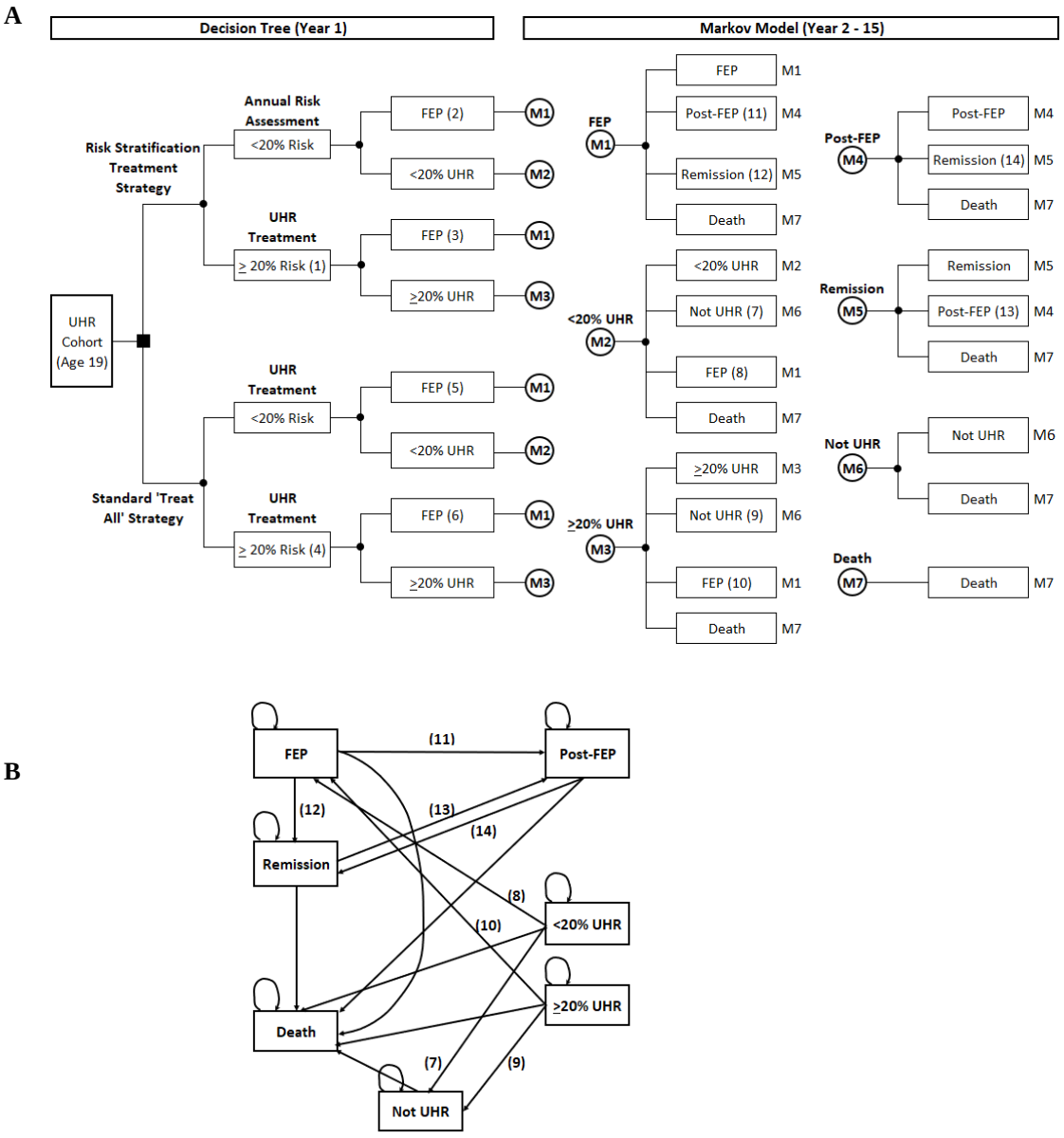

Figure 3.1 The (A) decision tree and Markov model and (B) state-transition diagram. The Markov model is adapted from 'PsyMod' in the study by Wijnen and collegues[81]

The numbers in the decision tree and Markov model correspond to the 'Transition Number' in Table 3.1. 'M' represents the Markov node. UHR participants begin in the (A) decision tree for one year, then enter the Markov model in the following year (M1-M3). In the third year and until the end of the Markov time horizon (14 years total), people may enter the remaining states (M1-M7). The Markov model has a one-year cycle, so people move between states once a year. The health states are defined as: <20% ultra-high risk for psychosis (<20% UHR), ≥20% ultra-high risk for psychosis (≥20% UHR), recovery from the ultra-high risk state (Not UHR), First-episode psychosis (FEP), Remission from FEP (Remission), incomplete remission from FEP (Post-FEP), and Death.

3.3.2 Transition Probabilities

Transition probabilities for the decision tree and Markov model were derived predominately from the NAPLS literature. Where parameter data could not be obtained from the NAPLS study, Canadian values – where possible – were instead retrieved from a focused search strategy in MEDLINE (**Appendix F**) and by handsearching references.

The transition probabilities for conversion to the FEP state differed based on whether one received treatment for UHR or not. To specify, the latter group only received an annual risk assessment with the NAPLS calculator. For those receiving UHR treatment, the transition probability to FEP was based on the NAPLS study in which participants were given risk scores and received a mix of medication or therapy.[22] Since the NAPLS study reported two-year transition probabilities, we converted them to annual probabilities to align with the model cycle length. Annual probabilities were estimated by first converting the two-year probabilities to an instantaneous event rate, and then to a one-year transition probability. The following formulas were used and assumed that the events had a constant rate:

$$r = \frac{-[\ln(1-p)]}{t}$$

$$p = 1 - \exp\{-rt\}$$

where r is the rate, p is the probability, and t is the time period of interest.[92]

For individuals not receiving UHR treatment, the annual transition probability for conversion to FEP was calculated by adjusting the probability in the UHR treatment group. This adjustment is based on a previous meta-analysis by van der Gaag and collegues.[93] The meta-analysis reported a relative risk (RR) of 0.463 (95% CI = 0.33–0.64) at 12 months to convert to psychosis for those enrolled in early psychosis intervention (generally medication and CBT) compared to a less intensive, control condition (generally placebo and monitoring or placebo and supportive therapy).[93] The conversion risk in the ‘not treated’ group was calculated by dividing the probability of the

treated group to convert to psychosis by the RR (**Appendix G**, Section G.1.1). It has also been found that, in the long-term, annual probabilities to convert to psychosis decreases within the UHR population.[90,93,94] There is little known about how this applies to subpopulations of the UHR group that are risk-stratified by NAPLS scores. Therefore, the conservative long-term assumption was made that the risk to convert to psychosis remained unchanged over time (3+ years) in both groups. Details on the probabilities to convert to psychosis in both treatment arms are available in Table 3.1, but are also available in the Appendix (**Appendix G**, Table G.1). Sensitivity analyses on how results would change with different values for conversion to psychosis are presented in the Appendix (**Appendix G**, Figure G.1), and are presented in the results (see Section 3.4.4).

Age-dependent mortality probabilities for the general population were derived from Statistics Canada.[95] There is evidence of higher mortality among those experiencing psychotic disorders.[96] The additional mortality may be partially attributed to increased risk of suicide, but there are also factors such as physical comorbidities, and antipsychotic medication use to consider.[96–99] Therefore, to provide mortality estimates for those in the FEP and Post-FEP states, we applied age-specific standardized mortality ratios from an Ontario FEP population (in press)[100] to the general population mortality probabilities (**Appendix G**, Table G.2). The focused MEDLINE search did not return any Canadian mortality probabilities for the UHR states. Therefore, the general population mortality was used on the UHR groups. There is also past precedent of using general mortality estimates for the UHR group in the original PsyMod publication.[81] The transition probabilities used in the model and their sources can be found in Table 3.1.

Table 3.1 Annual transition probabilities for the decision tree and Markov model

Transition Number	State Transition	Parameter	Distribution	Source†
Decision Tree				
Risk Stratification Treatment Strategy				
1	Proportion who score ≥20% upon entry into the UHR clinic	0.349	Beta	Cannon et al,[22] 2016
2	Year 1: <20% UHR State to FEP State (Annual Risk Assessment)	0.077	Lognormal	Cannon et al,[22] 2016 & van der Gaag et al,[93] 2013
3	≥20% UHR State to FEP State (UHR Treatment)	0.148	Beta	Cannon et al,[22] 2016
Standard 'Treat All' Strategy				
4	Proportion who score ≥20% upon entry into the UHR clinic	0.349	Beta	Cannon et al,[22] 2016
5	Year 1: <20% UHR State to FEP State (UHR Treatment)	0.036	Beta	Cannon et al,[22] 2016
6	≥20% UHR State to FEP State (UHR Treatment)	0.148	Beta	Cannon et al,[22] 2016
Markov Model				
Risk Stratification Treatment Strategy & Standard 'Treat All' Strategy				
2	Year 2: <20% UHR State to FEP State (Annual Risk Assessment)	0.056	Estimate‡	Estimate
2	Year 3+: <20% UHR State to FEP State (Annual Risk Assessment)	0.036	Beta	Estimate
5	Year 2+: <20% UHR State to FEP State (UHR Treatment)	0.036	Beta	Cannon et al,[22] 2016
7	<20% UHR State to Not UHR State	0.184	Beta	Addington et al,[101] 2019
8	<20% UHR State to FEP State (General Mental Health Services)	0.036	Beta	Cannon et al,[22] 2016 & van der Gaag et al,[93] 2013
9	≥20% UHR State to Not UHR State	0.184	Beta	Addington et al,[101] 2019
10	≥20% UHR State to FEP State (General Mental Health Services)	0.148	Beta	Cannon et al,[22] 2016 & van der Gaag et al,[93] 2013
11	FEP State to Post-FEP State	0.678	Dirichlet	Jordan et al,[102] 2014
12	FEP State to Remission State	0.300	Dirichlet	Jordan et al,[102] 2014
13	Remission State to Post-FEP State	0.496	Dirichlet	Wijnen et al,[81] 2019
14	Post-FEP State to Remission State	0.350	Dirichlet	Wijnen et al,[81] 2019

Abbreviations: FEP, First Episode Psychosis; UHR, Ultra-High Risk.
Note that mortality is not included in this table because it is an age-dependent transition probability. In addition, the probability of staying in the same state (ex. FEP to FEP) was not included in this table because it is always equal to "1- (all other probabilities)"
†Assumptions for the sources can be found in Appendix G.
‡The distribution is the average between the distribution from Transition Number 2 (Year 1) and Transition Number 2 (Year 3).

3.3.3 Service Use

Information on standard of UHR care and service use was based on expert opinion from the PROdromal Symptoms of Psychosis – Early identifiCation and Treatment (PROSPECT) clinic in London, Ontario and generally followed the Canadian UHR treatment guidelines (**Table 3.2**).[49,103] The risk stratification treatment strategy provided an annual risk assessment to those under the risk score cutoff (<20% risk to convert to FEP). Annual risk assessment involved an annual one-hour session with a psychiatrist per person. In this session, the psychiatrist would use the NAPLS calculator to reassess the predicted risk score to convert to FEP. People with scores equal to or above the risk cutoff (≥20% risk to convert to FEP), and everyone in the standard 'treat all' strategy, would receive UHR treatment. UHR treatment involved case monitoring by a nurse, visits with a psychiatrist as needed, psychotherapy by a psychologist, vocational services by a counsellor, and antidepressant medication prescribed by a psychiatrist. All services were provided as individual sessions, with the exception of psychotherapy, which was provided in groups of ten. We assumed 12 one-hour sessions annually for case monitoring and psychotherapy, sessions annually with a psychiatrist as needed, and four one-hour sessions annually with vocational support services. We also assumed that UHR patients would be prescribed fluoxetine (40 mg/day). This intensive UHR treatment protocol was provided for two years, at which point, patients would then receive care from general mental health services, provided that they did not convert to psychosis and require support from an FEP program. In these general mental health care services, people who were UHR and had risk scores at or above the cutoff received out-patient support from a psychiatrist, whereas those below this cutoff received care from a family physician. Finally, patients who recovered from the UHR state saw a psychiatrist four times a year. Table 3.2 provides further information on sessions and duration.

Details regarding FEP service use was obtained from expert opinion from the PROSPECT clinic, unless otherwise specified. Specifically, people who converted to FEP were assumed to receive the same 'UHR treatment' strategy outlined above in the context of an early psychosis intervention program, but were additionally prescribed antipsychotic medication (risperidone, 4 mg/day) or antipsychotic injections, and had

their lipid and glucose levels monitored biannually. Finally, those in remission from FEP received eight sessions annually with a psychiatrist.

Table 3.2 Service use and cost of services

Service	Service Provider	Patients per Session	Annual Frequency of Service	Length of each session (hours)	Annual Salary (Median)	Unit cost ($)	Annual Mean Cost ($)	Source†
NAPLS Assessment								
Equipment Cost of NAPLS Calculator	N/A	N/A	N/A	N/A	N/A	0.00	0.00	https://riskcalc.org/napls/
Consultation Using NAPLS Risk Calculator	Psychiatrist	1	1	1	FFS	216	216	Ontario SOB – (pg. A155 & A157)
Active Case Management								
UHR, FEP, and Post-FEP								
Case Monitoring	RPN	1	12	1	$56,000	34	405	Calculated from salary
Visits with a Psychiatrist	Psychiatrist	1	8	0.5	FFS	87	695	Ontario SOB – (pg. A162)
Psychotherapy (ABC-Coping Skills Group)	Psychologist	10	12	1	$110,500	67	80	Calculated from salary
Vocational Support	Counsellor	1	4	1	$46,000	28	111	Calculated from salary
FEP and Post-FEP								
Metabolic Monitoring (Glucose and Lipid Levels)	N/A	1	2	N/A	FFS	39	77	Ontario SOB – (pg. J68 and J64)
Pharmacotherapy								
UHR and 1/3 of FEP and Post-FEP								
Depression Medication – Fluoxetine 40 mg/day	N/A	1	365	N/A	N/A	20 mg = 0.331 (x2 pills)	242	Ontario drug formulary (https://www.formulary.health.gov.on.ca/formulary/)
1/2 FEP and Post-FEP								
Antipsychotic Medication – Risperidone 4 mg/day	N/A	1	365	N/A	N/A	2	746	Ontario drug formulary (https://www.formulary.health.gov.on.ca/formulary/)

1/2 FEP								
Antipsychotic Injection – Paliperidone palmitate (Invega Sustenna) 150mg/month	N/A	1	9	N/A	N/A	636	2861	Ontario drug formulary (https://www.formulary.health.gov.on.ca/formulary/)
Consultations for UHR and FEP Prescriptions								
Initial Consultation	Psychiatrist	1	1	1	FFS	216	216	Ontario SOB – (pg. A155 & A157)
Repeat Consultation	Psychiatrist	1	4	0.5	FFS	87	347	Ontario SOB – (pg. A162)
Injection Nurse (FEP)	RPN	1	9	0.5	$56,000	34	152	Calculated from salary
General Mental Health Services								
<20% UHR								
Pharmacotherapy offered by a GP	GP	1	1	0.5	FFS	68	68	Ontario SOB – (pg. A19)
≥20% UHR								
Referral by a GP	GP	1	1	0.5	FFS	68	68	Ontario SOB – (pg. A19)
Initial Consultation for Pharmacotherapy Prescription	Psychiatrist	1	1	1	FFS	216	216	Ontario SOB - (pg. A155 & A157)
Repeat Consultation	Psychiatrist	1	1	0.5	FFS	87	87	Ontario SOB – (pg. A162)
Not UHR								
Initial Consultation	Psychiatrist	1	1	1	FFS	216	216	Ontario SOB – (pg. A155 & A157)
Repeat Consultation	Psychiatrist	1	4	0.5	FFS	87	347	Ontario SOB – (pg. A162)
Remission								
Initial Consultation	Psychiatrist	1	1	1	FFS	216	216	Ontario SOB – (pg. A155 & A157)
Repeat Consultation	Psychiatrist	1	8	0.5	FFS	87	695	Ontario SOB – (pg. A162)

Abbreviations: ABC, Adversity Belief Consequence; FEP, First Episode Psychosis; FFS, Fee-for-service; GP, General Practitioner; NAPLS, North American Prodrome Longitudinal Study; RPN, Registered Practical Nurse; SOB, Schedule of Benefits; UHR, Ultra-High Risk.

[†]Service use was assumed to be expert opinion from the London (PROSPECT) clinic unless otherwise specified.

Hospitalizations and ED visits were included for the UHR, FEP, and Post-FEP states in Table 3.3, with details on additional assumptions in the Appendix (**Appendix G**, Table G.3). Service use for ED visits and hospitalizations were informed from the PROSPECT clinic (L.P) or additional Canadian publications.[16,104] Only some people (see Table 3.3, "Proportion in State") used these services. For ED visits and hospitalizations, the <20% UHR group was assumed to use half the services of the ≥20% UHR group. Changes to this assumption were addressed in a scenario analysis. Total annual costs for each person (UHR or FEP) using ED services and hospitalization services were about $483 and $9819, respectively. These values were derived from a 2016 Ontario study by de Oliveira and colleagues, which estimated net costs for service use in individuals with chronic schizophrenia.[14] These annual costs may not accurately reflect the costs for people identified as UHR or with FEP, but uncertainty was addressed using sensitivity analyses.

Table 3.3 Service use and cost of hospitalization and the emergency department

Service	Service Use (Proportion in State)†	Annual Cost ($) (per person per Year)	Sources
ED Visits			
Risk Stratification Strategy			
<20% UHR and ≥20% UHR	0.122	483	Service Use: Expert Opinion (L.P) Cost: de Oliveira et al,[14] 2016
UHR Treatment Strategy			
<20% UHR	0.061	483	Service Use: Expert Opinion (L.P) Cost: de Oliveira et al,[14] 2016
≥20% UHR	0.122	483	Service Use: Expert Opinion (L.P) Cost: de Oliveira et al,[14] 2016
Hospitalizations			
Risk Stratification Strategy			
<20% UHR and ≥20% UHR	0.069	9819	Service Use: Expert Opinion (L.P) Cost: de Oliveira et al,[14] 2016
UHR Treatment Strategy			
<20% UHR	0.035	9819	Service Use: Expert Opinion (L.P) Cost: de Oliveira et al,[14] 2016
≥20% UHR	0.069	9819	Service Use: Expert Opinion (L.P) Cost: de Oliveira et al,[14] 2016
General Mental Health Services			
ED Visits			
<20% UHR	0.122	483	Service Use: Estimation Cost: de Oliveira et al,[14] 2016
≥20% UHR	0.245	483	Service Use: Anderson et al,[104] 2018 Cost: de Oliveira et al,[14] 2016
FEP	0.141	483	Service Use: Anderson et al,[16] 2018 Cost: de Oliveira et al,[14] 2016
Post-FEP	0.082	483	Service Use: Anderson et al,[16] 2018 Cost: de Oliveira et al,[14] 2016
Hospitalizations			
<20% UHR	0.069	9819	Service Use: Estimation Cost: de Oliveira et al,[14] 2016
≥20% UHR	0.139	9819	Service Use: Anderson et al,[104] 2018 Cost: de Oliveira et al,[14] 2016
FEP	0.144	9819	Service Use: Anderson et al,[16] 2018 Cost: de Oliveira et al,[14] 2016
Post-FEP	0.057	9819	Service Use: Anderson et al,[16] 2018 Cost: de Oliveira et al,[14] 2016

Abbreviations: FEP, First Episode Psychosis; UHR, Ultra-High Risk.
†This refers to the proportion of people in the indicated state and strategy who use the indicated service.

3.3.4 Costs

The costing perspective of this model was the health system perspective (Ontario Ministry of Health and Long-Term Care). Total costs were calculated by determining the product of unit costs and service use (**Table 3.2**). Unit costs were retrieved from the 2020 Ontario Schedule of Benefits for physicians.[105] For nonphysicians, their applied hourly salary was used as a proxy for unit costs, similar to methods used elsewhere in the Canadian literature.[106] Additional details on the assumptions for costs can be found in Appendix G (see *Section G.3*). For those below the cutoff score in the risk stratification treatment strategy, there were no costs associated with acquisition of the NAPLS calculator because it is freely accessible online at https://riskcalc.org/napls/, but assessment by a psychiatrist to attain a risk score had an associated fee ($216).

The annual cost for UHR treatment was estimated to be $2,312 per person. In the standard 'treat all' arm, the cost of risk screening using NAPLS was excluded ($2,096). Both cost and outcomes were discounted at an annual rate of 1.5%, as per the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines.[107] No baseline costs were included, as it was assumed that because the participants were young, they were unlikely to have previous instances of significant health care service consumption – this rationale has also been used in other cost-effectiveness analyses on the UHR population.[20,79] Costs for each state can be found in Table 3.4.

3.3.5 Health Outcomes

Quality-adjusted life-years (QALYs) were used as the effectiveness measure – they are derived using a measure of the quality of life in a given health state multiplied by the length of time in that state.[73] The quality of life is usually represented by utility values: a preference weight scaled between zero (death) to one (perfect health).[73] We searched for Canadian quality-of-life values relevant to our model, but none were found. As a result, most utilities were derived from a Dutch cost-effectiveness study using the PsyMod model.[20,81] This study used the 3-level version of the EQ-5D (EQ-5D-3L) instrument,

with UK tariffs to value health states.[20] For the purposes of the current study, we assumed that these utilities were generalizable to the Canadian population (**Table 3.4**).

While most utilities were retrieved from PsyMod, utilities for the UHR states (<20% UHR and ≥20% UHR) and the Remission state were estimated instead. Given that there is evidence that the risk to convert is influenced by prodromal symptom severity, decline in social functioning, and verbal learning and memory scores,[22] we assumed that the utility values for the <20% UHR state and ≥20% UHR state would differ – those with a lower risk for conversion would have a higher utility value than those at a higher risk for conversion. Our focused MEDLINE search did not return relevant values for these two UHR state utilities. Therefore, the <20% UHR state utility was estimated by averaging the utilities between the 'Not UHR' state and the UHR state from the original PsyMod publication.[81] Similarly, the average of the UHR state and the FEP state utilities was calculated to estimate the ≥20% UHR state utility (see Appendix G, Section G.4). Sensitivity analysis was performed to determine how our main results would change in a scenario where both UHR state utilities had the same value from the original PsyMod publication (0.640).[81] The results are presented in Appendix G (**Figure G.1**). In the original PsyMod publication, the 'Not UHR' state utility and Remission state utility were the same. In order to establish rank ordering for the sensitivity analysis – to account for inappropriate iterations where a 'better' health state (such as UHR) had lower utilities than another (such as FEP) – the Remission state utility was modified from the original PsyMod publication.[81] Based on clinical opinion (L.P), the Remission state utility was estimated to be closer to the <20% UHR state utility than the 'Not UHR' state. This is because those in remission from FEP may experience more cognitive difficulties and social stigma than those in the 'Not UHR' state. Sensitivity analysis was completed on this parameter to assess its influence on the main results. For the Post-FEP state utility, we used a UK utility value for moderately functioning outpatients with schizophrenia, retrieved from the focused MEDLINE search.[108,109]

Table 3.4 Cost and utility values for each health state

State	Cost ($) (SE)†	Cost Distribution	Utility (95% CI)	Utility Distribution
Decision Tree				
Risk Stratification Treatment Strategy				
<20% UHR (Annual Risk Assessment)	952 (238)	Gamma	N/A‡	N/A
≥20% UHR (UHR Treatment)	3048 (762)	Gamma	N/A‡	N/A
Standard 'Treat All' Strategy				
<20% UHR (UHR Treatment)	2469 (617)	Gamma	N/A‡	N/A
≥20% UHR (UHR Treatment)	2833 (708)	Gamma	N/A‡	N/A
Markov Model				
Not UHR	563 (141)	Gamma	0.756 (0.729 – 0.782)	Beta
<20% UHR	1046 (261)	Gamma	0.698 (0.669 – 0.726)	Beta
≥20% UHR	2095 (524)	Gamma	0.503 (0.472 – 0.534)	Beta
FEP	6880 (1720)	Gamma	0.366 (0.336 – 0.396)	Beta
Post-FEP	2662 (666)	Gamma	0.490 (0.459 – 0.521)	Beta
Remission	910 (228)	Gamma	0.720 (0.692 – 0.747)	Beta
Death	0	Gamma	0	Beta

Abbreviations: CI, Confidence Interval; FEP, First Episode Psychosis; SE, Standard Error; UHR, Ultra-High Risk.
†The SE is calculated similarly to a 2018 Ontario Health Technology Assessment,[106] where the SE was estimated to be ± 25% of the mean cost.
‡Note that QALYs are accrued in the decision tree, but only at the end of the year. This happens once someone converts (FEP), or remains UHR (<20% UHR or ≥20% UHR). These utility values can be found in the Markov section of this table.

3.3.6 Base Case Analysis

In both the decision tree and Markov model, costs and associated QALYs were assigned based on the state people were in. Given that events were expected to occur any time throughout a cycle, a half-cycle correction was included, which provided an unbiased assumption that the average event would occur in the middle of the cycle – instead of the traditional assumption that movement to different health states occur at the end of each cycle.[110] The differences in cost and QALYs between the risk stratification and the standard 'treat all' strategy was quantified using the incremental cost-effectiveness ratio (ICER):[73,92]

$$ICER = \frac{C_1 - C_2}{E_1 - E_2}$$

where C_i and E_i are the cost (Canadian dollars) and effectiveness measures (QALY), respectively.[92] C_1 and E_1 refers to the risk stratification treatment strategy, whereas C_2 and E_2 refers to the standard 'treat all' strategy.

3.3.7 Sensitivity Analyses

Deterministic sensitivity analyses (DSA) and probabilistic sensitivity analyses (PSA) were used to account for parameter uncertainty and assess the robustness of the model base case results to changes in parameter values. DSA varies the parameter values to see how the values affect the model results.[73] A one-way DSA varies one parameter at a time, whereas a multi-way analysis (one variation being a scenario analysis), would change multiple parameters of interest.[73] The PSA quantifies model uncertainty by providing specific distributions for each parameter. Values can then be randomly sampled from these distributions repeatedly to repeat the main analysis several times.[73]

DSAs were completed by varying: (i) the cost of the annual risk assessment if it were provided by a trained psychologist instead of a psychiatrist ($67 instead of $215); (ii) the prevalence of those at ≥20% risk (34.89% to 57.89%); and (iii) the state-specific utilities values: <20% UHR (0.640 to 0.756), ≥20% UHR (0.366 to 0.640), Post-FEP (0.362 to 0.490), and Remission (0.720 to 0.756) state. Scenario analyses were also performed in order to test whether cost-effectiveness would be substantially affected if the probability to convert to psychosis increased in the second year of UHR treatment for those <20% UHR in the 'treat all' strategy, rather than remaining unchanged in the expected two years of treatment. This was done to demonstrate a scenario where treatment adherence does not occur over the full course of treatment, which is common in treatments involving medication.[111] We also examined how increasing the use of the ED (from 12.2% to 24.5% of the cohort) and increased hospitalizations (from 6.9% to 13.9% of the cohort) within the <20% UHR group affected results. This analysis was performed to model uncertainty around the base case model assumption that those at <20% risk to convert to FEP used half the ED and hospitalization services of those at ≥20% risk. Evidence suggests that the <20% risk cutoff for treatment decision (used in the base case analysis) is appropriate because so few convert,[22] but we also evaluated the impact of

other cutoff values for risk stratification to see if the increased risk for conversion (lower QALYs) was suitably offset by the lower costs from the risk stratification treatment strategy.

For the PSA, we completed 1000 iterations of the main analysis. Uncertainty for transition probabilities and utilities were generally represented by beta distributions, while the gamma distribution was used to vary costs. A rank order was enforced for the utilities in the PSA to account for inappropriate iterations where a 'better' health state (such as UHR) had lower utilities than another (such as FEP). The rationale for the chosen range of values in the DSA, the probabilities used in the scenario analysis, and the distributions for the PSA can be found in Appendix G (see *Section G.5* to *Section G.7*).

3.4 Results

3.4.1 Base Case Analysis Results

The cost of the risk stratification treatment strategy to the health system was about $16,459, with QALY gains of 8.331. In the standard 'treat all' practice, this was $17,652 with QALY gains of 8.408. Compared to treating all UHR patients (standard practice), only treating those with ≥20% risk of conversion to FEP (risk stratification treatment strategy) resulted in a cost reduction of $1,193 and a loss of 0.077 QALYs. The ICER for risk stratification, compared to the standard 'treat all' strategy, was $15,466 per QALY and lies in the southwest quadrant of a cost-effectiveness plane – this means that cost savings can only occur in the risk stratification strategy if the health opportunity cost due to lost QALYs are acceptable.

3.4.2 One-Way Deterministic Sensitivity Analysis Results

One-way DSAs were conducted to examine how the base case results would change if: (i) the annual risk assessment was provided by a trained psychologist instead of a psychiatrist; (ii) the prevalence of those at ≥20% risk increased; and (iii) health state utilities for the <20% UHR state, ≥20% UHR state, Post-FEP, and Remission state were varied (**Figure 3.2**). The ICERs for the risk stratification strategy (compared to the

standard ‘treat all’ practice) were higher than the base case when the cost of the annual risk assessment was decreased, when the utility value of the <20% UHR state was reduced, and when the Remission state utility was increased. The ICERs were lower when the prevalence of the people at ≥20% increased, when the <20% UHR state utility was increased, and when the Post-FEP state utility was reduced. ICER values changed only slightly by adjustments to the ≥20% UHR state utility parameter, as most people did not spend significant time in this state, compared to the <20% UHR state. In all DSAs, changes to model parameters resulted in a range of ICERs between $11,000 to $18,000 per QALY gained for the risk stratification strategy, compared to the standard ‘treat all’ treatment strategy. All ICERs remained in the southwest quadrant. Similarly, in all cases in the DSA, the risk stratification treatment strategy continued to have lower costs than the standard ‘treat all’ practice, but produced worse health outcomes. Generally, ICERs that were larger than the base case ICER suggested that the incremental costs were large (i.e., an increase in the difference in costs between the treatment strategies, suggesting more cost savings in risk stratification) or incremental QALYs were small (i.e., a decrease in the difference in QALYs between the treatment strategies, suggesting that risk stratification had similar health outcomes to the standard ‘treat all’ strategy).

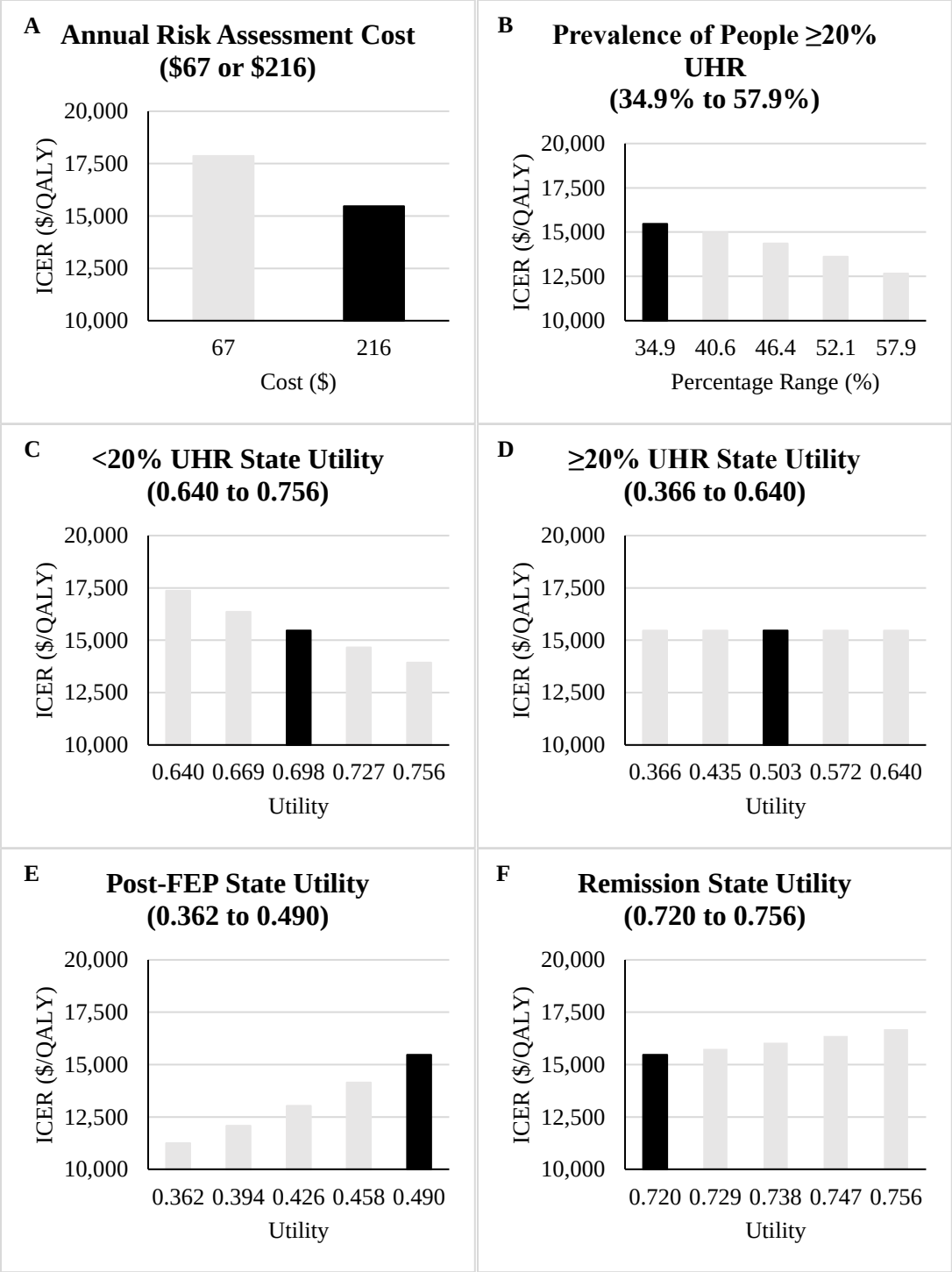

Figure 3.2 Deterministic sensitivity analysis comparing the risk stratification treatment strategy to the standard 'treat all' practice

The black bars indicate the base case results, while the grey bars indicate the different ICERs derived from changes made to the: (A) cost of the NAPLS assessment; (B) prevalence of those who are ≥20% risk for psychosis; (C) <20% UHR state utility; (D) ≥20% UHR state utility; (E) Post-FEP state utility; and (F) Remission state utility.

3.4.3 Scenario Analysis Results

The following scenarios were modeled to examine how they impacted the cost-effectiveness results: (i) UHR treatment non-adherence in the standard 'treat all' practice group in the second year (treatment effectiveness in the first year only) (ii) an increase in use of the ED and hospitalizations for those who were at <20% risk for psychosis to equal the service use in the ≥20% risk group; and (iii) scenarios where different risk score cutoff values for UHR treatment decision were employed.

First, a scenario was modelled where <20% UHR people in the standard 'treat all' strategy did not adhere to the full two-year UHR treatment plan. To model this scenario, the probability to convert to psychosis within this group was increased in the second year (**Table 3.5**). When modeling this scenario, the risk stratification strategy costs and QALYs remained unaffected, but the standard 'treat all' strategy became more expensive and returned worse outcomes (lower QALYs) compared to the base case results. As a result, the ICER (southwest quadrant) for the risk stratification strategy compared to the standard 'treat all' strategy – $25,199 per QALY gained – returned a higher value than the base case results.

Table 3.5 Results of changes in adherence to UHR treatment in the standard 'treat all' strategy

Adherence Scenario	Risk Stratification Treatment		Standard 'Treat All' Practice		Difference		ICER
	Cost ($)	QALY	Cost ($)	QALY	Cost ($)	QALY	($)/QALY
Base Case (Full Adherence of UHR Treatment)	16,459	8.331	17,652	8.408	-1,193	-0.077	15,466
No Adherence in Second Year of UHR Treatment†	16,459	8.331	17,817	8.385	-1,358	-0.054	25,199

†This scenario models a situation where <20% risk people in the standard 'treat all' strategy do not adhere to the UHR treatment plan in the second year, which is equivalent to a risk to convert to psychosis of 5.6% in the second year, instead of 3.6%.

Next, we modeled a scenario where ED and hospitalization services were increased in the <20% UHR group and modified from the assumption of half the service use of the ≥20% UHR group (**Figure 3.3**). While the QALYs remained unchanged, the difference in costs between the strategies decreased, resulting in fewer cost savings from risk stratification.

As a result, the ICER was $10,721 for the risk stratification strategy compared to the standard ‘treat all’ strategy in the scenario where service use was identical in the two risk groups. This value – in the southwest quadrant – was lower than the base case value. In this scenario, the standard ‘treat all’ strategy remained relatively inexpensive for each additional QALY.

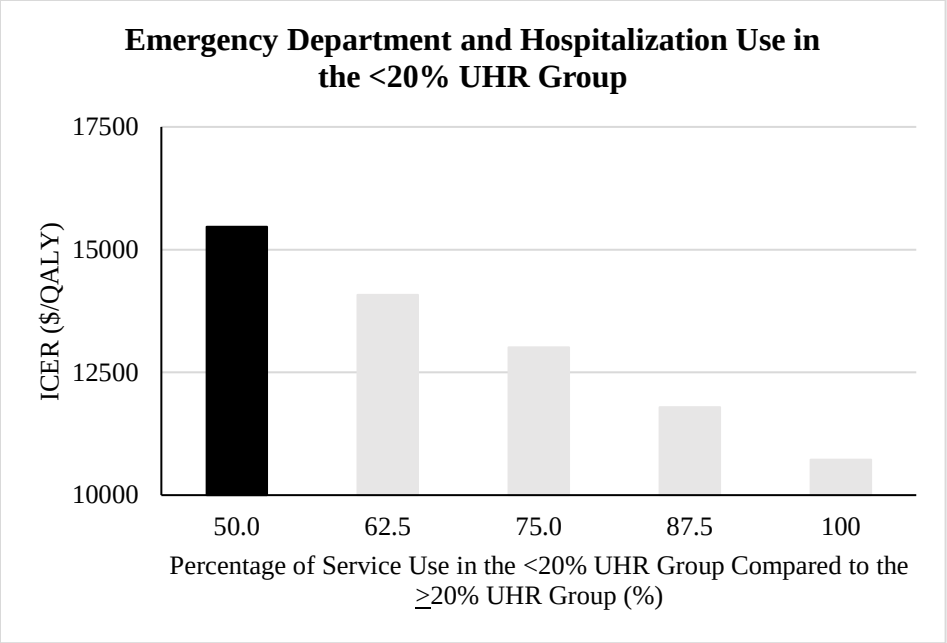

Figure 3.3 Incremental cost-effectiveness ratios comparing risk stratification to the standard ‘treat all’ practice for changes in emergency department use and hospitalization

The black bars indicate the base case results, while the grey bars indicate the different ICERs derived from changes in the percentage of service use in the <20% UHR group compared to the ≥20% UHR group.

Next, we investigated how changing the cut-off for UHR treatment decision in the risk stratification strategy affected the results (see Appendix G, Table G.6 for probabilities to convert at different risk levels). As the cutoff ranges increased – meaning that the proportion of people untreated increased – the ICERs for the risk stratification strategy decreased (**Figure 3.4**). This decline was due to the greater losses of QALYs in the risk stratification strategy because some people did not receive UHR treatment and were therefore more likely to convert to FEP. Once again, all ICERs would be in the southwest quadrant of a cost-effectiveness plane.

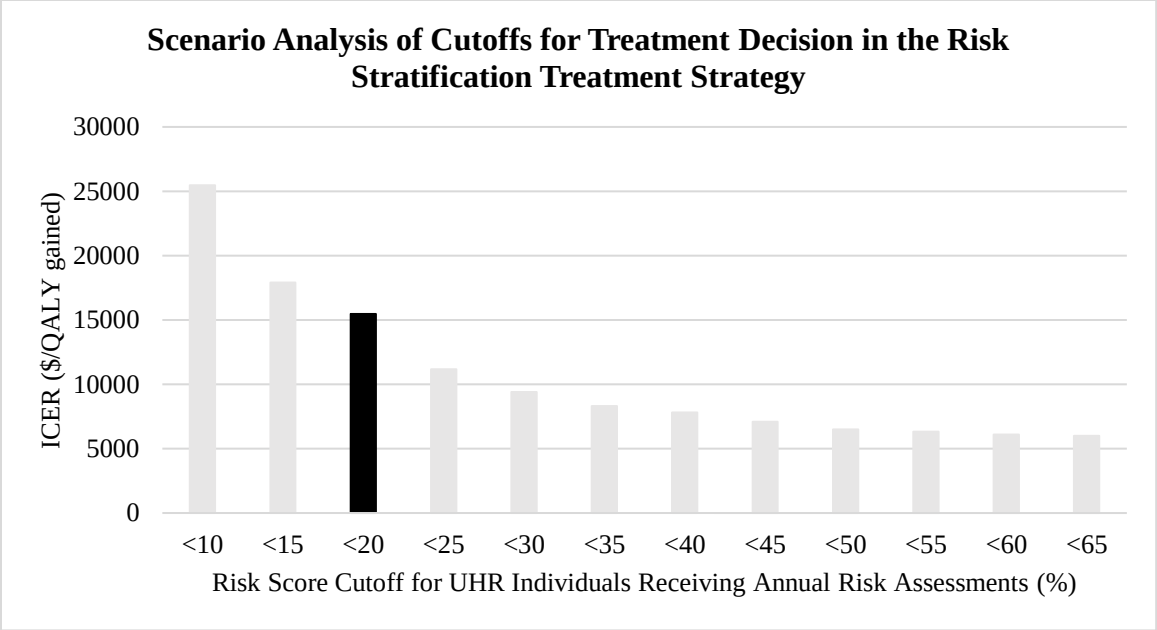

Figure 3.4 ICERs comparing the risk stratification treatment strategy to the standard 'treat all' strategy at different risk cutoff scores from the NAPLS calculator

The black bar indicates the base case results. The grey bars indicate the different ICERs for the risk stratification strategy. Under the risk stratification treatment strategy, UHR people with scores under these cutoff scores would receive the annual risk assessment, while those equal to or above these scores would receive UHR treatment.

3.4.4 Probabilistic Sensitivity Analysis Results

A PSA was also conducted to account for parameter uncertainty and repeated the main analysis over 1000 iterations (**Figure 3.5**). The PSA showed that: 86.9% of the time, the risk stratification strategy had lower costs and produced lower QALYs when compared to the standard 'treat all' strategy. These ICERs were found in the southwest quadrant of the cost-effectiveness plane. The median ICER for the risk stratification strategy over 1000 iterations was about $15,260 per QALY.

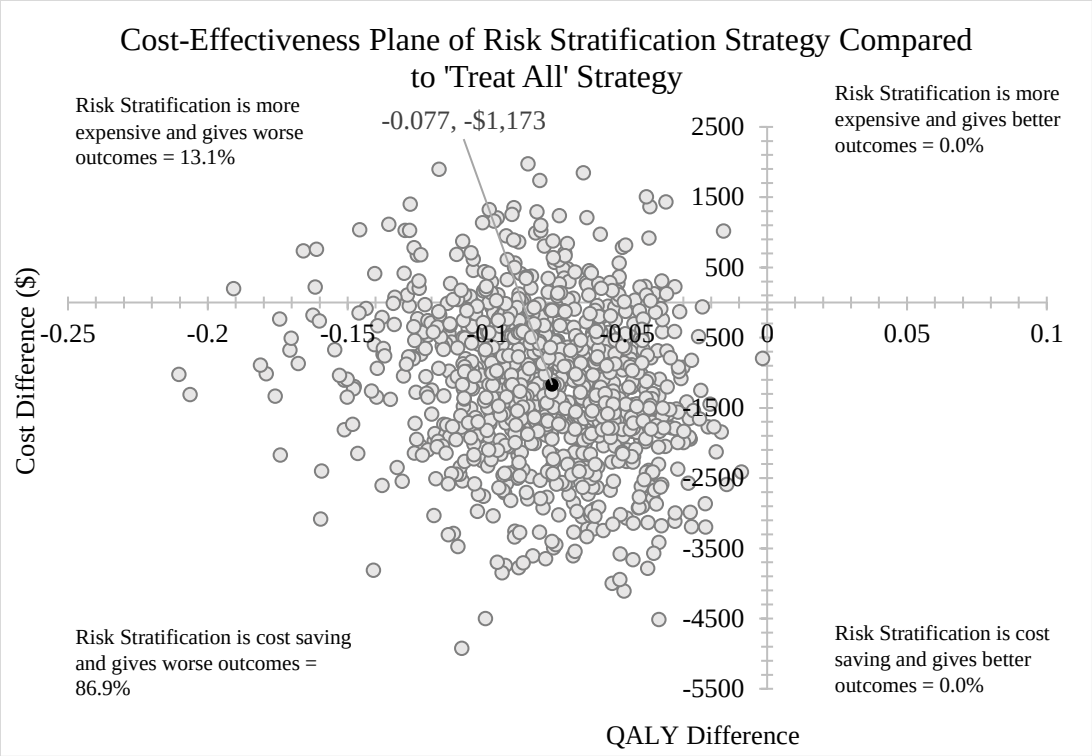

Figure 3.5 Cost-effectiveness plane showing 1000 iterations of the main analysis between the risk stratification treatment strategy and the standard ‘treat all’ practice

The black point indicates the median QALY difference and cost difference, respectively, for the risk stratification treatment strategy compared to the standard ‘treat all’ strategy.

3.5 Discussion

3.5.1 Summary of Findings

This analysis sought to estimate the cost-effectiveness of a risk stratification treatment strategy compared to a standard ‘treat all’ strategy for people at UHR for psychosis from the Canadian health system perspective. Our main findings suggest that the risk stratification treatment strategy is less expensive than the standard ‘treat all’ strategy, but returned lower health outcomes. The base case results suggest that treating all people who present to the UHR program – irrespective of their risk to convert to psychosis – had a small incremental cost for additional favorable outcomes (QALYs). For all sensitivity analyses, ICERs (in the southwest quadrant) larger than the base case value ($15,466 per

QALY gained) generally favored risk stratification more so than the standard ‘treat all’ strategy, but lower ICER values generally favored the standard ‘treat all’ strategy. More specifically, changes in individual parameters in the DSA highlight the robustness of the main findings, with ICERs ranging between $11,000 to $18,000 per QALY gained for the risk stratification treatment strategy, compared to the standard ‘treat all’ strategy. Results from the scenario analysis supported the main results as well. The treatment nonadherence scenario returned a substantially higher ICER ($25,199) than the base case results and demonstrated that the model is sensitive to changes in the proportion of people converting to psychosis while in the UHR program. In the scenario where ED and hospitalization use was increased in the <20% risk group to more closely resemble the ≥20% risk group, we saw fewer cost savings from risk stratification and therefore, lower ICERs. In the final scenario, different cutoff scores for treatment decision were examined. We saw a decline in the ICERs as the cutoff increased – in favor of the standard ‘treat all’ strategy – largely due the fact that the risk stratification strategy would return worse outcomes as more people were left untreated (i.e., there were a greater number of conversions to psychosis and associated health system costs). Overall, the scenario analysis showed that the risk stratification strategy would become a more desirable strategy to adopt if: (i) the UHR treatment became less effective, resulting in a greater number of conversions to psychosis in the standard ‘treat all’ strategy; (ii) those at <20% risk used acute care services at a much lower frequency than the ≥20% risk group, thereby further reducing costs for the risk stratification treatment strategy; and (iii) the risk score cutoff for treatment decision remained low and subsequently reduced the number of conversions in the risk stratification strategy. Finally, the PSA demonstrated that the main findings were robust to changes – the risk stratification strategy was cost saving and returned worse outcomes 86.9% of the time.

3.5.2 Discussion of the Findings

Our main findings demonstrated that risk stratification reduces costs, but returns worse outcomes, and that the standard ‘treat all’ practice is the preferred strategy because it is reasonably inexpensive to the health system to gain additional QALYs. The results suggest that risk stratification is a cost saving strategy (with savings of $1,193 per

person) and has a health opportunity cost of 0.077 QALYs. The ICER was $15,466 per QALY and lies in the southwest quadrant of a cost-effectiveness plane. Therefore, the decision to adopt or reject risk stratification depends on the willingness-to-accept (WTA) threshold. Interventions in the field of psychosis with similar ICERs have been suggested to have good value for money. For example, an Ontario study found that CBT for psychosis provided by nonphysician therapists offered good value for money at $21,520 per QALY gained, relative to usual care.[106] Even strategies with considerably higher ICERs have been suggested to provide good value for money – internet-delivered CBT for anxiety in Ontario, which had an ICER of $43,214 per QALY gained compared to unguided therapy, is one such example.[112] The risk stratification treatment strategy would only be considered to be a reasonable alternative in instances where the cost to provide treatment for all UHR patients is untenable – which may be a possibility because UHR programs are costly[113] – or if there is an alternate non-specialized form of care for low risk people that provides similar outcomes as UHR programs. These general mental health services do exist, but the field is still fairly nascent.[114,115]

The scenario analyses returned results that were generally expected, based on clinical evidence. When modeling low program adherence, the higher ICER (southwest quadrant) for risk stratification compared to the standard 'treat all' strategy ($25,199) suggested that the model is sensitive to changes to the probability to convert to psychosis. In a real-world setting, low adherence to treatment – such as medication for schizophrenia[111] – is linked to many negative outcomes, including increased risk of relapse, remission, and hospitalization.[111,116] This directly increases costs, as evidenced in literature,[117,118] and to a lesser extent, our model of low program adherence. There is also evidence showing that the UHR population is heterogeneous in terms of functioning and symptom severity, which in turn impacts their long-term outcomes.[119,120] Yet, there is a paucity of literature available examining service use or treatment effectiveness differences between the risk groups based on the NAPLS calculator.[22] Therefore, the additional scenario analyses completed in this thesis that tested the assumption of service use between different UHR classes and the cost-effectiveness at different risk cutoffs were exploratory in nature, and only served to support the robustness of the main results. More specifically, the scenario analysis examining the different risk cutoffs likely underestimated costs at higher ranges,

given that costs were only estimated for the perceived service use of people at <20% risk for psychosis and ≥20% risk for psychosis. Therefore, costs were not adjusted for the presumed increase in service use expected if people with higher risk scores went untreated. This may explain why the ICERs were impacted more by changes in QALYs between the two treatment strategies, rather than costs.

Overall, our results consistently showed – as evidenced in the PSA – that the risk stratification strategy remained an incrementally low-cost strategy, compared to the standard treat all' strategy, but returned worse outcomes.

3.5.3 Model Limitations

Our model had several limitations. Most notably, we assumed that the NAPLS risk scores remained static over time, meaning that people could not move between the two UHR states. The Markov model examined the average outcomes of the cohort and could not follow individual patients and their outcomes, unlike patient-level state-transition models, such as microsimulations.[107] Costs in the model were valued based on service use under ideal conditions and expert opinion from the PROSPECT UHR clinic, implying that patients would adhere to all aspects of the treatment, including antipsychotic medication regimens, which are known to have low adherence.[111] To address this limitation, efforts were made to assess the impact of low adherence in sensitivity analyses. In addition, hospitalization and ED unit costs were derived from a study examining the economic burden of health service use in an Ontario population of people with chronic schizophrenia,[14] which may not accurately reflect the costs for people identified as UHR or with FEP. However, we attempted to account for cost uncertainty – and uncertainty in other parameters – by completing a PSA. We also recognize that the duration of psychotic illness and other symptoms vary, and that a one-year cycle length (with utilities lasting for one year) may not reflect variability in these health states adequately. Also, resource use data (expert opinion) was mainly derived from one Canadian UHR clinic with small sample sizes, which may not be representative of other clinics in Canada. Mortality estimates for the UHR group were based on general population mortality estimates, as seen in the original PsyMod publication.[81] We recognize that those at UHR

for psychosis may have an increased risk for mortality compared to the general population – attributed to suicide for example[83] – but did not have adequate data to inform this mortality parameter. Finally, studies examining the long-term outcomes of UHR patients found that the annual risk to convert to psychosis declines over time.[90,94] Although our model only considered a declining risk to convert to psychosis over three years in the untreated group (with the probability to convert in the third year persisting indefinitely), we found that the proportion of people who remained UHR at the end of the 15 years in the model (~2% of the modelled cohort) was similar to those who remained as UHR in a long-term study of UHR people after 15 years (~1%).[90] With the added understanding that there is a paucity of data available on the long-term annual probabilities to convert to psychosis within groups stratified by NAPLS risk scores, it was determined that no further modification to the conversion probability would be done.

3.5.4 Implications for Future Research and Conclusions

This economic evaluation focused on risk stratification for treatment decision and was informed by prespecified NAPLS score cutoffs. The NAPLS risk calculator may show promise in informing treatment allocation in instances where the cost savings outweigh negligible losses in QALYs. The difference in costs between the treatment strategies were not very large, whereas, the difference in QALYs were small. In addition, there is uncertainty in the parameters. Therefore, careful consideration must be made by decision-makers in weighing the small benefits in costs with the uncertainty of the estimates and other literature published in this field. In interpreting the ICER (southwest quadrant) from this study, a WTA threshold would have to be considered as well to determine if there is an amount of QALYs a decision-maker is willing to forego in favor of additional resources (i.e. cost savings) that can be invested into other interventions or treatment plans in the field that can offer more QALY gains elsewhere. Overall, caution must be exercised when examining our findings as future research is needed.

Future research requires a more rigorous method of valuing costs for the different risk classes. There is also a need for more Canadian data in community settings to determine the sensitivity and specificity of this calculator. In addition, given that there is already

evidence of different levels of conversion risk impacting long-term health outcomes of UHR people,[22,119,120] future research may benefit from clinical trials examining long-term outcomes of risk stratification for treatment decision compared to a standard 'treat all' strategy. This may better inform transition probabilities for future economic evaluations related to conversion risk and recovery among those not receiving the complete resource-intensive UHR treatment. Alternatively, future studies could also consider different intensity treatments or personalized treatment plans based on these risk scores.

3.6 Conclusion

The risk stratification treatment strategy, where UHR treatment was only provided to those who had a ≥20% NAPLS risk score, resulted in an ICER of $15,466 per QALY to the Canadian health system, relative to treating all people at UHR for psychosis. This ICER lies in the southwest quadrant of a cost-effectiveness plane, meaning that risk stratification resulted in lower costs and lower QALYs compared to treating everyone identified as UHR. The cost reduction from the risk stratification treatment strategy may not be worth the loss in QALYs. More precise cost valuation methods are needed to determine how much the health system would be saving by not providing resource-intensive, specialized UHR services to those with low risk of conversion to psychosis. A decision would also have to be made regarding an acceptable quantity of QALYs that can be foregone in order to reallocate finite resources towards more severe UHR cases – that is the WTA.

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3.8 Declaration of Conflicting Interests

K.K.A, O.M.O, and S.A declare that there is no conflict of interest to disclose. L.P reports personal fees from Otsuka Canada, SPMM Course Limited, UK, Canadian Psychiatric Association; book royalties from Oxford University Press; investigator-initiated educational grants from Janssen Canada, Sunovion and Otsuka Canada outside the submitted work.

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Chapter 4

4 Extended Discussion and Conclusion

In this chapter, the results of the systematic review and economic evaluation will be summarized and synthesized. An extended discussion of the contributions to the literature and a detailed description of study limitations will follow. Finally, future directions in the field will be discussed.

4.1 Summary of Results

The overarching objective of this thesis was to examine the state of the literature on economic evaluations of ultra-high risk (UHR) for psychosis programs, and to then use the findings to inform a novel economic model for identifying and treating people in UHR programs from the Canadian perspective. First, a systematic review was conducted to summarize and evaluate the literature, which included a qualitative synthesis of all economic evaluation studies examining the cost and cost-effectiveness of interventions for people identified as UHR (Chapter 2).[1] This chapter provided the context necessary for the subsequent cost-effectiveness analysis, which evaluated the use of risk stratification based on the probability of conversion to psychosis for treatment decisions in a UHR program, compared to the standard 'treat all' practice (Chapter 3).

Of the partial (cost) and complete (cost-effectiveness) economic evaluations of UHR programs included in our systematic review (n=6), all cost-effectiveness studies and one cost analysis suggested that UHR programs were potentially cost-effective and cost saving, respectively. Despite these results, there were limitations to the included studies, including: inconsistent valuation of outcomes, cost perspectives limited to the health system perspective, and heterogeneity in results that may be due to methodological or reporting errors. Although there was some evidence suggesting that UHR programs are cost-effective (Chapter 2),[1] the absence of a firm consensus is mirrored in the lack of high-quality evidence available to more definitively show that UHR interventions are clinically effective (see Chapter 1).[54] These observations contributed to the decision to

examine risk stratification treatment strategies in our economic evaluation, rather than focus on any particular intervention. Similarly, the systematic review also helped summarize the limitations to prior studies that could potentially be addressed in the economic evaluation completed for this thesis.

The main objective of the economic evaluation was to examine whether the cost-effectiveness of UHR programs from the Canadian health system perspective was impacted by the use of a risk stratification treatment strategy that provided treatment to those at or above a 20% predicted risk of conversion to psychosis, relative to the standard practice of treating all UHR patients. Risk scores were based on the North American Prodrome Longitudinal Study (NAPLS) risk calculator.[22] The NAPLS calculator provides a percentage score of the predicted risk to convert to psychosis among people identified as UHR, and is described in detail elsewhere.[22] In the risk stratification treatment strategy, those below the 20% risk cutoff would receive an annual risk assessment with the NAPLS calculator to monitor risk levels. Those at or above the cutoff, as well as those in the standard 'treat all' practice strategy, would receive UHR treatment (which primarily consisted of active case management). Many sensitivity analyses were completed to evaluate parameter uncertainty, in addition to scenario analyses – most notable was an examination of how different cutoff scores for UHR treatment decisions in the risk stratification strategy would affect the base case cost-effectiveness results. The economic evaluation found that treating those at ≥20% risk to transition – and only providing annual risk assessments for those at <20% risk for psychosis – resulted in lower costs and lower QALYs compared to treating everyone identified as UHR. Compared to the standard 'treat all' strategy, the incremental cost per QALY estimate for only treating those at ≥20% risk to convert to psychosis was $15,466. The ICER was in the southwest quadrant of the cost-effectiveness plane, implying that cost savings can only be made if the health system decision-maker is willing to accept the health opportunity cost due to lost QALYs. We concluded that interpretations of these results must be carefully assessed due to limitations on two fronts: (i) the NAPLS calculator is novel and is currently only used for research purposes (not clinical practice), which therefore limits the available literature to inform the economic model; and (ii) there is a

paucity of data on service use available at the different risk levels, which limits the ability to accurately value costs to the health system.

Both the systematic review and the economic analysis highlight the need for more economic evaluations on UHR programs. There is a high rate of service use among people with psychosis,[86] and with UHR programs increasingly available worldwide,[19,50] it is imperative that research in this field continues in order to determine whether UHR programs prevent or delay the onset of a first psychotic episode (FEP), lower service use costs, and improve patient outcomes.

4.2 Contributions to the Literature and Policy Implications

Our systematic review (Chapter 2)[1] contributes to the literature by providing an update to the evidence base on both partial and complete economic evaluations exclusively focused on UHR populations. Other systematic reviews of economic evaluations have examined UHR programs, but have also included FEP programs. For example, a systematic review from 2012 examined whether UHR programs are cost-saving in different health care settings, but included both recent-onset psychosis and UHR populations.[66] Similarly, a 2019 systematic review on early intervention for psychosis also included both UHR and FEP populations.[31] Our systematic review provides a more recent update to the evidence base (March 2020) and uses a rigorous search strategy. In addition, grey literature databases were also searched to potentially mitigate the effects of publication bias – a phenomenon where negative studies may be missed by systematic reviews because they are more likely to be published in other formats less likely to be accessed.[85] Finally, results from this systematic review suggest a need for more economic evaluation of UHR programs, which are sentiments echoed in other published systematic reviews.[31,66]

Our economic evaluation (Chapter 3) is the first to consider a risk stratification approach for treatment decision in UHR programs and the first to be done from the perspective of the Canadian health care system. In addition, attempts were made to strengthen the economic model by addressing the limitations of previous models identified by our

systematic review. In particular, the systematic review concluded that future economic evaluations would benefit from more consistent valuation of outcomes, longer-term assessments of UHR programs, assessments of cost from the societal perspective, and the use of transparent guidelines for economic evaluations. Our economic evaluation used the Canadian Agency for Drugs and Technologies in Health (CADTH)-approved quality-adjusted life-year (QALY) as our effectiveness measure,[107] we examined outcomes from a fifteen-year time horizon, and we used the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist[89] to report our findings transparently. Finally, while we considered using costs from the societal perspective, this was not feasible due to the lack of available data to inform parameters.

Completing economic evaluations using QALYs as an outcome measure has benefits. QALYs provide both a measure of the quality and quantity of life[73] and allow an easier comparison between different interventions on different health outcomes.[121,122] These characteristics make QALYs highly desirable for policy makers when allocating resources across different health sectors.[121,122] Though this may be true, economic evaluations are encouraged to be completed alongside clinical trials in order to make informed mental health policy decisions.[121] To the author's knowledge, there are currently no published clinical trials that have examined the use of risk stratification treatment strategies in the UHR population, and the impact on resource use and effectiveness. Therefore, the results from this thesis would not serve to imply the need for policy change, but instead serve as an exploratory analysis to suggest the potential benefits of prioritizing treatment to those with a higher risk of transitioning to psychotic disorder. Future decision-making using the ICER from this study are subject to uncertainty within the estimates (especially because of the small incremental differences in costs and QALYs in the model), the paucity of literature in the field, and the need to establish a suitable willingness-to-accept threshold.

4.3 Thesis Limitations

Although both the systematic review and economic evaluation make their own unique contributions to literature, they are not without limitations.

4.3.1 Limitations of the Systematic Review

It was not possible to complete a meta-analysis for the systematic review. This was largely due to heterogeneity in study results, including: differences in the effectiveness measures used and differences in the types of economic evaluations conducted. The search strategy was also limited to English studies, which may introduce publication bias.

4.3.2 Limitations of the Economic Evaluation

As mentioned previously, the economic evaluation adds a unique Canadian perspective to the literature on priority-based treatment using a novel risk calculator currently used for research purposes, with hopes of future clinical use. This study provides a novel contribution to the literature, but this novelty also presented challenges on several fronts.

In terms of our outcome data, it was challenging to find utilities from the Canadian perspective relevant to the modified states of our Markov model, so the utilities used predominantly relied on ones retrieved from a Dutch study.[20,81] However, it is well-known that utilities are hard to attain for specific populations, particularly in the field of mental health.[121,122] It is especially challenging to derive utilities from populations with certain mental illnesses, as there may be differences in participants' capacity to understand or make judgements on utility-measuring activities, especially in more severe manifestations of disorder or where there is significant cognitive impairment.[122] Some state utilities were also estimated based on assumptions, but any uncertainty was addressed in extensive sensitivity analyses.

Another limitation is that our estimates for service utilization (expert opinion) assumed that there would be 100% engagement in all aspects of the program. We would then be underestimating the real-world costs associated with poor outcomes from program drop-outs or low program adherence, although we completed a sensitivity analysis to assess the latter. Similarly, while costs due to lost productivity are likely to be significant in patients with psychosis,[13] our own model did not examine a perspective that accounts for these costs, namely the societal perspective. This limitation is consistent across most economic evaluations examining UHR programs – our systematic review only found two studies

conducted from a societal perspective.[20,77] However, even when the societal perspective was employed in the included studies, factors such as criminal justice costs or caregiving were not included.[77] As is the consensus from our systematic review, and from the discussion of the original PsyMod publication,[81] there is a paucity of data available to properly value societal costs. In addition, although our model did not value the costs and service use for the different risk levels in the scenario analysis, it is important to remember that NAPLS is still being used for research purposes only. Consequently, there is no published data available on service-related outcomes stratified by risk score in the NAPLS cohort, such as presentations to the emergency department and psychiatric hospitalizations.

We obtained our transition probabilities from the Canadian literature, where available, however some transition probabilities originated from international sources. In addition, though the risk to convert to psychosis could be derived for the groups receiving treatment, the transition probabilities for untreated groups (those receiving annual risk assessments) had to be estimated indirectly from other parameters.[93] This is due to the fact that most clinical trials have control groups that are treated,[45] so literature is sparse on the outcomes for people identified as UHR who remain untreated. Finally, not all transition probabilities used in our economic model considered how these may vary between those with different risk scores – for example, the mortality risk among those with a risk score of <20% versus ≥20%.

4.3 Future Directions

People who access UHR programs tend to be distressed and are at a greater risk of long-term negative outcomes.[18] Our risk stratification treatment strategy implies that those below a certain cutoff may not require treatment from an UHR clinic, but it does not mean that they are not in need of comprehensive mental health care. UHR programs are highly specialized, and people identified as UHR who are experiencing milder symptoms and have a low probability of transitioning to psychosis may be better suited for other services or treatment regimens. Future studies could examine the effectiveness of providing different intensities of treatment based on risk scores, or by shifting away from

UHR programs toward youth mental health services that broaden the accessibility to people who may not necessarily meet the UHR criteria.

To the author's knowledge, there is currently no clinical evidence on the effectiveness of risk stratification for treatment decision for people identified as UHR for psychosis, but the interest in risk scores or risk stratification for treatment decision is not unique to this field.[123,124] There are examples of different assessment tools available to predict transition risk,[59] and there is evidence to suggest that people with lower predicted risk scores have less severe symptoms.[22] How this knowledge should translate to treatment planning for the UHR population is a topic for future studies. Our economic model only presents one potential scenario, and future studies may explore how different intensities of treatment based on risk score may impact effectiveness and cost-effectiveness.

An alternative way to address the heterogeneity of symptoms and varying levels of conversion risk among people accessing UHR programs is to provide services to a broader population – that is, people in need of general mental health services. Doing so may identify a greater number of help-seeking people who meet the UHR criteria. This will lead to a shift towards a transdiagnostic approach – the rejection of single-diagnosis classification in favor of a new classification system that considers disease comorbidities.[125] Efforts have been made to promote an alternative service model that provides primary mental health care, including general mental health assessments and treatment. Examples include the Headspace initiative in Australia[114] and the Canadian equivalent, ACCESS Open Minds.[126] Headspace provides a broad point of entry for help-seeking distressed youth between the ages of 12 and 25.[114] These centers tend to be less diagnosis-driven, with more of a focus towards needs-based psychotherapeutic techniques.[114] Services like Headspace are still in their early stages, and to date, have been shown to provide small to moderate improvements in patient health.[115] Similarly, information on the cost-effectiveness of Headspace services is still in its early stages.[115] Whether future research moves towards risk stratification strategies for UHR treatment decision in order to identify those most in need of specialized services, or towards broadening the criteria to provide treatment for all youth regardless of clinical presentation, it is clear that more work needs to be done.

4.4 Conclusions

The main objectives of this thesis were to examine the state of the literature on economic evaluations of UHR programs, then to use this knowledge to help inform an economic model comparing the cost-effectiveness of a risk stratification treatment strategy to the standard ‘treat all’ practice. Our findings suggest that there is potential value for money in UHR programs, and that not treating a proportion of the cohort results in losses of good health outcomes, despite a reduction in costs. Both studies highlight the paucity of clinical and economic evidence on treatment for the UHR population. Understanding the contributions that specialized programs, like UHR clinics, may have on lessening the health burden of psychotic disorders is important for improving health outcomes of people in need of additional support[18] and for lessening the economic burden on the health system.[86]

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Appendices

Appendix A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) checklist[72]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	15
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	16
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	17-19
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	17-19
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	19
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	19-20
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	19
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	19
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	19-21
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	20-21
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	20
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	20-21
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	21
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	21

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	21 & Figure 2.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	23 & Table 2.1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	30 & Table 2.3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	23-27 & Table 2.2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	32-34
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	34
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	34-35
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	35-36

Appendix B Complete electronic and grey literature search strategy

Electronic Database Search strategy

The initial search strategy and results below are from inception to 9/23/2019. The updated search strategy used the same search terms from 9/23/2019 to 3/09/2020.

Medline (Ovid)		
1	exp Prodromal Symptoms/	
2	(at risk mental state* or ARMS* or psychosis risk* or psychosis prediction* or psychosis onset* or prodrom* or prodromal psychosis* or high risk* or ultra-high risk* or ultra high risk* or UHR or CHR or clinical high risk* or clinical-high risk* or high clinical risk* or referr* or help seeking* or progression to first-episode psychosis*).ti,ab,tw.	
3	1 or 2	
4	exp cost-benefit analysis/	
5	exp "Costs and Cost Analysis"/	
6	(economic evaluation* or health economic* or cost-effectiveness* or cost-benefit* or cost analysis*).ti,ab,tw.	
7	4 or 5 or 6	
8	exp Schizophrenia/	
9	exp Psychotic Disorders/	
10	(Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder* or psychiatric crisis* or crises*).ti,ab,tw.	
11	8 or 9 or 10	
12	3 and 7 and 11	**Results: 152**

Embase (Ovid)		
1	exp prodromal symptom/	
2	(at risk mental state* or ARMS* or psychosis risk* or psychosis prediction* or psychosis onset* or prodrom* or prodromal psychosis* or high risk* or ultra-high risk* or ultra high risk* or UHR or CHR or clinical high risk* or clinical-high risk* or high clinical risk* or referr* or help seeking* or progression to first-episode psychosis*).ti,ab,tw.	
3	1 or 2	
4	exp economic evaluation/	
5	exp "cost benefit analysis"/	
6	exp "cost minimization analysis"/	
7	exp "cost utility analysis"/	
8	exp "cost effectiveness analysis"/	
9	exp health economics/	
10	(economic evaluation* or health economic* or cost-effectiveness* or cost-benefit* or cost analysis*).ti,ab,tw.	
11	4 or 5 or 6 or 7 or 8 or 9 or 10	
12	exp schizophrenia/	
13	exp psychosis/	
14	exp affective psychosis/	
15	exp schizoaffective psychosis/	
16	(Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder* or psychiatric crisis* or crises*).ti,ab,tw.	
17	12 or 13 or 14 or 15 or 16	
18	3 and 11 and 17	**Results: 623**

PsycINFO (Ovid)		
1	exp Prodrome/	
2	(at risk mental state* or ARMS* or psychosis risk* or psychosis prediction* or psychosis onset* or prodrom* or prodromal psychosis* or high risk* or ultra-high risk* or ultra high risk* or UHR or CHR or clinical high risk* or clinical-high risk* or high clinical risk* or referr* or help seeking* or progression to first-episode psychosis*).ti,ab,tw.	
3	1 or 2	
4	exp "Costs and Cost Analysis"/	
5	exp Health Care Economics/	
6	(economic evaluation* or health economic* or cost-effectiveness* or cost-benefit* or cost analysis*).ti,ab,tw.	
7	4 or 5 or 6	
8	exp Schizophrenia/	
9	exp Psychosis/	
10	exp Affective Psychosis/	
11	exp Schizoaffective Disorder/	
12	(Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder* or psychiatric crisis* or crises*).ti,ab,tw.	
13	8 or 9 or 10 or 11 or 12	
14	3 and 7 and 13	**Results: 97**

Cochrane		
1	MeSH descriptor: [Prodromal Symptoms] explode all trees	
2	(at risk mental state* or ARMS* or psychosis risk* or psychosis prediction* or psychosis onset* or prodrom* or prodromal psychosis* or high risk* or ultra-high risk* or ultra high risk* or UHR or CHR or clinical high risk* or clinical-high risk* or high clinical risk* or referr* or help seeking* or progression to first-episode psychosis*):ti,ab,kw	
3	#1 or #2	
4	MeSH descriptor: [Cost-Benefit Analysis] explode all trees	
5	MeSH descriptor: [Costs and Cost Analysis] explode all trees	
6	(economic evaluation* or health economic* or cost-effectiveness* or cost-benefit* or cost analysis*):ti,ab,kw	
7	#4 or #5 or #6	
8	MeSH descriptor: [Schizophrenia] explode all trees	
9	MeSH descriptor: [Psychotic Disorders] explode all trees	
10	(Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder* or psychiatric crisis* or crises*):ti,ab,kw	
11	#8 or #9 or #10	
12	#3 and #7 and #11	**Results: 566**

Grey Literature Search Strategy

Dissertations & Theses		
1	noft("at risk mental state" OR "ultra high risk" OR "clinical high risk")	**Results: 76**

Scopus		
1	TITLE-ABS-KEY ("at risk mental state*" OR "ARMS*" OR "psychosis risk*" OR "psychosis prediction*" OR "psychosis onset*" OR "prodrom*" OR "prodromal psychosis*" OR "high risk*" OR "ultra-high risk*" OR "ultra high risk*" OR "UHR" OR "CHR" OR "clinical high risk*" OR "clinical-high risk*" OR "high clinical risk*" OR "referr*" OR "help seeking*" OR "progression to first-episode psychosis*")	
2	TITLE-ABS-KEY ("economic evaluation*" OR "health economic*" OR "cost-effectiveness*" OR "cost-benefit*" OR "cost analysis*")	
3	TITLE-ABS-KEY ("Psychosis" OR "psychotic" OR "schizophreni*" OR "sever* mental ill*" OR "sever* mental disorder*" OR "psychiatric crisis*" OR "crises*")	
4	#1 AND #2 AND #3	**Results: 302**

Appendix C International Society of Pharmacoeconomics and Outcomes Research (ISPOR) checklist for model-based evaluations[75]

S. no.	Helper questions to consider	Question	Valmaggia et al 2009	McCrone et al 2013	Perez et al 2015	Wijnen et al 2019
Relevance						
1	Are the demographics similar?	Is the population relevant?	Yes	No	Yes	No
	Are risk factors similar?					
	Are behaviors similar?					
	Is the medical condition similar?					
	Are comorbidities similar?					
2	Does the intervention analyzed in the model match the intervention you are interested in?	Are any critical interventions missing?	No	No	No	No
	Have all relevant comparators been considered?					
	Does the background care in the model match yours?					
3	Are the health outcomes relevant to you considered?	Are any relevant outcomes missing?	Yes	Yes	No	No
	Are the economic end points relevant to you considered?					
4	Is the geographic location similar?	Is the context (settings and circumstances) applicable?	Yes	No	No	Yes
	Is the health care system similar?					
	Is the time horizon applicable to your decision?					
	Is the analytic perspective appropriate to your decision problem?					
Credibility						
Validation						
1	Has the model been shown to accurately reproduce what was observed in the data used to create the model?	Is external validation of the model sufficient to make its results credible for your decision?	No	No	No	Yes
	Has the model been shown to accurately estimate what actually happened in one or more separate studies?					
	Has the model been shown to accurately forecast what eventually happens in reality?					

2	Have the process of internal verification and its results been documented in detail?	Is internal verification of the model sufficient to make its results credible for your decision?	No	No	No	Yes
	Has the testing been performed systematically?					
	Does the testing indicate that all the equations are consistent with their data sources?					
	Does the testing indicate that the coding has been correctly implemented?					
3	Does the model contain all the aspects considered relevant to the decision?	Does the model have sufficient face validity to make its results credible for your decision?	Yes	No	Yes	Yes
	Are all the relevant aspects represented and linked according to the best understanding of their characteristics?					
	Have the best available data sources been used to inform the various aspects?					
	Is the time horizon sufficiently long to account for all relevant aspects of the decision problem?					
	Are the results plausible?					
	If others have rated the face validity, did they have a stake in the results?					
Design						
4	Was there a clear, written statement of the decision problem, modeling objective, and scope of the model?	Is the design of the model adequate for your decision problem?	Yes	Yes	Yes	Yes
	Was there a formal process for developing the model design (e.g. influence diagram, concept map)?					
	Is the model concept and structure consistent with, and adequate to address, the decision problem/objective and the policy context?					
	Have any assumptions implied by the design of the model been described, and are they reasonable for your decision problem?					
	Is the choice of model type appropriate?					
	Were key uncertainties in model structure identified and their implications discussed?					

Data						
5	All things considered, do you agree with the values used for the inputs? Did the approaches to obtaining and processing the data inputs meet the criteria from their corresponding questionnaires?	Are the data used in populating the model suitable for your decision problem?	Yes	Yes	Yes	Yes
Analysis						
6		Were the analyses performed using the model adequate to inform your decision problem?	No	No	No	Yes
7		Was there an adequate assessment of the effects of uncertainty?	Yes	Yes	Yes	Yes
Reporting						
8	Did the report of the analyses provide the results needed for your decision problem? Was adequate nontechnical documentation freely accessible to any interested reader? Was technical documentation, in sufficient detail to allow (potentially) for replication, made available openly or under agreements that protect intellectual property?	Was the reporting of the model adequate to inform your decision problem?	Yes	No	Yes	Yes
Interpretation						
9		Was the interpretation of results fair and balanced?	Yes	Yes	Yes	Yes
Conflict of Interest						
10		Were there any potential conflicts of interest?	No	No	No	No
11		If there were potential conflicts of interest, were steps taken to address these?	Yes	Yes	Yes	Yes

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[redacted]

Appendix E Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist[89]

Section/item	Item no.	Recommendation	Reported on page no/line no
Title and Abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as ‘‘cost-effectiveness analysis’’, and describe the interventions compared	37
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions	37
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions	38-39
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analyzed, including why they were chosen	40-43
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made	40-43
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated	52
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen	40
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate	40
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate	52
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed	52-53
Measurement of effectiveness	11a	Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data	N/A
	11b	Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data	Appendix F & G
Measurement and valuation of preference-based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes	N/A
Estimating resources and costs	13a	Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of	N/A

		its unit cost. Describe any adjustments made to approximate to opportunity costs	
	13b	Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs	46-52 & Appendix G
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate	46-52 & Appendix G
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended	40-42
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model	Figure 3.1 & Appendix G
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty	55-56 & Appendix G
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended	55-56 & Appendix G
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios	56
Characterizing uncertainty	20a	Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective)	N/A
	20b	Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions	56-62
Characterizing heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information	N/A
Discussion			

Study findings, limitations, generalizability, and current knowledge	22	Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge	62-67
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support	68
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations	68

Appendix F Focused MEDLINE Search Strategy

Both search strategies were attempted to find parameter values for the decision tree (search strategy 1) and Markov model (search strategy 2) on 11/5/19 and 11/16/19 respectively. Examining the references of search results and hand-searching was also completed.

Search Strategy #1 - Medline (Ovid)		
1	exp Prodromal Symptoms/	
2	(at risk mental state* or ARMS* or psychosis risk* or psychosis prediction* or psychosis onset* or prodrom* or prodromal psychosis* or high risk* or ultra-high risk* or ultra high risk* or UHR or CHR or clinical high risk* or clinical-high risk* or high clinical risk* or referr* or help seeking* or progression to first-episode psychosis*).ti,ab,tw.	
3	1 or 2	
4	exp Schizophrenia/	
5	exp Psychotic Disorders/	
6	(Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder* or psychiatric crisis* or crises*).ti,ab,tw.	
7	4 or 5 or 6	
8	exp Canada/	
9	(Canada or Canadian or Ontario or London or Quebec or Montreal).ti,ab,tw.	
10	8 or 9	
11	3 and 7 and 10	**Results: 258**

Search Strategy #2 - Medline (Ovid)		
1	exp Prodromal Symptoms/	
2	(at risk mental state* or ARMS* or psychosis risk* or psychosis prediction* or psychosis onset* or prodrom* or prodromal psychosis* or high risk* or ultra-high risk* or ultra high risk* or UHR or CHR or clinical high risk* or clinical-high risk* or high clinical risk* or referr* or help seeking* or progression to first-episode psychosis*).ti,ab,tw.	
3	1 or 2	
4	exp Schizophrenia/	
5	exp Psychotic Disorders/	
6	(Psychosis or psychotic or schizophreni* or sever* mental ill* or sever* mental disorder* or psychiatric crisis* or crises*).ti,ab,tw.	
7	4 or 5 or 6	
8	3 and 7	
9	(first episode psychosis or first-episode psychosis or FEP or first psychotic episode or first episode of schizophrenia or early onset psychosis or early onset schizophren* or early psycho* or early schizophren* or early admission* or first admission*).ti,ab,tw.	
10	exp Canada/	
11	(Canada or Canadian or Ontario or London or Quebec or Montreal or British Columbia or Alberta or Saskatchewan or Newfoundland or Nova Scotia).ti,ab,tw.	
12	10 or 11	
13	(8 or 9) and 12	**Results: 555**

Appendix G Technical Appendix

G.1 Transition Probabilities

The presented transition probabilities in this appendix correspond with the 'Transition Number' in Table 3.1 and Figure 3.1.

G.1.1 Transition Probabilities for Annual Risk Assessment and UHR Treatment

The probabilities to convert to FEP, given treatment for two years, were based on Figure 1 in the original North American Prodrome Longitudinal Study (NAPLS) examining the NAPLS risk calculator.[22] In this publication, UHR participants were treated based on the standard of care available in each of the eight data collection sites (UHR treatment centers). They examined the proportion of the sample who converted (converters = 84 people) and did not convert (non-converters = 512 people) in their respective risk classes.[22]

The following formula was used to determine probability to convert to FEP, given treatment for two years in the UHR population:

$$p(Annual\ convert\ to\ FEP\ |\ Trt\ (2\ yrs)) = \frac{Number\ of\ people\ who\ converted\ in\ risk\ category}{Total\ number\ of\ people\ in\ risk\ category} \qquad \textit{Eq. 1}$$

To convert our two-year transition probabilities to one-year transition probabilities, we used *Eq. 2* to convert the two-year transition probabilities to annual rates and *Eq. 3* to convert these rates to one-year transition probabilities. These equations assume that the events that occur have a constant rate.

$$r = \frac{-[\ln(1-p)]}{t} \qquad \textit{Eq. 2}$$

$$p = 1 - \exp\{-rt\} \qquad \textit{Eq. 3}$$

where r is the rate, p is the probability, and t is the time period of interest.[92]

Using *Eq. 1-3*, we estimated the one-year transition probability used in the model:

$$p(Annual\ convert\ to\ FEP\ |\ Trt\ (2\ yrs)) = \frac{27}{388} = 0.070$$

$$Annual\ Rate = r = \frac{-[\ln(1-0.070)]}{2} = 0.036$$

$$p(Annual\ convert\ to\ FEP\ |\ Trt\ (1\ yr)) = 1 - \exp\{-0.036 \times 1\} = 0.036$$

Therefore, the one-year transition probability for a treated UHR individual with a NAPLS risk score <20% to convert to FEP was about 3.6% (**Transition Number 5**).

To calculate the estimated probability for conversion to FEP, given no treatment (i.e. annual risk assessment) for one year in the <20% risk group, we adjusted the probability for the treated group to convert to psychosis (3.6%) using the relative risk (RR) from a previous meta-analysis by van der Gaag and collegues.[93] The meta-analysis reported a RR of 0.463 (95% CI = 0.33–0.64) at 12 months to convert to psychosis for those enrolled in early psychosis intervention (generally medication and cognitive behavioral therapy) compared to a control condition (generally placebo and monitoring or placebo and supportive therapy). We used the RR to estimate the risk increase expected if the treated group was suddenly untreated. *Eq. 4* was used below.

$$p(Annual\ convert\ to\ FEP\ |\ No\ Trt, yr\ 1) = \frac{p(Annual\ convert\ to\ FEP\ |Trt, yr\ 1)}{RR\ in\ year\ 1\ (Trt\ vs.\ No\ Trt)} \qquad Eq.\ 4$$

Using *Eq.4*:

$$p(Annual\ convert\ to\ FEP\ |\ No\ Trt, yr\ 1) = \frac{3.6\%}{0.463} = 7.7\%$$

Therefore, the one-year transition probability for an untreated UHR individual, given an annual risk assessment, with a NAPLS risk score <20% to convert to FEP was about 7.7% (**Transition Number 2**).

The above equations (*Eq. 1 – 3*) were also used to calculate the probability for conversion to FEP, given treatment for one year in the ≥20% risk group (UHR treatment or **Transition Number 3 and 6** = 14.8%). The untreated probability was not calculated for this risk group because the model called for those at ≥20% risk to be treated with UHR treatment in both the risk stratification strategy and the standard 'treat all' strategy.

Evidence suggests that the risk to convert to FEP reduces over time.[90,93] In the second year of treatment, the probability to convert for the untreated group who were <20% risk was calculated based on the average between the probability in the third year and the first year for those under the annual risk assessment strategy using *Eq.5* (See Table G.1 for parameter values).

$$P(Annual\ Convert\ to\ FEP \mid No\ Trt, yr\ 2) = \frac{p(Annual\ convert\ to\ FEP \mid No\ Trt, yr\ 1) + p(Annual\ convert\ to\ FEP \mid No\ Trt, yr\ 3)}{2} \qquad Eq.\ 5$$

Using *Eq.5*:

$$p(Annual\ Convert\ to\ FEP \mid No\ Trt, yr\ 2) = \frac{7.7\% + 3.6\%}{2} = 5.6\%$$

Following two years of the UHR treatment or annual risk assessments at a specialized UHR clinic, UHR patients then received health care from general mental health services (3+ years). There is no literature available to inform the long-term projection of conversion risk within an UHR population stratified by NAPLS risk scores (3+ years), so the probability to convert was assumed and can be seen in the table below for the <20% risk population (**Table G1**). The ≥20% risk group was treated regardless of what strategy they were enrolled in (i.e. Risk stratification strategy or Standard 'treat all' strategy). The risk to convert was assumed to remained steady over the 15 years at 14.8% in this group (**Transition Number 10**). The uncertainty around these parameter values were assessed in comprehensive sensitivity analyses (**Table G.5** or **Table G.7**).

Table G.1 Probabilities to convert to psychosis for the <20% UHR group

Year	Transition Number	p(Annual convert to FEP | No Trt, yr x)	Transition Number	p(Annual convert to FEP | Trt, yr x))
1	**2**	0.077	**5**	0.036
2	**2**	0.056	**5**	0.036
3+	**8**	0.036	**8**	0.036

Abbreviations: FEP, First Episode Psychosis; p, probability; RR, Relative Risk; Trt, Treatment; Yr, Year.

G.1.2 Transition Probabilities for Mortality in the FEP and Post-FEP States

Age-dependent mortality probabilities for the general population were derived from Statistics Canada.[95] Since there is evidence to suggest that mortality is higher in those experiencing psychosis in disorders such as schizophrenia,[96] age-specific standardized mortality ratios (SMR) from an unpublished study on the Ontario FEP population (in press)[100] was used to estimate mortality for those in the psychosis states: FEP and Post-FEP states. We multiplied the general population mortality rate by the SMR (*Eq. 6*) and converted this to a one-year probability for use in the model.

$$mortality\ rate\ for\ psychosis, at\ specified\ age = (general\ mortality\ rate) \times SMR \qquad Eq.\ 6$$

Table G.2 specified the age-dependent SMRs used as the cohort aged over the 15 years.

Table G.2 Standard mortality ratios for the psychosis and post-psychosis states

Age Range	SMR
16-24	10.4
25-29	13.5
30-34	11.9

Abbreviations: SMR, Standard Mortality Ratio.

G.1.3 Transition Probabilities to the 'Not UHR' State

The study used was a two-year follow up of people originally enrolled in the NAPLS study.[101] The study found that about 33.5% were symptomatic ("symptomatic but not currently meeting criteria for a prodromal risk syndrome").[101] This value was converted to a 1-year transition probability using *Eq. 2* and *Eq. 3* (18.4%). Since there is a paucity of literature available for outcomes for recovery from the UHR state, we assumed that

this probability would be used for both the <20% risk state and ≥20% risk state to transition to the 'Not UHR' state (**Transition Number 7 and 9**). Uncertainty around this parameter was assessed by extensive sensitivity analyses (**Table G.5** or **Table G.7**).

G.1.4 Transition Probabilities from FEP to Post-FEP or Remission

The focused MEDLINE search strategy returned a study by Jordan and colleagues, which examined FEP service data in Montreal, Canada over one year.[102] We assumed that Post-FEP was incomplete remission of positive remission symptoms only, whereas, remission refers to remission from both positive and negative symptoms and followed the consensus for remission criteria by Andreason and colleagues.[91] The study determined that 30% of their cohort was in total remission for 12 months, while 67.8% were in positive remission for about seven months.[102] They were used for the transition probability from the FEP state to the Remission state and Post-FEP state, respectively (**Transition Number 12 and 11**, respectively).

G.1.5 Transition Probabilities Between Remission and Post-FEP

The focused MEDLINE search returned no results on Canadian studies with probabilities to transition from the Remission state to Post-FEP (incomplete remission) or Post-FEP to Remission. As a result, the values from the original PsyMod model were used (**Transition Number 13 and 14**) and the methods on how these were derived are available elsewhere.[81]

G.2 Service Use

Service use was predominantly retrieved from the Prodromal Symptoms in Psychosis Early Clinical Treatment (PROSPECT) clinic. Hospitalization and Emergency Department (ED) service use for the UHR, FEP, and Post-FEP states were gathered from two key 2018 Canadian publications from Anderson and colleagues (**Table G.3**).[16,104] Data used to estimate hospitalization and ED use for the UHR group was converted to annual transition probabilities using *Eq. 2* and *Eq. 3.* Since the data did not stratify service use by risk class, we operated under the assumption that these adjusted annual probabilities for ED and hospitalization use represented the higher risk group (≥20%)

more than the <20% risk group. We assumed the <20% risk group used half the services of the ≥20% risk group. We also acknowledge that the data used in this study may have included people who did not meet the UHR criteria – as no UHR clinics existed in this time to confirm – though they likely displayed prodromal symptoms.[104] For the data collected in literature to determine ED and hospitalization use for the FEP and Post-FEP states, we assumed that those who had left the program were in incomplete remission (Post-FEP).[16]

Table G.3 Emergency department and hospitalization service use data

State	Source	Assumptions	Annual Probability (%)
During UHR Treatment or Annual Risk Assessment			
ED visits			
≥20% UHR	UHR treatment reduces service use by 50% (L, Palaniyappan, Personal Communication)	Under UHR treatment, we assume half the ED use compared to general mental health services.	12.2
<20% UHR	Same source as above	(i) While receiving annual risk assessments, we assume the same amount of ED use as general mental health services; (ii) Under UHR treatment, we assume half the ED use as general mental health services	(i) 12.2; (ii) 6.1
Hospitalizations			
≥20% UHR	Same source as above	Under UHR treatment, we assume half the hospitalizations compared to general mental health services.	6.9
<20% UHR	Same source as above	(i) While receiving annual risk assessments, we assume the same amount of hospitalizations as general mental health services; (ii) Under UHR treatment, we assume half the hospitalizations compared to general mental health services.	(i) 6.9; (ii) 3.5
Post-UHR Treatment (General Mental Health Services)			
ED visits			
≥20% UHR	13.1% in six months (Anderson et al,[104] 2018)	We applied this data to the probability of ED visits in general mental health services	24.5
<20% UHR	Estimation	Assumed to be half the ED use of those at ≥20% risk	12.2
FEP	26.2% in two years (Anderson et al,[16] 2018)	Converted to a one-year probability	14.1
Post-FEP	22.6% in three years (Anderson et al,[16] 2018)	We took data from the percentage of people out of an FEP program (three years after) who visited the ED and converted it to a one-year probability	8.2
Hospitalizations			
≥20% UHR	7.2% in six months (Anderson et al,[104] 2018)	We applied this data to the probability of hospitalization in general mental health services	13.9
<20% UHR	Estimation	Assumed to be half the hospitalization use of those at ≥20% risk	6.9
FEP	26.7% in two years (Anderson et al,[16] 2018)	Converted to a one-year probability	14.4
Post-FEP	16.2% in three years (Anderson et al,[16] 2018)	We took data from the percentage of people out of an FEP program (three years after) who were hospitalized and converted it to a one-year probability	5.7

Abbreviations: ED, Emergency Department; FEP, First Episode of Psychosis; UHR, Ultra-High Risk.

G.3 Cost Methods

To determine costs used in the model, the following general formula was applied:

$$Total\ cost = cost\ per\ U \times service\ use \qquad \textit{Eq. 7}$$

Unit costs (*cost per U*) were derived from the Ontario schedule of benefits (SOB),[105] but these *cost per U* only applied to physicians (i.e. psychiatrists).

When unit costs were readily available (only for physicians), the following formula below was used to determine the annual cost to the health system per patient:

$$Annual\ cost\ to\ health\ system\ per\ patient\ (Physicians) = \frac{cost\ per\ U \times Annual\ frequency\ of\ service \times \left(\frac{length\ of\ each\ session}{U}\right)}{Patients\ per\ session} \qquad \textit{Eq. 8}$$

where unit (U) = 0.5 hours (as per SOB guidelines).

A sample calculation follows below:

The cost to the health system per patient for repeat consultations with a psychiatrist (see Table 3.2, Consultations for UHR and FEP Prescriptions) can be calculated using *Eq. 8*:

From the service use table (**Table 3.2**), we determined the: (i) *Annual frequency of service* (expert opinion from PROSPECT clinic) was 4 consultations per year; (ii) *Length of each session* (expert opinion from PROSPECT clinic) was 0.5 hours per session; (iii) *Cost per U* or unit cost (SOB code K198) was $86.85 per 0.5 hours for out-patient psychiatric care; and (iv) *Patients per session* (expert opinion from PROSPECT clinic) was 1 patient in consultation with psychiatrist at a time.

$$Annual\ cost\ to\ health\ system\ per\ patient\ for\ consultations\ with\ psychiatrist = \frac{86.85 \times 4 \times \left(\frac{0.5}{0.5}\right)}{1} = \$347.40$$

In situations where *unit costs* were not available (for services offered by nonphysicians), methods derived from the 2018 Ontario technology health assessment for cognitive behavioral therapy for psychosis (pg.58-60) were used to calculate the applied hourly salary as a proxy for unit costs.[106]

Applied hourly salary was calculated based on the formula below:

$$Applied\ hourly\ salary = \boldsymbol{cost\ per\ U} = \frac{Annual\ salary}{\left(7.5\frac{hours}{day} \times 5\frac{day}{week} \times 52\frac{weeks}{year}\right) * 0.85\ applied\ rate} \qquad Eq.\ 9$$

where the applied rate of 85% is the time spent by staff on clinical work, and 1,950 hours (i.e., $7.5 \times 5 \times 52$) is the number of hours of work per year a full-time employee is expected to complete.

For example, the cost to the health system per patient for a registered practical nurse (RPN; annual median salary = $56 000 from the PROSPECT clinic) to perform a UHR program service was calculated by applying *Eq. 9*:

$$cost\ per\ U\ for\ RPN = \frac{56000}{\left(7.5\frac{hours}{day} \times 5\frac{day}{week} \times 52\frac{weeks}{year}\right) * 0.85\ applied\ rate} = \$33.79$$

The above *unit cost* could then be applied to a modified version of *Eq. 8* to determine annual costs to the health system per patient (*Eq. 10)*:

$$Annual\ cost\ to\ health\ system\ per\ patient\ (non-physicians) = \frac{cost\ per\ U \times Annual\ frequency\ of\ service \times length\ of\ each\ session}{Patients\ per\ session} \qquad Eq.\ 10$$

Unit costs can be found in the main text (**Table 3.2**), and additional assumptions for costs and service use can be found in Table G.4.

Table G.4 Assumptions for service use and cost of services

Service	Assumptions
NAPLS Assessment	
Equipment Cost of NAPLS Calculator	The NAPLS risk calculator can be freely accessed online and is assumed to cost nothing to access
Consultation Using NAPLS Risk Calculator	Fee for general psychiatric consultation (code: A195)
Active Case Management	
UHR, FEP, and Post-FEP	
Case Monitoring	Based on the salary of a registered practical nurse
Visits with a Psychiatrist	Fee for out-patient psychiatric care (code: K198). Note that we assume that those in the Post-FEP state have a less intensive form of case management and do not receive this service. Their case is mostly managed by their case management nurse
Psychotherapy (ABC-Coping Skills Group)	Based on the salary of a psychologist
Vocational Support	Based on the salary of a counsellor
FEP and Post-FEP	
Metabolic Monitoring (Glucose and Lipid levels)	Fee for glucose, quantitative or semi-quantitative lab test (code: G002) and the fee for a sputum lab test for general assessment (for lipids in this case, code: L815)
Pharmacotherapy	
UHR and 1/3 of FEP and Post-FEP	
Depression Medication – Fluoxetine 40 mg/day	Cost for generic fluoxetine (Apo-Fluoxetine 20mg Cap, where 1 unit = 1 pill). Patients need to take 2 pills to meet the 40mg dosage requirement. We assume 1/3 of FEP patients and Post-FEP patients will continue to receive this medication
1/2 FEP and Post-FEP	
Antipsychotic Medication – Risperidone 4 mg/day	Cost for generic Risperidone (Mylan-Risperidone ODT 4mg Orally Disintegrating Tab, where 1 unit = 1 pill). Everyone in Post-FEP receives this, but half of those with FEP will receive antipsychotic injections instead
1/2 FEP	
Antipsychotic Injection – Paliperidone palmitate (Invega Sustenna) 150mg/ month	Cost of (Paliperidone palmitate) Invega Sustenna 150mg Injection (where 1 unit = 1 injection). Only half of those with FEP receives this

Consultations for UHR and FEP Prescriptions	
Initial Consultation	Fee for general psychiatric consultation (code: A195)
Repeat Consultation	Fee for out-patient psychiatric care (code: K198)
Injection Nurse (FEP)	Based on the salary of a registered practical nurse
General Mental Health Services	
<20% UHR	
Pharmacotherapy offered by a GP	Fee for individual primary health care consultation per unit (code: K005)
≥20% UHR	
Referral by GP	Fee for individual primary health care consultation per unit (code: K005)
Initial Consultation for Pharmacotherapy Prescription	Fee for general psychiatric consultation (code: A195)
Repeat Consultation	Fee for out-patient psychiatric care (code: K198)
Not UHR	
Initial Consultation	Fee for general psychiatric consultation (code: A195)
Repeat Consultation	Fee for out-patient psychiatric care (code: K198)
Remission	
Initial Consultation	Fee for general psychiatric consultation (code: A195)
Repeat Consultation	Fee for out-patient psychiatric care (code: K198)

Abbreviations: ABC, Adversity Belief Consequence; FEP, First Episode Psychosis; GP, General Practitioner; NAPLS, North American Prodrome Longitudinal Study; RPN, Registered Practical Nurse; SOB, Schedule of Benefits; UHR, Ultra-High Risk.

G.4 Utility Modifications and Rank Ordering

There is evidence to suggest that the risk to convert is influenced by prodromal symptom severity, decline in social functioning, and verbal learning and memory scores.[22] As a result, we assumed that the two UHR risk states would have different utilities. The original PsyMod model only had one UHR state utility (not stratified by risk=0.640). We made assumptions about our two UHR risk state utilities (<20% UHR and ≥20% UHR) to reflect clinical evidence suggesting that outcomes differ between these two risk classes.[22] We assumed that the utilities for the <20% risk state was between the 'no UHR' state utility (0.756) and the UHR state utility (0.640) from the original PsyMod model. As a result, we calculated the average between these two values to derive the <20% state utility value. We made similar assumptions for the ≥20% risk state utility – we took the average of the UHR state (0.640) and the FEP state utilities (0.366). Extensive sensitivity analyses were performed on both these UHR state utilities in order to address the uncertainty surrounding the true state utility values for both these risk classes (**Table G.5** and **Table G.9**).

$$< 20\%\ UHR\ state\ utility = \frac{(0.756 + 0.640)}{2} = 0.698$$

$$\geq 20\%\ UHR\ state\ utility = \frac{(0.640 + 0.366)}{2} = 0.503$$

Rank ordering of the best to the worst outcomes was established for probabilistic sensitivity analysis (PSA) based on the new utility values and was confirmed by expert clinical opinion (L Palaniyappan, personal communication):

$$(Perfect\ health, 1) > (no\ UHR, 0.756) > (Remission, 0.720) > (< 20\%\ risk, 0.698) > (\geq 20\%\ risk, 0.503) > (Post - FEP, 0.490) > (FEP, 0.366) > (death, 0)$$

G.5 Methodology for Deterministic Sensitivity Analyses

One-way deterministic sensitivity analysis (DSA) was completed for several parameters. A one-way DSA changes one value at a time and re-runs the analysis to see

how the new results differ from the base case result. Table G.5 provides reasons for the proposed ranges, while Figure G.1 presents the results of the last two DSAs.

Table G.5 Deterministic sensitivity analysis assumptions

Parameter Description	Base Case Value (Range)	Lower Range Assumption	Upper Range Assumption
Cost of the Annual Risk Assessment	$215.65 ($66.67 or $216.65)	Estimated unit cost for a one-hour session with a trained psychologist (calculated)[106]	Unit cost for a one-hour session with a psychiatrist based on the Ontario SOB[105]
Prevalence of the ≥20% risk state	34.9% (34.9% – 57.9%)	From the NAPLS study[22]	Observations from the London PROSPECT clinic (L Palaniyappan, personal communication)
<20% risk state utility	0.698 (0.640 – 0.756)	UHR state utility from the original PsyMod publication[81]	'No UHR' state utility from the original PsyMod publication[81]
≥20% risk state utility	0.503 (0.366 – 0.640)	FEP state utility from the original PsyMod publication[81]	UHR state utility from the original PsyMod publication[81]
Post-FEP state utility	0.490 (0.362 – 0.490)	Post-FEP state utility from the original PsyMod publication[81]	Estimated UK utility value for outpatients with schizophrenia who had moderate functioning.[108,109]
Remission state utility	0.720 (0720 – 0.756)	Expert clinical opinion (L Palaniyappan, personal communication)	Remission state utility from the original PsyMod publication[81]
Year 2: <20% UHR State to FEP State (Annual Risk Assessment)†	5.6% (4.9% – 6.3%)	1/3 of the distance between the year 2 and year 3 probability	1/3 of the distance between the year 1 and year 2 probability
Probability to transition from the <20% risk state to the 'Not UHR' state†	18.4% (18.4% – 44.7%)	From the NAPLS study[101]	From the original PsyMod publication[81]

Abbreviations: FEP, First Episode Psychosis; PROSPECT, PROdromal Symptoms of Psychosis – Early identifiCation and Treatment; SOB, Schedule of Benefits; UHR, Ultra-High Risk.
†The results of these analyses are presented only in Figure G.1.

We also included a two-way DSA (**Figure G.1**) that assessed what the base case result would be in a scenario where both the UHR state utilities remained unchanged from the value used in the original PsyMod publication (i.e. 0.640).[81]

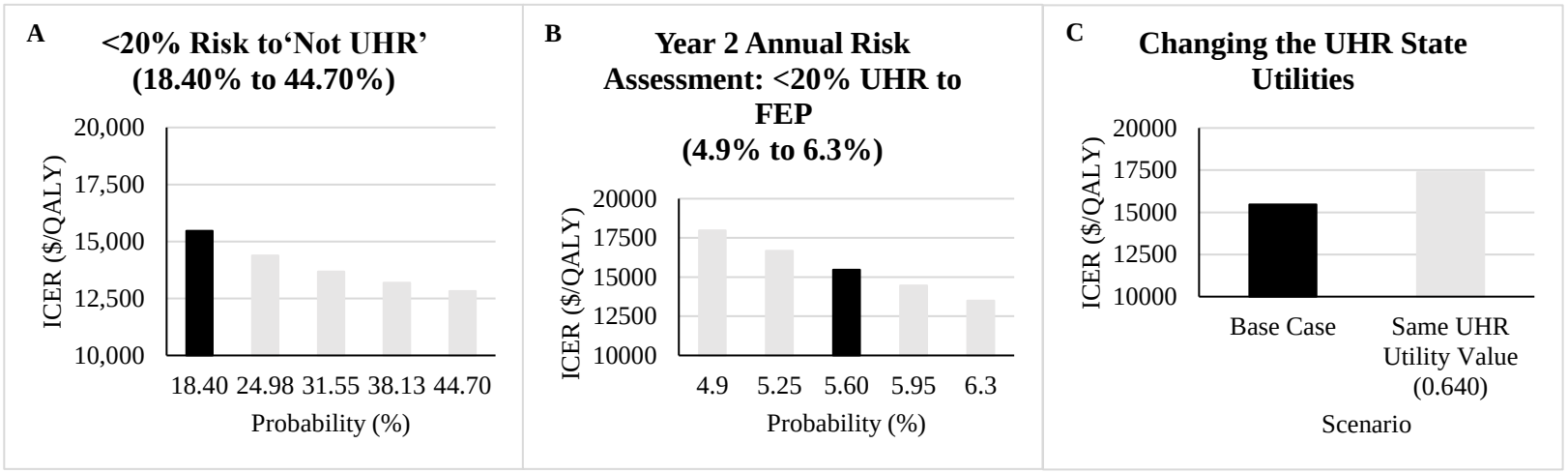

Figure G.1 Deterministic sensitivity analyses comparing the risk stratification treatment strategy to the standard 'treat all' practice

The black bars indicate the base case results, while the grey bars indicate the different ICERs derived from changes made to the: (A) probability to recover from the UHR state in the <20% UHR group; (B) probability of the <20% UHR group to convert to psychosis in year 2 of the annual risk assessment; and (C) giving both the <20% UHR state utility and the ≥20% UHR state utility the same value (0.640).

G.6 Scenario Analysis

The scenario analysis employed different cutoffs for treatment decision in the risk stratification strategy to see how the cost and effectiveness would change compared to the standard 'treat all' strategy. The effect of the different cutoff strategies were only reflected in the different transition probabilities for conversion to FEP from the UHR states. Table G.6 below displays the probabilities to convert to psychosis in the first year for both the group receiving treatment and not receiving treatment (i.e., annual risk assessment), but not the second year. The formula remains the same to calculate the second-year probabilities, as seen in *Eq.5*.

Table G.6 Probabilities for different treatment cutoffs in the scenario analyses

Trt Cutoff (n%)[†]	**Proportion of cohort ≥n**[‡]**% risk**	**<n% p(Annual convert to FEP | No Trt, yr 1)**	**<n% p(Annual convert to FEP | Trt, yr 1)**	**≥n% p(Annual convert to FEP | Trt or No Trt, yr 1)**
10	0.816	0.021	0.010	0.088
15	0.545	0.061	0.028	0.112
20	0.349	0.077	0.036	0.148
25	0.215	0.102	0.047	0.175
30	0.124	0.117	0.054	0.221
35	0.080	0.128	0.059	0.251
40	0.050	0.134	0.062	0.315
45	0.027	0.143	0.066	0.373
50	0.015	0.151	0.070	0.335
55	0.007	0.153	0.071	0.449
60	0.004	0.157	0.073	0.259
65	0.000	0.158	0.073	0.000

Abbreviations: FEP, First Episode Psychosis; p, probability; Trt, Treatment; Yr, Year.

[†]UHR patients with scores for predicted risk to transition to psychosis under the cutoff receive an annual risk assessment for two years, while those with scores equal to or greater than the cutoff are treated with UHR treatment for two years. Note that scores are available up until 64% risk because no UHR patients in Cannon et al[22] scored higher than this value.

[‡] n refers to the treatment cutoff value

G.7 Methodology for the Probabilistic Sensitivity Analyses

For the probabilistic sensitivity analysis (PSA), different distributions were used for the parameters: Dirichlet distribution, beta distribution, lognormal distribution, and Gamma distribution. The beta distribution was used often in situations where parameter values were bound between zero and one (i.e. transition probabilities and utilities), and in instances where there were only dichotomous transition probability outcomes available (transition to FEP or remain as UHR).[92] For polytomous transitions (in the Markov model) with multiple possible outcomes available for an individual in any one state, the Dirichlet distribution was often used.[92] Cost uncertainty was represented by the gamma distribution, since this distribution is appropriate for skewed data – common in cost data – and is bound between zero and infinity.[92] Also, since it is not possible to have negative costs, the gamma distribution was also the appropriate choice for the cost data. Finally, the rank ordering for the utility values (see section G.4) was also upheld in all 1000 iterations of the PSA.

With the exception of the Dirichlet distribution alpha and beta values (which are used to derive one-year transition probabilities for the PSA), Table G.7 displays the alpha and beta values for two-year transition probabilities. Two-year transition probabilities were converted to one-year transition probabilities for every iteration in the PSA.

Table G.7 Distributions for transition probabilities

State Number	State Transition	Parameter	Distribution	Alpha	Beta
Decision Tree					
1	Proportion who score ≥20% upon entry into the UHR clinic	0.349	Beta	208	388
2	Year 1: <20% UHR State to FEP State (Annual Risk Assessment)	0.077	Lognormal†	N/A	N/A
3	≥20% UHR State to FEP State (UHR Treatment)	0.148	Beta	57	151
4	Proportion who score ≥20% upon entry into the UHR clinic	0.349	Beta	208	388
5	Year 1: <20% UHR State to FEP State (UHR Treatment)	0.036	Beta	27	361
6	≥20% UHR State to FEP State (UHR Treatment)	0.148	Beta	57	151
Markov Model					
2	Year 2: <20% UHR State to FEP State (Annual Risk Assessment)	0.056	Estimate‡	Estimate‡	Estimate‡
5	Year 2: <20% UHR State to FEP State (UHR Treatment)	0.036	Beta	27	361
7	<20% UHR State to Not UHR State	0.184	Beta	93	185
8	<20% UHR State to FEP State (General Mental Health Services)	0.036	Beta	27	361
9	≥20% UHR State to Not UHR State	0.184	Beta	93	185
10	≥20% UHR State to FEP State (General Mental Health Services)	0.148	Beta	57	151
11	FEP State to Post-FEP State	0.678	Dirichlet	678	322
12	FEP State to Remission State	0.300	Dirichlet	298	702
13	Remission State to Post-FEP State	0.496	Dirichlet	496	504
14	Post-FEP State to Remission State	0.350	Dirichlet	350	650

Abbreviations: FEP, First Episode Psychosis; N/A, Not Applicable; UHR, Ultra-High Risk.

†Uncertainty is assessed by dividing the values retrieved from the beta distribution for the 1-Year probability of treatment for the treated group by the lognormal distribution for the 1-Year RR.
‡The distribution is the average between the distribution from Transition Number 2 (Year 1) and Transition Number 2 (Year 3).

Table G.8 shows the one-year alpha and beta values used for the cost data in the PSA.

Table G.8 Distributions for costs

State	Cost ($)	Alpha	Beta
Decision Tree			
<20% UHR (Annual Risk Assessment)	952	16	60
≥20% UHR (UHR Treatment)	3048	16	191
<20% UHR (UHR Treatment)	2469	16	154
≥20% UHR (UHR Treatment)	2833	16	177
Markov Model			
Not UHR	389	16	24
<20% UHR	1046	16	65
≥20% UHR	2095	16	131
FEP	6880	16	430
Post-FEP	2662	16	166
Remission	910	16	57

Abbreviations: FEP, First Episode Psychosis; UHR, Ultra-High Risk.

Table G.9 shows the one-year alpha and beta values used for the state utilities in the PSA.

Table G.9 Distributions for state utilities

State	Utility	Alpha	Beta
Not UHR	0.756	756	244
<20% UHR	0.698	698	302
≥20% UHR	0.503	503	497
FEP	0.366	366	634
Post-FEP	0.490	490	510
Remission	0.720	720	280
Death	0	756	244

Abbreviations: FEP, First Episode Psychosis; UHR, Ultra-High Risk.

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Poster Presentations:

Ologundudu, Olajumoke M., Lau, Tammy., Palaniyappan, Lena., Ali, Shehzad & Anderson, Kelly K. Interventions for people at ultra-high risk for psychosis: A systematic review of economic evaluations. Mental Health Research and Innovation Day. November 2020. London, Ontario.