PhD thesis
Lene Halling Hastrup

Exploring methodological issues in mental health economic evaluations:
illustrated in relation to community mental intervention among persons with first-episode psychosis
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Lene Halling Hastrup
Author
Lene Halling Hastrup, MSc (Economics)
Psychiatric Research Unit, Region Zealand

Supervisors
Dorte Gyrd-Hansen, Professor, PhD, Institute of Public Health, Southern Danish University &
Australian Centre for Health Economic Research on Health, University of Queensland,
Merete Nordentoft, Professor, MD, DMSc, Psychiatric Center Copenhagen, Mental Health
Services in the Capital Region of Denmark and Faculty of Health Sciences, University of
Copenhagen
Christian Kronborg, Associate Professor, MSc., PhD, Institute of Public Health, Southern
Danish University
&
Erik Simonsen, Professor, MD, PhD, Dr.h.c., Psychiatric Research Unit, Region Zealand and
Faculty of Health Sciences, University of Copenhagen

Review committee
Chairperson: Professor Jan Sørensen, Southern Danish University
Professor Carl Hampus Lyttkens, Lunds Universitet
Associate Professor Ulrika Enemark, University of Aarhus

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Foreword

This thesis is the result of three years of work at Psychiatric Research Unit, Region Zealand. I was enrolled two years at the University of Copenhagen and the final year at the Institute of Public Health at University of Southern Denmark. Region Zealand financed the Ph.D. project. The idea to the project came up when I was working as Project manager at Storstrøms County evaluating an Assertive Community Treatment (ACT) project, which was carried out at Falster and Southern Zealand. For me as an economist, the psychiatry was a new and interesting field, and I realized during my employment that there was an increasing interest from researchers and decision makers for health economic research of mental health interventions.

I am indebted to many people who have helped me in various ways.
First of all, I am indebted to my supervisors. I would like to thank my main supervisor Dorte Gyrd-Hansen for being optimistic and at the same time realistic about the project all the way through and for continuously helping and inspiring me with her pragmatic way of thinking. Even though, Dorte has lived in Australia for most of the time, I have never felt that her help and support was far away.
I would like to thank Merete Nordentoft, who was the first to introduce me to schizophrenia and other severe mental illnesses and community mental health interventions. Merete has also inspired and encouraged me to do this thesis, and she has been interested in and supported my work with mental health economics all the way through.
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Executive summary
The thesis aims to contribute to mental health economics by answering four methodological and policy relevant questions. The research questions constitute important areas of research relating to economics of community mental health care, with focus on current lack of economic evidence and methodological issues identified in Chapter 1 and 2. Four research questions were addressed in the thesis by way of four original research journal articles (Article 1 to 4).

1) Is early intervention in first-episode psychosis cost-effective?
Since the current economic evidence of early intervention in first-episode psychosis is ambiguous, this study aimed to conduct an economic evaluation of the largest RCT study to date. Adopting a comprehensive public sector perspective, the economic evaluation of the OPUS study found the two-year specialized early intervention program (OPUS) could be implemented at the same costs as treatment as usual, but with better outcome. It is concluded that a longer observation period (5 years) will affect cost effectiveness outcomes.

2) Are mental health care resources distributed to those individuals mostly in need?
Mentally ill patients can have difficulties in engaging with services and are at a greater risk of being lost to the system. The association between individual baseline characteristics of newly diagnosed first-episode psychosis patients and their future consumption of health care services was assessed. It was found that personal characteristics, which indicate severe illness (higher symptom level, lower functional level, having a substance abuse, and being homeless) was statistically significantly associated with higher future costs. The findings suggest that within this specific Danish community mental health setting, resources are distributed according to need.

3) Do caregivers of patients with mental illness experience a higher subjective caregiver burden than other caregivers?
Current evidence suggests that caregivers to patients with mental illnesses suffer from a substantial burden. In a sample of 865 Dutch informal caregivers it was found that being informal caregiver to a care recipient with a mental illness was associated with an added subjective and objective caregiver burden measured by the Caregiver Strain Index (CSI). A higher caregiver burden was experienced by carers who are a child or partner of care recipient,
have a paid job, have a low health-related quality of life or suffer from illness. It is concluded that including the cost of caregiving is highly relevant in the context of mental health.

4) Is it appropriate to apply a generic preference based quality of life measure (EQ-5D) in the context of mental health?

Current evidence suggests that using existing preference-based generic quality of life instruments may be problematic in mental health populations. Using baseline data of 103 patients with schizophrenia spectrum disorders and cannabis abuse, it was assessed how quality of life aspects as measured by MANSA (used for quality of life assessment in psychiatric populations) were associated with the generic preference-based outcome measure, the EQ-5D. Although some correlation between instruments was present, the instruments were found to be largely complementary and it is recommended that both instruments be applied in future economic evaluations.
List of articles

Article 1:
The article is under review at British Journal of Psychiatry (final review round).

Article 2:
Hastrup LH, Nordentoft M, Bertelsen M, Jeppesen P, Jørgensen P, Petersen L, Gyrd-Hansen D. Analyzing the relationship between individual characteristics of first-episode psychosis patients and future resource use in order to ascertain if resources are allocated according to need.
The article has been submitted to Social Psychiatry and Psychiatric Epidemiology.

Article 3:

Article 4:
Hastrup LH, Nordentoft M, Hjorthøj C, Gyrd-Hansen D. Does the EQ-5D measure quality of life in Schizophrenia?
Outline of the thesis

The chapters of the thesis are organized as follows:

**Chapter 1** comprises an introduction to schizophrenia spectrum psychosis and outlines the historical development of community treatment of patients with severe mental illnesses. The clinical evidence of community mental health treatment especially with focus on patients in their first-episode of psychosis is briefly described. Finally, health economic evidence of early intervention treatment in first-episode psychosis is outlined.

**Chapter 2** introduces the welfare economic foundation for health economic evaluation including the welfare production framework that gives a conceptual contribution to understanding the mental health practice and policy. Furthermore, the chapter outlines the types of economic evaluations and gives a summary of cost assessment in health economic evaluation. Available methods for measuring, valuing and incorporating informal caregiving in economic evaluations are described with focus on mental health. Finally, outcome measures in relation to health economic evaluation are outlined and discussed in relation to mental health.

**Chapter 3** presents the central research questions that are the focus of this thesis. The research questions constitute important areas of research relating to mental health economic research, with a focus on current lack of economic evidence and important methodological issues identified in Chapter 1 and 2. Four research questions are addressed in the thesis by way of four original research journal articles (Articles 1 to 4) of which one is published, one is under review, and two are submitted to international peer-reviewed journals.

**Chapter 4** constitutes Article 1: "Cost and effectiveness of early intervention in first episode psychosis: economic evaluation of a randomized controlled trial (the OPUS trial)" which reports the findings of a cost-effectiveness analysis of a two-year intensive early intervention program (OPUS) compared with standard treatment over an observation period of 5 years.

**Chapter 5** consists of Article 2: "Analyzing the relationship between individual characteristics of first-episode psychosis patients and future resource use in order to ascertain if resources are allocated according to need”. This article analyses the association between future costs and severity of illness and other characteristics of newly diagnosed patients within the schizophrenic spectrum.

**Chapter 6** outlines empirical data from a Dutch study of informal caregivers who have been in contact with support centres in Article 3, which is entitled "Do informal caregivers in mental
illness feel more burdened? A comparison of mental versus somatic illnesses”. The study compares the subjective burden of informal caregivers in mental health with other caregivers.

**Chapter 7** consists of Article 4: "Does the EQ-5D measure quality of life in Schizophrenia?", which compares the preferred outcome measure in health economic evaluations, EQ-5D, with a quality of life measure developed for use in psychiatric populations in order to assess the appropriateness of EQ-5D in mental health economic evaluations.

**Chapter 8** provides an extended summary of the findings of the thesis, and reports the answers to the four research questions. Finally, some concluding remarks are made with a focus on scope for future research.
Chapter 1 Introduction

The focus of this thesis is the health economics of community mental health treatment of patients with first-episode psychosis patients who suffer from diseases within the schizophrenia spectrum psychosis. This chapter first gives a brief introduction to schizophrenia and schizophrenia spectrum disorders. Secondly, the historical development of community-based mental health treatment and the clinical evidence of community mental health treatment of patients with schizophrenia are briefly described. Finally, the chapter outlines the clinical and health economic evidence of early-intervention treatment in first-episode psychosis.

1.1 Schizophrenia

Schizophrenia is a psychotic illness and is regarded as one of the most severe chronic and recurrent mental illnesses (1). In addition to clinical symptoms, it often causes marked impairments in social, occupational, cognitive and global functioning, increased mortality and co-morbidity, and stigma (2). Thus, the illness has serious impact on the patient's lives through interference with family, social live and work situation (3). Besides, many patients with schizophrenia often suffer from substance abuse, depression, and are often associated with high rates of violence and legal problems and suicide (4, 5).

The current idea is that schizophrenia occurs with a wide range of symptoms. Symptoms are generally classified as positive (including hallucinations, delusions, thought disorder and emotional withdrawal) and negative symptoms (including social withdrawal, self-neglect, emotional blunting, paucity of speech, loss of motivation and initiative) (6).

Schizophrenia is being described as a multifactorial disorder, and the greatest risk factor is a positive family history (6). Patients who have developed schizophrenia probably have inherited several risk genes, which interact with each other and the environment to cause schizophrenia once a critical threshold is crossed (6).

The incidence of schizophrenia is varying. In a systematic review, Saha et al, 2005, found that the incidence is relatively low (15.2 per 100,000 per year) with a lifetime risk in the general population of just below 1% (7). Because of the lifelong disability and continuous course with frequent relapses, the prevalence of schizophrenia is high (about 7.2 per 1000) (7).

The first psychotic break down usually strikes in the prime of life, during late adolescence and early adulthood (6).
The disease path of schizophrenia is often described in the following phases (Figure 1): premorbid, prodrome, active, remission, and some patients experience relapse. The period immediately preceding the onset of psychosis, during which behaviour and functioning deteriorates from a stable premorbid level of functioning is referred to as the prodromal phase. Remission can be defined as a sustained reduction of or at best absence of psychotic symptoms beneath a predefined threshold level at endpoint (8). The residual phase is regarded as remission from positive symptoms while negative symptoms can still appear. Relapse can be defined as a recurrence of psychotic symptoms above the threshold line.

![Psychotic phases diagram](image)

**Figure 1. Psychotic phases (adapted from (9))**

**1.2 Community based treatment of mental illnesses**

The treatment of schizophrenia usually includes primary antipsychotic drug treatment, psychotherapy, social skills training, psycho-education and work rehabilitation. Nowadays the focus of treatment is on outpatient services. Before the 1960’s, large psychiatric institutions were the dominant form of provision for people with severe and chronic mental health needs in the Western countries (10). In the past thirty years, care of persons with severely mentally illnesses has shifted toward forms of community treatment, which denotes a shift in location away from hospitals. After the deinstitutionalization of psychiatry, the patients were treated in outpatient clinics, day centres or community mental health centres (11).

Assertive Community Treatment (ACT) (12) was developed in the early 1970’s to address the difficulties of caring for people with severely mental illnesses in the community, since the
Community services were not able to meet the complex psychiatric and social needs of this group of patients. The result was often loss of contact with patients due to low patient engagement which resulted in increasing readmission rates at psychiatric hospitals (11).

The main goals of ACT were to keep the people with severe mental illnesses in contact with services, to reduce psychiatric in-patient admissions and to improve outcome, especially social functional level and quality of life.

The key elements of ACT have been described by (13) as follows:

- A core services team is responsible for helping individual patients to meet all of their needs and provides a bulk of clinical care
- The primary goal is improved patient functioning in employment, social relations and activities of daily living
- Patients are directly assisted in symptom management
- The ratio of staff to patients are not greater than 1:15
- Each patient is assigned a key worker who is responsible for ensuring comprehensive assessment, care and review by themselves or by the whole ACT team
- Treatment plans are individual to each patient and may change over time
- Patients are engaged and followed up in an assertive manner
- Treatment is provided in community settings because skills learnt in the community can be better applied in the community
- Care is continuous both over time and across functional areas.

Other types of community based care, including community psychiatric nursing, have been described in the literature. In this thesis, the focus is on ACT and intensive case management models, which have received most attention and have been evaluated extensively in different settings in the literature during the last 20-30 years.

1.3 Clinical results of ACT among persons with severe mental illness

ACT is probably the most evaluated psychiatric non-pharmaceutical intervention and the literature on this model is large. This section only presents a brief overview of the most important results.
The original American randomized controlled ACT trial that was published by (12, 14) found significantly reduced readmission rates, improved clinical outcome, better adherence to antipsychotic medication, and improved social functional level and quality of life. A systematic review by Marshall and Lockwood, which was published in 1998 and based on 17 randomized controlled trials mostly conducted in USA, concluded that ACT reduced psychiatric inpatient care, improved accommodation, employment, and patient satisfaction, when the treatment was targeting severely mentally ill patients with high service use of inpatient admissions (15). However, these results have not been replicated in later European studies (16-20), which found higher patient satisfaction, but no reduction of psychiatric inpatient service use among ACT patients.

In 2007, a systematic review including meta-regression of 52 randomized controlled trials of intensive case management for people with severe mental illness found that trials with high use of inpatient services before the intervention or in the control group were more likely to find that intensive case management reduced inpatient service use(16). Furthermore, the review found that teams, which were organized according to the ACT model, were more likely to reduce the use of psychiatric inpatient service, although this result tended to be less robust in sensitivity analysis.

The review concluded that the inconsistencies between the early findings in United States and the later studies in Europe could be explained by different baseline levels of psychiatric inpatient service use and the authors stated that low levels of hospital use could be interpreted as a proxy for good community service, which meant that even intensive case management teams would find it difficult to have an impact on the inpatient service use. Conversely, it might be fairly easier to reduce inpatients service use in settings with lower level of community service. The authors finally concluded that it was important that the team focused on being organized in accordance with the ACT requirements rather than focusing on the staff requirements.

1.4 Clinical evidence of early intervention in first-episode psychosis

Early intervention in psychosis is a potentially confusing term and refers to the timing of treatment as well as to providing treatment specifically for needs associated with the early phase of the illness (21). Since psychotic disorders can only be diagnosed by symptoms or combinations of symptoms and since causal risk factors that predict onset of psychotic disorder
with any specificity are unknown, primary prevention is currently out of reach (22). Early intervention, therefore, means early secondary prevention (22).

In broad terms, early intervention has two objectives: the first is to prevent the onset of schizophrenia in people with prodromal symptoms, and the second is to provide effective treatment to people in the early stages of schizophrenia with the goal of reducing the ultimate severity of illness (23).

The trajectories of long-term outcome in schizophrenia may be identified and determined within the first 5 years of the illness, which has been described as the critical period (24). This implies that the window for interventions to influence the longer-term outcome is relatively narrow (25).

Duration of untreated psychosis, which is usually expressed as DUP, is the time between the onset of psychotic symptoms and the onset of adequate antipsychotic treatment (26). The association between DUP and symptoms and functional outcome has been confirmed in the literature (27-29). The idea that a longer duration of untreated psychosis leads to worse outcome (29) and that a reduction in DUP will be reflected in improved outcome has led to an expansion in early intervention services in first-episode psychosis patients in many Western countries (6).

Early intervention studies can be divided into i) studies that seek to prevent development of psychosis and ii) studies that seek to improve outcome in diagnosed first episode-psychosis (23):

i) Trials to prevent development of psychosis.

Interventions during the prodromal phase of psychotic illnesses have been attracting significant attention in recent years. However, the results are inconclusive (23). It is unclear whether the prodromal interventions target people in a pre-psychotic state or if the interventions treat people with milder level of psychotic symptoms (30). Before interventions during the prodromal phase are accepted as evidence-based practice, further research is needed to show greater benefits and minimal risks of such preventive interventions beyond what can be achieved through early intervention services provided promptly to people with a diagnosable first-episode psychosis (30).

ii) Trials to improve outcome in first-episode psychosis

Evidence so far has suggested that a specialized early intervention treatment of first-episode psychosis patients resulted in higher benefits through high rates of remission, better control of
symptoms, and greater adherence and retention in treatment in the short term (18 month to 2 years) (31, 32). Furthermore, the treatment has shown benefits related to functional outcome, patient satisfaction and quality of life.

Three 5-year follow-up studies both found that the results did not sustain after transition to standard treatment (33-35). (35) found that patients who were treated in early intervention service for 15 months and then transferred to standard treatment showed poor outcome and high relapse rates and disability rates at 5-year follow-up. In the OPUS trial, the patients received early intervention treatment for 2 years and were then transferred to standard treatment. At 5 years follow-up, the difference in outcome between intervention and control group had disappeared and the early intervention patients had more symptoms and lower functional level (33). In a 5 years follow-up study of the LEO trial, the number of psychiatric bed days was assessed by case-note review (34). Although the study was underpowered, it found that the difference between the specialist intervention group and standard treatment in the number of bed days at 18-month follow-up were not sustained at the 5 years follow-up.

Current evidence suggests that many first-episode psychosis patients benefit from specialized services. It may be that some patients require a longer period of specialized care, perhaps up to 5 years rather than the 18 months up to 2 years generally funded now (36).

1.5 Health economic evidence of early intervention treatment in first-episode psychosis

This section summarizes the current health economic evidence of early intervention in first-episode psychosis patients. The current economic evidence is limited and based on one randomized controlled study and four case control and cohort studies. Furthermore, one model study has been published. In the following, the health economic evidence from the studies of first-episode psychosis treatment is outlined.

Randomized controlled studies

Only one health economic evaluation of early intervention services in first-episode psychosis was found during the literature search. McCrone et al, 2010, evaluated the cost-effectiveness of the intervention of the LEO trial in South London, which was targeting patients in their first episode of psychosis or patients who had previously discontinued treatment (37). The study evaluated 144 patients within a time horizon of 18 months. Primary outcome measures of the clinical study were rates of relapse and hospitalization. Secondary outcomes, which were chosen as outcome measures of the economic evaluation, were quality of life, measured by
MANSA, and vocational recovery, which was defined as a return to or taking up full-time recovery.

The perspective of the evaluation was that of the public sector. The costs items included inpatient and outpatient care (both mental and somatic), primary care services, social care services and contacts with the criminal justice system.

The study found a statistically significantly higher quality of life measured by MANSA at the 18 months follow-up among patients in the LEO trial. The LEO early intervention group had a higher number of contacts with psychiatrists, psychologists, health care assistants, community mental health nurses, and day-care services than the control group during the first 6 months after randomization. However, over the 18 months follow-up, the inpatient costs of the early intervention group were around 33% lower in the early-intervention group. Likewise, total cost were about 17% lower (although this difference was not statistically significant). Since the LEO group had a higher MANSA score and better vocational outcome (although the latter result was statistically insignificant) than the control group, the study concluded that the early intervention appeared to be cost-effective.

The authors acknowledge that the study had some limitations. The study had a relatively short follow-up period and all unit cost information (except for inpatient care) relied on information, which was collected from the patients. Furthermore, all cost data (except for psychiatric inpatient care) between 6 and 12 months were imputed, as these data were not available for this part of the observation period.

Another limitation was that missing outcome or costs were not replaced with imputed values, which may be a source of bias if there are differences between complete cases and patients who dropped out.

Case-control and cohort studies

In the Australian EPPIC study, community-oriented treatment delivered by the Early Psychosis Prevention and Intervention Centre was compared with standard treatment. A before-and-after study compared 51 patients treated in 1993 and 1994 with 51 matched retrospective (historical) controls who had received the pre-treatment model between 1989 and 1992 (38). The follow-up period was 12 months.

The outcome assessed was quality of life and negative symptoms. The cost assessments were limited to mental health care services and consisted of inpatient mental health services,
outpatient mental health services, community mental health teams, general practitioners and private therapy and contacts with psychiatrists.

The EPPIC treatment was found to be less costly than the pre-treatment model, but the study did not give any indication of the statistical significance of the result. The cost savings were due to reductions in psychiatric inpatient service, which out-weighted the increase in community services.

The study had a number of methodological limitations, but encourages the view that early intervention services can be more cost-effective than standard treatment.

In a 7.5 year follow-up study of EPPIC, the long-term cost-effectiveness was assessed (39). Long-term outcome measures were improved (BPRS) and negative symptoms (SANS), functional outcome (GAF) and quality of life (QLS and WHOQOL-BREF). The EPPIC group displayed a lower level of psychotic symptoms and a higher functional level measured by GAF. The perspective of the evaluation was that of the mental health sector, with specific focus on specialised treatment costs: psychiatric bed days, outpatient services, and medication. The total mean mental health service cost per patient was approximately one third of the cost of the control group. The difference was due to lower inpatient and outpatient costs in the EPPIC group, while there was no difference in medication costs.

The conclusions of the study have some important caveats. The original sample is relatively small and follow-up data was only available on 64% of the original cohort, although the authors state that they are confident that the smaller follow-up cohort is representative of the original cohort. Also the study only considered costs from a narrow perspective and did not include costs such as primary health care, community based specialist care, and private inpatient services. Further, the authors state that the improved clinical course of the EPPIC patients may have positive economic consequences not captured in the evaluation such as improved work force participation and hence productivity gains.

Cullberg, et al, 2006, investigated the costs and benefits associated with first-episode treatment of a cohort of 61 first-episode patients with schizophrenia in the Parachute Project compared with two control groups comprising a matched historical comparison group (n = 41) and a prospective control group (n =25) (40). The follow-up period was 3 years. The evaluation found that after the first year, the Parachute group had better symptomatic (BPRS, PANSS) and functional outcomes (GAF) compared with the historical control group. When using the
prospective group as comparator, the Parachute group fared no better. The cost elements included were psychiatric inpatient and outpatient costs. The evaluation also included number of bed days in a residential/crisis home and found that compared to the historical group, the Parachute group had significantly fewer bed days within 3 years, although the cost savings were not assessed. Compared to the prospective group, the total costs of year one were statistically significantly lower in the Parachute group due to lower inpatient costs. These differences between the Parachute group and prospective group became smaller and statistically insignificant in the second and third year of follow-up.

Goldberg et al, 2006 evaluated the impact of a new early intervention service in Canada for first-episode psychosis patients 3 years before the introduction and 3 years after introduction of the new treatment (41). Case records for all first hospital admissions of patients diagnosed within a non-affective psychosis were examined within the study period. A total of 146 pre-PEEP patients and 159 post-PEEP patients were included. Cost items were psychiatric inpatient services, intensive observation unit and emergency rooms. The study found significant differences in characteristics of the two patient groups, which indicated that the patient groups before introduction of PEEP were older and a higher proportion suffered injuries.

The study found statistically significantly lower costs with respect to inpatient beds and emergency room costs among the post-PEEP patients compared to pre-PEEP patients, although the authors concluded that they were unable to definitely confirm that the reductions were attributed to the introduction of the new specialized treatment.

Model studies

Serretti et al, 2009, analysed costs of early intervention services by using a simulation model. The study estimated direct costs for Italian patients with usual care derived from a retrospective prevalence-based multicenter cost-of-illness study that recruited 100 patients with schizophrenia in 10 Italian community-based mental health centres (42). The EPPIC study was used to estimate the type and number of interventions of the experimental model of first-episode psychosis and an application to the Italian setting was simulated. The study found that the experimental model yielded an increase in outpatient service and a decrease in inpatient services, which resulted in 6.1% lower total costs. The study did not
report any information on statistical significance tests. The main limitation of the study is that it was solely based on simulation of published data from another setting.

1.6 Summary
So far the current evidence regarding cost-effectiveness of early intervention services are limited and based on very few studies. Most studies were based on less rigorous design (historical control studies), had small sample sizes, or a relatively short follow-up period. Except for the LEO study, which had a broader public sector perspective (including health care costs, social care and criminal costs) all other studies adopted a narrow health care or mental health care perspective. Only disease-specific instruments were used to measure outcome. All the studies can be regarded as cost-consequence analysis, since they reported outcomes using more than one instrument without specifying which one of the instruments were the most important.

Across the studies found in the literature (of which the quality is varied), the main finding was that specialized interventions targeting first-episode psychosis patients appear to lead to a decrease in psychiatric inpatient in the short-run (18 month to 3 years), which in a narrow mental health perspective outweighed increasing psychiatric outpatient contacts. However, whether such interventions are cost-effective when a broader perspective is adopted, and whether conclusions hold if the observation period is extended remains unanswered. This thesis presents an economic evaluation of the largest RCT study to date (the OPUS trial), which has tested a two-year specialized early intervention treatment in first-episode psychosis with a follow-up period of 5 years (Chapter 4).
Chapter 2 The theoretical framework

The following chapter provides a brief outline of the welfare economic foundation for economic analysis in health care as well as an overview of the various types of economic evaluations. This is followed up by a discussion of which cost components should be included in an economic evaluation of psychiatric interventions and the challenges involved in determining unit cost. The presentation includes a discussion of methods of assessing informal caregiver costs, a cost item which is especially pertinent in the context of mental illness. Choice of outcome measures generally and specifically relating to psychiatric interventions is then described. Finally, the most important methodological challenges described in the literature in relation to economic evaluation of mental health interventions are summarized.

2.1 Welfare economic foundation

According to the theory of welfare economics, health care services are considered as factors that contribute to produce social welfare. When goods or services are allocated to those people who gain most utility from them, social welfare is optimized. The Pareto principle states that distribution of a resource is considered to be optimal when any change in the distribution makes someone worse off, even if others are better off (allocative efficiency). However, if a reallocation of the resources makes at least one person better off and no one worse off, the reallocation is considered as a Pareto improvement. In the case where a reallocation creates gainers and losers, the reallocation of resources is only considered to be a potential Pareto improvement, if the gainers can compensate the losers and remain better off themselves after compensating the losers (also known as the Kaldor-Hicks criterion) (43).

The key elements in the provision of services and the links between services have been described within a conceptual theoretical framework. The welfare production framework can contribute to an understanding of mental health care practice and policy in a number of ways and can be a framework on which to base an evaluation (44).

The production of welfare in Figure 3.1 is a simplification of the links between staff and other resources employed in the production of a health care service, and the health, behavioural and quality of life outcomes that the services will provide for the service users, their families and relevant others (45).
The welfare production framework shows the connections between (46):

- Needs of individuals for care and support, defined by reference to national and local policies, agreed service objectives and the views of service users and relevant others
- Resource inputs used in promoting better health and improvement of quality of life
- Costs of the resource inputs in monetary terms
- Outputs (or intermediate outcome), which is service volumes and quality achieved by combining the resource inputs
- Outcomes (or final outcomes), which are changes over time in the health, welfare and quality of life from prevention, treatment, care and rehabilitation, principally for individual service users. These are gauged in terms of symptom alleviation, changes in behavioural patterns, better personal and social functioning, improved quality of life for the service users and families, and perhaps some wider social consequences.
- Non-resource inputs, which do not have a readily identified cost but which exert influences on outcomes and also mediate the influences of the resource inputs. This could be the care environment, service users’ attitude and personal experiences, e.g. previous treatment or care experiences. Other examples could be attitudes of the staff.

![Diagram of the production of welfare framework](image)

Figure 2.1 The production of welfare framework (adapted from (46))

The production of welfare framework emphasizes that the success of a care system in meeting needs by health and quality of life improvements depends on the mix, volume and deployment
of resource inputs and the services they deliver, which in turn are dependent on the finances made available (46). A good care system aims to offer the services most suitable to meeting patient needs and responding to patient preferences.

2.2 Health economic evaluations

At any given period of time, the amount of resources available to society is scarce, which implies that choices have to be made concerning how to allocate the available resources to maximize social welfare. As described in Chapter 2.1 health care services are considered as factors contributing to produce social welfare, which is optimized when goods or services are allocated to the people who can gain the most utility from them. In absence of individual preferences and utilities, extra-welfarists argue that the objective of the health care sector is to produce as much health benefit as possible suggesting that resources ought to be allocated to the most cost-effective or technical efficient activity or program (43).

Economic evaluation has been defined as the comparative analysis of alternative courses of action in terms of both their costs and consequences (43). The basic tasks of any economic evaluation, including health economic evaluation, are to identify, measure, value and compare the costs and consequences of the alternative being considered. Every decision to fund a service or treat a patient in a resource constrained health system is associated with a loss of health gains elsewhere, which is also known as opportunity costs.

In order to perform a full economic evaluation, it is necessary to perform a comparative analysis of alternative course of action. Choice of comparator is important as it can influence the size of difference in costs and effects. Thus choosing a comparator, which is ineffective and costly, will make the new treatment appear more cost-effective. In a gold standard economic evaluation, the comparator should be the next best alternative. The comparator in mental health evaluations is commonly usual care.

A full economic evaluation can be performed as a cost-benefit analysis (CBA), a cost-effectiveness analysis (CEA) or a cost-utility analysis (CUA). In the following, CBA and CUA are only briefly described, while CEA is outlined in greater detail.
Cost-benefit analysis

The cost-benefit analysis (CBA) is directly founded on the potential Pareto improvement criterion and is a method for assessing if a given policy provides positive net benefits to society. CBA has a broader scope than CEA and CUA, as it can include all welfare generating outcomes and does not require an ex ante definition of goals. Outcomes are generally measured in terms of willingness-to-pay estimates, which are most often elicited using stated preference methods. Since CBAs are rarely conducted in the context of mental health care evaluations because of difficulties in applying monetary values to mental health outcomes, this method is not further described in the thesis.

Cost-effectiveness analysis

The cost-effectiveness analysis (CEA) is the most commonly used alternative to CBA. CEA can be regarded as a method to identify the potentials for economic efficiency. The main difference between CBA and CEA is that CEA measures effectiveness in natural units. In CEA focus is on optimising health gains, and not utility. CEA combines cost information with data on a single outcome measure. In community mental health interventions, a condition-specific measure, for example social functioning or psychotic symptoms is often applied as outcome measure.

Programs that are more effective and less costly than its comparator (scenario II in figure 2) represent a potential for improving the economic efficiency, whereas implementation of a program that would result in a loss of effectiveness and higher costs would lead to a deterioration of economic efficiency. This implies that programs that both are more costly and less effective than the alternatives (scenario IV) should be ruled out. However, it is unclear whether or not a new intervention should be adopted if outcomes are better but costs are higher (scenario I). In this case it is a question of whether the health gain is higher or lower than the health loss incurred due to resources being allocated towards this new intervention and away from other health care services. Likewise, the appropriateness of an intervention is ambiguous if an intervention saves money but is less effective (scenario III).
The horizontal axis in the diagram represents the difference in effect between a given intervention (A) and the relevant alternative (O), and the vertical axis represents the difference in costs, while the alternative O could be status quo or a competing treatment programme. Scenario I and III involve a non-trivial decision, and the cost and effectiveness of two programmes are therefore compared by calculating the incremental cost-effectiveness ratio (ICER) (47): 

\[
\Delta C/\Delta E = \text{Cost}_A - \text{Cost}_B / \text{Effect}_A - \text{Effect}_B
\]

Where \(\text{Cost}_A\) is the arithmetic mean cost for treatment A and \(\text{Cost}\) is the arithmetic mean cost for treatment B; \(\text{Effect}\) is the arithmetic mean effect for treatment A and \(\text{Effect}\) is the arithmetic mean for treatment B; \(\Delta C\) is the difference in cost and \(\Delta E\) is the difference in effect.

Ranking all potential health care interventions in terms of their cost-effectiveness ratios (in the form of a QALY-league table), a decision maker can chose the programmes from the lowest to the highest cost-effectiveness ratio to the point where the resource budget is exhausted.
Clearly, a full list of all possible health care services and their cost effectiveness is unattainable, which means that optimal technical efficiency is difficult to reach due to lack of full information. Nevertheless, the more information that is generated on the cost-effectiveness of health care services, the greater the move toward improved technical efficiency.

The ICERs rely on point estimates of costs and outcomes and yet there will be uncertainty around both of the estimates, which has led to the development of cost-effectiveness acceptability curves. These show the probability that one intervention is more cost-effective than another for alternative values or thresholds placed on a unit improvement in outcome.

A disadvantage of CEA is that the unit of outcome is uni-dimensional and cannot comprise a more complex set of outcomes. Therefore, in cases where there are multiple objectives of treatments or programmes, one approach is to present an array of the differential achievements, along each dimension, for the various alternatives to the decision-makers, so that they can make their own trade-off between effects (43). This form of evaluation is called cost-consequence analysis.

Cost-utility analysis

CUA is a special version of CEA where the outcome is measured in quality-adjusted life years (QALYs) gained or a variant such as disability-adjusted life years (DALYs). The advantage of QALYs as a health outcome is that it simultaneously captures the gains from reduced morbidity and reduced mortality and combines these into a single measure using weights derived from citizens preferences (43). This allows for a comparison of cost-effectiveness across interventions targeting different diseases with the aim of either improving life expectancy and/or improving quality-of-life.

Perspective of the evaluation

It is important to establish the appropriate perspective of the evaluation, which entails ascertaining, which costs should be included and excluded. The choice of perspective defines which policy questions are answered. Generally, if the policy aim is to optimise resource use in society, a societal perspective should be applied in order to avoid sub-optimisation. Also, the greater and the more diverse patient needs are, the broader the range of services likely to be utilised and the greater the number of outcome dimensions an evaluation will need to include in order to gauge impact (44). The societal perspective means that everyone affected by an
All significant outcomes and costs that flow from the intervention should be counted regardless of who experiences the outcomes and costs. In many contexts, but specifically in the context of mental health, the appropriate perspective is the societal perspective, since persons with mental health problems often have more complex needs that necessitate contact with a multitude of service providing sectors (48).

### 2.3 Assessment of costs

It is important to address all the relevant resource dimensions in an economic evaluation to obtain a comprehensive picture of the consequences of alternative care policies or treatment interventions.

#### Resource use

The relevant resource items to include as costs in economic evaluation have been described in four categories (43).

- **Health care resources:**
  - Costs of organizing and operating the programme (including dealing with adverse events caused by the programme)
  - Variable costs
  - Fixed overhead costs (such as light, heat, rent, or capital costs).

- **Patient and family resources:**
  - Out-of-pocket expenses incurred by patients or family members
  - Value of any resources that they contribute to the treatment process.

- **Productivity losses:**
  - Lost time from work as a consequence of participating in the treatment programme under evaluation.

- **Resources consumed in other sectors.**

Accounting for resources consumed in other sectors is relevant in relation to mental health care programmes, which often reach outside the health care sector. In the context of mental health care, it is appropriate to collect information on use of all resources, including apparently unrelated resources, rather than applying a narrow focus which only measures costs related to pre-identified resource items, since it can be difficult to ex ante
identify which types of resource use that are related to the mental health problem and impacted by the intervention in question. Furthermore, in a comparative analysis, the inclusion of apparently unrelated resources does not matter, because with successful randomization, these resources should be equally distributed between the groups.

**Costs**

When the relevant range of costs has been identified, the individual items must be measured and valued. That is, costing has two elements: measurement of the quantities of resource use and assignment of unit costs (43). The measurement of resource quantities often depends on the context of the evaluation and may be collected by different sources, such as case report forms, a review of patient charts, routine data systems, or official registers. Some resources may only be estimated by asking patients, or by having the patients keep a diary. Collecting reliable non-service costs (in order to reflect a societal perspective), such as caregiver costs is considered as being very difficult (49).

From a societal perspective, the appropriate unit cost for a resource is its opportunity cost, which is the value of the forgone benefits because the resource is not available in its best alternative use. If goods are bought on a perfectly competitive market, prices will reflect opportunity cost (in equilibrium \( p=mc \)). However, there are situations where such market prices are not available and unit costs must be derived through adjustment of existing prices, use of tariffs or expert judgement.

**Cost assessment in mental health economics**

In a review of economic evaluations of community mental health treatment, Roberts et al, 2005 found that inclusion of relevant cost items varied widely (50). Early studies of community treatment have simply focused on psychiatric inpatient admissions (51). Later studies included a wider range of health care costs, e.g. outpatient contacts and medication utilization. Besides disability, mortality and health care systems, mental health problems tend to impact upon many aspects of life and welfare. Indirect costs, which fall to the social care, education, housing, criminal justice, social security systems, and informal caregivers, were often overlooked in mental health economic evaluations (52). Another neglected cost is patient time spent using services (53). In economics generally, time is valued using information on supply of labour as a function of wages net-of-tax, but the majority of patients with severe mental illnesses are not
in work, and have not willingly chosen to leave the workforce. This does not mean, however, that the value of time is zero, since time spent in other activities will still have to be forgone in order to use the services.

2.4 Measuring and valuation of informal caregiving

It is difficult to put an economic value on informal care and earlier studies have shown that the costs are high, but informal caregiver costs were more likely to go unaccounted for in mental health economic evaluations (50), which implies that the costs are often overlooked in policy and practice discussions (54).

When the societal perspective is adopted, informal care needs to be incorporated in economic evaluations, since informal care plays a substantial role in the total care provided especially for care of patients with chronic diseases. There is growing evidence of adverse effects on informal caregivers in terms of, for example, opportunity costs due to forgone paid work and quality of life or wellbeing, and informal caregiving is increasingly being considered as a valuable substitute and complement of expensive formal care (55). Informal care is, however a less visible part in terms of costs and effects, and is therefore often ignored in economic evaluations and subsequent policymaking (55).

A definition of informal care is not straightforward. Van den Berg et al, 2004, defined informal care as follows:

"Nonmarket composite commodity consisting of heterogeneous parts produced (paid or unpaid) by one or more members of social environment of the care recipient as a result of the care demands of the care recipient”,

Where heterogeneous parts besides being related to differences in time investment and duration of care also include care tasks provided:

a) Home keeping 
b) Personal care 
c) Support with mobility 
d) Administrative tasks 
e) To some extent socializing.
Not all these tasks are necessarily informal care. Only additional housework chores and administrative tasks due to the disease of the care recipient should be seen as informal care. Furthermore, if a care recipient and caregiver are sharing the same household it makes it more difficult to separate informal tasks from normal household activities. In addition there may be differences in terms of the freedom of choice to become an informal caregiver. A person outside the household may enter a caregiving situation more voluntarily compared to persons sharing a household with the care recipient who may feel more obliged to care. The relationship (e.g. spouse, parent, child, sister, neighbour, or friend) between care recipient and informal caregiver may also affect the way the provision of care is perceived.

The starting point and course of a caregiving episode can also be a source of heterogeneity and have implications for the measurement of informal care (55). When the starting point is slowly evolving, the caregiver grows in her or his role and is gradually taking on more and more tasks, with no clear distinction between before and after becoming an informal caregiver. When the caregiver situation arises abruptly, the forgone normal activities and additional informal care efforts are clearer. This definition leaves open for the possibility for informal caregivers to be paid.

Since informal caregiver costs are to some extent related to the time input of informal caregivers, valid measurements of the time input are necessary. Two frequently applied methods of collecting time budget are the diary method, which is normally considered as gold standard, and the recall method (56).

**Valuation methods**

Different methods for the valuation of informal care have been discussed in the literature. Van den Berg and his colleagues, 2004 have described the methods in three categories:

1) Revealed preference methods where preferences of informal caregivers are deduced from informal caregivers’ decisions or from decisions in the market for close substitutes of informal care (57):

   a. The opportunity cost method assesses the informal caregiver’s benefits forgone due to spending time on providing informal care. The forgone benefits are approximated by the individual's net market wage, which represents the caregiver's value of leisure. The value of informal caregiving equals the net market wage rate multiplied by hours spent on informal caregiving.
b. Proxy good method (or market cost method) distinguishes between different care tasks and values time spent on informal care at the (labour) market prices of a close marked substitute. This approach requires the availability of a marked substitute for the nonmarket good, which is assumed to be almost perfect. The time spent on informal care is valued at the marked wage of, for example, a professional house worker. It remains unclear, whether this market wage rate should be the gross wage (the real opportunity costs to society) or the net wage rate (for which the professional is willing to sacrifice leisure) (57).

2) Stated preference methods which measure and value respondents' preferences mostly for nonmarket commodities through surveys (either oral or written):
   a. Contingent valuation can be used to value informal caregiving by for example assessing the minimum amount of money that an informal caregiver would need to receive to be willing to provide a certain or an additional amount of informal care (58).
   b. Conjoint analysis is a method for the analysis of respondents' preferences for a set of multiattribute alternatives by using different techniques such as ranking, rating or discrete choice experiments. Respondents' preferences are elicited by asked them to rate different states of the world (vignettes) (59).

3) Others measures or methods:
   a. Objective burden assesses the time invested in caregiving, the seriousness of the care recipients' illness, and the care tasks performed.
   b. Subjective burden assessment relates to the strain of care as experienced by the informal caregiver. Many subjective burden instruments are disease-specific and focus often on the negative aspects of caring. The instruments do no value, but merely register the subjective burden.
   c. Health-related quality of life measurement can be used to assess the impact of providing informal care on informal caregivers' health.
   d. Well-being measurement
      i. Well-being valuation method produces a complete monetary valuation of informal care, capturing all the costs (and benefits) faced by informal caregivers in terms of utility. The instrument is a broad concept of well-being, which combines information on happiness, income and time spent
on informal care to derive an implicit trade-off between income and hours of informal care. The trade-off is taken as the monetary value of providing an additional hour of informal care (60).

ii. The CarerQol instrument is measuring care-related quality of life and is attempting to provide a complete valuation of informal caregiving in terms of happiness (60, 61). The instrument describes the impact of informal care on seven main dimensions of subjective burden (fulfilment, relationships, mental health, social support, financial support, perceived support and physical health) and makes an assessment of the total valuation of this impact from the caregivers’ perspective in terms of happiness, using a visual analogue scale.

Incorporating informal care in economic evaluations

Economic evaluations can incorporate a monetary value of informal care (60, 62). The revealed preference methods and stated preference methods yield monetary values that can be used directly on the cost side of CBA, CEA and CUA. On the effect side of CEA or CUA, the health effects for the caregiver can be measured in natural units or QALYs can be combined with cost estimates, based on the revealed preference methods. In CBA, stated preference methods are appropriate tools of valuation of informal caregiving. Measurement of objective burden, subjective burden, health-related quality of life and well-being yields non-monetary outcomes. Utility-based health-related quality of life changes in informal caregivers could in principle be included in CUA, but it is unclear how to combine these changes with the changes in care recipients’ health related quality of life. The measures of objective burden, subjective burden, health-related quality of life and well-being may therefore be seen as a measure of the impact of informal care in ‘natural units’ in economic evaluations. The broader, non-monetary valuation techniques require a broader evaluation framework than CEA or CUA, such as for example cost-consequence analysis.

2.5 Choice of outcome measure

Health economic evaluations should help decision makers to maximize utility or health gains subject to available budgets. In the case where the objective is maximization of health gains
the challenge is to measure outcome on a scale, which allows for comparison of treatments across a range of diseases and conditions.

*Types of outcome measure*

Improvement in health-related quality of life is one of the main economic benefits of treatment, which implies that it clearly needs to be incorporated in economic evaluations (43, 60).

There are three main types of quality of life scales:

i) Disease-specific quality of life measures focus on health outcomes specific to an individual disease, medical condition or patient population and usually concentrate on dimensions of quality of life that are most relevant to the disease under study.

ii) General health profiles are more comprehensive measures of health-related quality of life and include typically items such as physical functioning, ability of self-care, psychological status, level of pain and distress, and social integration.

iii) Preference-based measures are including several dimensions that can be summarized to a single score using utility theory and preferences elicited from the population.

Type ii) and iii) are generic instruments including a broad number of dimensions to measure quality of life in the general populations, while the disease-specific measures are designed to measure quality of life in specific conditions. Examples of common disease-specific quality of life measures in mental health care are Lehman’s Quality of Life Index (QOLI), Heinrichs Quality of Life Scale (QLS), and Manchester Assessment of Need (MANS), while the most common preference-based measures are EQ-5D, 15D or SF6D(63).

The most commonly applied preference-based measure for subjectively describing and valuing health related quality of life is the EQ-5D, which generates a health profile as well as a preference-based index score, which can be used as weights for calculating QALYs. The instrument includes five dimensions or attributes that measure current problems: ‘mobility’, ‘self-care’, ‘usual activities’, ‘pain/discomfort’, and ‘anxiety/depression’. Responses in each dimension have three ordinal levels: 1) no problem, 2) some problems, and 3) major/severe problems, thus defining $3^5 = 243$ possible health states with the state ‘11111’ (perfect health) and death being assigned values of 1 and 0. Preferences for the scoring function were measured with the Time Trade-Off (TTO) technique. The Danish EQ-5D index scores, which were
obtained from a random sample of 1332 members of the Danish population, are ranging between -0.550 (health state worse than death) and 1 (perfect health) (64).

Despite an increasing use of generic preference-based outcome measures, mental health economic evaluations are still mostly based on disease-specific outcomes measures, e.g. instruments that measure symptom improvement, improvement of functional level, management of side effects, or quality of life (65, 66). Also the review of economic evaluations in Chapter 1.5 of first-episode psychosis studies reported only disease-specific outcome measures.

Generic preference-based measures allow for comparisons across different disease groups, providing information useful to support health policy decisions through the application of cost-effectiveness analysis. According to the recommendations of NICE, a generic preference-based outcome measure is the preferred outcome measure in health economic evaluations(67). EQ-5D has been the preferred preference-based outcome measure. However, in recent years, concern has been raised over the tendency in health economic evaluations to solely rely on preference-based outcome measures (51) and specifically the use of EQ-5D in mental health populations. Recent evidence suggests problems of validity and usefulness of generic preference-based measures, especially the EQ-5D, in psychiatric populations and a number of studies has advised that further research is needed on how to appropriately use generic preference-based measures in psychiatric populations (53, 68-72).

2.6 Summary
The demand for economic evaluations as an integral part of research evaluations in order to generate sufficient information to guide mental health decision makers has grown during the last 20 years (51, 53). Although, the number and sophistication of economic evaluations within the area of mental heath has increased, there has been published more health economic evaluations of pharmaceutical treatment of psychiatric patients than well-conducted economic evaluations of community mental health treatment (50).

A number of methodological challenges in relation to conduct economic evaluations in the mental health field have been brought up in the literature. Some of these issues may also be important in the context of other chronic illnesses. In this section, some of the important methodological issues related to conducting economic evaluations are addressed with a special focus on interventions in community-based mental health treatment.
Chapter 1 described how the ACT model was developed to reach persons with severe mental illnesses in community mental health settings with difficulties in accessing community services. As described in Chapter 2.1, the production of welfare framework emphasises that the success of a care system in meeting needs by health and quality of life improvements depends on the mix, volume and deployment of resource inputs and the services they deliver. In a community mental health setting, this implies that the resources are distributed to the patients who have the highest need.

Although a comprehensive societal perspective needs to be taken in mental health economic evaluations, most economic evaluations in community mental health have adopted a more narrow perspective. Chapter 2.3 concluded that even though a number of methods have been developed over the last ten years for measuring and valuing informal care, very few evaluations have actually assessed informal caregiver costs in economic evaluations of community-based mental health interventions. This may be an important omission as many community-based interventions could well increase the necessity for care from family members and friends.

Choice of relevant outcome measure in mental health economic evaluation has also been described as a challenge. Most economic evaluations in community-based mental health care interventions applied disease-specific outcome measures, which cannot be used to compare interventions across different diseases.

The thesis aims to address the described lack of current economic evidence and methodological issues identified in Chapter 1 and 2. Four research questions are formulated and will be presented in Chapter 3. The research questions are addressed in the thesis by way of four original research journal articles (Articles 1 to 4)
Chapter 3 Research questions

On the basis of the current lack of clinical and economic evidence of community mental health treatment of patients with first episode psychosis (as discussed in Chapter 1) as well as important methodological issues in relation to health economic evaluation of community mental health treatment (as discussed in Chapter 2), the following four research questions were formulated.

1) Is early intervention in first-episode psychosis cost-effective?

The literature review in Chapter 1.4 found that the evidence of the clinical effects of early intervention in first-episode psychosis is still limited. Furthermore the long-term consequences of the treatment have not yet been justified. Chapter 1.5 concluded that there remain unanswered questions in relation to the cost-effectiveness of early intervention in first-episode psychosis. Article 1 contributes to the health economics of intensive specialized treatment of patients with first-episode psychosis by conducting a cost-effectiveness analysis of the OPUS trial. The OPUS trial randomized 547 first-episode psychosis patients aged between 18 and 45 years to either a two-year specialized early intervention treatment or standard community-based treatment. The study is the largest RCT study to date and has a follow-up period of five years. All cost data was extracted from Danish official registers.

2) Are mental health care resources distributed to those individuals mostly in need?

The distributional aspects of health care services as described by the ‘production of welfare’ framework were discussed in relation to mental health in Chapter 2.1. Current clinical evidence of the patient group under study, which was outlined in the introduction, suggests that mentally ill patients may have greater difficulties in engagement with services and there may be a greater risk of patients being lost to the system. The challenge for mental health care services is therefore to secure that resources are distributed according to need in order to optimize use of resources. Article 2 addresses, whether health care resources were allocated to high-need patients in their early phase of psychotic illness, by analyzing the association between baseline patient characteristics and future costs.
3) Do caregivers of patients with mental illness experience a higher subjective caregiver burden than other caregivers?

In Chapter 2.2, the importance of a comprehensive assessment of costs in health economic evaluations was discussed. Various methods have been developed to measure and valuate informal caregiving, but current evidence suggests that informal caregiver costs are rarely assessed in mental health economic evaluations. Article 3 focuses on the informal caregiver burden in the context of mental health, by analysing whether caregivers to patients with mental illnesses experience a higher subjective burden than other caregivers and which specific caregiver characteristics are associated with the subjective caregiver burden. The study was based on a dataset of 865 Dutch informal caregivers collected by postal questionnaires as a part of a larger investigation into the situation of informal caregivers. The respondents were recruited through 40 regional support centres for informal caregivers that offer information, organize self-help groups and help with directions to formal care.

4) Is it appropriate to apply a generic preference based quality of life measure (EQ-5D) in the context of mental health?

Choosing an appropriate instrument to measure outcome was discussed in Chapter 2.2. Current evidence suggests that using a preference-based generic quality of life measure may be problematic in mental health populations, as it may not capture all relevant health aspects associated with mental health. Article 4 explores the appropriateness of the EQ-5D among patients in community mental health treatment, by analysing how quality of life aspects as measured by MANSA (an instrument developed for quality of life assessment in psychiatric populations) are associated with the generic preference-based outcome measure, EQ-5D. The dataset of the study was baseline data from the CapOpus project and consisted of 103 patients with schizophrenia spectrum disorder and abuse of cannabis. The patients were recruited through early-psychosis detection teams, community mental health centres, and assertive community treatment teams to a randomised controlled trial of specialized addiction intervention during the period from 2007 to 2009.
Chapter 4
The chapter presents Article 1, which addresses the research question “Is early intervention in first-episode psychosis cost-effective?”

Title: Costs and effectiveness of early intervention in first episode psychosis: economic evaluation of a randomized controlled trial (the OPUS study). The article has been submitted to British Journal of Psychiatry.

Authors:
Lene Halling Hastrup, MSc. Economics, Project manager and Ph.D.student, Region Zealand, Psychiatric Research Unit, Toftebakken 9, DK-4000 Roskilde & University of Southern Denmark
lhhs@regionsjaelland.dk, lenehastrup@yahoo.dk (corresponding author)

Christian Kronborg, Associate Professor, Southern Danish University

Mette Bertelsen, Associate Professor, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Pia Jeppesen, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Per Jørgensen, Medical Director, Board for Mental and Social Affairs, Central Region of Denmark

Lone Petersen Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Anne Thorup, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Erik Simonsen, Professor, Psychiatric Research Unit, Region Zealand

Merete Nordentoft, Professor, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen
Abstract

**Background** Current economic evidence of early intervention treatment in first-episode psychosis is limited and ambiguous.

**Aims** To evaluate the cost-effectiveness of the largest RCT study to date that compared intensive early intervention program of first-episode psychosis patients with standard treatment.

**Method** An incremental cost-effectiveness analysis was applied over 2 and 5 years.

**Results** Adopting a comprehensive public sector perspective, the economic evaluation found that the two-year OPUS intervention can be implemented at the same costs as standard treatment, but with a better outcome. This leads to the conclusion that the specialized early intervention treatment is cost-effective.

**Conclusions** The results suggest that although the total costs over the full observation period did not differ across the treatment groups, there may be cost savings beyond the intervention period due to lower costs at supported living facilities.

**Declaration of interests** The authors declare that they have no conflict of interest.

**Introduction**
Schizophrenia is a severe and chronic illness\(^1\). The first psychotic break down is usually seen in adolescence or early adulthood. The illness has serious impact on the young patient’s lives through interference with the emotional and behavioural balance, social life and working situation\(^2\). Besides, many patients with schizophrenia often suffer from substance abuse and depression, and are often associated with high rates of suicide attempts, violence and legal problems. The attention on first-episode psychosis arises because delayed detection and treatment of the illness predicts poor outcome \(^3\)\(^-\)\(^5\). Furthermore, longer periods of untreated psychosis are associated with poorer outcomes \(^5\). Therefore, it is important to identify possibilities for prevention and treatment of the illness. Early intervention psychiatric services in psychosis seek to help persons who are in their early stages of the illness and are experiencing their first episode of psychosis. The treatment combines Assertive Community Treatment (ACT) with psycho-education and family intervention. The evidence on the effectiveness of early intervention services targeting people in early phases of a diagnosed psychosis has been demonstrated in various studies \(^6\). In particular, randomized controlled trials such as the OPUS study in Denmark and the LEO study in United Kingdom have demonstrated better outcome of specialized early intervention programs over standard treatment on a broad range of outcomes including psychotic and negative symptoms, vocational outcome, social functioning, and reduced inpatient care and treatment adherence \(^7\)\(^-\)\(^9\).
In spite of a fast development of early intervention service offers for persons experiencing their first episode of psychosis during the last decade, the evidence base of the health economics of these services is still limited. So far only a few published studies have investigated the health economic consequences of an early intervention in psychotic disorders. The current evidence on cost-effectiveness is based on studies, which are either less rigorous designed or without enough power in terms of number of patients to answer health economic questions definitely. Especially, the question regarding the long-term cost-effectiveness of early intervention service has not yet been justified. In this study, we aimed to analyze the cost-effectiveness of the OPUS trial, which is the largest trial to date comparing an intensive early-intervention program with community standard treatment.

**Methods**

*Setting and subjects*

This cost-effectiveness analysis was based on a single-blinded, randomized, controlled clinical study comparing intensive early-intervention program (called OPUS) with standard treatment (community mental health centres) in Copenhagen and Aarhus in Denmark. A total of 547 patients in contact with inpatient or outpatient mental health services for the first time were consecutively included in the study from January 1998 to December 2000.

At the time of inclusion, patients were between 18 and 45 years of age and had a clinical diagnosis within the schizophrenia spectrum (ICD 10 codes in the F2 category). None of the patients had previously received antipsychotic medication for more than 12 continuous weeks.

Full details of the study design and intervention is described in the papers presenting the clinical results of the OPUS trial.

*OPUS*

The intensive early intervention programme consisted of an enriched Assertive Community Treatment (ACT) inspired by Stein & Test, psycho-educational family treatment and social skills training. Each patient was offered treatment for 2 years by a multidisciplinary team providing the integrated treatment. The caseload was planned to 1 staff member for each 10 patients. A primary team member was designated for each patient and was responsible for maintaining contact and coordinating treatment within the team and across different treatment and support facilities. Patients were visited in their homes or other places in their community or at their primary team member’s office according to the patient’s preference. A crisis plan was developed.
for each patient. Treatment responsibility was transferred to the hospital during hospitalisations with the primary team member visiting the patient once a week. The office hours were Monday to Friday, 8 am to 5 pm. The patients could leave a message on one of the team member’s answering machine outside office hours and be sure that the team would respond the next morning. The patients were encouraged to take responsibility for their own affairs as soon as possible during the process of recovery. If the patient was reluctant to continue treatment, the team tried to motivate the patient and stayed in contact.

The team offered medication according to the low-dose recommendations for patients with first-episode psychosis using atypical drugs as first choice. Careful attention was paid to the patient's adherence to treatment, using psycho-educational methods. Patients with impaired social skills assessed by the Disability Assessment Schedule 21 were offered social skills training with focus on medication, coping with symptoms, conversations, problem-solving and conflict-solving skills in a group with a maximum of six patients and two therapists. The patients who were unable to work in a group were offered individual training. Patients who were evaluated to not need social skills training received individual psycho-education. Psycho-educational family treatment modelled on McFarlane's manual of multiple-family groups was offered to patients and their family members or friends 22.

Standard treatment

Standard treatment consisted of the standard routines offered by the mental health services in Copenhagen and Aarhus at that time and patients with first-episode psychosis were mixed in with a spectrum of other mental disorders. Contacts were usually made in the local community mental health centres and the patients were in contact with a physician, a psychiatric nurse, and in some cases, a social worker. Caseload varied between 1:20 and 1:30. Administration of antipsychotic medication was based on the same principles as the OPUS treatment.

Type of evaluation, perspective and time horizon

The evaluation adopted a comprehensive public sector perspective, explained below, when considering the costs associated with early intervention services. In order to conduct the economic evaluation, we first determined the utilization of resources for each patient in the sample, i.e. what and which amount of different types of services they received during the study period. Secondly, we determined the costs of each of the services in unit cost per service and finally we calculated the total cost of services for each patient in OPUS and in the control group.
Direct costs of psychiatric in-patient care, other mental health services, general health care services including prescription drugs and services provided by supported houses for mentally ill persons were included in the study.

The time horizon of the study was 5 years.

**Resource use**

We extracted all resource data covering 1998 to 2007 for all patients in the study by their personal identification number registered in the Danish Civil Registration System. Since the patients were consecutively enrolled into the study, we classified the use of services in one-year intervals from 1 to 5 years after the inclusion date.

Data on psychiatric inpatient and outpatient treatment, and contacts on psychiatric emergency departments was collected from the Danish Psychiatric Central Register. At the beginning of the OPUS trial, there appeared to be technical difficulties in reporting the correct number of psychiatric outpatient contacts to the register. We compared the data extracted from the register to the clinicians' own reports on the number of psychiatric outpatient contacts during the intervention period on basis of all 547 patient files. The numbers of outpatient contacts extracted from the register were lower than the number of outpatient contacts registered in the patient files. It appears as if the data on outpatient contacts, at least at the beginning of the OPUS trial, were underreported in the register. Hence, we decided to use the data on psychiatric outpatient contacts during the intervention period collected on basis of accessing the patient files in this study.

Data on somatic inpatient and outpatient treatment and visits to hospital accident and emergency rooms were extracted from the National Patient Registry which is a central registry of all discharges of individual patients from publicly owned hospitals including outpatient visits and accident and emergency department visits. The National Board of Health administers the National Patient Register. Each discharge was classified in accordance with the Danish diagnosis-related grouping system (DRG). Furthermore, we estimated the number of bed days and counted the number of outpatient visits and visits at hospital accident and emergency wards. Data on the use of services from GP's and other medical specialists, dentists, physiotherapists, chiropractors, chiropodists, and psychological counsellors were obtained from the National Health Insurance Service Register, which is a central registry of health care services that are reimbursed by the National Health Insurance. The registry contains information on the date the service was received, type of service, and fee paid to the provider.
Data on all patients’ use of prescription drugs were collected from the Register of Medicinal Product Statistics, which is a central registry based on transaction reports from the dispensing pharmacies. It is administered by the Danish Medicines Agency. The transaction reports were identifiable from the patients’ personal identification number. From each transaction report, we extracted information on the date the receipt was presented at the pharmacy, the package identifier, and the number of packages issued. Data on over-the-counter medication were not available.

We collected information on number of days living in supported homes for patients with mental health problems by combining a database with addresses for all supported housing facilities in Denmark with address information in the Civil Status Register.

We extracted all records for all patients in the study from the registry. That is, we included all resources used regardless of whether the resource use was directly associated with the intervention program. Improvements in mental health might cause individuals to change their demand for other health care services as a consequence of improved mental health.

**Costs**

The resource volumes were combined with unit costs to obtain a cost per person over their time in the study. The unit costs were included as an approximation to society's valuation of each resource item, which is also known as opportunity costs. All costs in the study were calculated in 2009 values of Danish kroners and converted to Euros (1 € = 7.44 DKK), both undiscounted and in present values using a 3%, 5% and 6% discount rate.

Since DRG charges for psychiatric services had not yet been developed in Denmark, we estimated cost of bed days at psychiatric hospital, outpatient visits and contacts at emergency wards by multiplying with a fixed price obtained from the Danish National Board of Health.

We used DRG charges as unit costs for somatic hospital treatment. The DRG charges were provided by the Danish National Board of Health and reflect the average costs for treating patients with similar conditions and processes of care in a Danish hospital. For patients who stayed beyond the number of days covered by the DRG charge an additional charge per day in excess of the number of days covered was added to the hospital costs in accordance with the Danish DRG charge guidelines. In Denmark, hospital treatment is provided free of charge to the patient. National DRG charges are used for reimbursements between regional health care authorities providing hospital treatment if a patient from one region is treated at a hospital in another region.

The unit costs of GP services and services from other healthcare providers were based on the prevailing National Health Insurance fee schedules. The fee reimbursed at the point of
consumption was provided along with the data on resource use. A fixed fee between €7 and €10 per patient was added to the total cost of GP services for every 3 months to reflect that GPs are paid by a mixture of capitation and fee for service. We added patient co-payment for physiotherapy, chiropractic treatment, and dental services as appropriate in accordance with national fee schedules. Since the fees were fixed by fiat, we assumed that the fees equalled opportunity cost to physicians and other private practicing healthcare providers.

The total charge for each pharmacy transaction was provided along with the data on prescription drug consumption. The total charge was the sum of the patient's out-of-pocket expenses, reimbursement from the National Health Insurance, and the reimbursement from the local health authorities. Thus the total charge equalled the retail price, which included the cost price for the pharmacy, the prescription fee charged by the pharmacy and value added taxes before reimbursement at the point of consumption, and covered the full product cost irrespective of who incurred the costs.

We estimated the costs of living in supported housing facilities by multiplying the number of days in supported houses by a mean charge that represents the reimbursement that supported houses receive from local authorities. This charge varies between the different supported houses depending on the size and support facilities. Since we have no information on which of the supported houses in the area that the patients have been assigned for, we used information from the National Board of Social Services to estimate a mean charge on basis of the reimbursement that the housing facilities in the Copenhagen and Aarhus area receive for a bed day. Missing data for patient who died during the study period were replaced with zero while other missing data were replaced with the last observed value. In sensitivity analysis, we examined the way that the charge of supported housing affected the overall costs.

We counted the total costs of OPUS and the control group by summing all the costs items. The increased psychiatric outpatient costs capture at least a part of the costs of the OPUS intervention. In this case, we were not certain that the psychiatric outpatient cost could be applied as an approximation of the intervention and treatment cost as seen in earlier studies. Therefore, we further estimated the intervention costs and the costs of standard treatment. For comparison, we reported both results of the cost estimation.

To assess the intervention cost of OPUS, we estimated the staff cost of an OPUS team: 1 full time psychiatrist, 1 full time psychiatric nurse, 1 full time psychologist, 1 full time social worker, 1 full time occupational therapist and 1 full time secretary staffed one OPUS team. Further, 1 full time labour market/educational guide was recruited to the Copenhagen teams in 2000. We added variable
costs at transportation, medical drugs and educational and supervision costs of the staff. Fixed costs/operating costs (i.e. rent, electricity, heating and water) were also included.

In sensitivity analysis, we analyzed the ways in which the staff costs affected the overall costs. Since some early intervention teams were established in existing mental health centres, we also examine how exclusion of fixed costs affected the overall costs.

Costs of standard treatment were assessed by estimating staff costs a physician, a psychiatric nurse and a social worker and included variable and fixed costs. Since we have no information of the exact caseload of standard treatment, we assumed a caseload of 1 staff to 25 patients as base case. Further, we examined in sensitivity analysis how different caseloads of standard treatment (1:20 and 1:30) affected the overall costs.

**Outcome**

Since no generic preference based outcome measures or other quality of life measures were available for this study, assessment of overall mental health functioning using the Global Assessment of Functioning (GAF) scale was applied for this economic evaluation. GAF is on a 1-100 scale divided into ten deciles, each of which provides a description of functioning level. A higher score on GAF denotes a better functional level. Figure 1 show that the GAF score was statistically significantly higher in the OPUS group than the control group at two-years follow-up, while this difference in GAF score has disappeared at the 5 years follow-up. GAF has been applied as outcome measure in other health economic evaluations of community mental health interventions (e.g.28,29).

(Figure 1)

**Statistical analysis**

Data was analysed on an intention-to-treat basis. No statistical differences were found between treatment groups at baseline in either clinical or socio-demographic characteristics. Resource use and cost data were analyzed on annual basis and in accordance with the two years and five years follow-up of the clinical trial. We calculated mean costs and mean resource use with their standard deviations for both treatment groups. Mean differences between both groups are presented with their 95% confidence intervals. We estimated confidence intervals by non-parametric bootstrapping as a check of the robustness of the standard parametric t-test. Since we found only minor differences, which did not influence the results, the non-parametric tests are not reported here.
The mean total costs were counted within the study periods of two and five years and added intervention cost during the first two years after inclusion for respectively OPUS and standard treatment. Eventually, we examined the robustness of the results using sensitivity analysis by controlling for the effect of a number of cost items on the total mean costs (table 1). Since OPUS started as a trial with consecutively enrolment of patients, the full capacity of the treatment was not in use from the beginning of the study. We varied the intervention cost from low intervention costs (full capacity) to high intervention costs (lower capacity). We also varied the intervention costs of OPUS by excluding fixed costs and by including higher staff costs. Further, since we do not know the exact costs of standard treatment, we varied the costs by using different levels of caseload of the standard treatment. Finally, we varied the unit cost of a bed day of supported houses in accordance with respectively the lowest and highest price, which was found on supported housing facilities for patients with mental illnesses in areas of Copenhagen and Aarhus.

All data were analyzed using STATA SE 11.0 at Statistics Denmark’s server via remote access.

Results

Resource use

The patients’ resource use is summarized in Table 2. Within the first two years of intervention period the mean number of psychiatric bed days was 28 (CI, 95% -54.96 to -1.33) days lower in the OPUS group than in the control group. After an additional three years the difference was 46 (CI, 95% -89.38 to –3.87) bed days between OPUS and the control group. Thus, more than half of the reduction in psychiatric bed days takes place within two out of five years of observation, which means that the service use of psychiatric bed days remains low after end of the intervention.

Furthermore, as expected the intervention increased the number of psychiatric outpatient visits in OPUS compared with standard treatment. Hence, the mean number of psychiatric outpatient visits was three times higher in OPUS than the control group during the intervention period, i.e. during the first two years of the observation study period. In the following years the difference in the mean number of psychiatric outpatient visits decreased to the same level as the control group. Thus, in total within the 5-year study period the mean number of psychiatric outpatient visits was twice the number of outpatient visits in the control group.

We found no difference in number of days in supported housing facilities during the intervention period. By the year 4 and year 5, the number of days is statistically lower in OPUS than standard treatment.
No other differences in resource use between OPUS and the control group were identified.

**Costs**
The largest mean difference between OPUS and the control group in psychiatric hospital costs appears during the first and third year after inclusion (figure 2). By 4 and 5 years after inclusion, both treatment groups had reached a low level of psychiatric inpatient costs. Also, we found no differences in other annual health care cost items. By year 5, the mean annual costs per patient of supporting living facilities were € - 5176 (€ –9322 to € –1012) lower in OPUS than the control group (figure 3).

Within 2 years, there were marked differences in total health care costs due to psychiatric inpatient treatment (table 4). By the end of OPUS intervention, the mean psychiatric inpatient costs per patient were € 11138 lower than standard treatment (€ -21755 to € -521). There were no differences between the treatment groups in total costs by the end of 2 years.

By the end of 5 years after inclusion, the mean health care costs per patient were € 18337 lower in OPUS than standard treatment due to lower psychiatric inpatient costs (€ -36541 to € -132) (Figure 4). We found no differences in total costs between the treatment groups by the end of 5 years (Table 5).

Within the two-year study period, the mean total costs in OPUS within the intervention period equalled those in the control group, but the OPUS intervention has in earlier studies shown to be more effective than standard treatment.

By the end of five years, there was no difference in effect of primary outcome measures, and we could not reject the hypothesis that the mean total costs in OPUS equalled the total costs in the control group. The incremental cost-effectiveness ratio (ICER), which measures a cost per point improvement of functional level, is only informative if one intervention is both more effective and more costly than its comparator 31. Thus, in this case it was not relevant to calculate the ICER.

Table 6 shows in sensitivity analysis that the variations of the cost items only changed the magnitude of the difference between the OPUS and control group. No matter how the cost items were varied, OPUS was not more expensive than the standard treatment.

**Discussion**
Key findings
In the present economic evaluation, early intervention treatment is shown to be both more effective on the short run (t=2 years) and possible to implement at the same costs as treatment as usual. As such, OPUS may be regarded as cost-effective.

In the five year term, the total cumulative costs of OPUS were equal to standard treatment. Our results show, however, that the higher costs of the OPUS intervention are outweighed by the lower psychiatric inpatient costs and even though there was no statistically significant difference in total costs between the treatment groups, the mean health care costs per patient were lower in the OPUS group. Further, the OPUS group has lower cost at supported housing facilities on the longer run (year 4 and 5), which results in lower total costs of OPUS in year 5.

Thus if only health care services are included in the cost analysis, the mean costs per patient are lower in OPUS than the control group. In this case, the psychiatric outpatient costs were used to approximate the intervention costs.

The sensitivity analysis, where unit costs of days in supported housing facilities and assumptions of intervention costs and costs of standard treatment were varied, showed a robust result. No matter how the cost items were varied, OPUS was not more expensive than standard treatment. The evaluation of the trial was undertaken before the OPUS program was implemented with a full caseload. Hence, the calculations of the intervention costs in OPUS were based on a lower caseload than expected, which means that the intervention costs per treated patient were higher compared to a fully implemented OPUS treatment. The sensitivity analysis showed that a fully implemented OPUS treatment with a caseload of 1 staff member per 10 patients might be even more cost-effective.

Comparisons with other studies
To our knowledge, no other studies have analyzed cost-effectiveness of early intervention in psychosis based on randomized controlled trial in such a large patient group of 547 patients during an extended 5 years follow-up period. In the LEO study in south London, 114 patients with newly diagnosed psychosis were randomized to an intervention by a multidisciplinary assertive outreach team. Follow-up period in this study was 18 month. The intervention was comparable with the OPUS intervention and consisted of cognitive-behavioural therapy, family therapy, vocational...
rehabilitation and low-dose medication regimes. Standard treatment was provided by community mental health with no training in dealing with first-episode psychosis. As in the OPUS evaluation, the overall costs showed no statistically significant differences between the treatment groups. The LEO study found a reduction of one third of psychiatric in-patient costs in the early intervention group compared with the control group during 18 months. Also the psychiatric inpatient costs in OPUS were reduced by one third during the first 3 years after inclusion compared with standard treatment and after 3 years reached the same level as standard treatment. In an extension of the follow-up period with the same LEO patient group, the gains of early intervention during the first 1-2 years were lost when transferred to standard treatment 

In the EPPIC study from Australia, a cohort of 51 first episode psychotic patients who received high-quality care were compared at one-year follow up with a historical matched control group of 51 patients who received community care. After the first year of treatment the EPPIC group had significantly better functional and symptomatic outcomes. The improved outcome was demonstrated in association with a reduction in mental health service costs due to a halving of the use of psychiatric in-patient services, which was more than able to compensate for a doubling in the intensity and costs of the EPPIC treatment.

In an extension of the EPPIC study, the long-term cost-effectiveness was assessed at the follow-up after approximately 7.5 years. Complete follow-up data were available for 65 of the original 102 patients. In contrast to the present study, the EPPIC study found an advantage both in terms of clinical outcomes and treatment costs, which was maintained beyond the period over which the intervention was provided. The EPPIC patients had higher functional outcome (GAF) and lower positive psychotic symptoms (BPRS total) than the historical controls at follow-up. Moreover, the mean total costs per EPPIC patient including mental health care and medication costs were one-third of the costs of the control group. The authors, however, acknowledge the caveats of the study that among others include small sample size and large attrition (36%) of the original cohort of 102 patients. In the Swedish 'Parachute Project', 61 first episode psychotic patients were followed over 3 years and compared to two other treatment groups. The study assessed mental health care costs and found that the psychiatric inpatient costs in the first episode group were one-third of the control group, while the outpatient costs were more than four times higher in the first episode group. The study found no differences in costs during two and three years after inclusion.
Strengths and weaknesses of the study

A major strength of the present study is the design of the trial, which was conducted as a randomized controlled trial in routine psychiatric outpatient settings with a relatively large patient sample and a long-term follow-up period. Further, the study relies on data drawn from official Danish registers, which are known to be of high quality and characterized by a high degree of completeness and validity. Limitations: The study did not include indirect cost, as contacts with the criminal justice system or care provided by informal caregivers, like family and friends. Informal caregiving is unpaid but may clearly carry an economic cost since the time used for informal caregiving usually could be used for other purposes. Earlier studies among patients with schizophrenia have shown that informal caregiving is substantial in this patient group.

Productivity loss was neither included in the study, but we calculated the costs of early age pension as an indicator of the patients’ ability to be a part of the labour force. There appeared to be no difference between the treatment groups in the costs of early age pension during 2 and 5 years after inclusion. Likewise, there was no difference in the proportion of patients who had a job or was being educated after five years (data not shown here).

Implications for clinical practice and for policymakers

The results of this economic evaluation indicate that the OPUS intervention is a cost-effective treatment due to lower psychiatric inpatient costs during the intervention period that offset the higher costs of psychiatric outpatient care.

Since the difference in effect on the primary outcome measures disappear during the period of three years after transition to standard treatment, it is has been suggested that the two years intervention period is too short at least for some of the patients. At this point of time, there is no evidence for the optimal duration of the specialized early intervention treatment to prevent relapse or which specific elements of the early intervention that needs to be offered for an extended period to prevent relapse. Birchwood hypothesized that there is a critical period up to five years after onset of psychotic illness, which represents a window of opportunity where the long-term course can be influenced. A randomized controlled trial, OPUS-II, is being carried out in Denmark these years in order to test whether an extension of the specialized intervention up to five years will allow the beneficial effects to continue beyond the critical phase, through consolidation of improved social and functional outcomes. In the light of this evaluation, the costs of a five years intervention seem to depend on the intensity of the intervention in terms of costs and on supported housing facility
costs since the psychiatric inpatient costs reached the same low level in both treatment groups 4 years and in particular 5 years after the intervention.

Conclusion
This economic evaluation shows that the integrated early intervention treatment is not more expensive than standard treatment within the two years intervention period. Moreover, the OPUS patients have a better outcome, which leads us to the conclusion that the OPUS treatment is cost-effective.

During the two years of active treatment, and during the first five years of follow-up, there were significantly lower health care costs in the OPUS group compared to standard treatment group.

During the five years, there was no statistically significant difference in total cumulative mean costs between OPUS and standard treatment. However, the costs at supported housing facilities were lower 4 and 5 years after inclusion in the OPUS group compared to standard treatment group, which led to statistically significantly lower total costs of OPUS in year 4. This finding indicates that there might be long term cost differences between the intensive early intervention treatment and standard treatment for patients with first episode psychosis.

Declaration of interest
None

Reference List


(37) Awad AG, Voruganti LN. The burden of schizophrenia on caregivers: a review. *Pharmacoconomics* 2008; **26**:149-162.
Figure 1. Mean GAF score at baseline, 2 and 5 years
Figure 2. Mean psychiatric hospital cost (Euro, 2009 prices). OPUS and control group, 1 to 5 years after inclusion.
Figure 3. Mean cost difference per patient between OPUS and control group at supported housing facilities (Euro, 2009 prices). 1 to 5 years after inclusion.
Figure 4. Mean total cost difference per patient between OPUS and control group. Year 1 to year 5 (Euro, 2009 prices)
Table 1. Main unit costs and assumptions used in costs analysis and interval for sensitivity analysis, 2009 Euro

<table>
<thead>
<tr>
<th>I. OPUS Intervention costs per year</th>
<th>Base case</th>
<th>Applying lowest observed unit cost</th>
<th>Applying highest observed unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Fixed costs excluded</td>
<td>8459</td>
<td>7370</td>
<td>9647</td>
</tr>
<tr>
<td>I. Higher staff costs</td>
<td>9774</td>
<td>8574</td>
<td>11173</td>
</tr>
</tbody>
</table>

II. Costs of standard treatment: caseload (staff/patient ratio) of standard treatment

<table>
<thead>
<tr>
<th>II. Cost standard treatment per year ( \text{staff/patient ratio} = 1:25 )</th>
<th>Base case</th>
<th>Applying lowest observed unit cost</th>
<th>Applying highest observed unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>II. Cost standard treatment per year ( \text{staff/patient ratio} = 1:30 )</td>
<td>437</td>
<td>2864</td>
<td>4229</td>
</tr>
<tr>
<td>II. Cost standard treatment per year ( \text{staff/patient ratio} = 1:20 )</td>
<td>878</td>
<td>3231</td>
<td>4847</td>
</tr>
</tbody>
</table>

III. Mean estimated cost per day of supported homes

<table>
<thead>
<tr>
<th>III. Mean estimated cost per day of supported homes</th>
<th>Base case</th>
<th>Applying lowest observed unit cost</th>
<th>Applying highest observed unit cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>321 25</td>
<td>3</td>
<td>512</td>
</tr>
</tbody>
</table>

\(^1\) Equals cost of OPUS at full capacity (Euro 8445)

\(^2\) Equals cost of OPUS at base case (Euro 9694)
Table 2. Resource used within 2 years and 5 years after inclusion to OPUS and control group, selected items

<table>
<thead>
<tr>
<th>Service use within 2 yrs</th>
<th>OPUS</th>
<th>Control</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. bed days in psychiatric hospital</td>
<td>94.08 ± 8.86</td>
<td>122.22 ± 10.39</td>
<td>-28.15 (-54.96 to -1.33)</td>
</tr>
<tr>
<td>No. psychiatric outpatient visits</td>
<td>73.64 ± 2.63</td>
<td>25.27 ± 1.94</td>
<td>48.37 (41.93 to 54.80)</td>
</tr>
<tr>
<td>No. visits psychiatric emergency rooms</td>
<td>1.36 ± 1.66 ±</td>
<td>1.66 ±</td>
<td>( to)</td>
</tr>
<tr>
<td>No. bed days in somatic hospital</td>
<td>2.05 ± 1.41 ±</td>
<td>( to)</td>
<td></td>
</tr>
<tr>
<td>No. outpatient visits</td>
<td>0.87 ± 0.14</td>
<td>0.65 ± 0.10</td>
<td>0.23 (-0.11 to 0.56)</td>
</tr>
<tr>
<td>No. visits emergency rooms</td>
<td>0.43 ± 0.03</td>
<td>0.44 ± 0.04</td>
<td>-0.01 (-0.11 to 0.09)</td>
</tr>
<tr>
<td>No. GP consultations</td>
<td>6.45 ± 0.48</td>
<td>6.84 ± 0.72</td>
<td>-0.39 (-2.09 to 1.30)</td>
</tr>
<tr>
<td>No. telephone consultations</td>
<td>5.56 ± 0.49</td>
<td>6.67 ± 0.64</td>
<td>-1.11 (-2.69 to 0.48)</td>
</tr>
<tr>
<td>No. consultations psychiatrist</td>
<td>0.23 ± 0.08</td>
<td>0.23 ± 0.09</td>
<td>0.00 (-0.24 to 0.24)</td>
</tr>
<tr>
<td>No. consultations psychologist</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>No. of packages Prescriptive drugs</td>
<td>21.99 ± 2.12</td>
<td>24.53 ± 3.19</td>
<td>-2.54 (-10.04 to 4.79)</td>
</tr>
<tr>
<td>No. of days in supported housing facilities</td>
<td>30.19 ± 6.37</td>
<td>33.56 ± 7.36</td>
<td>-3.37 (-22.42 to 15.68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Service use within 5 yrs</th>
<th>OPUS</th>
<th>Control</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. bed days in psychiatric hospital</td>
<td>147.25 ± 13.67</td>
<td>193.88 ± 16.97</td>
<td>-46.63 (-89.38 to -3.87)</td>
</tr>
<tr>
<td>No. psychiatric outpatient visits</td>
<td>109.65 ± 4.48</td>
<td>56.46 ± 3.96</td>
<td>53.18 (41.43 to 64.93)</td>
</tr>
<tr>
<td>No. visits psychiatric emergency rooms</td>
<td>3.27 ± 0.39</td>
<td>3.82 ± 0.54</td>
<td>-0.55 (-1.86 to 0.76)</td>
</tr>
<tr>
<td>No. bed days in somatic hospital</td>
<td>3.57 ± 0.88</td>
<td>3.71 ± 0.89</td>
<td>-0.14(-2.59 to 2.32)</td>
</tr>
<tr>
<td>No. outpatient visits</td>
<td>2.07 ± 0.32</td>
<td>1.57 ± 0.19</td>
<td>0.49 (-0.24 to 1.23)</td>
</tr>
<tr>
<td>No. visits emergency rooms</td>
<td>2.16 ± 0.28</td>
<td>2.20 ± 0.32</td>
<td>-0.05 (-0.88 to 0.79)</td>
</tr>
<tr>
<td>No. GP consultations</td>
<td>16.79 ± 1.01</td>
<td>17.43 ± 1.71</td>
<td>-0.64(-4.53 to 3.25)</td>
</tr>
<tr>
<td>No. telephone consultations</td>
<td>19.80 ± 1.33</td>
<td>19.33 ± 1.53</td>
<td>-0.47(-3.98 to 4.91)</td>
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<tr>
<td>No. consultations psychiatrist</td>
<td>1.11 ± 0.28</td>
<td>0.90 ± 0.28</td>
<td>0.20(-0.58 to 0.98)</td>
</tr>
<tr>
<td>No. consultations psychologist</td>
<td>0.12 ± 0.07</td>
<td>0.03 ± 0.03</td>
<td>0.09(-0.06 to 0.25)</td>
</tr>
<tr>
<td>No. of packages Prescriptive drugs</td>
<td>82.22 ± 9.41</td>
<td>83.28 ± 11.45</td>
<td>-1.06(-30.14 to 28.03)</td>
</tr>
<tr>
<td>No. of days in supported housing facilities</td>
<td>84.27 ± 17.37</td>
<td>141.92 ± 24.07</td>
<td>-57.65 (-115.55 to 0.25)</td>
</tr>
</tbody>
</table>

Values are means ± SE
<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric hospital</strong></td>
<td>-7555 (-14184 to -927)</td>
<td>-3583 (-8880 to 1714)</td>
<td>-4679 (-9005 to 353)</td>
<td>-2400 (-6265 to 1466)</td>
<td>-302 (-4183 to 3579)</td>
</tr>
<tr>
<td><strong>Outpatient visits (Psychiatric)</strong></td>
<td>5618 (4730 to 6507)</td>
<td>3942 (3318 to 4567)</td>
<td>1076 (437 to 1716)</td>
<td>87 (-490 to 664)</td>
<td>204 (-907 to 499)</td>
</tr>
<tr>
<td><strong>Emergency rooms (psychiatric)</strong></td>
<td>-28 (-86 to 28)</td>
<td>-31 (-99 to 37)</td>
<td>-49 (-122 to 24)</td>
<td>22 (-35 to 80)</td>
<td>-24 (-98 to 50)</td>
</tr>
<tr>
<td><strong>Somatic hospital</strong></td>
<td>-119 (-487 to 248)</td>
<td>-350 (-795 to 245)</td>
<td>-232 (-567 to 104)</td>
<td>-207 (-818 to 403)</td>
<td>-174 (-607 to 258)</td>
</tr>
<tr>
<td><strong>Outpatient visits and emergency rooms</strong></td>
<td>4 (-45 to 52)</td>
<td>37 (-28 to 102)</td>
<td>16 (-59 to 92)</td>
<td>42 (-50 to 134)</td>
<td>-9 (-113 to 90)</td>
</tr>
<tr>
<td><strong>Prescriptive drugs</strong></td>
<td>-72 (-271 to 128)</td>
<td>-64 (-330 to 201)</td>
<td>-5 (-331 to 322)</td>
<td>130 (-239 to 498)</td>
<td>244 (-136 to 623)</td>
</tr>
<tr>
<td><strong>Medical specialists</strong></td>
<td>89 (-313 to 492)</td>
<td>-17 (-267 to 233)</td>
<td>38 (-108 to 184)</td>
<td>161 (-67 to 389)</td>
<td>-179 (-544 to 187)</td>
</tr>
<tr>
<td><strong>Supported housing facilities</strong></td>
<td>-942 (-3014 to 1130)</td>
<td>-523 (-3953 to 2907)</td>
<td>-1225 (-5073 to 2623)</td>
<td>4186 (-8487 to 1115)</td>
<td>-5167 (-9322 to 1012)</td>
</tr>
<tr>
<td><strong>Total costs incl. psychiatric outpt. care excl. intervention cost</strong></td>
<td>-3005 (-10209 to 4199)</td>
<td>-589 (-7166 to 5989)</td>
<td>-5058 (-11295 to 1179)</td>
<td>-6350 (-12651 to -50)</td>
<td>-5816 (-12125 to 494)</td>
</tr>
<tr>
<td><strong>Total costs excl. psychiatric outpt. care incl. intervention costs</strong></td>
<td>-2807 (-10064 to 4450)</td>
<td>1285 (-5314 to 7885)</td>
<td>-5058 (-11295 to 1179)</td>
<td>-6350 (-12651 to -50)</td>
<td>-5816 (-12125 to 494)</td>
</tr>
</tbody>
</table>

1 Information based on OPUS data during the intervention period (year 1 and 2), while data during year 3-5 was extracted from Danish Psychiatric Central Register.
2 Mean charge: 321 Euro per day (2009-prices)
3 Total mean costs (base case) including psychiatric outpatient care excl. intervention costs
4 OPUS intervention costs of 9644 Euro per year in year 1 and year 2; caseload for standard treatment 1:25; psychiatric outpatient costs during the intervention period are not included.
# Table 4. Mean total cumulative costs per person 0 to 2 years after inclusion, 2009 Euro, undiscounted

<table>
<thead>
<tr>
<th></th>
<th>OPUS N=275</th>
<th>Control N=272</th>
<th>Diff. ± S.E.</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric hospital</strong></td>
<td>37257 ±3510</td>
<td>48396 ±4116</td>
<td>-11138 ±5405</td>
<td>(-21755 to -521)</td>
<td>&lt;0.039</td>
</tr>
<tr>
<td><strong>Outpatient visits (Psychiatric)</strong></td>
<td>579 ±521</td>
<td>5003 ±384</td>
<td>9576 ±648</td>
<td>(8302 to 10850)</td>
<td>&lt;0.000</td>
</tr>
<tr>
<td><strong>Emergency rooms (psychiatric)</strong></td>
<td>269 ±31</td>
<td>329 ±48</td>
<td>-60 ±56</td>
<td>(-171 to 51)</td>
<td>&lt;0.291</td>
</tr>
<tr>
<td><strong>Somatic hospital</strong></td>
<td>800 ±140</td>
<td>1064 ±276</td>
<td>-265 ±308</td>
<td>(-870 to 340)</td>
<td>&lt;0.391</td>
</tr>
<tr>
<td><strong>Outpatient visits and emergency rooms</strong></td>
<td>305 ±34</td>
<td>265 ±32</td>
<td>40 ±46</td>
<td>(-51 to 51)</td>
<td>&lt;0.386</td>
</tr>
<tr>
<td><strong>Prescriptive drugs</strong></td>
<td>1558 ±159</td>
<td>1694 ±149</td>
<td>-136 ±218</td>
<td>(-564 to 293)</td>
<td>&lt;0.533</td>
</tr>
<tr>
<td><strong>Medical specialists</strong></td>
<td>954 ±284</td>
<td>881 ±114</td>
<td>72 ±307</td>
<td>(-530 to 676)</td>
<td>&lt;0.814</td>
</tr>
<tr>
<td><strong>Total health care costs</strong></td>
<td>41076 ±3532</td>
<td>52767 ±4234</td>
<td>-11690 ±5508</td>
<td>(-22511 to -870)</td>
<td>&lt;0.034</td>
</tr>
<tr>
<td><strong>Supported housing facilities</strong></td>
<td>95 ±1621</td>
<td>9160 ±1870</td>
<td>-1464 ±2473</td>
<td>(-6322 to 3393)</td>
<td>&lt;0.5540</td>
</tr>
<tr>
<td><strong>Total costs incl. psychiatric outpt. care excl. intervention costs</strong></td>
<td>373 ±4172</td>
<td>66967 ±4910</td>
<td>-3594 ±6438</td>
<td>(-31009 to 9054)</td>
<td>&lt;0.577</td>
</tr>
<tr>
<td><strong>Total costs excl. psychiatric outpt. care incl. intervention costs</strong></td>
<td>68160 ±4158</td>
<td>69682 ±4971</td>
<td>-1522 ±6474</td>
<td>(-14240 to 11196)</td>
<td>&lt;0.814</td>
</tr>
<tr>
<td><strong>3 % discount rate</strong></td>
<td>65349 ±3982</td>
<td>66863 ±4760</td>
<td>-1514 ±6200</td>
<td>(-13692 to 10664)</td>
<td>&lt;0.814</td>
</tr>
<tr>
<td><strong>5 % discount rate</strong></td>
<td>63590 ±3872</td>
<td>65098 ±4628</td>
<td>-1508 ±6028</td>
<td>(-13349 to 10333)</td>
<td>&lt;0.803</td>
</tr>
<tr>
<td><strong>6 % discount rate</strong></td>
<td>62742 ±3818</td>
<td>64247 ±4564</td>
<td>-1505 ±5945</td>
<td>(-13183 to 10174)</td>
<td>&lt;0.800</td>
</tr>
</tbody>
</table>

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3 Total mean costs (base case) including psychiatric outpatient care excl. intervention costs
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<table>
<thead>
<tr>
<th></th>
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<th>Control N=272</th>
<th>Diff. ± S.E.</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric hospital</strong></td>
<td>58502 ± 5437</td>
<td>77021 ± 6748</td>
<td>-18519 ± 8656</td>
<td>(-35523 to -1515)</td>
<td>&lt; 0.032</td>
</tr>
<tr>
<td><strong>Outpatient visits (Psychiatric)</strong></td>
<td>83 ± 891</td>
<td>11249 ± 789</td>
<td>10534 ± 1191</td>
<td>(8195 to 12874)</td>
<td>&lt; 0.000</td>
</tr>
<tr>
<td><strong>Emergency rooms (psychiatric)</strong></td>
<td>650 ± 79</td>
<td>760 ± 107</td>
<td>-110 ± 133</td>
<td>(-372 to 151)</td>
<td>&lt; 0.407</td>
</tr>
<tr>
<td><strong>Somatic hospital</strong></td>
<td>2064 ± 284</td>
<td>3118 ± 737</td>
<td>-1053 ± 787</td>
<td>(-2599 to 492)</td>
<td>&lt; 0.181</td>
</tr>
<tr>
<td><strong>Outpatient visits and emergency rooms</strong></td>
<td>889 ± 97</td>
<td>800 ± 93</td>
<td>89 ± 134</td>
<td>(-174 to 352)</td>
<td>&lt; 0.507</td>
</tr>
<tr>
<td><strong>Prescriptive drugs</strong></td>
<td>5544 ± 465</td>
<td>5311 ± 465</td>
<td>233 ± 657</td>
<td>(-1058 to 1524)</td>
<td>&lt; 0.723</td>
</tr>
<tr>
<td><strong>Medical specialists</strong></td>
<td>2607 ± 367</td>
<td>2513 ± 235</td>
<td>93 ± 437</td>
<td>(-766 to 953)</td>
<td>&lt; 0.831</td>
</tr>
<tr>
<td><strong>Total health care costs</strong></td>
<td>77451 ± 5624</td>
<td>95787 ± 7382</td>
<td>-18337 ± 9268</td>
<td>(-36541 to -132)</td>
<td>&lt; 0.048</td>
</tr>
<tr>
<td><strong>Supported housing facilities</strong></td>
<td>77 ± 4496</td>
<td>35818 ± 5744</td>
<td>-12042 ± 7285</td>
<td>(-26352 to 2268)</td>
<td>&lt; 0.098</td>
</tr>
<tr>
<td><strong>Total costs incl. psychiatric outpt. care excl. intervention cost</strong></td>
<td>15 829 ± 8141</td>
<td>136646 ± 11139</td>
<td>-20818 ± 13774</td>
<td>(-47875 to 6239)</td>
<td>&lt; 0.131</td>
</tr>
<tr>
<td><strong>Total costs excl. psychiatric outpt. care incl. intervention costs</strong></td>
<td>120615 ± 8140</td>
<td>139361 ± 11193</td>
<td>-18746 ± 13817</td>
<td>(-45887 to 8395)</td>
<td>&lt; 0.175</td>
</tr>
<tr>
<td><strong>3 % discount rate</strong></td>
<td>112032 ± 7488</td>
<td>128834 ± 10245</td>
<td>-16802 ± 12669</td>
<td>(-41688 to 8084)</td>
<td>&lt; 0.815</td>
</tr>
<tr>
<td><strong>5 % discount rate</strong></td>
<td>106878 ± 7100</td>
<td>122536 ± 9683</td>
<td>-15658 ± 11988</td>
<td>(-39206 to 7889)</td>
<td>&lt; 0.192</td>
</tr>
<tr>
<td><strong>6 % discount rate</strong></td>
<td>104452 ± 6919</td>
<td>119579 ± 9420</td>
<td>-15127 ± 11669</td>
<td>(-38049 to 7795)</td>
<td>&lt; 0.195</td>
</tr>
</tbody>
</table>

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Table 6. Sensitivity analysis: Effect on mean differences in cost per patient by changes in cost items within 2 years and 5 years after inclusion. (2009 Euro), undiscounted

<table>
<thead>
<tr>
<th>Mean difference in costs (95% CI)</th>
<th>Costs within 2 years</th>
<th>Costs within 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Base case</td>
<td>-18746 (-45887 to 8395)</td>
<td>1522 (-14240 to 11196)</td>
</tr>
<tr>
<td>Fixed cost excluded</td>
<td>-21217 (-48357 to 5924)</td>
<td>3992 (-16711 to 8725)</td>
</tr>
<tr>
<td>Higher unit costs of supported living facilities</td>
<td>-25918 (-60160 to 8325)</td>
<td>2394 (-16912 to 12124)</td>
</tr>
<tr>
<td>Lower unit cost of supported living facilities</td>
<td>-16216 (-41065 to 8634)</td>
<td>1214 (-13398 to 10970)</td>
</tr>
<tr>
<td>Higher costs of standard treatment (caseload 1:20)</td>
<td>-25918 (-60160 to 8325)</td>
<td>3461 (-16172 to 9257)</td>
</tr>
<tr>
<td>Lower costs of standard treatment (caseload 1:30)</td>
<td>-17454 (-44594 to 9687)</td>
<td>230 (-12948 to 12488)</td>
</tr>
<tr>
<td>Higher OPUS intervention costs</td>
<td>-15980 (-43121 to 11161)</td>
<td>44 (-11474 to 13962)</td>
</tr>
<tr>
<td>Fixed cost excluded</td>
<td>-18854 (-45994 to 8287)</td>
<td>1629 (-14347 to 11088)</td>
</tr>
<tr>
<td>Higher unit costs of supported living facilities</td>
<td>-23152 (-57394 to 11090)</td>
<td>2 (-14146 to 14890)</td>
</tr>
<tr>
<td>Lower unit cost of supported living facilities</td>
<td>-13450 (-38299 to 11399)</td>
<td>52 (-10632 to 13735)</td>
</tr>
<tr>
<td>Higher costs of standard treatment (caseload 1:20)</td>
<td>-17919 (-45060 to 9222)</td>
<td>695 (-13413 to 12023)</td>
</tr>
<tr>
<td>Lower costs of standard treatment (caseload 1:30)</td>
<td>-14688 (-41829 to 124523)</td>
<td>-2536 (-10182 to 15254)</td>
</tr>
<tr>
<td>Lower OPUS intervention costs</td>
<td>-21243 (-48384 to 5897)</td>
<td>4019 (-16737 to 8699)</td>
</tr>
<tr>
<td>Fixed cost excluded</td>
<td>-23392 (-50532 to 3749)</td>
<td>6168 (-18886 to 6550)</td>
</tr>
<tr>
<td>Higher unit costs of supported living facilities</td>
<td>-28415 (-62657 to 5827)</td>
<td>4892 (-19409 to 9626)</td>
</tr>
<tr>
<td>Lower unit cost of supported living facilities</td>
<td>-18713 (-43562 to 6136)</td>
<td>3712 (-15895 to 8472)</td>
</tr>
<tr>
<td>Higher costs of standard treatment (caseload 1:20)</td>
<td>-23182 (-50323 to 3959)</td>
<td>5958 (-18676 to 6760)</td>
</tr>
<tr>
<td>Lower costs of standard treatment (caseload 1:30)</td>
<td>-19951 (-47092 to 7190)</td>
<td>2727 (-15445 to 9991)</td>
</tr>
</tbody>
</table>
Chapter 5

The chapter presents Article 2, which addresses research question 2: “Are resources distributed to those individuals mostly in need?”.

Title: Analyzing the relationship between individual characteristics of first-episode psychosis patients and future resource use in order to ascertain if resources are allocated according to need.

The article has been submitted to Social Psychiatry and Psychiatric Epidemiology.

Authors
Lene Halling Hastrup, MSc. Economics, Project manager and Ph.D.student, Region Zealand, Psychiatric Research Unit, Toftebakken 9, DK-4000 Roskilde & University of Southern Denmark
lhhs@regionsjaelland.dk, lenehastrup@yahoo.dk (corresponding author)

Merete Nordentoft, Professor, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Mette Bertelsen, Associate Professor, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Pia Jeppesen, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Per Jørgensen, Medical Director, Board for Mental and Social Affairs, Central Region of Denmark

Lone Petersen Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

Professor Dorte Gyrd-Hansen, (i) Institute of Public Health, University of Southern Denmark, Winslowsvej 9, DK-5000 Odense C, (ii) Australian Centre for Health Economic Research on Health, University of Queensland, Herston, Q4006, Australia
Abstract

**Aim:** Coupling data on future resource consumption with baseline characteristics can provide vital information of future consumption patterns for newly diagnosed patients. The aim of this study was to explain the association between baseline variables such as demographic characteristics, diagnosis and severity of illness of first-episode psychosis patients and future costs and to test whether a higher need (as measured by severity of illness) of newly diagnosed patients was associated with higher future service costs.

**Method:** A sample of 547 patients between 18 and 45 years randomized to the OPUS trial was analyzed in the study. Multiple regression analysis was applied to analyze the impact of the explanatory variables on mean total costs, which consisted of total health care costs and costs at supported living facilities.

**Results:** The study found that patient baseline characteristics such as lower age, higher level of symptoms (GAF-s), lower functional level (GAF-f), having a substance abuse, and being homeless were associated with higher total costs over 5 years.

**Conclusion:** The association between future costs and severity of illness of newly diagnosed patients suggests that higher needs among patients were associated with higher resource input level. Strength of the study was that resource data was extracted from official Danish registers and caregiver characteristics were collected by interviewers of the OPUS trial. Given the results are likely to be context specific being reflecting Danish treatment practices, we perceive that the results can be generalised to settings with similar treatment practices.
Introduction
In recent years, analysis of patient characteristics has become increasingly important in explaining and predicting individual health service use and resource consumption in mental health research [Dunn et al. 2003; Kilian et al. 2003]. Various approaches of modelling health care cost data have been described in the literature [Gregori et al. 2011].

The present study uses data from a randomized controlled trial of an early-intervention programme (OPUS) conducted in Denmark [Jorgensen et al. 2000]. Using information on base-line characteristics of patients at inclusion and detailed registration of resource consumption over a 5 year period, we examine the relationship between the characteristics of the patients at baseline and future costs. In a literature search, we found previous studies that have focused on the relationship between costs and various individual characteristics among patients with longer duration of severe mental illnesses and previous contacts to community mental health treatment. However, we found no studies investigating the relationship between later costs and baseline patient characteristics in first-episode psychosis. Coupling data on future resource consumption with base-line characteristics at first-episode psychosis can provide vital information for prediction of future consumption patterns for newly diagnosed patients.

The aim of this study was to explain the impact of baseline characteristics of first-episode psychosis patients on the total costs over a period of 5 years and to test whether a higher need (as measured by severity of illness) of the first-episode patients at baseline were associated with higher future service costs. On the basis of prior studies among patients with schizophrenia and other psychosis [Bonizzato et al. 2000; Byford et al. 2001; Carr et al. 2003; Carr et al. 2004; Johannessen et al. 2005; Knapp et al. 2002; McCrone et al. 2001; Mirandola et al. 2004; Rund and Ruud 1999], we hypothesized that the future costs would be associated with:

1) Demographic characteristics
2) Diagnosis
3) Severity of the illness

Methods
Sample
The sample consisted of 547 patients who were in contact with inpatient or outpatient mental health services for the first time and were randomized to either an intensive early-intervention program
(OPUS) or standard treatment in Copenhagen and Aarhus in Denmark (modified assertive community treatment or standard treatment in a community mental health centre). The patients were between 18 and 45 years and had a clinical diagnosis within the schizophrenia spectrum. Full details of the clinical trial and the intervention are described elsewhere [Jorgensen et al. 2000]. The individual patient characteristics have previously been examined and no statistical differences were found between the treatment groups at baseline in either clinical or socio-demographic characteristics [Petersen et al. 2005]. Descriptive statistics of all variables are presented in table 1. The mean age of the patients in the sample was 26 years, and 59% were males. Two thirds of the patients were diagnosed with schizophrenia (F20) and 27% had a substance abuse. A recent study of the long-term cost implications of introducing the early-intervention program suggests that the intervention is resource neutral, i.e. the resources investments invested in early initiatives lead to equivalent savings in resource consumption over the subsequent 5 years [Hastrup LH et al 2011]. The patterns of resource consumption are likely to be somewhat context specific and will partly be a result of Danish treatment practices. However, the fact that base-line characteristics are equally distributed across intervention and control group, and the observation that the intervention is cost neutral suggests that variations in consumption patterns across patient characteristics are unlikely to be majorly affected by the specific intervention setting.

Costs
Costs included psychiatric health care services, somatic health care services, general practitioners and other medical specialists, medication, supported living facilities and intervention costs. All resource data were extracted from Danish registers and combined with unit costs to obtain a cost per patient over their time in the study. The total costs consisted of a summarization of all the described cost items. The cost data were analyzed on an annual basis and summarized over five years. All cost data were reported in 2009 Euro (exchange rate 1 Euro ~ 7.448 DDK). The resource items and costs calculations are described in detail elsewhere [Hastrup LH et al 2011].

Explanatory variables
The potential explanatory baseline variables were the following:
  i) Demographic variables: sex, age, citizenship, and living situation; dummy of 1 if homeless (other=0), and dummy of 1 if living in supported housing facilities (other=0).
ii) Diagnosis: dummy of 1 if schizophrenia diagnosis based on ICD 10 codes in the F2 category (other=0), and dummy of 1 if the patient has a substance abuse (other=0)

iii) Severity of illness: duration of untreated psychosis (DUP), baseline psychotic symptom level (GAF-S), and baseline global functional level (GAF-F).

**Statistical analysis**

Age was recoded into a categorical variable grouped by quartiles (18-21 years, 22-24 years, 25-31 years, and 32-45 years). DUP was recoded into dummy variable of 1 if duration of untreated psychosis exceeded 6 months.

Standard ordinary least squares regression method (OLS) was first applied on untransformed cost data. The regression coefficients of the linear OLS model indicate the change of the costs in Euro (€) caused by a change of the independent variables by one unit. Total costs were slightly skewed (Table 2). Since Breusch-Pagan tests showed that the residuals were heteroscedastic, we computed robust standard errors (and confidence intervals) using the sandwich estimator with the *robust* option in STATA.

Further, a log transformation (ln(y)) was applied to the dependent variables. An OLS model was computed with the natural log of total costs and the same set of explanatory variables. After the log transformation of data, skewness of data was reduced, and the Breusch-Pagan test did not reject the hypothesis of homoscedasticity.

When the primary goal of an analysis is explanatory modelling and in cases where the dependent cost variable has no zero-cost, a generalised linear model (GLM) with a log link and gamma family has been suggested [Gregori et al. 2011; Kilian et al. 2002; Moran et al. 2007]. To model this function, a link function and a family based on the data has to be identified [Glick H et al. 2007]. The link function specifies the relationship between the mean and the linear specification of the covariates. The family corresponds to a distribution that reflects the mean-variance relationship. Specification of a gamma family assumes variance is proportional to the square of the mean. The correct specification of family was selected by performing the modified Parks test as suggested by [Glick H et al. 2007]. We applied GLM as a check of the other two models.
**Results**

Table 2 presents results of the OLS, OLS (log) and GLM regression models. The models are not hugely different with respect to outcomes. Coefficients largely have the same sign, and the p-values are for most candidate explanatory variables of the same order of magnitude.

**Demographic variables**

Age, citizenship, and living situation had statistically significantly impact on the mean total costs (Table 2). The regression coefficients of the linear OLS model indicate the change of the mean total cost caused by a change of the explanatory baseline variable by one unit. Compared to the reference group, (25-31 years) the oldest patient group (32-45 years) tended to have had lower total cost of €42021 (OLS: p = 0.017; OLS (log): p=0.051; GLM: p=0.020) while the youngest patient group (18-21 years) had €61274 higher total costs (OLS: p = 0.018; OLS(log): p=0.008; GLM: p=0.007). Danish citizenship increased the mean total costs by €57367 within 5 years (OLS: p=0.001; OLS(log): p=0.075; GLM: p=0.008) compared to patients with other citizenships. Being homeless increased the total cost by a mean of as much as €141359 (OLS: p=0.001; OLS(log): p=0.001; GLM: p=0.010). Supported living demonstrated a similar increase in costs (€161765), but with lower significance levels (OLS: p=0.185; OLS(log): p=0.128; GLM: p=0.072) which is most likely explained by the fact that only 1.2% of our sample were living in supported housing facilities at baseline. Gender very clearly had no statistically significant impact on costs (OLS: p = 0.651; OLS(log): p=0.505; GLM: p=0.453).

**Severity of illness**

Level of psychotic symptoms and functional level showed an impact on the mean total costs. Improvement in the GAF-symptom score by one unit decreased the mean costs by €1811 (OLS:p=0.053; OLS(log): p=0.002; GLM: p=0.022) and improvement in the GAF-function score by one unit decreased the mean costs by €1035 (OLS: p=0.091; OLS(log): p=0.002; GLM: p=0.06). Having a substance abuse increased the mean total costs by €36702 (OLS: p=0.02; OLS(log): p=0.015; GLM: p=0.076) compared to other patients in the study. Main diagnosis (F20) very markedly did not add further explanatory power to the cost variations (OLS: p=0.915; OLS(log): p=0.802; GLM: p=0.606), nor did durations of undiagnosed psychosis (DUP) ((OLS: p=0.802; OLS(log): p=0.557; GLM: p=0.257).
Discussion

Previous studies have attempted to identify factors related to health care costs, especially psychiatric costs. Generally these studies have concentrated on the associations between costs and socio-demographic and clinical characteristics as well as patterns of service utilization. Focus has been on specific aspects of community mental treatment or selected subsamples of patients with severely mental illnesses and with a prior utilization of services. The present study concentrates on a specific group of psychiatric patients, namely patients in contact with services with a first-episode psychosis.

The estimated models of future total costs by individual characteristics had a low $R^2$ (0.16 –0.18). Since our main focus was to predict future costs given conditions at baseline, the explanatory variables used were baseline characteristics. As many other factors during the observed period may impact on resource patterns, the low $R^2$ is not surprising. Other studies with baseline characteristics as independent variables and a similar sample size have estimated $R^2$ at the same level [Mirandola et al. 2004]. Endogeneity may arise if level of resource consumption over the observation period affects severity of illness in the same time period, in which case the causal relationship between health status and level of resource consumption would be reversed. In order to avoid problems of endogeneity, only indicators of initial severity of disease at base-line were included as potential explanatory variables, as these are unaffected by subsequent resource consumption (i.e. exogenous).

In contrast with previous studies [Carr et al. 2004; Knapp et al. 2002; Rund and Ruud 1999], we found no impact of gender on future costs (p>0.45 for all models). We found that younger age groups (18-21 years) tended to have higher resource consumptions, whilst the 32-45 years olds had lower resource consumption than those who were 25-31 years. Previous studies of the relationship between age and costs have mixed results. The association between younger age groups and increased costs has been noted in earlier studies among patients with severe mental illnesses and may reflect several factors. The UK700 study among severe mentally ill patients aged between 18 and 65 years, found higher costs of care among patients younger than 29 years [Byford et al. 2001]. A possible explanation of higher costs among young age groups could be that young patients may have parents who advocate for them. Furthermore, Byford et al, 2001[Byford et al. 2001], argue that there is evidence to suggest that health professionals may concentrate efforts on the young and acute. Also, age of the patient at the onset of psychotic symptoms is known to be a prognostic indicator for schizophrenia and related psychotic disorders. The younger one is at the onset of
positive psychotic symptoms, the poorer the outcome tends to be [Bellino et al. 2004; Tuulio-Henriksson et al. 2004]. In the present study, all patients are first-episode psychosis patients and may as such be considered as acute when they enter the study whereas in earlier studies, the patients are a mix of patients with both shorter and longer duration of illness. Carr et al., 2004, found that young age at illness onset were associated with higher costs, which correspond with the finding of this study [Carr et al. 2004]. McCrone et al., 2001, analyzed a patient group aged between 18 and 65 years and found higher age associated with higher total costs [McCrone et al. 2001]. The authors explain the finding with the fact that patients, when they get older, lose the support of informal caregivers, which leads to higher societal costs. Furthermore, expensive residential services tend to be more geared toward older people. In our study the upper age is 45 years, and so we cannot verify such a pattern of events.

We found that being homeless increased the future costs markedly. This suggests that being homeless is likely to be an indicator of severe mental illness, which is associated with a high level of need and high a high level of resource consumption. Despite the individuals being homeless our results suggest that access to health care services is not impaired.

Diagnosis of schizophrenia was not in itself a significant predictor in the multiple regression models (p>0.606 for all models) but a bivariate analysis showed that the presence of schizophrenia was associated with increased costs (albeit weakly: p=0.051), which supports the findings of [Bonizzato et al. 2000; Carr et al. 2004; McCrone and Strathdee 1994].

In prior studies patients with a diagnosis of substance abuse were shown to initiate lower total costs [Carr et al. 2004](Carr, 2004). These authors suggested that this resource pattern may be a reflection of poorer patient engagement with services. Alternatively, there might be some therapeutic pharmacological benefits from substance abuse in context of psychosis. In our study we did not find the same resource consumption pattern. Although our results are not strongly statistically significant (0.015 ≤ p ≤ 0.076 across models), the size of the coefficient (€ 36702) does not support the hypothesis that there is a therapeutic benefit of street drugs, but suggests that in a Danish setting access to health care services are to a greater extent secured despite patients being drug abusers.
Higher level of psychotic symptoms (GAF) was associated with higher costs. This confirms earlier findings that severity of illness during the early course of illness is associated with later costs [Bonizzato et al. 2000;Byford et al. 2001;Kilian et al. 2003].

Longer duration of untreated psychosis (DUP) has been shown to be associated with poorer outcome among patients with first-episode psychosis [Johannessen et al. 2005;Marshall et al. 2005], but we found no evidence in the literature on the relationship between DUP and later costs. In this study, we found a small correlation of DUP and later costs when running a bivariate regression analysis (p=0.018), but when controlling for the other patient characteristics in the multiple regression analysis, there was no statistically significant impact on the costs (p>0.257 across all models).

There are some limitations to our study. Firstly, the overall sample size is relatively small (n=547), and therefore, for some subgroup analysis (such as those on supported living and the homeless) the sample sizes are reduced to very few individuals and the statistical power is markedly reduced. Given that we are looking for a number of base-line characteristics, it could be argued that we should have applied Bonferroni adjustment in order to ensure appropriate significance levels for multiple significance levels, thereby avoiding chance results. We would, however, argue that Bonferroni correction is less appropriate for the present study, as we are testing hypothesis based on previous finding in the literature (and are therefore not on a “data mining” expedition). Further, Bonferroni correction controls the probability of false positives only. In the present study we as interested in retaining the null hypothesis as are in rejecting it, and in the former case the Bonferroni correction is non-conservative.

We have chosen to present the results of all three variants of the regression models (OLS, OLS(log) and GML in order to openly demonstrate the impact on p-values of choosing different analytical strategies. However, we do find that there is a clear pattern in the magnitude of p-values, which contributes to the robustness of the results.

Finally, we acknowledge that our results are likely to be context specific, and that the consumption patterns demonstrated here are likely to be (at least partly) a result of the study being based on Danish data and reflecting Danish treatment practices. Also, study is based on a randomized
controlled trial, which involved a particular intervention (modified assertive community treatment versus treatment in a community mental health centre). That 50% of the patients were subject to an intervention for the first two years of the observation period could in principle affect results. We would, however, argue that the implications are bound to be minimal on the grounds that that baseline characteristics are equally distributed across intervention and control group, and the observation that the intervention is cost neutral [Hastrup LH et al 2011] suggests that variations in consumption patterns across patient characteristics are unlikely to be majorly affected by the specific intervention setting. We therefore perceive that our results can be generalized to other setting with similar treatment practices.

Strength of this study was that cost data was extracted from official Danish Registers, which are known to be of high quality and characterized by a high degree of completeness and validity [Andersen et al. 1999; Munk-Jørgensen and Mortensen 1997; Olivarius et al. 1997]. Furthermore, interviewers collected the data on patient characteristics as a part of the randomized controlled trial, which also guarantees for the validity of data.

**Conclusion**

In this study it was found that the following individual baseline characteristics; lower age, higher symptom level, lower functional level, having a substance abuse and being homeless were associated with higher future costs when controlling for other variables in a sample of first-episode psychosis patients. The association between young age and higher future costs is likely to reflect earlier findings of age as prognostic factor for schizophrenia and other psychosis. The association between the later costs and severity level (including being homeless) indicates that higher needs are associated with higher level of resource input. In accordance with the present recommendations of regression modelling with cost data, we applied OLS, log-transformed OLS, and GLM, and found similar overall results, confirming the robustness of our results.
Reference List


<table>
<thead>
<tr>
<th>Variable</th>
<th>Description</th>
<th>Mean %</th>
<th>Standard deviation</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Dummy of 1, if patient is male</td>
<td>59.05</td>
<td>0.02</td>
<td>0-1</td>
</tr>
<tr>
<td>Age</td>
<td>Continuous variable</td>
<td>26.62</td>
<td>6.35</td>
<td>18-45</td>
</tr>
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<td>Age 18-21</td>
<td>Dummy of 1, if the patient is 18-21 years</td>
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<td>0-1</td>
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<tr>
<td>Age 22-24</td>
<td>Dummy of 1, if the patient is 22-24 years</td>
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<td>0-1</td>
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<tr>
<td>Age 25-31</td>
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<td>27.8</td>
<td>0.02</td>
<td>0-1</td>
</tr>
<tr>
<td>Age 32-45</td>
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<td>0.01</td>
<td>0-1</td>
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<tr>
<td>Citizen</td>
<td>Dummy of 1 if the patient is a Danish citizen</td>
<td>93.5</td>
<td>0.01</td>
<td>0-1</td>
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<tr>
<td>DUP &gt; 6 months</td>
<td>Dummy of 1 if duration of untreated psychoses is more than 6 months</td>
<td>75.2</td>
<td>0.02</td>
<td>0-1</td>
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<tr>
<td>F21</td>
<td>Dummy of 1 if diagnosis of F21 (Schizophrenia)</td>
<td>66.2</td>
<td>0.02</td>
<td>0-1</td>
</tr>
<tr>
<td>F22</td>
<td>Dummy of 1 if diagnosis of F22 (Schizotypal disorder)</td>
<td>14.4</td>
<td>0.01</td>
<td>0-1</td>
</tr>
<tr>
<td>F23</td>
<td>Dummy of 1 if diagnosis of F23 (Delusional disorder)</td>
<td>4.5</td>
<td>0.01</td>
<td>0-1</td>
</tr>
<tr>
<td>F25</td>
<td>Dummy of 1 if diagnosis of F25 (Acute psychosis)</td>
<td>4.4</td>
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</tr>
<tr>
<td>F31</td>
<td>Dummy of 1 if diagnosis of F31 (Schizoaffective disorder)</td>
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<tr>
<td>Dual diagnosis</td>
<td>Dummy of 1, if the patient has a substance abuse</td>
<td>26.7</td>
<td>0.02</td>
<td>0-1</td>
</tr>
<tr>
<td>GAF-symptoms</td>
<td>Global Assessment of functioning – symptom scale; Continuous variable (0-99); High score indicates lower symptom level</td>
<td>33.53</td>
<td>10.68</td>
<td>10-80</td>
</tr>
<tr>
<td>GAF-function</td>
<td>Global Assessment of functioning – function Scale; Continuous variable (0-99); High score indicates higher functional level</td>
<td>41.32</td>
<td>13.34</td>
<td>10-80</td>
</tr>
<tr>
<td>Homeless</td>
<td>Dummy of 1 if patient is homeless</td>
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<tr>
<td>Supported living</td>
<td>Dummy of 1 if patient lives at institution</td>
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<td>0.01</td>
<td>0-1</td>
</tr>
<tr>
<td>Total costs 5 years</td>
<td>Continuous variable; Summarization of health care costs, cost of supported living facilities and intervention costs within 5 years</td>
<td>129936</td>
<td>161696</td>
<td>7990-885755</td>
</tr>
<tr>
<td>Ln(Total costs 5 years)</td>
<td>Logtransformed Total costs of 5 years</td>
<td>11.16</td>
<td>1.09</td>
<td>8.99-13.69</td>
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Table 2. Multiple regression analysis. Total costs in 2009 € over 5 years after inclusion by individual baseline characteristics

<table>
<thead>
<tr>
<th>Total costs, 5 years</th>
<th>OLS</th>
<th>OLS (log)</th>
<th>GLM</th>
</tr>
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<tr>
<td></td>
<td>β</td>
<td>p</td>
<td>β</td>
</tr>
<tr>
<td>Constant</td>
<td>147667</td>
<td>0.019*</td>
<td>11.81</td>
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<tr>
<td>DUP (dummy: DUP &gt; 6 months)</td>
<td>4342</td>
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<td>0.072</td>
</tr>
<tr>
<td>Sex</td>
<td>5891</td>
<td>0.651</td>
<td>-0.063</td>
</tr>
<tr>
<td>Age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-21 years</td>
<td>61274</td>
<td>0.018*</td>
<td>0.369</td>
</tr>
<tr>
<td>22-24 years</td>
<td>-14539</td>
<td>0.396</td>
<td>-0.145</td>
</tr>
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<td>32-45 years</td>
<td>-42021</td>
<td>0.017*</td>
<td>-0.242</td>
</tr>
<tr>
<td>Citizenship</td>
<td>57367</td>
<td>0.001**</td>
<td>0.322</td>
</tr>
<tr>
<td>Main diagnosis: F20</td>
<td>1655</td>
<td>0.915</td>
<td>0.027</td>
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<tr>
<td>Dual diagnosis</td>
<td>36702</td>
<td>0.020*</td>
<td>0.257</td>
</tr>
<tr>
<td>(Drug/alcoholabuse)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>GAF-symptoms</td>
<td>-1811</td>
<td>0.053</td>
<td>-0.016</td>
</tr>
<tr>
<td>GAF-function</td>
<td>-1035</td>
<td>0.091</td>
<td>-0.012</td>
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<tr>
<td>Homeless</td>
<td>141359</td>
<td>0.007**</td>
<td>0.749</td>
</tr>
<tr>
<td>Supported living</td>
<td>161765</td>
<td>0.185</td>
<td>0.764</td>
</tr>
<tr>
<td>R²</td>
<td>0.163</td>
<td>0.173</td>
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<tr>
<td>Root MSE</td>
<td>1.4e+05</td>
<td>0.991</td>
<td></td>
</tr>
<tr>
<td>F (significance)</td>
<td>9.20 (0.00)</td>
<td>11.17 (0.00)</td>
<td></td>
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<tr>
<td>Breusch-Pagan</td>
<td>131.56 (0.00)</td>
<td>1.92 (0.17)</td>
<td></td>
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<td>heteroscedasticity test; Chi^2 (significance)</td>
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<tr>
<td>Skewness</td>
<td>2.12</td>
<td>0.29</td>
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Reference value age 25-31 years; *p<0.05, **p<0.01, ***p<0.001
Chapter 6
The chapter presents Article 3. Title: Do informal caregivers in mental illness feel more burdened? A comparative study of mental versus somatic illnesses.

Do informal caregivers in mental illness feel more burdened? A comparative study of mental versus somatic illnesses

LENE H. HASTRUP1,2, BERNARD VAN DEN BERG3 & DORTE GYRD-HANSEN2,4,5

1Psychiatric Research Unit, Region Zealand, DK-4000 Roskilde, Denmark, 2Institute of Public Health, University of Southern Denmark, Winsløwej 9, DK-5000 Odense C, Denmark, 3Centre for Health Economics, University of York, York, UK, 4DSI Institute for Health Services Research, Dampfærgevej 27-29 DK-2100 Copenhagen, Denmark, and 5Australian Centre for Economic Research on Health, University of Queensland, Australia

Abstract
Aims: This study investigates a possible added subjective burden among informal caregivers to care recipients with a mental illness or a combination of mental and somatic illnesses compared with caregivers to care recipients with a somatic illness. The study also investigates the subjective caregiver burden by caregivers' characteristics and objective burden.

Methods: The association between subjective caregiver burden and socio-demographic factors, objective burden, and health-related quality of life was analyzed in a population of 865 Dutch informal caregivers, using multiple linear regression analysis.

Results: Controlling for other factors in the analysis, we found that caring for a recipient with mental illness or a combination of mental and somatic illness was associated with an extra subjective caregiver burden (measured by Caregiver Strain Index). Objective burden, in terms of more than 50 hours of care provision per week, less than three years of caregiving, or living together with the care recipients was associated with higher subjective caregiver burden. Other factors associated with higher subjective caregiver burden were being partners or a child of care recipient, having a paid job, a low health-related quality of life (EQ-5D), or having an illness.

Conclusions: This study suggests that caregivers to care recipients with a mental and especially a combination of mental and somatic illnesses have a higher subjective caregiver burden compared with caregivers to care recipients with a somatic illness. Because the study is not representative of all caregivers, more research focusing on identifying and contacting informal caregivers is needed to confirm the result.

Key Words: Caregiver strain index, informal caregiving, mental illness, objective caregiver burden, subjective caregiver burden

Background
Informal care is recognized as a significant part of the total care provided to care recipients with chronic illnesses [1]. Informal caregiving can be defined as a non-market composite commodity consisting of heterogeneous parts produced (paid or unpaid) by one or more members of the social environment of the care recipient as a result of the care recipients care demands [2]. This definition stresses that informal care is heterogeneous and includes personal care and housework. Moreover, it emphasizes that there is a social relation between informal caregivers and their care recipients.

The caregiver burden has been explained theoretically from psychological perspectives of stress and coping [3]. The contextual characteristics of the caregiver and care recipient, e.g. socio-demographic variables, have an influence on the caregiver’s adaptation to the stress related to caregiving [4,5]. This implies that the primary stress factors in relation to caregiving can proliferate in other areas of the caregiver’s life and provoke negative repercussions.
on the free time, leisure activities, social relations, and the economic and employment situation of the caregiver. The subjective assessment of these consequences can lead to diminished self-esteem, expertise, sense of self, and competency.

Caregiver burden has been defined in terms of objective and subjective burden [6]. Objective burden refers to problems relating to negative effects of the care recipients’ illness on the caregiver and the caregiving demands placed on carers [7], such as the time spent on informal caregiving, constraints in social, leisure and work activities, and possible financial problems. Subjective burden refers to the physical, psychological, social and emotional impact caregivers experience in providing care, e.g. feelings of loss, depression, anxiety, and embarrassment in social situations. This description of caregiver burden is still the most common definition, although the term “burden” has been criticized for being damaging because it restricts caregivers’ reactions to the negative and does not allow for positive aspects of caregiving [8].

In this study, we wanted to investigate whether caregivers to people with mental illnesses or a combination of mental and somatic illnesses experience a higher subjective burden compared with caregivers to people with (only) somatic illness. Mental illnesses comprise a broad range of illnesses, e.g. dementia, Alzheimer’s disease, psychosis including schizophrenia and bipolar diseases, depression, anxiety, and are understood as clinically significant conditions characterized by alterations in thinking, mood or behaviour associated with personal distress and/or impaired functioning [9].

The literature suggests associations between caregiver's socio-demographic variables (age, gender, education, income, relationship with care recipient) and subjective caregiver burden. Female caregivers and younger caregivers tend to be more burdened [10]. Lower income has also been found to predict higher caregiver burden [11]. Better quality of life and health status among caregivers are associated with low caregiver burden [12,13].

Objective factors, which are characterized by long duration of caregiving, daily caregiver involvement, and residential situation between carer and care recipient, are likewise associated with increased caregiver burden [14,15]. Care recipient’s characteristics, such as symptoms, illness-related deficits, and higher age of the patient are predictors of caregiver burden in mental illness [16]. Furthermore, there is increasing evidence of behavioural problems of care recipients with mental illnesses that may represent an extra source of subjective caregiver burden for their caregivers compared with other caregivers [17–22] e.g. threatening or embarrassing behaviour by the care recipients, and also self-blame of the caregiver and feelings of guilt in relation the care recipients’ illness [23]. Moreover, different aspects of social stigma attached to mental illness seem to become a part of a caregiver’s subjective burden [8,24].

In the literature search, we found only one comparative study of the caregiver burden among care recipients with mental illness versus care recipients with somatic illnesses [21]. This study compared caregivers of care recipients with schizophrenia to caregivers of care recipients with brain diseases, heart disease, renal diseases and lung diseases and reported a higher subjective caregiver burden among care recipients with mental illnesses and brain diseases compared with other somatic illnesses. We did not find studies comparing the subjective burden among caregivers to care recipients with comorbidity of mental and somatic illnesses with other caregiver types.

Aims

The aim of this paper was twofold. First, we compared the subjective burden in a broad group of caregivers to care recipients with mental illnesses or a combination of mental and somatic illnesses, with caregivers to care recipients with somatic illnesses in order to test for a possible extra subjective caregiver burden in mental illnesses. Secondly, we tested for an association between the subjective caregiver burden and caregivers’ characteristics and objective burden. This knowledge can be a helpful tool in identifying and supporting caregivers at high risk of subjective caregiver burden.

Methods

Study population

The data analyzed in this study were based on postal questionnaires collected as part of a larger investigation into the situation of informal caregivers and valuation of informal care, which has been described elsewhere [25]. The respondents were recruited through Dutch regional support centres for informal caregivers, which offer information, organize self-help groups and help with directions to formal care. From the 52 centres that were asked to participate, 40 centres were willing to join the study by means of distributing a questionnaire to informal caregivers that were registered at the centre. Caregivers were registered at the centres if they participated in a support group, had contacted the centre by phone at
some point in time, or had participated in at least one meeting. Consequently, caregivers with only sporadic contact with the centres were also invited to participate. As only names and postal addresses were documented, there was no information about the characteristics of the caregiver population or their reasons for contacting the support centres.

During the period November 2001 to February 2002, postal questionnaires were sent to 3,258 Dutch informal caregivers known to one of the 40 regional support centres. The final sample consisted of 865 informal caregivers. The response rate was 26.6%. As no information on the population characteristics were available, and we cannot control for factors that may characterize non-responders, we sought to control for all observable factors that may vary across the different types of caregivers.

Information on the care recipients’ illness or illnesses was based on caregivers’ reports in the questionnaire. The caregiver could either indicate if the care recipient had a mental illness, a somatic illness or a combination of mental and somatic illnesses.

**Measures**

**Subjective caregiver burden**

The subjective caregiver burden was measured using Caregiver Strain Index (CSI) [26]. CSI contains 13 questions that measure strain related to care provision in the following domains: employment, financial, physical, social, and time. CSI has shown reasonable construct validity in relation to caregivers’ subjective perceptions of the relationship with the care recipients, and the physical and emotional health of the caregivers [26].

**Objective caregiver burden**

To assess the objective burden, the respondents were asked to report the number of years that they had been providing informal care. Respondents were also asked to recall time invested in care tasks per day as well as the number of hours per week used on care tasks. Assuming that respondents take joint production into account, the recall method has been shown to be a valid method to measure time spent on providing informal care compared with the diary method, which is considered the gold standard [27]. The respondents also reported whether they share the same house as the care recipient, which has been applied as another indicator of objective burden [21].

**Caregiver socio-demographics**

The informal caregivers reported their socio-demographic characteristics (age, gender, educational level, income level, and occupation), and their relation to the care recipient (parent, partner, child, or other).

**Health-related quality of life among caregivers**

Caregivers’ health-related quality of life was assessed using the generic EQ-5D index, which has been validated in various illnesses as a measure of health-related quality of life. Available tariffs were used to value the health states [28]. Caregivers were also asked to directly indicate in the postal questionnaire whether they suffer from illness.

**Statistical analysis**

We investigated caregiver characteristics (socio-demographics, health-related quality of life and objective burden) (Table I), subjective and objective burden (Table II), using t test and chi² test to test for differences across caregiver types (mental vs. somatic, mental vs. both mental and somatic, and both mental and somatic vs. somatic). The following variables were recoded into categorical variables: age (14–49 years, 50–59 years, 60–69 years, 70+ years), duration of caregiving in years (0–3 years, 4–9 years, 10+ years), time invested in care tasks in hours per week (0–24 hours, 25–49 hours, 50–75 hours, and 76+ hours). The association between the subjective caregiver burden, measured by CSI and the caregiver characteristics, and objective burden was investigated, using multiple regression analysis (Table III). We tested for whether caregiver type (mental, somatic, or both mental and somatic) has an impact on CSI per se. In order to verify the relative impact of mental illness (versus somatic illness), we included a dummy variable (=1 if mental illness; otherwise zero) to capture the possible added impact of mental illness on CSI relative to somatic illness. Further, we included a dummy variable (=1 if mental and somatic illness; otherwise zero) to verify whether the combination of illnesses add to CSI relative to somatic illness. We estimated two models (A and B). In order to test for a linear association between age, duration of caregiving in years and time invested in care tasks in hours per week, these three variables were included as continuous variables in model A. Model B was estimated with the same three variables coded as categorical variables to test for a non-linear association between these variables and CSI.
Table I. Caregivers’ socio-demographic and health profile.

<table>
<thead>
<tr>
<th>Socio-demographic</th>
<th>Caregivers to care recipients with:</th>
<th>Test of differences in proportions/mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mental illness (MI) n = 158</td>
<td>Somatic illness (SI) n = 428</td>
</tr>
<tr>
<td></td>
<td>MI vs. SI p-values</td>
<td>MI vs. BMS p-values</td>
</tr>
<tr>
<td>Age, mean (std)</td>
<td>59.92 (13.22)</td>
<td>59.78 (11.86)</td>
</tr>
<tr>
<td>15–49 years %</td>
<td>0.89</td>
<td>0.67</td>
</tr>
<tr>
<td>50–59 years %</td>
<td>0.29</td>
<td>0.20</td>
</tr>
<tr>
<td>60–69 years %</td>
<td>0.03*</td>
<td>0.12</td>
</tr>
<tr>
<td>70+ years %</td>
<td>0.00**</td>
<td>0.04*</td>
</tr>
<tr>
<td>Male %</td>
<td>0.03*</td>
<td>0.12</td>
</tr>
<tr>
<td>Married %</td>
<td>71.15</td>
<td>78.82</td>
</tr>
<tr>
<td>Children %</td>
<td>68.99</td>
<td>64.72</td>
</tr>
<tr>
<td>Educational level: %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>90.00</td>
<td>86.96</td>
</tr>
<tr>
<td>Medium</td>
<td>10.00</td>
<td>11.96</td>
</tr>
<tr>
<td>High</td>
<td>0</td>
<td>1.09</td>
</tr>
<tr>
<td>Net monthly income in Euro, mean (std)</td>
<td>1,485.64 (822.86)</td>
<td>1,524.81 (741.77)</td>
</tr>
<tr>
<td>Income level: %</td>
<td>0.62</td>
<td>0.71</td>
</tr>
<tr>
<td>Low income</td>
<td>10.42</td>
<td>7.64</td>
</tr>
<tr>
<td>Medium income</td>
<td>49.31</td>
<td>53.45</td>
</tr>
<tr>
<td>High income</td>
<td>40.28</td>
<td>38.92</td>
</tr>
<tr>
<td>Caregiver has a paid job, %</td>
<td>0.77</td>
<td>0.91</td>
</tr>
<tr>
<td>Relationship between caregiver and care recipient</td>
<td>0.30</td>
<td>0.53</td>
</tr>
<tr>
<td>Patient is partner, %</td>
<td>35.90</td>
<td>54.46</td>
</tr>
<tr>
<td>Patient is parent, %</td>
<td>22.44</td>
<td>25.12</td>
</tr>
<tr>
<td>Patient is child, %</td>
<td>19.87</td>
<td>7.28</td>
</tr>
<tr>
<td>Patient is someone else, %</td>
<td>03.16</td>
<td>2.80</td>
</tr>
<tr>
<td>Caregivers' health-related quality of life</td>
<td>0.93</td>
<td>0.77</td>
</tr>
<tr>
<td>EQ-5D index score, mean (std)</td>
<td>0.73</td>
<td>0.78</td>
</tr>
<tr>
<td>Caregiver has an illness, %</td>
<td>0.06</td>
<td>0.73</td>
</tr>
<tr>
<td>Caregiver has an illness, %</td>
<td>72.15</td>
<td>69.39</td>
</tr>
</tbody>
</table>

*p < 0.05,

**p < 0.01,

***p < 0.00 (t-test and Chi²-test).
The models were estimated using SPSS 17.0. We tested for multi-collinearity and multiplicative effects by including interaction variables and multiplied variables. None of these effects were statistically significant. Logistic regression with substantial burden (CSI > 6) as dependent variable by the explanatory variables did not contribute with more information to the analysis and is therefore not presented here.

Results

Comparison of caregiver characteristics and subjective/objective burden across caregiver types

Table I shows only small differences across caregiver types in socio-demographic and socioeconomic characteristics such as gender, having children, educational level and income level.

Compared with the other caregiver groups, those caring for recipients with mental illness tended to be older (70+ years) (p < 0.037), fewer were married (71.15; p < 0.05), they would more often be a partner (35.9%; p > 0.001) or a parent (19.9%; p < 0.00) of the care recipient and they were less likely to share accommodation with the recipient (46%; p < 0.000). Further, the time investment in caregiver tasks per week was lower (60 hours per week; p < 0.04) compared with the other caregiver groups (68.85–70.17 hours per week). In comparison with the somatic group, the caregivers to care recipients with mental illness had a lower health-related quality of life measured by EQ-5D (p < 0.06).

Compared with the other caregiver groups, the caregivers to care recipients with both mental and somatic illnesses had lower income (p < 0.04) and were less likely to have a paid job (p > 0.07). A higher percentage reported that they suffered from illness (p < 0.001) and the quality of life score was statistically significantly lower (p < 0.001) than those caring for recipients with a somatic illness only.

No differences across caregiver types were found with respect to the number of years that the respondents have been providing care to the care recipients. We found a statistically significantly higher (p < 0.01) caregiver burden among caregivers to care recipients with a combination of mental and somatic illness (mean = 8.68) compared to patients with a somatic illness (mean = 7.28) and mental illness (mean = 7.82).

Association between subjective burden and caregiver characteristics, health-related quality of life and objective burden

Table III presents the two estimated regression models of CSI by caregiver characteristics and objective burden. Model A included age, time investment in care tasks, and duration of caregiving as continuous variables, while the three variables were

---

Table II. Caregivers’ objective and subjective burden.

<table>
<thead>
<tr>
<th>Caregivers to care recipients with:</th>
<th>Test of differences in proportions/mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MI vs. SI</td>
</tr>
<tr>
<td>Mental illness (MI) n = 158</td>
<td></td>
</tr>
<tr>
<td>Somatic illness (SI) n = 428</td>
<td></td>
</tr>
<tr>
<td>Both MI and SI (BMS) n = 260</td>
<td></td>
</tr>
<tr>
<td>Objective burden</td>
<td></td>
</tr>
<tr>
<td>Live in same house as patient %</td>
<td>46.20</td>
</tr>
<tr>
<td>Duration of caregiving in years, mean (std)</td>
<td>8.14</td>
</tr>
<tr>
<td>0–3 years</td>
<td>26.58</td>
</tr>
<tr>
<td>4–9 years</td>
<td>34.80</td>
</tr>
<tr>
<td>10 years +</td>
<td>29.10</td>
</tr>
<tr>
<td>Time invested in care tasks in hours per week, mean (std)</td>
<td>60.09</td>
</tr>
<tr>
<td>0–24 hours</td>
<td>31.6</td>
</tr>
<tr>
<td>25–75 hours</td>
<td>24.1</td>
</tr>
<tr>
<td>&gt;75 hours</td>
<td>41.8</td>
</tr>
<tr>
<td>Subjective burden</td>
<td></td>
</tr>
<tr>
<td>Caregiver Strain Index (CSI), mean (std)</td>
<td>7.81</td>
</tr>
<tr>
<td>Caregiver indicates substantial burden, % (CSI score &gt; 6)</td>
<td>66.41</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, ***p < 0.00 (t test and Chi²-test).
Do informal caregivers in mental illness feel more burdened? Comparative study

Table III. Linear regression of subjective burden (Caregiver Strain Index) by explanatory variables.

<table>
<thead>
<tr>
<th>Model A</th>
<th>Model B</th>
</tr>
</thead>
<tbody>
<tr>
<td>(R^2 = 0.378)</td>
<td>(R^2 = 0.367)</td>
</tr>
<tr>
<td><strong>Coeff.</strong></td>
<td><strong>p-values</strong></td>
</tr>
<tr>
<td>Constant</td>
<td>9.403</td>
</tr>
<tr>
<td>Care recipient has a mental illness</td>
<td>Yes = 1</td>
</tr>
<tr>
<td></td>
<td>No = 0</td>
</tr>
<tr>
<td>Care recipient has a combination of mental and somatic illnesses</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Socio-demography</td>
<td>No = 0</td>
</tr>
<tr>
<td>Age</td>
<td>15–49 years</td>
</tr>
<tr>
<td></td>
<td>50–59 years</td>
</tr>
<tr>
<td></td>
<td>60–69 years</td>
</tr>
<tr>
<td>Gender</td>
<td>0.174</td>
</tr>
<tr>
<td>Marital status</td>
<td>Male = 1</td>
</tr>
<tr>
<td></td>
<td>married = 1</td>
</tr>
<tr>
<td>Caregiver has children</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Caregiver has a paid job</td>
<td>No = 0</td>
</tr>
<tr>
<td>Relationship to care recipient</td>
<td>0.937</td>
</tr>
<tr>
<td>Care recipient is partner</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Care recipient is child</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Care recipient is someone else</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Caregivers health status</td>
<td>0.701</td>
</tr>
<tr>
<td>EQ-5D Index score</td>
<td>–3.180</td>
</tr>
<tr>
<td>Caregiver suffers from illness</td>
<td>Yes = 1</td>
</tr>
<tr>
<td>Objective burden</td>
<td>0.023</td>
</tr>
<tr>
<td>Duration of caregiving, years</td>
<td>0–3 years</td>
</tr>
<tr>
<td></td>
<td>4–9 years</td>
</tr>
<tr>
<td>Time invested in care tasks, hours per week</td>
<td>25–49</td>
</tr>
<tr>
<td></td>
<td>50–75</td>
</tr>
<tr>
<td></td>
<td>&gt;75 hours</td>
</tr>
<tr>
<td>Caregiver and care recipient live in same house</td>
<td>Yes = 1</td>
</tr>
</tbody>
</table>

*p < 0.05, **p < 0.01, ***p < 0.00.

Model A: Age, duration of caregiving in years, and time invested in care tasks are defined as continuous variables. Model B: Age, duration of caregiving in years, and time invested in care tasks are defined as ordinal variables. Reference group: care recipient has a somatic illness. Reference group: age \(\geq 70\). Reference group: care recipient is parent. Reference group: years of caregiving \(\geq 10\) years. Reference group: hours of care giving < 25 hours per week.

Recoded into categorical variables in model B. Both models show that when controlling for all other factors, being caregiver to a care recipient with a mental illness is positively and statistically significantly associated with a larger subjective burden \((p < 0.01)\). Relative to the subjective burden associated with caring for a care recipient with somatic illness, the caregiver burden is increased by approximately 0.9 on the CSI.

Being caregiver to a care recipient with both a mental and somatic illness has a marked statistically significant impact on the burden score \((p < 0.001)\) when controlled for other explanatory factors. The caregiver burden increases with approximately 1 unit on the CSI relative to the burden of caring for a care recipient with somatic illness only.

Both models show that caregivers with a paid job score higher on the CSI \((p < 0.02)\). The coefficient is 0.69. Other socio-demographic variables (age, gender, marital status, educational level) were not statistically significantly associated with subjective caregiver burden. Partners and children of care recipients experience a substantially higher subjective burden \((p < 0.001)\).

We found a statistically significant impact of the caregivers’ self-reported illness \((p < 0.02)\) and health-related quality of life \((p < 0.001)\) on CSI. A higher level of health-related quality of life decreases the
caregiver burden. Likewise, caregivers' self-reported illness was associated with higher CSI.

The objective burden has an impact on the subjective caregiver burden. Living together with the care recipient increased the CSI \( (p < 0.07) \) by approximately 0.6. The number of years of care provision was insignificant when included in model A as a continuous variable. When we included number of years of care provision as an ordinal variable in model B, there was an impact on CSI although only near-statistically significant. Caregivers who have provided care for up to three years tended to have a higher burden score \( (p < 0.06) \) than caregivers with more than three years of care provision. The number of hours per week spent on care provision had a statistically significant impact on the caregiver burden. In model A, when assuming a linear effect of the variable and including hours per week as a continuous variable, the variable was statistically significant but the coefficient was very small. When hours per week was included as a categorical variable, we found that caregivers who spend between 50 and 75 hours per week on care provision also have a higher subjective burden \( (p < 0.02) \) compared with other caregivers. A high number of hours of care provision (more than 75 hours per week) increased the CSI by 1.7 \( (p < 0.001) \) relative to caregivers spending less than 25 hours per week.

It is worth noting that if Bonferroni adjustments are made to correct for multiple significance tests, the results are only considered to be statistically significant at \( p \)-levels of less than 0.01.

Discussion

The aim of the study was first to investigate differences in subjective burden in a broad sample of informal caregivers in order to find a possible extra subjective caregiver burden of caregivers to care recipients with a mental illness or a combination of mental and somatic illnesses. Secondly, we wanted to identify the association between socio-demographic factors and objective burden and the subjective caregiver burden. This is important in relation to identifying the types of caregivers that experience a higher subjective caregiver burden, which could be helpful in developing caregiver support programmes.

The data analyzed were collected by postal questionnaire as part of a larger Dutch study investigating the value of informal caregiving. The respondents were recruited through the local support centres. Postal questionnaires were sent to all caregivers known by the support centres. The response rate of 26.6% was very low. Since we have no information on non-responders and those not invited, we cannot verify whether our sample is representative of the general population of caregivers. We suspect that this sample is not representative of the Dutch population of informal caregivers, but it remains unclear to which degree it may be unrepresentative. Respondents were a self-selected group of carers who had contacted a support centre, but they were not necessarily carers who were strongly associated with these centres. Those seeking help and support at centres may be individuals who feel they have a very heavy burden, but they may also be carers who have extra time and energy to make contact. Among those invited, non-responders may reflect respondents who are less engaged in the question of carer burden, or carers who do not have sufficient free time on their hands to fill out questionnaires. Unfortunately, it is a very difficult task to identify the full sample of caregivers in the Netherlands and elsewhere, and therefore there is bound to be some degree of uncertainty regarding sample bias in any similar study. Since this study focuses mainly on the variation in caregiver burden within the selected sample of carers and does not attempt to estimate the absolute magnitude of caregiver burden, the issue of self-selection bias may be less of an issue, given that self-selection follows the same patterns across the carer groups.

Our categorization of caregivers into caregiver types is entirely based on information that caregivers provided. Caregivers were asked to indicate whether their care recipients had a mental, somatic or a combination of mental and somatic illnesses. Our information on the care recipients' illness is therefore restricted to these three categories of illnesses. Since these categories are clearly very broadly defined and are likely to contain care recipients with different diagnoses and socio-demographic characteristics, this may have resulted in a high degree of heterogeneity within the groupings.

The association between subjective caregiver burden and socio-demographic factors, and objective variables was estimated using a multiple linear regression models. The models explained, respectively, 36% and 37% of the total variation of the caregiver strain index, which is relatively low.

The result of the regression model suggests that being a caregiver to a care recipient with a mental illness or a combination of mental and somatic illness is associated with an added subjective caregiver burden measured by the CSI compared with caregivers to care recipients with somatic illness. This is in line with the findings of Magliano et al. [21], where the subjective caregiver burden was measured by the Family Problem Questionnaire (FPQ).
These authors found a statistically significantly higher caregiver burden among care recipients with mental illness (mean = 2.5) and brain diseases (mean = 2.4) compared with somatic illnesses (mean < 2.0). FPQ has 34 questionnaires and covers a broader range of topics related to caregiving, e.g. objective and subjective caregiver burden, professional support and support received by social network, and the caregivers’ attitude toward the care recipient, than the CSI, which mainly focuses on subjective caregiver burden.

Also, caregivers to care recipients with a combination of mental and somatic illnesses reported an even higher burden (mean = 8.7) compared with the caregivers to care recipients with mental or somatic illnesses. This finding is in accordance with a recent review [29], which found that the presence of somatic illness in addition to the mental illness can magnify the difficulties that the caregivers are experiencing daily. At this point in time, there is, however, limited evidence on the excess subjective burden of caregivers to care recipients with a combination of mental and somatic illnesses.

The socio-demographic variables were generally not associated with the subjective caregiver burden. In line with Jacob et al. [14], we found that caregivers who are partners to or children of care recipients are more burdened than other caregivers. We did not find any association between income and caregiver burden, but the model suggests that having a paid job was associated with higher subjective caregiver burden. As we expected, better health-related quality of life and no self-reported illness of the caregiver are associated with a lower subjective caregiver burden. In our sample, caregivers to care recipients with, respectively, mental illness or a combination of mental and somatic illness have a statistically significantly lower EQ-5D index score compared with caregivers to care recipients with somatic illness. This is in accordance with the findings of Andres et al. [12], who reported that caregivers with a lower health profile tended to experience higher subjective caregiver burden.

The objective burden in terms of time spent on providing care is positively association on the perceived caregiver burden. This confirms earlier findings [15,21] of a correlation between the number of daily hours with the care recipient and subjective caregiver burden.

We found that caregivers to care recipients with a mental illness have a lower objective burden in terms of time investment in caregiver tasks, which may be related to the fact that fewer caregivers were married to and/or living together with the care recipient in the mental group compared with the two other groups.

There was no difference across caregiver types in the number of years that they had provided informal care tasks for the care recipient but there was a positive association between providing care for less than three years compared with providing care for more than 10 years. This suggests that caregivers “adapt” to the caregiver role, because the subjective caregiver burden was higher among respondents who were caregivers for less than three years compared with respondents who have been caregivers for more than 10 years.

Earlier studies found it appropriate to include care recipients’ aspects such as socio-demographics, severity of the illness, health-related quality of life, and social support in the analysis of subjective caregiver burden [6]. In addition, scarce contact between caregiver and health professionals has been shown to increase subjective caregiver burden [14,15]. We did not have access to this type of information in the present study, but such factors might explain some of the observed variation in the subjective caregiver burden.

Conclusion

This study suggests that caregivers to care recipients with mental and especially a combination of mental and somatic illnesses experience a higher subjective caregiver burden compared with care recipients with a somatic illness. This is especially true when we control for factors representing the objective burden and socio-demographic factors. Since the study is not representative of the whole population of caregivers, care should be taken in generalizing the results. The subject needs more investigation in a representative population of caregivers to care recipients with mental and somatic illnesses.

Our literature search has shown that comparison of informal caregiver burden in mental and somatic illness is an under-researched area. The reason for this is likely to be the methodological difficulties associated with obtaining a representative sample due to problems of identifying and contacting relevant informal caregivers. Furthermore, it is difficult to ensure an unselected sample, because caregivers who are very burdened may be reluctant to spend the time to participate in the research. It is therefore important to develop methods of data collection that ensure a representative sample by making sure there is a minimum degree of self-selection. This could be done firstly by identifying the care recipients and secondly, by contacting their caregivers. This may be a complicated recruitment procedure but may also ensure the representativeness of the caregiver
population. We expect that future studies could reach a higher response rate if data is collected through face-to-face interviewing as, e.g. [21] instead of using postal questionnaires sent to the caregivers as in this study.

We suggest that future comparative studies of informal caregiver burden across mental and somatic illnesses also collect information on the care recipients’ socio-demographic factors, the severity of the care recipients’ illness and health-related quality of life, and the level of social support and contact with professional health care. Caregivers’ contact with health professionals may also be a useful indicator of caregiver burden in future studies.

Although the data presented here involve the experiences of caregiver burden, other studies have found that caregivers actually benefit from being caregivers and feel that care recipients contribute to the caregiver’s life [30]. Greater knowledge about the differences in subjective burden across different caregiver types, caregivers’ resources and benefits of caregiving and their input in effective health service delivery will allow for interventions and policies to enhance the relationship between caregiver and care recipient.

Acknowledging the shortcomings of this study, the presented results suggest that there is a high degree of variation in caregivers’ burden, and that it is possible to predict which types of caregivers experience a higher degree of subjective burden, and who therefore needs support. Hopefully, the present study will inspire other researchers to initiate further research in this field in order to obtain valid information that can inform policy making.

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References


Do informal caregivers in mental illness feel more burdened? Comparative study


Chapter 7
The chapter presents Article 4, which addresses the fourth research question.

Title: Does the EQ-5D measure quality of life in schizophrenia?


Authors and their affiliations:
1. Lene Halling Hastrup
2. Professor Dorte Gyrd-Hansen, (i) Institute of Public Health, University of Southern Denmark, Winslowsvej 9, DK-5000 Odense C, (ii) Australian Centre for Health Economic Research on Health, University of Queensland, Herston, Q4006, Australia
3. Ph.D. student, Carsten Hjorthøj, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen
4. Professor Merete Nordentoft, Department of Psychiatry, Bispebjerg Hospital, University of Copenhagen

1 Corresponding author: Lene Halling Hastrup, (i) Psychiatric Research Unit, Region Zealand, Toftebakken 9, DK-4000 Roskilde, Denmark, (ii) Institute of Public Health, University of Southern Denmark, Winslowsvej 9, DK-5000 Odense C
E-mail: lhhs@regionsjaelland.dk, lenehastrup@yahoo.dk

Word count
Abstract: 463
Text excluding abstract, tables and reference list: 3687
Number of tables: 5
Abstract

Background Most health economic evaluations in mental care include outcome measures aimed at specific aspects of health, like symptom improvement, functional improvement and quality of life instead of generic preference based outcome measures. The health economic guidelines (NICE) recommend to include a generic preference based outcome measure, like EQ-5D, in health economic evaluations in order to allow for comparisons of health related quality of life of patient groups across different diseases, providing information particular useful to support health policy decisions and cost-effectiveness analysis.

Although the EQ-5D is by far the most widespread outcome measure within the context of economic evaluations, its validity in psychiatric populations has not yet been established unambiguously. An increasing number of articles have tested the validity of the EQ-5D in comparisons with clinical measures in mental health, but only few studies have addressed the correlation between the EQ-5D and a condition-specific quality of life measure in mental health.

Aims of the study The aim of the article is to test for a potential correlation between the preferred generic outcome measure in health economic evaluations EQ-5D and Manchester Short Assessment of Quality of Life (MANSA) in order to assess to what extent quality of life dimensions measured by a psychiatric quality of life measure are captured in the EQ-5D in a population of patients with schizophrenia and cannabis abuse.

Methods Data analysed is a part of a study of 103 patients with schizophrenia and abuse of cannabis participating in a randomized controlled trial testing a specialized addiction intervention during the period 2008-09.

The correlation of the EQ-5D and scores of MANSA was assessed using the Spearman’s correlation coefficient. In addition, we tested how the EQ-5D and MANSA correlated with PANSS, GAF and WHO-DAS in order to make comparisons with earlier studies.

Results We found moderate, statistically significant correlations between the EQ-5D index score and MANSA total score (rho = 0.358**). The dimensions ‘Mobility’, ‘Self-Care’ and ‘Pain/discomfort’ on the EQ-5D were overall not sensitive in this population, while the dimensions ‘Usual activities’ and ‘Anxiety/depression’ was moderately correlated with MANSA. The EQ-5D and MANSA both showed statistically significant moderate correlations with the clinical measures in the study PANSS, GAF and WHO-DAS.

Discussion Our results suggest that the EQ-5D and MANSA are complementary measures rather than substitutes.
Implications for Health Policies Mental health interventions seek to improve the patients’ quality of life in a broader perspective, like improving the patients’ relationship with family, friends and other network, financial situation, employment and accommodation. If the EQ-5D is used as a single outcome in health economic evaluations of e.g. mental health community interventions, these factors may be overlooked. Based on a relatively small sample, we therefore recommend applying the EQ-5D together with condition-specific quality of life measures in future health economic evaluations in mental health.
Introduction

For the purposes of policy decision-making, it is important to decide which outcome measure to include in health economic evaluations. Generic measures allow for comparisons across different disease groups, providing information useful to support health policy decisions and cost-effectiveness analysis. Despite an increasing use of preference based outcome measures, mental health economic evaluations are still mostly based on outcomes aimed specifically at patients with mental illness, e.g. symptom improvement, improvement of functional level, management of side effects and quality of life.

The EQ-5D is the most commonly used generic, preference-based health related outcome measure in economic evaluations. The instrument may be used to compare health related quality of life in the general population. It has been extensively validated and has been shown to be sensitive to changes in health related quality of life and internally consistent. The EQ-5D is the preferred measure of health related quality of life in health economic evaluations according to The National Institute for Health and Clinical Excellence (NICE) recommendations. Despite widespread use, increasing evidence suggests problems of validity and usefulness of the EQ-5D in psychiatric populations. A recent systematic review of generic health status measures in schizophrenia found mixed evidence for properties of convergent validity and responsiveness of the EQ-5D. As a consequence of the chronic nature of schizophrenia, which often interferes with many life domains and roles, mental health interventions, especially in community treatment, often have a broader focus than many physical conditions. Besides improving clinical measures, they will often seek to improve e.g. the patients’ relationship to family, friendship and network, vocational recovery and accommodation.

One of the most commonly used outcome measures in mental health is Manchester Short Assessment of Life (MANSA). MANSA is a subjective well-being oriented quality of life measure, which has been designed for use in psychiatric populations. A recent cost-effectiveness study of early intervention used MANSA as outcome measure.

In contrast to the EQ-5D, which is a narrow instrument and focuses on functioning in relation to health-related quality of life, MANSA has a broader quality of life construct and measures the patient’s satisfaction with a number of different aspects of quality of life. This study investigates the association between the EQ-5D and MANSA. We found two earlier studies that have examined the correlation between the EQ-5D and quality of life assessed by an instrument designed for
psychiatric patients. Barton et al., 2009, found no correlation between the EQ-5D and the psychiatric quality of life measure QLS, while Auquier et al., 2003, found moderate statistically significant correlations between the EQ-5D and S-QoL. We also examine the correlation between the EQ-5D and objective measures of psychiatric symptoms (PANSS), functional level (GAF) and a subjective measure for disability level (WHO-DAS). Earlier studies found evidence of a small to moderate correlation between the EQ-5D and psychiatric symptom and functional scales. However, the EQ-5D has been shown to be problematic for use in serious mental illnesses like psychosis. One of the problems that have been discussed is whether schizophrenia has quality of life implications not adequately described by the five dimensions of the EQ-5D, since only one of five dimensions refers specifically to mental problems. This dimension is concerning the patient’s problems with anxiety and/or depression, which may not necessarily be capturing the relevant problems of patients with e.g. schizophrenia.

The focus of this article is to compare the EQ-5D with a psychiatric quality of life measure and measures for symptom level and functional level in order to contribute with more knowledge in using the EQ-5D in populations of patients with schizophrenia. This may help choosing outcome measure in future evaluations of mental health interventions and will be of special relevance if the intervention is supposed to include a health economic evaluation.

**Objective**
In order to address the use of EQ-5D as outcome measure in health economic evaluations in a psychiatric population, the present study tests whether the EQ-5D responds to variations in the quality of life among patients with schizophrenia and cannabis abuse as measured by Manchester Short Assessment of Life (MANSA).

In order to make comparisons with earlier findings, we further examine the correlation between the EQ-5D and PANSS, GAF and WHO-DAS.

**Subjects and methods**

**Subjects**
The data analysed is baseline data from a study of 103 patients diagnosed with schizophrenia spectrum disorder according to ICD-10 F2 and abuse of cannabis (ICD-10 F12). They were
recruited through early-psychosis detection teams, community mental health centres, and assertive community treatment teams to a randomised controlled trial of specialized addiction intervention during the period from 2007 to 2009. The CapOpus project is described elsewhere 19.

**Measures**

**EQ-5D**

EQ-5D is a simple generic instrument for subjectively describing and valuing health related quality of life 20. It generates a health profile as well as a preference-based index score that may be used as weights for calculating quality-adjusted life years, known as QALYs, in health economic evaluation.

The questionnaire comprises five questions relating to current problems in the dimensions 'mobility', 'self-care', 'usual activities', 'pain/discomfort', and 'anxiety/depression'. Responses in each dimension are divided into three ordinal levels coded 1) no problems, 2) some problems and 3) severe problems. The self-classifier provides a five-dimensional description of health status, which can be defined by a five-digit number. Theoretically, \(3^5 = 243\) different health states can be defined.

The EQ-5D index represents societal preference values for the full set of 243 EQ-5D health states with the state '11111' (perfect health) and 'death' being assigned values of 1 and 0, respectively. Time-Trade-Off 1 was used to derive a value set for the 243 health states of the EQ-5D 21. The Danish EQ-5D index scores, ranging between –0.550 (health state worse than death) and 1 (perfect health) that we used in the present study were obtained from a random sample of 1332 members of the Danish population 22.

**Psychiatric Quality of Life Profile MANSA**

The Manchester Short Assessment of Quality of Life (MANSA) has been developed as a condensed and slightly modified instrument for routine use. MANSA is based on experiences and empirical evidence gained in studies using Lancashire Quality of Life Profile (LQLP) 23. The MANSA was applied in a sample of community care patients and showed high correlations with LQLP and psychopathology which suggests a high face and construct validity of MANSA 24.

The questionnaire consists of 16 questions. Four of these are termed objective and to be answered with yes or no. Twelve questions are strictly subjective and assess the patient's satisfaction with items like life as a whole, job situation, financial situation, friendship, leisure activities, personal

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1 Time-Trade-Off is a health economic method to value health states, which are being used to determine quality of life.
safety, sex life, mental health, and physical health. Satisfaction is rated on 7-point rating scales, ranging from 1 (negative extreme) to 7 (positive extreme). The total score is the average of the item score. The score is not preference based and cannot be applied as a weight for calculating QALYs.

Psychopathology PANSS

The Positive and Negative Syndrome Scale (PANSS) is a 30-item rating instrument for objectively evaluating the presence or absence and severity of positive, negative and general psychopathology of schizophrenia in the previous week. Positive symptoms is composed of florid symptoms, such as delusions, hallucinations, paranoia, and disorganized thinking while negative symptoms are characterized by deficits in cognitive, affective, and social functions, including blunted affect and passive withdrawal. General symptoms are characterized by e.g. anxiety, depression, and poor attention.

All 30 items are rated on a 7-point Likert scale ranging from 1 (absent) to 7 (extreme). From the 30 items, scores of 4 scales can be derived, namely ‘positive’ (scores between 7 and 49), ‘negative’ (scores between 7 and 49), ‘general’ (scores between 16 and 111) and ‘total’ (scores between 30 and 210) by summing up the respective item scores. Total PANSS score is being considered as 'mildly ill' if the score is less than or equal to 58, 'moderately ill' if the score is more than 58 and less than or equal to 75, 'markedly ill' if the score is more than 75 and less than or equal to 95 and 'severely ill' if score more than 95.

Functional and symptom level GAF

Global Assessment of Functioning Scale (GAF) assesses symptom level and psychological, social and occupational functioning on a 1-100 rating scale that is divided into ten deciles, each of which provides a description of functioning and symptom level. A higher score on the GAF denotes a better response (lower symptom level or higher functional level).

Disability level WHO DAS

The 12-item interviewer administered version of the WHO Disability Assessment Schedule II (WHO DAS II) was developed by the World Health Organization as an international instrument to measure disability. The instrument provides a summary measure of functioning and disability that is reliable and valid across geographic regions, diagnostic groups, ages, and genders. The WHO DAS II can measure severity, monitor impact of programs, determine the score of individuals or
groups in relation to the general population, compare groups with respect to their disability. All items are rated on a 5-point scale ranging from 1 (no difficulty) to 5 (extreme difficulty) and summing up the respective item scores derives a total score.

**Data Analytic Procedures**

We tested the correlation between EQ-5D/ MANS A and PANSS, GAF and WHO-DAS, respectively. Since most data tended not to be normally distributed (tested by Kolmogorov-Smirnov Z-test) the correlations were assessed using Spearman’s rho correlation coefficient. Correlations greater or equal to 0.5 are considered large, correlations less than 0.5 and more than or equal to 0.3 are considered moderate, whereas correlations less than 0.3 are considered small. We expect that fewer problems on the EQ-5D dimensions and thus higher EQ-5D index score correlate with higher satisfaction on MANS A, fewer psychiatric symptoms (lower PANSS score), higher functional level (higher GAF score) and lower disability level (lower WHO DAS score).

The relationship between the EQ-5D and the quality of life as measured by MANS A was investigated using simple multiple regression analysis (Table 3). All calculations were estimated using SPSS 17.0.

**Results**

One hundred and three patients diagnosed with schizophrenia and cannabis abuse were recruited to the study. Baseline demographic and disease-related characteristics of patients are presented in table 1. The mean age is 28.8 years (SD 6.2), ranging from 17 to 42 years and 75% of the patients are males. As many as 54% are unemployed, and 15% are retired, while only 14% have a paid job or are students. 12% of the patients are married or in a relationship. 71% live independent, while 17% of the patients live assisted and 12% are hospitalized.

The mean score on the GAF symptom scale is 43.3 (SD 11.1, minimum 0 and maximum 68). GAF-symptom scores from 41 to 50 are described as severe symptoms. The mean score on the GAF function scale is 43.0 (SD 9.6, minimum 22 and maximum 71). GAF function score from 41 to 50 are characterized with serious impairment in social, occupational or school functioning (e.g., no friends, unable to keep a job).
In total, 95 of the 103 patients completed the EQ-5D at baseline. The mean index score equal to 0.69 (SD. 0.23, median = 0.765). Table 1 shows the patient’s perception of their problems on the EQ-5D dimensions.

The dimensions ‘Mobility’ (70.5%) and ‘Self Care’ (63.3%) are the areas where most of the patients assess that they have no problems at baseline, while only 25.3% of the patients indicate that they have no problems with ‘Usual activities’. 49.5% of the patients assess that they have no problems on the dimension ‘Pain/Discomfort’ and 31.6% have no problems on the dimension ‘Anxiety/depression’.

(Table 1 here)

The patients’ satisfaction with quality of life measured on MANSA is shown in table 1. More than half of the patients assess that they are dissatisfied with the items ‘mental health’ (55.8%), ‘job/main occupation’ (53.7%) and ‘financial situation’ (63.2%), while almost half of the patients are dissatisfied with ‘life as a whole’ (46.4%) and ‘sex life’ (43.2%). 34.7% of the patients indicate not to be satisfied with their ‘health’ as measured on MANSA.

(Table 2 here)

The correlation analysis of the EQ-5D index and MANSA total score (table 2) showed that the measures were statistically significantly correlated, but the correlation was moderate (rho=0.358**). Analysis of correlations between the dimensions of the two measures generally showed coefficients of equal or lower magnitude. We found that the dimensions ‘Usual activities’ (rho = 0.4 **) and ‘Anxiety/depression’ (rho= 0.5**) both had moderate to large correlations with the total MANSA score. The dimensions ‘Mobility’, ‘Self care’, and ‘Pain/discomfort’ on the EQ-5D did not correlate with the total MANSA score.

The dimensions on the MANSA that were statistically significant and moderately correlated with the EQ-5D index were ‘Satisfaction with life as a whole’ (rho = 0.34**), ‘Satisfaction with leisure activities’ (rho = 0.27**), ‘Satisfaction with personal safety’ (rho = 0.35**), and ‘Satisfaction with mental health’ (rho = 0.44**). The dimensions ‘Satisfaction with health’ (rho=0.23*) and
‘Satisfaction with sex life’ (rho=0.21*) on MANSA had a statistically significant but small correlation with the EQ-5D index.

(Table 3 here)

The relationship between health-related quality of life, measured by the EQ-5D index, and the MANSA items was investigated, using a multiple linear regression analysis (table 3). The estimated regression model explained 30.4% of the variation of the EQ-5D index. The dimensions ‘Satisfaction with mental health’ and ‘Satisfaction with personal safety’ had a statistically significant impact on the EQ-5D index score.

(Table 4 here)

The results of the correlation analysis of the EQ-5D and functional level GAF and symptom level PANSS (Table 4) showed that the instruments were statistically significantly correlated with the EQ-5D index, except for the PANSS negative symptom scale. Higher functional level and lower symptom level was associated with better health on the EQ-5D index, but the correlation rates were small to moderate. The dimensions ‘Mobility’ and ‘Self care’ on the EQ-5D scale were not captured in either GAF or PANSS.

Comparing the EQ-5D with the disability instrument WHO-DAS, we found a large correlation (rho = -0.625**) between the total WHO-DAS score and the total EQ-5D index score. This indicates that a lower disability level was associated with a higher index score on EQ-5D (better health). All five dimensions on the EQ-5D were moderately correlated with the dimensions on the WHO-DAS.

(Table 5 here)

MANSA was moderately statistically significantly correlated with GAF, PANSS and WHO-DAS (table 5), except for PANSS negative symptom scale. Even though the total MANSA score does not correlate with the negative symptom PANSS, three items on the MANSA scale are moderately correlated with the negative symptoms, namely ‘satisfaction with number and quality of friendships’ (rho=-0.375***), ‘satisfaction with sex life’ (rho=-0.359***) and ‘satisfaction with leisure activities’ (rho=-0.217*). Overall, MANSA was moderately correlated with WHO-DAS...
(rho=-0.399**). The MANSA dimensions ‘Satisfaction with life as a whole’, ‘Satisfaction with leisure activities’, ‘Satisfaction with personal safety’, and ‘Satisfaction with mental health’ were all correlated with the total WHO-DAS score.

**Discussion**

The purpose of this study was to investigate whether a correlation exists between the EQ-5D and a psychiatric quality of life measure MANSA in order to assess whether the EQ-5D captures quality of life measured by an instrument designed for psychiatric patients.

The study used a sample of patients with schizophrenia and cannabis abuse of predominately male patients recruited through early-psychosis detection teams, community mental health centres, and assertive community treatment teams. Cannabis abuse in combination with schizophrenia may maintain and aggravate the disease and has shown detrimental effects like reduced compliance to therapy, psychiatric medication and increased level of psychotic-dimension symptoms. The population is relatively young and with a high proportion of males. Given the specific characteristics of our sample we should be wary of any generalisation. We did not, however, find any impact of gender and age on the EQ-5D. The mean EQ-index score of 0.69 (SD 0.23) is also similar to values found in other studies of patients with schizophrenia. In comparison, other samples of patients with schizophrenia found EQ-5D index scores equal to 0.75 (SD 0.45), 0.62 (SD 0.28), and 0.68 (SD 0.29). Barton et al, 2009 found a EQ-5D index score equal to 0.67 (95% CI 0.604 – 0.748) in a population of patients with non-affective psychosis recruited to early intervention teams.

In this study, we found moderate statistically significant correlations between the EQ-5D and MANSA. A simple linear regression model of EQ-5D index by the MANSA dimensions explained only 30% of the variation of the EQ-5D index score, which indicates that EQ-5D and MANSA to some extent measure different aspects of quality of life.

Although patients reported problems on the EQ-5D dimensions ‘Mobility’, ‘Self-Care’ and ‘Pain/discomfort’, this was not reflected on the MANSA score. Conversely, a number of MANSA dimensions such as ‘financial situation’, ‘job/main occupation’, ‘friendship’, ‘accommodation’, and ‘relationship with family’ had no impact on the EQ-5D score. A need for a broader focus than
merely on health related issues has previously been questioned since mental health by its nature extends beyond conventional definitions of health. Besides improving psychiatric symptoms and functional level, mental health interventions, especially in e.g. community mental health treatment, often have a broader focus and are targeting to improve the patients relationship to family, friendship and network, vocational recovery, accommodation etc. Our study shows that the EQ-5D does not correlate much with those factors, although the dimension ‘Usual activities’ may capture information about ‘Satisfaction with leisure activities’, ‘Satisfaction with job/main occupation’ and ‘Personal safety’.

It is difficult to determine how correlated EQ-5D and MANSA should be in theory. Barton et al, 2009, found no correlation between EQ-5D index and the 21-item psychiatric instrument QLS (rho=0.025). The missing correlation may probably be caused by the fact, that the two instruments have different constructs and only few overlaps. QLS was rated by clinicians and has specific focus on assessing the deficit syndrome in schizophrenia including four categories, which relates to ‘Intrapsychic foundations’ (e.i. cognition, conation and affectivity), ‘Interpersonal relations’, ‘Instrumental role’ category (social roles) and ‘Common objects and activities’. Auquier et al, 2003, found statistically significant correlations between the EQ-5D index and the 41-item health related quality of life instrument S-QoL (rho=0.48*). Especially, the items ‘Self-esteem’ (rho=0.56*), ‘Psychological well-being’ (rho=0.46*) and ‘Physical well-being’ (rho=0.46*) was associated with the EQ-5D index. Compared to MANSA, S-QoL has more overlaps than QLS.

Clearly, EQ-5D and MANSA are moderately correlated. Relevant dimensions relating to health such as mobility, self-care and pain/discomfort appear to be best captured by the EQ-5D. In contrast, quality of life relating directly to every-day life such as satisfaction with occupation and social life is best reflected in the MANSA. Our results suggest that the MANSA and EQ-5D are complementary measures rather than substitutes, and that using the EQ-5D as a single outcome in health economic evaluations of e.g. mental health community interventions might result in overlooking important quality-of-life factors, which are not health related. At the same time use of the MANSA as a quality of life indicator may overlook health related issues, but such problems will to some extent be reflected in the array of clinical measures available. This supports the point of Meier et al, 2002, that the choice of quality of life instrument also is a choice of content, which needs careful considerations of which aspects of quality of life one aims to capture and critical evaluation in relation to the research question that needs to be answered.
The objective measures indicate severe problems with psychotic symptoms and functional level of the patients. The baseline total PANSS mean score was found to be 75.9 (SD 18.3) and GAF functional score was equal to 43.0 (9.6). In comparison, König et al, 2007, found lower levels of psychotic symptoms and better functional level (PANSS total mean score = 55.1(SD 15.2) and GAF function mean score = 51.5(SD 17.0))\(^{15}\).

We found that EQ-5D index had a weak to moderate correlation with the objective measures (PANSS, GAF) while there was a large correlation between the EQ-5D index and the subjective measure of disability (WHO DAS). This is in line with König et al, 2007, who found a stronger correlation between the EQ-5D index and subjective measures than objective measures\(^{15}\) who explained these findings by a lowering of expectations as a result of patients’ adaption to health related problems, patients’ lack of awareness of illness and differences in patients’ and clinicians’ preferences. We found no correlation between the EQ-5D and PANSS negative symptom scale. We explain this finding by lack of self-insight which characterizes this patient group\(^{37}\). This implies that the patients are not aware of problems caused by negative symptoms like deficits in cognitive, affective, and social functions. A subjective instrument does not capture these deficits unless the patients are asked specific questions relating to the details of such problems\(^{38,39}\). That we find a correlation between the negative PANSS symptoms and MANSA dimensions that relate to more extroverted activities like friendship, sex life and leisure activities suggests that it is necessary to ask specifically to these problems in order to adequately identify deficits caused by negative symptoms. The EQ-5D is more highly correlated with WHO-DAS than MANSA, which most likely is explained by the fact that Both WHO-DAS and EQ-5D focus on disability with self-care and daily living activities. Our results indicate that some of the disability items, like ‘difficulties washing your whole body’ and ‘difficulties getting dressed’ are captured in the EQ-5D item ‘Self-care’, while these disability items are only partly captured in MANSA. The items of the WHO-DAS that are mostly correlated with MANSA are ‘Emotionally affected by health problems’, ‘Difficulties maintaining a friendship’, and ‘Self-rated health’, which relate to the ‘mental health’ MANSA dimension. These results suggest that MANSA does not fully capture problems in daily living activities.
In comparison with the EQ-5D other generic preference based measures like e.g. 15D and SF-6D have broader defined constructs. However, earlier studies also found limitations in applying these measures in populations of patients with mental illnesses. Developing a new quality-of-life measure as described by Brazier and his colleagues which adequately encompasses all facets of mental health should therefore be a priority.

**Conclusion**

Based on our relatively small sample, which includes a specific group of dual diagnosis patients, we find that the EQ-5D in comparison with MANSAs does not appear to work as single measure that adequately captures the relevant quality of life dimensions in the context of mental health. On the other hand, if MANSAs is used as single outcome measure, our analysis suggests that important health-related aspects of quality of life may be overlooked.

Our analysis questions the validity of applying EQ-5D as the single instrument for measuring outcomes in the context of interventions targeting patients with schizophrenia. The results presented here suggest that evaluations in mental health may be more appropriately conducted using softer evaluations where (costs and) consequences are described by way of various instruments. This weakens the evidence base, and makes it difficult to evaluate the relative performance of community mental health interventions, as well as the relative merits of such interventions relative to other health care interventions.

**Acknowledgements**

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**Conflict of interest**

The authors have not transmitted any conflicts of interest.
Reference List


10. Papaioannou D, Brazier J, Parry G. How valid are generic health state measures, such as the EQ-5D and SF-36, in schizophrenia? A systematic review. In Press 2011.


Table 1 Baseline demographic and disease-related characteristics of participants.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age:</strong> mean years (SD)</td>
<td>28.8 (6.2)</td>
</tr>
<tr>
<td><strong>Male:</strong> % (n)</td>
<td>75.7 (103)</td>
</tr>
<tr>
<td><strong>Marital status:</strong> % (n)</td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>80.9 (76)</td>
</tr>
<tr>
<td>Married/cohabiting</td>
<td>11.7 (12)</td>
</tr>
<tr>
<td>Separated/divorced</td>
<td>7.5 (7)</td>
</tr>
<tr>
<td><strong>Working situation:</strong> % (n)</td>
<td></td>
</tr>
<tr>
<td>Work/student</td>
<td>13.8 (20)</td>
</tr>
<tr>
<td>Retired</td>
<td>14.9 (14)</td>
</tr>
<tr>
<td>Unemployed</td>
<td>54.4 (56)</td>
</tr>
<tr>
<td>Other</td>
<td>3.9 (4)</td>
</tr>
<tr>
<td><strong>Living situation:</strong> % (n)</td>
<td></td>
</tr>
<tr>
<td>Independent in community</td>
<td>70.7 (65)</td>
</tr>
<tr>
<td>Assisted living</td>
<td>17.4 (16)</td>
</tr>
<tr>
<td>Hospitalized</td>
<td>12.0 (11)</td>
</tr>
<tr>
<td><strong>GAF-S:</strong> mean (SD)</td>
<td>43.3 (11.1)</td>
</tr>
<tr>
<td><strong>GAF-F:</strong> mean (SD)</td>
<td>43.0 (9.6)</td>
</tr>
<tr>
<td><strong>PANSS-P:</strong> mean (SD)</td>
<td>18.5 (6.1)</td>
</tr>
<tr>
<td><strong>PANSS-N:</strong> mean (SD)</td>
<td>18.3 (6.9)</td>
</tr>
<tr>
<td><strong>PANSS-G:</strong> mean (SD)</td>
<td>39.2 (9.3)</td>
</tr>
<tr>
<td><strong>PANSS-T:</strong> mean (SD)</td>
<td>75.9 (18.3)</td>
</tr>
<tr>
<td><strong>EQ-5D index score:</strong> mean/median (SD)</td>
<td>0.69/0.765 (0.23)</td>
</tr>
<tr>
<td><strong>EQ-5D dimensions:</strong> % (n)</td>
<td></td>
</tr>
<tr>
<td>Mobility</td>
<td>70.5 28.4 1.1</td>
</tr>
<tr>
<td>Self care</td>
<td>63.2 36.8 0</td>
</tr>
<tr>
<td>Usual activities</td>
<td>25.3 66.3 8.4</td>
</tr>
<tr>
<td>Pain/discomfort</td>
<td>49.5 45.3 5.3</td>
</tr>
<tr>
<td>Anxiety/depression</td>
<td>31.6 53.7 14.7</td>
</tr>
<tr>
<td><strong>MANSA total score:</strong> mean (SD)</td>
<td>4.02 (0.76)</td>
</tr>
<tr>
<td><strong>MANSA dimensions:</strong> % (n)</td>
<td></td>
</tr>
<tr>
<td>Satisfaction with life as a whole</td>
<td>31.6 22.1 46.4</td>
</tr>
<tr>
<td>Satisfaction with main occupation</td>
<td>26.3 20.0 53.7</td>
</tr>
<tr>
<td>Satisfaction with financial situation</td>
<td>23.2 13.7 63.2</td>
</tr>
<tr>
<td>Satisfaction with number and quality of friendship</td>
<td>60.1 17.9 22.1</td>
</tr>
<tr>
<td>Satisfaction with leisure activities</td>
<td>33.7 16.8 49.5</td>
</tr>
<tr>
<td>Satisfaction with accommodation</td>
<td>44.2 17.9 37.9</td>
</tr>
<tr>
<td>Satisfaction with personal safety</td>
<td>64.2 22.1 13.7</td>
</tr>
<tr>
<td>Satisfaction with people you live with/or living alone</td>
<td>56.3 20.2 23.4</td>
</tr>
<tr>
<td>Satisfaction with your sex life</td>
<td>33.6 23.2 43.2</td>
</tr>
<tr>
<td>Satisfaction with family relationship</td>
<td>54.8 27.4 17.9</td>
</tr>
<tr>
<td>Satisfaction with health</td>
<td>39.9 25.3 34.7</td>
</tr>
<tr>
<td>Satisfaction with mental health</td>
<td>35.3 18.9 55.8</td>
</tr>
</tbody>
</table>
Table 2: Correlations\(^i\) between the EQ-5D dimensions/index score and MANSA at baseline

<table>
<thead>
<tr>
<th></th>
<th>Mobility</th>
<th>Self Care</th>
<th>Usual Activities</th>
<th>Pain/Discomfort</th>
<th>Anxiety/Depression</th>
<th>EQ-5D index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satisfaction with life as a whole</td>
<td>0.071</td>
<td>0.015</td>
<td>0.506**</td>
<td>0.063</td>
<td>0.503**</td>
<td>0.344**</td>
</tr>
<tr>
<td>Satisfaction with job/main occupation</td>
<td>0.044</td>
<td>-0.104</td>
<td>0.200*</td>
<td>0.005</td>
<td>0.113</td>
<td>0.059</td>
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<tr>
<td>Satisfaction with financial situation</td>
<td>0.098</td>
<td>-0.043</td>
<td>-0.183</td>
<td>0.014</td>
<td>0.197</td>
<td>0.125</td>
</tr>
<tr>
<td>Satisfaction with number and quality of friendship</td>
<td>0.073</td>
<td>-0.061</td>
<td>0.070</td>
<td>-0.004</td>
<td>0.137</td>
<td>0.076</td>
</tr>
<tr>
<td>Satisfaction with leisure activities</td>
<td>0.156</td>
<td>-0.131</td>
<td>0.386**</td>
<td>0.038</td>
<td>0.444**</td>
<td>0.266**</td>
</tr>
<tr>
<td>Satisfaction with accommodation</td>
<td>0.026</td>
<td>0.035</td>
<td>0.031</td>
<td>0.018</td>
<td>0.060</td>
<td>0.030</td>
</tr>
<tr>
<td>Satisfaction with personal safety</td>
<td>0.107</td>
<td>0.153</td>
<td>0.319**</td>
<td>0.293**</td>
<td>0.293**</td>
<td>0.352**</td>
</tr>
<tr>
<td>Satisfaction with the people you live with/or living alone</td>
<td>-0.036</td>
<td>-0.071</td>
<td>0.112</td>
<td>-0.099</td>
<td>0.101</td>
<td>-0.049</td>
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<tr>
<td>Satisfaction with your sex life</td>
<td>0.080</td>
<td>-0.104</td>
<td>0.191</td>
<td>0.109</td>
<td>0.318**</td>
<td>0.208*</td>
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<tr>
<td>Satisfaction with relationship with family</td>
<td>-0.036</td>
<td>-0.117</td>
<td>-0.043</td>
<td>0.087</td>
<td>0.128</td>
<td>0.078</td>
</tr>
<tr>
<td>Satisfaction with health</td>
<td>0.009</td>
<td>0.181</td>
<td>0.107</td>
<td>0.335**</td>
<td>0.127</td>
<td>0.226*</td>
</tr>
<tr>
<td>Satisfaction with mental health</td>
<td>0.203*</td>
<td>0.022</td>
<td>0.484**</td>
<td>0.262</td>
<td>0.498**</td>
<td>0.447**</td>
</tr>
<tr>
<td>Total score</td>
<td>0.089</td>
<td>-0.080</td>
<td>0.400**</td>
<td>0.195</td>
<td>0.501**</td>
<td>0.358**</td>
</tr>
</tbody>
</table>

Spearman’s rho correlations *p<0.05, **p<0.01, ***p<0.001

\(^i\) Positive correlation indicates that higher score on EQ-5D (better health) is associated with higher satisfaction on MANSA
Table 3: Linear regression analysis of baseline data: EQ-5D index by MANSA dimensions

<table>
<thead>
<tr>
<th></th>
<th>Coeff.</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R</strong></td>
<td>0.551</td>
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<tr>
<td><strong>F (sig.)</strong></td>
<td>2.944 (0.00)</td>
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<th></th>
<th>Coeff.</th>
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<td>Satisfaction with accommodation</td>
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<td>0.673</td>
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<tr>
<td>Satisfaction with the people you live with/or living alone</td>
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<tr>
<td>Satisfaction with relationship with family</td>
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</tr>
<tr>
<td>Satisfaction with health</td>
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<tr>
<td>Satisfaction with mental health</td>
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<td>0.033*</td>
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*p<0.05
Table 4: Correlations of the EQ-5D and GAF, PANSS, WHO-DAS at baseline

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<tr>
<th></th>
<th>Mobility</th>
<th>Self Care</th>
<th>Usual Activities</th>
<th>Pain/discomfort</th>
<th>Anxiety/Depression</th>
<th>EQ-5D index</th>
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<tr>
<td>GAF-S i)</td>
<td>0.206</td>
<td>0.089</td>
<td>0.363**</td>
<td>0.304**</td>
<td>0.451**</td>
<td>0.405**</td>
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<tr>
<td>GAF-F ii)</td>
<td>0.242*</td>
<td>0.210</td>
<td>0.482**</td>
<td>0.238*</td>
<td>0.380**</td>
<td>0.395**</td>
</tr>
<tr>
<td>PANSS iii) Positive symptoms</td>
<td>0.162</td>
<td>0.145</td>
<td>0.189</td>
<td>0.256*</td>
<td>0.216*</td>
<td>0.295**</td>
</tr>
<tr>
<td>PANSS ii) Negative symptom</td>
<td>0.021</td>
<td>-0.214</td>
<td>0.004</td>
<td>0.148</td>
<td>0.129</td>
<td>0.046</td>
</tr>
<tr>
<td>PANSS iii) General symptoms</td>
<td>0.138</td>
<td>0.079</td>
<td>0.323**</td>
<td>0.337**</td>
<td>0.259**</td>
<td>0.389**</td>
</tr>
<tr>
<td>PANSS iii) Total</td>
<td>0.142</td>
<td>-0.031</td>
<td>0.237*</td>
<td>0.299**</td>
<td>0.289**</td>
<td>0.298**</td>
</tr>
<tr>
<td>WHO-DAS iv)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing for long periods such as 30 minutes</td>
<td>0.178</td>
<td>0.262*</td>
<td>0.183</td>
<td>0.391**</td>
<td>0.249*</td>
<td>0.416**</td>
</tr>
<tr>
<td>Taking care of your household responsibilities</td>
<td>0.262*</td>
<td>0.388**</td>
<td>0.383*</td>
<td>0.105</td>
<td>0.225*</td>
<td>0.418**</td>
</tr>
<tr>
<td>Learning a new task, e.g. learning how to get to a new place</td>
<td>0.128</td>
<td>0.236*</td>
<td>0.154</td>
<td>0.053</td>
<td>0.129</td>
<td>0.170</td>
</tr>
<tr>
<td>Problems joining in community activities in the same way as anyone else can</td>
<td>0.309**</td>
<td>0.296**</td>
<td>0.367</td>
<td>0.073</td>
<td>0.403*</td>
<td>0.441**</td>
</tr>
<tr>
<td>Emotionally affected by health problems</td>
<td>0.183</td>
<td>0.134</td>
<td>0.299**</td>
<td>0.359**</td>
<td>0.471**</td>
<td>0.486**</td>
</tr>
<tr>
<td>Difficulty concentrating on doing something for ten minutes</td>
<td>0.129</td>
<td>0.345**</td>
<td>0.244*</td>
<td>0.135</td>
<td>0.239*</td>
<td>0.355**</td>
</tr>
<tr>
<td>Difficulty walking a long distance such as a kilometre</td>
<td>0.186</td>
<td>0.187</td>
<td>0.197</td>
<td>0.211*</td>
<td>0.347**</td>
<td>0.366**</td>
</tr>
<tr>
<td>Difficulty washing your hole body</td>
<td>0.135</td>
<td>0.614**</td>
<td>0.192</td>
<td>0.172</td>
<td>0.079</td>
<td>0.304**</td>
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<tr>
<td>Difficulty getting dressed</td>
<td>0.000</td>
<td>0.368**</td>
<td>0.179</td>
<td>0.095</td>
<td>-0.013</td>
<td>0.145</td>
</tr>
<tr>
<td>Difficulty dealing with people you do not know</td>
<td>0.201</td>
<td>0.315**</td>
<td>0.442**</td>
<td>0.235</td>
<td>0.386**</td>
<td>0.486**</td>
</tr>
<tr>
<td>Difficulty maintaining a friendship</td>
<td>0.084</td>
<td>0.111</td>
<td>0.227*</td>
<td>0.071</td>
<td>0.267**</td>
<td>0.210*</td>
</tr>
<tr>
<td>Difficulty to day work</td>
<td>0.138</td>
<td>0.315**</td>
<td>0.392**</td>
<td>0.112</td>
<td>0.433**</td>
<td>0.464**</td>
</tr>
<tr>
<td>Self rated health</td>
<td>0.169</td>
<td>0.242*</td>
<td>0.302**</td>
<td>0.173</td>
<td>0.391**</td>
<td>0.344**</td>
</tr>
<tr>
<td>Total score</td>
<td>0.316**</td>
<td>0.489**</td>
<td>0.478**</td>
<td>0.282**</td>
<td>0.484**</td>
<td>0.625**</td>
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</table>

Spearman’s rho correlations *p<0.05, **p<0.01, ***p<0.001
i) Fewer symptoms on GAF-S is associated with better health on EQ-5D
ii) Higher functional level on GAF-F is associated with better health on EQ-5D
iii) Fewer symptoms on PANSS is associated with better health on EQ-5D
iv) Lower disability on WHO-DAS is associated with better health on EQ-5D.
Table 5. Correlation between MANSA and GAF-S, GAF-F, PANSS and WHO-DAS at baseline

<table>
<thead>
<tr>
<th>Satisfaction with:</th>
<th>life as a whole</th>
<th>job or education</th>
<th>financial situation</th>
<th>Number and quality of friendships</th>
<th>leisure activities</th>
<th>Accommodation</th>
<th>personal safety</th>
<th>people you live with</th>
<th>sex life</th>
<th>family relationship</th>
<th>physical health</th>
<th>mental health</th>
<th>Total MANSA score</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAF-S (*i)</td>
<td>0.248*</td>
<td>0.066</td>
<td>-0.092</td>
<td>0.245*</td>
<td>0.150</td>
<td>0.010</td>
<td>0.290**</td>
<td>-0.033</td>
<td>0.134</td>
<td>0.224*</td>
<td>0.069</td>
<td>0.349**</td>
<td>0.285**</td>
</tr>
<tr>
<td>GAF-F (*ii)</td>
<td>0.288</td>
<td>0.113</td>
<td>-0.033</td>
<td>0.232*</td>
<td>0.248*</td>
<td>0.099</td>
<td>0.307**</td>
<td>-0.053</td>
<td>0.116</td>
<td>0.224*</td>
<td>0.102</td>
<td>0.307**</td>
<td>0.327**</td>
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<td>PANSS (*iii)</td>
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<td></td>
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<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Positive symptoms</td>
<td>-.049</td>
<td>-.094</td>
<td>-0.043</td>
<td>-0.120</td>
<td>0.028</td>
<td>-.143</td>
<td>-.234**</td>
<td>-.176</td>
<td>-.022</td>
<td>-.211*</td>
<td>-.161</td>
<td>-.109</td>
<td>-.272**</td>
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<td>Negative symptom</td>
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<td>General symptoms</td>
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<td>-.226*</td>
<td>-.195</td>
<td>-.062</td>
<td>-.285**</td>
<td>-.010</td>
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<td>-.179</td>
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<td>Total PANSS</td>
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<td>-.126</td>
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<td>-.281**</td>
<td>-.165</td>
<td>-.056</td>
<td>-.255**</td>
<td>-.058</td>
<td>-.227*</td>
<td>-.174</td>
<td>-.095</td>
<td>-.260**</td>
<td>-.335**</td>
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<td>WHO-DAS (*iv)</td>
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<td>1Standing for long periods such as 30 minutes</td>
<td>-.152</td>
<td>-.169</td>
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<td>-.103</td>
<td>-.010</td>
<td>-.077</td>
<td>0.135</td>
<td>-.209*</td>
<td>-.295**</td>
<td>-.252*</td>
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<tr>
<td>3Learning a new task, e.g. learning how to get to a new place</td>
<td>-.145</td>
<td>-.048</td>
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<td>-.121</td>
<td>-.187</td>
<td>-.146</td>
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<td>-.072</td>
<td>-.071</td>
<td>-.065</td>
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<td>-.200</td>
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<td>0.026</td>
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<td>-.301**</td>
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<td>-.003</td>
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<td>-.248*</td>
<td>-.112</td>
<td>0.057</td>
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<td>-.083</td>
<td>-.143</td>
<td>-,509***</td>
<td>-.404***</td>
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<td>-.171*</td>
<td>-.086</td>
<td>-.266*</td>
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<td>-.036</td>
<td>-.152</td>
<td>-.232*</td>
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<td>-.044</td>
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<td>-.241*</td>
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<td>8Difficulty washing your hole body</td>
<td>9Difficulty getting dressed</td>
<td>10Difficulty dealing with people you do not know</td>
<td>11Difficulty maintaining a friendship</td>
<td>12Difficulty to day work</td>
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<td>-.353**</td>
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<td>-.043</td>
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<td>-.169</td>
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</tr>
</tbody>
</table>

Pearson’s rho correlations: *p<0.05, **p<0.01, ***p<0.001

i) Fewer symptoms on GAF-S is associated with higher satisfaction on MANSA
ii) Higher functional level on GAF-F is associated with higher satisfaction on MANSA
iii) Fewer symptoms on PANSS is associated with higher satisfaction on MANSA
iv) Lower disability on WHO-DAS is associated with higher satisfaction on MANSA.
Chapter 8 Summary and concluding remarks

This thesis aims to contribute to mental health economics by giving input to methodological and policy relevant questions relating to community mental health care issues, which have been identified as important in the current literature.

This chapter concludes the findings of the thesis by answering the four research questions one by one.

1. Is early intervention in first-episode psychosis cost-effective?

The review of studies of early intervention in first-episode psychosis in Chapter 1.5 concluded that to date only few studies have included health economic aspects in evaluations. The current evidence base regarding cost-effectiveness is limited. Most studies were either based on a less rigorous design (based on historical controls), had small sample sizes or a relatively short follow-up period. Furthermore, most evaluations adopted a narrow costing perspective, which may give a less than a full picture of overall resource implication and thus possibly lead to sub-optimal decision making. Also, the economic evaluations applied various disease-specific outcome measures without specifying the most important outcome measure. Such cost-consequence analyses may be less useful for decision making as there is no weighting of the relative importance of goals. Applying disease specific measure as opposed to generic health related quality of life measures also restricts the usefulness of the application, as such measures do not allow for prioritization across disease areas. The main finding of the literature review was that a specialized intervention targeting first-episode psychosis patients leads to a decrease in psychiatric inpatient costs in a short-run perspective, which goes from 18 months to 3 year.

The OPUS trial is the largest study of first-episode psychosis patients to date. In this study 547 patients aged between 18 and 45 years were randomized to either a two-year specialized early intervention program or standard treatment. Adopting a comprehensive public sector perspective, the economic evaluation found that the two-year OPUS intervention can be implemented at the same costs as standard treatment, but with a better outcome. This leads to the conclusion that the specialized early intervention treatment is cost-effective. In line with earlier studies, the psychiatric inpatient costs outweighed the increase in psychiatric outpatient treatment cost caused by the intervention. Other health care costs and supported living facility costs were not affected by the intervention over the 2 years period. An important contribution to the literature is that the study also evaluated cost-effectiveness over
5 years, i.e. over a longer observation period than previously applied in the literature. In this long term perspective the difference in outcome between OPUS and standard treatment had disappeared at the 5 years follow-up. Furthermore, we did not find statistical significant differences in total costs between the treatment groups. The statistically significant difference in psychiatric inpatient costs observed during the first 3 years after inclusion was not maintained 4 and 5 years after inclusion. An interesting finding was that costs relating to supported housing facilities did not differ between the treatment groups until year 4, after which the costs of supported living facilities were lower in OPUS. Moreover, total costs in year 5 were statistically significantly lower in OPUS. The results suggest that, although, the total costs over the full observation period did not differ across the treatment groups, there may be cost savings beyond the intervention period.

Major strengths of the trial were the design and the relatively large sample included in the study. The collection of clinical data allowed for a follow-up period of the economic evaluation of 5 years. Furthermore, an important strength was that all resource data were extracted from Danish official registers, which are known to be of high quality, completeness and validity.

A weakness of the economic evaluation was that a full societal perspective was not adopted. Lost productivity, which could possible be affected by the OPUS intervention, was not included in the study. As an indicator of the patient's ability to be part of the labour force, a calculation of the costs of early age pension was performed and there appeared to be no difference between OPUS and standard treatment, which suggests that the productivity of the patients was not affected by the intervention. Other omitted costs were indirect cost items such as contacts with criminal justice and informal caregiver costs. Both cost items could potentially be affected by the intervention.

In the OPUS intervention, caregivers or family members were directly involved in part of the treatment via psycho-educational family treatment. According to Chapter 2.4 and the results of article 3 (presented in Chapter 6), the evaluation should account for the time used by caregivers to directly participate in the treatment as this investment is not trivial in the context of mental health. Revealed preference methods could possibly be applied to valuing caregiver time.
2. Are health care resources distributed to those individuals mostly in need?
The specific group of patients with first-episode psychosis is among the most severely mentally ill. These patients are known to have difficulties in engaging with services and are at a great risk of being lost to the system. The thesis used a welfare economics framework to understand the necessary conditions for welfare optimal mental health practice and policy. Both from an efficiency perspective and from an equity perspective it is important to ascertain that services are allocated to patients with the highest need. The relationship between individual characteristics of newly diagnosed patients and future costs was analysed in order to ascertain whether resources were sufficiently accessible to those who were more severely mentally ill.

Data on future resource consumption were coupled with baseline patient characteristics on demographic characteristics, diagnosis and severity of illness (GAF-f, GAF-s and DUP). Endogeneity may arise if level of resource consumption over the observation period affects severity of illness in the same time period, in which case the causal relationship between health status and level of resource consumption would be reversed. In order to avoid problems of endogeneity, only indicators of initial severity of disease at base-line were included as potential explanatory variables, as these are unaffected by subsequent resource consumption (i.e. exogenous).

Article 2 found that personal characteristics such as lower age, higher symptom level, lower functional level, having a substance abuse, and being homeless were associated with higher costs. Other factors in the study such as sex, diagnosis and DUP did not offer further explanation to the variations in future costs in a multivariate regression analysis.

The association between young age and higher future costs is likely to reflect earlier findings of age as prognostic factor for schizophrenia and other psychosis. The younger age at the onset of positive psychotic symptoms, the poorer the outcome tends to be. The association between future costs and other factors that may be interpreted as indicators of the severity of illness (GAF-f, GAF-s, substance abuse and being homeless) suggests that a higher need at onset of illness was indeed associated with a higher resource input. That the study shows that the homeless and substance abusers have a higher resource use is especially indicative of an effective delivery of services and a successful outreach policy, as these patients are often the most difficult to engage in services.
The findings suggest that within this specific Danish community mental health setting, the resources were distributed to patients in need at onset of illness.

3. Do caregivers of patients with mental illness experience a higher subjective caregiver burden than other caregivers?

The evidence base suggests that caregivers to patients with mental illnesses suffer from a substantial burden. Various methods have been developed to measure and valuate informal care, but current evidence suggests that informal caregiver costs are rarely assessed in mental health economic evaluations.

Article 3 seeks to answer the third research question by analyzing whether caregivers to patients with mental illnesses are experiencing a higher subjective burden than other caregivers and furthermore which specific caregiver characteristics are associated with the subjective caregiver burden. The study was based on a broad sample of 865 Dutch informal caregivers, and data was collected by postal questionnaires as a part of a larger investigation into the situation of informal caregivers. The respondents were a self-selected group of caregivers who had contacted one of 40 regional support centres for informal caregivers. These centres offer information, organize self-help groups and help with directions to formal care. The article found that when controlling for other factors in the analysis, being informal caregiver to a care recipient with a mental or a combination of mental and somatic illnesses was associated with an added subjective caregiver burden measured by the Caregiver Strain Index (CSI). Objective burden, in terms of hours of care provision per week, years of care giving, and living together with care recipient was associated with subjective caregiver burden. The subjective caregiver burden was higher amongst carers who lived together with the recipient and those who spent many hours care giving. Interestingly, subjective care burden was associated with fewer years of care giving, suggesting that adaptation to own caregiver situation may take place. Other factors which were associated with higher caregiver burden was being child or partner of care recipient, having a paid job, having a low health-related quality of life, or suffering from illness. Acknowledging that the response rate is relatively low and that the sample was a self-selected group of carers (who may not be representative of all carers), the article suggests that caregivers to care recipients with either a mental or a combination of mental and somatic illnesses experience a higher subjective burden. The study stresses that the burden of informal care giving is an under-researched
area, which is likely to the methodological difficulties in obtaining a representative sample due to problems of identifying and contacting caregivers.

4. **Is it appropriate to apply a generic preference based quality of life measure (EQ-5D) in the context of mental health?**

Current evidence suggests that using existing preference-based generic quality of life measure in economic evaluations, as recommended by health economic guidelines, may be problematic in mental health populations, as it may not capture all relevant health aspects associated with mental health. Unfortunately, methods for economic evaluation has in the past focused more on developing methods for measuring the health outcomes of somatic illnesses, and an often applied instrument (EQ-5D) has been criticized for not adequately measuring dimensions of health relevant for mental health. To answer the fourth research question, Article 4 analyzed how quality of life aspects as measured by MANSA (an instrument developed for quality of life assessment in psychiatric populations) are associated with the generic preference-based outcome measure, EQ-5D.

The study used baseline data from the CapOpus project, which consisted of 103 patients with schizophrenia spectrum disorder and abuse of cannabis. The patients were recruited through early-psychosis detection teams, community mental health centres, and assertive community treatment teams to a randomised controlled trial of specialized addiction intervention during the period from 2007 to 2009. The article found that the EQ-5D and MANSA were moderately correlated, and that health related dimensions such as mobility, self-care and pain/discomfort appeared to be best captured in the EQ-5D. Quality of life-dimensions such as satisfaction with occupation and social life were best captured by MANSA, while health-related dimensions may be overlooked by MANSA.

Since mental health interventions often seek to improve patients' quality of life in a broader perspective, using the EQ-5D as a single outcome measure will not capture factors like patient's relationship with family, friendships and other network, employment and accommodation, which may be important aspects of outcome in relation to interventions in community-based mental health. Conversely, MANSA does not seem to adequately capture dimensions relating to somatic illness, an often overlooked but important dimension of mental health (as mentioned in chapter 7). Based on this small study, Article 4 recommends
that EQ-5D should be used together with a disease-specific quality of life measure in future economic evaluation.

To conclude, this thesis has contributed to the mental health economic literature on several important issues. Needless to say, there is a vast scope for future research within the economics of mental health. Although this thesis does not cover them all, the finding of this thesis suggest that evaluations of mental health interventions in community setting should ensure that such interventions are assessed on a long term basis such that the resource use patterns over time are adequately captured. In addition, it may be important to focus on the efficiency of delivery of services to the more vulnerable sub-groups of the mental health population. For example, the literature suggests that community services may not be efficiently delivered to mentally ill substance users. Efficient delivery of services to mentally ill in the community is about tailoring the services such that services are delivered efficiently to all patients in the target group. Hence, economic evaluation is not only about assessing cost and outcomes at the aggregate, but also about analysing whether distribution of resources can be more efficiently delivered through more detailed analysis at the individual patient level.

Moreover, the thesis has highlighted the importance of applying a broader perspective when looking at the resource implications of interventions. Economic evaluations performed to date are often too narrowly focused and do not include potential important outcomes such as the mentally ill patients’ ability to maintain a job. Clearly, for some patients ensuring a job-market affiliation may result in productivity gains to society as well as quality-of-life enhancement. A focus of this thesis has also been on the cost of caregiving. This thesis has provided additional evidence on the cost of caregiving in the context of mental health. An important future research focus should therefore be to develop revealed or stated preference methods for establishing the value of informal caregiving in monetary terms such that this cost component can be appropriately included in economic evaluations, and is not ignored. Finally, this thesis has shed light on the inadequacy of current quality-of-life instruments in assessing the quality-of-life of mentally ill patients. It is recommended that future research focuses on developing a generic preference based instrument that is equally sensitive to changes in quality-of-life amongst somatic and psychiatric patients.
Dansk resume
Afhandlingens formål er at bidrage med sundhedsøkonomisk viden i forhold til interventioner i psykiatrien ved at besvare fire metodiske og policy-relevante forskningsspørgsmål inden for sundhedsøkonomisk evaluering af interventioner i psykiatrien med særlig fokus på distriktspsykiatriske indsatser. Disse fire spørgsmål er afdækket i den indledende litteraturgennemgang.
Afhandlingen indeholder fire artikler, som hver især besvarer de følgende forskningsspørgsmål.

1) Er specialiseret, integreret behandling af patienter med førstegangspsykose omkostningseffektiv?
2) Bliver sundhedsressourcer allokeret til patienter med det største behov?
Patienter med førstegangspsykose tilhører gruppen af patienter med svær psykisk sygdom, som kan have svært ved at udnytte eksisterende behandlingstilbud. Artikel 2 analyserede associationen mellem baseline karakteristika for patienter med førstegangspsykose og omkostninger til sundhedsydelser samt psykiatriske botilbud de følgende fem år. Formålet med analysen var at identificere om ressourcerne blev distribueret til patienter med det største behov. Analysen fandt en sammenhæng mellem omkostningerne over 5 år og faktorer, som indikerer sværere sygdom (højere symptomniveau, lavere funktionsniveau, misbrug, og hjemløshed). Resultatet tyder på, at større behov ved sygdomsstart var associeret med et større ressource input. Selvom resultatet sandsynligvis afspejler den konkrete kontekst og den estimerede model har en lav forklaringsgrad, tyder det på at i det specifikke distriktspsykiatrisk setting, var ressourcerne distribueret til de patienter, som havde det største behov ved sygdommens start.

3) Oplever pårørende (informal caregivers) til patienter med psykiatrisk sygdom en højere subjektiv byrde end andre "informal caregivers"?

4) Er et generisk præference baseret livskvalitetsmål (EQ-5D) velegnet i sundhedsøkonomiske evalueringer af psykiatriske interventioner?
Endelig indeholder afhandlingen et studie, der analyserer, om der er en potentiell korrelation mellem det mest anvendte generisk præferencebaserede outcomemål inden for
sundhedsøkonomisk evaluering, EQ-5D, og et psykiatrisk livskvalitetsmål. Artikel 4 undersøger i hvilken udstrækning, at livskvalitetsdimensioner i det psykiatriske livskvalitetsmål, MANSA, bliver opfanget i EQ-5D.

Undersøgelsen gennemførtes i en population af patienter med skizofreni og cannabismisbrug og viste en moderat korrelation mellem EQ-5D index score og MANSA total score. Dimensionerne i EQ-5D som vedrører "Bevægelighed", "Personlig pleje" og "Smerter/ubehag" var ikke sensitive, og givet det lille antal patienter i den anvendte population, tyder resultatet på, at EQ-5D er komplementære mål snarere end substitutter. Sundhedsøkonomiske interventioner i psykiatrien især i distriktspsykiatrien har ofte et bredere sigte, såsom at forbedre patienternes relation til familie, venner og andet netværk, forbedring af patienternes arbejdssituation og boligforhold. Afhandlingen anbefaler, at EQ-5D benyttes sammen med et psykiatrisk livskvalitetsmål i fremtidige sundhedsøkonomiske evalueringer i psykiatrien, især i interventioner indenfor distriktspsykiatrien.
Reference List


Papaioannou D, Brazier J, Parry G. How valid are generic health state measures, such as the EQ-5D and SF-36, in schizophrenia? A systematic review. 2011.


