Mortality prior to, during and after opioid maintenance treatment (OMT): A national prospective cross-registry study

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Abstract

Background: Opioid maintenance treatment (OMT) is generally considered to reduce mortality in opiate dependents. However, the level of mortality reduction is still uncertain. This study investigates mortality reductions in an “intention-to-treat” perspective including all dropouts. The mortality reducing effects of OMT are examined both within treatment and post-treatment. The study separates overdose and total mortality reductions.

Methods: The study is a prospective cross-registry study with up to 7 years follow-up. All opiate dependents in Norway who applied for OMT (a total of 3789 subjects) were cross-linked with data from the death registry from Statistics Norway. Date and cause of death were crossed with dates for initiation and termination of OMT, and subjects’ age and gender. A baseline was established from the waiting list mortality rate. Intention-to-treat was investigated by analysing mortality among the entire population that started OMT.

Results: Mortality in treatment was reduced to RR 0.5 (relative risk) compared with pre-treatment. In the “intention-to-treat” perspective, the mortality risk was reduced to RR 0.6 compared with pre-treatment. The patients who left the treatment programme showed a high-mortality rate, particularly males.

Conclusions: OMT significantly reduces risk of mortality also when examined in an intention-to-treat perspective. Studies that evaluate effects of OMT only in patients retained in treatment tend to overestimate benefits. Levels of overdose mortality will influence the risk reduction. Cross-registry studies as the current one are an important supplement to other observational designs in this field.

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Keywords: Maintenance treatment; Mortality; Opioid; Methadone; Buprenorphine; Intention-to-treat

1. Introduction

Mortality among untreated opioid dependents is internationally estimated with relatively wide variations; between 1 and 4 per 100 person years (Amato et al., 2005; Bargagli et al., 2006; Concool et al., 1979; Darke et al., 2007; Hser et al., 1993; Oppenheimer et al., 1994; Rossow and Lauritzen, 1999). As the majority of deaths among opiate dependents are reported to be overdose-related (Darke and Hall, 2003; Digiusto et al., 2004; Gossop et al., 2002), the level of overdose mortality is particularly influential.

Further, the level of mortality in a given population will be influenced by gender, age, drug administration, personality, general health status and treatment availability (Darke et al., 2007). The extent to which drug treatment is provided and easily accessible to dependent drug users, will impact substantially upon the rates of drug-related mortality amongst these populations (Darke et al., 2007). As risk reduction is influenced by baseline mortality, variation in mortality levels across different populations of illicit drug users is thus the result.

Opioid maintenance treatment (OMT) is generally considered to be the most important harm-reducing measure (Darke et al., 2007; van den Brink and Haasen, 2006; Zador, 2007), and it is often stated that “OMT saves lives” (Brugal et al., 2005; Gurnee and Gronbladh, 1981). While the evidence favours this view, there are several weaknesses in the research that underlie these results, particularly in regard to level of risk reduction. Still, estimating the level of risk reduction might be important both in treatment policy, in balancing the need for control with the need for availability, and in the management of the individual patients.
However, tragic, overdose deaths occur statistically infrequently, and research will need both adequate population size and follow-up period to attain sufficient statistical strength. Mortality has been included in the outcome measures of some randomized clinical trials (RCTs) with short follow-up periods, with little or no significant mortality reducing effects found (Dole et al., 1969; Strain et al., 1993). Even within opioid-dependent populations, research designs with large samples and long-term follow-up are needed, but difficult to apply in RCTs, in order to firmly examine mortality reducing effects (Faggiano et al., 2003). A systematic review concludes that it is not proven that OMT significantly reduces mortality (Amato et al., 2005). Nonetheless, the results from OMT research have been divergent on the issue. In a Swedish study, a clinical trial comparing buprenorphine maintenance to medically supervised buprenorphine withdrawal, observed a statistically significant difference in mortality rates favouring buprenorphine maintenance (Kakko et al., 2003). However, there are some problems comparing mortality after detoxification with that in treatment, and the findings might be disputed as the study size was rather small. Some years ago, Gunne compared a population-denied entrance to OMT with a group accepted for methadone maintenance treatment and found marked differences in mortality (Gunne and Gronbladh, 1981). However, that study was performed in a situation of policy conflict in Sweden and the group-denied treatment were in a rather vulnerable situation.

The mortality-reducing effects of OMT are primarily established through observational studies. However, these often exclude dropouts, sometimes lack clear selection criteria for treatment or might be seen as local area studies difficult to generalise from (Hser et al., 1993; Kleinman et al., 1977; Nich and Carroll, 2002). Findings are, as a result, mostly applicable to those selected by the treatment unit and maintained in treatment. Even well designed cohort studies face challenges with persons lost to follow-up (Soyka et al., 2006; Termorshuizen et al., 2005).

Programme characteristics such as treatment approach, inclusion and exclusion criteria may vary. Comparison of effect of different OMT programmes in different countries or regions is therefore not always appropriate. For example, a recent study from Stockholm found no opiate overdose deaths in their OMT population. However, the Stockholm programme did not include polydrug users and excluded patients with concurrent use of drugs (Fuglestad et al., 2007). The in-treatment effects of such a programme will be favourable, but the generalization is difficult.

In Norway, OMT is founded as a national system encompassing all systematic maintenance treatment offered (Waal, 2007). Applicants wait for treatment for some time, enabling a waiting list design, and establishing a pre-treatment mortality level within the study population.

Patient registers include information on periods both in and out of treatment.

According to current estimates there are between 8200 and 12 500 injecting opiate addicts in Norway (Bretteville-Jensen and Amundsen, 2006). Approximately 4600 persons are in OMT, of whom 90–95% are intravenous drug users. (Statistics from National OMT competence centre 2006). Buprenorphine was registered as a therapeutic OMT drug in 2001 and by 2003; 23% used buprenorphine, the rest used methadone. The average dosing of methadone and buprenorphine was 112 mg and 20 mg, respectively in 2005 (Statistics from National OMT competence centre 2006) (Waal, 2007).

Statistics Norway (SSB) receives all death certificates concerning deceased Norwegians (SSB, 2006). The relatively high quality and accessibility of electronic public registries in Norway permit a cross-registry study between an OMT patient registry and the death registry.

In this paper the mortality reducing effect in an entire national OMT population, with calculated baseline mortality prior to treatment, including all programme dropouts, is studied. The study is prospective and with a population size sufficient for appropriate statistical analysis. As nation wide registers are available, it is possible to study the effects of treatment in an “intention-to-treat” design. Our results complement previous findings.

1.1. Objectives

(1) To assess differences in mortality rates prior to, during and after OMT.
(2) To evaluate mortality reductions in an “intention-to-treat” perspective.
(3) To examine the distribution of drug overdose versus non-overdose as cause of death.

2. Materials and methods

2.1. Sample and data collection

The Norwegian OMT programme is designed to reach the population of severely addicted heroin users not benefiting from other types of treatment (Waal, 2007). The inclusion criteria for OMT are “several years of addiction dominated by opioid dependence”, verified prior to treatment. There has been a 25-year age limit for inclusion, although exceptions have been made. Persons with severe somatic or psychiatric co-morbidity have been given priority. Treatment is based on cooperation between social service centres, general practitioners and specialised OMT centres.

All opioid-dependent people who applied for and were accepted for OMT in Norway between 1 January 1997 and 31 December 2003 – a total of 3789 persons – were included in the data for this study, with a total observation time of up to 7 years. The design hence is a dynamic cohort, where persons were included as they applied for OMT, resulting in individual and varying observation times; from inclusion until 31 December 2003, which was the time set for examination of mortality.

2.2. Procedures

The sample has been divided into pre-treatment, (applicants qualifying for OMT, but prior to initiation of treatment = waiting list) in-treatment (in OMT) and post-treatment (after termination of OMT). A national OMT registry including national ID numbers was established based on the electronic record system in
each OMT centre. Each centre provided lists of all persons who had applied for, entered and left OMT during the observation period. These lists were sent to Statistics Norway and information on the date and cause(s) of any deaths were attached to the data files. The merging of data registers was performed towards the end of 2005. Thus, all deaths in the observation period (through 2003) are included in the register.

2.3. Measures and definitions

Death certificates registered with Statistics Norway are in most cases completed by a physician after examination of the deceased. In about one-third of cases, additional information as a result of autopsy is included (SSB, 2006). Death certificates include one principal cause of death, and up to four underlying causes (ICD 10 codes) (SSB, 2006; WHO, 2006). For the purposes of this paper, only the principal cause of death is used. Acute intoxications/deaths from all substances were combined in an “overdose” category. These comprise ICD 10 codes F11.0, F19.0, X42.0 and X44.0 diagnoses.

The non-overdose groups included both somatic and sudden/violent deaths (such as suicide, traffic accidents and homicide).

Some subjects included in the study (167 individuals) underwent several treatment periods. “In-treatment” refers in this study to the actual number of days in treatment (sum of days in treatment, excluding days “post-treatment” between treatment periods). “Post-treatment” is the number of days out of treatment both between and following treatment periods within the study period. If subjects had several application dates, the first date was chosen.

The registry initially contained some individuals that for varying reasons did not start treatment. Some were not fulfilling the criteria of opioid dependence. Others chose long-term drug-free residential treatment and some chose not to start for other reasons. These subjects had application dates, but no treatment initiation within 1 year, and were all re-examined and verification of the application status confirmed. Subjects who were ineligible or withdrew their application for OMT constitute a mixed group that is termed “ineligible for treatment” (403 persons in total). Possible cases of misclassifications between pre-treatment and ineligible groups cannot be ruled out, although the utmost care has been taken to reduce the problem by manually cross-checking the data with each centre. Mortality rate is not calculated for this group as a whole, as no definite observation time was available. Some persons with application status (pre-treatment) between 1 and 365 days, (i.e. included during the final year of observation (2003)), may have withdrawn the application prior to commencing treatment or been found non-eligible, without this being captured during data collection, as we have no information about the status of any subjects included beyond 31 December 2003.

“Intention-to-treat” in this paper includes every person who ever started on OMT.

2.4. Analyses

Most analyses and descriptive statistics were performed by SPSS version 14.0.2. (Inc., Chicago, IL, USA). Mortality rates were calculated per 100 person years, being equivalent in this case to mortality as percent per year, with 95% confidence intervals.

A Cox regression with a time-dependent covariate was performed (by SAS 9.2) (SAS Institute Inc.), to assess statistical differences between the treatment categories, as each individual could have changed status from pre-treatment to treatment and subsequently to post-treatment during the observation period.

The time-dependent covariate was defined according to a subject’s placement within the groups: pre-treatment, in-treatment and post-treatment. Calculated hazard ratios should be interpreted as relative risk (RR) between groups.

2.5. Ethics

The project was approved by the National Committees for Research Ethics and by the Data Inspectorate of Norway.

3. Results

3.1. Sample characteristics

Table 1 presents the study population and the treatment status at the end of 2003.

Female subjects constituted 31.9%. Ages ranged from 23 to 66 years of age. Twenty-three percent of the subjects, who had commenced OMT, terminated the treatment without restarting within the observation period. The mean age of male subjects was slightly higher than for the female subjects (live males 2.1

<table>
<thead>
<tr>
<th>Total, n</th>
<th>483</th>
<th>2382</th>
<th>711</th>
<th>3576</th>
<th>213</th>
<th>3789</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>71.6</td>
<td>67.6</td>
<td>66.8</td>
<td>68.0</td>
<td>70.9</td>
<td>68.1 (2582)</td>
</tr>
<tr>
<td>Female</td>
<td>28.4</td>
<td>32.4</td>
<td>33.2</td>
<td>32.0</td>
<td>29.1</td>
<td>31.9 (1207)</td>
</tr>
<tr>
<td>Mean age (S.D.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>39.3 (6.9)</td>
<td>42.7 (7.0)</td>
<td>42.1 (6.4)</td>
<td>42.1 (7.0)</td>
<td>44.5 (7.6)</td>
<td>42.1 (6.5)</td>
</tr>
<tr>
<td>Female</td>
<td>37.2 (7.2)</td>
<td>40.8 (6.9)</td>
<td>39.1 (6.7)</td>
<td>40.0 (7.0)</td>
<td>44.6 (7.5)</td>
<td>40.3 (7.1)</td>
</tr>
</tbody>
</table>

Percent and mean age. Mean age of subjects and (S.D.) (as on 31 December 2003) included in the study.
Table 2
Cause of mortality and observation time

<table>
<thead>
<tr>
<th>Cause of mortality</th>
<th>Pre-treatment</th>
<th>In-treatment</th>
<th>Post-treatment</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdose</td>
<td>61 (79)</td>
<td>24 (27)</td>
<td>28 (61)</td>
<td>113 (53)</td>
</tr>
<tr>
<td>Non-overdose</td>
<td>16 (21)</td>
<td>66 (73)</td>
<td>18 (39)</td>
<td>100 (47)</td>
</tr>
<tr>
<td>Total mortality (%)</td>
<td>77 (100)</td>
<td>90 (100)</td>
<td>46 (100)</td>
<td>213 (100)</td>
</tr>
</tbody>
</table>

Median no. of days in group (S.D.)

| Total mortality (%) | 169 (359) | 614 (532) | 349 (392) | – |

Total observation time (p.y.)

| Total observation time (p.y.) | 3181 | 6450 | 1303 | 10,934 |

Real numbers (percent). Chi-square $P = 0.001$. p.y.: person years.

years (mean) older than females). This was true for all groups except for deceased subjects, which had similar mean ages for both genders.

3.2. Overdose versus non-overdose

Overdose deaths comprised the majority of all deaths in all groups combined and 79% of deaths in the pre-treatment group (Table 2). For those leaving treatment, overdose mortality was not statistically different from that of the pre-treatment group.

The frequency of overdose deaths in treatment was clearly lower than pre- and post-treatment, but overdose was recorded in 24 cases. The in-treatment group is dominated by non-overdose causes which make up 73% of the deaths in that group. The number of days in the different treatment groups showed variation, but median pre-treatment time (on waiting list) was between 5 and 6 months, and in-treatment time close to 2 years. The total observation time (from the first application date to 31 December 2003 or date of death) was 10,934 person years, with a mean total observation time of 1053 days (S.D. 667) or close to 3 years per person. Of the total observation time, the in-treatment time made up the main bulk.

3.3. Gender and mortality

Table 3 shows gender-specific mortality rates differentiated between overdose and non-overdose deaths. A significant reduction in overdose mortality for the group in OMT (1.4) compared with the pre-treatment group (2.4) was found. Overdose mortality was particularly prevalent among males who had ceased treatment (4.1). From an “intention-to-treat” perspective the mortality reduction was smaller than the in-treatment results, with a significant reduction from 2.4 pre-treatment, to 1.8 in

<table>
<thead>
<tr>
<th>Total mortality</th>
<th>Pre-treatment</th>
<th>In-treatment</th>
<th>Post-treatment</th>
<th>Intention-to-treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>1.9 (1.6–2.1)</td>
<td>0.5 (0–1.0)</td>
<td>2.4 (2.1–2.7)</td>
<td>2.1 (1.8–2.4)</td>
</tr>
<tr>
<td>Female</td>
<td>1.8 (1.3–2.3)</td>
<td>0.5 (0–1.4)</td>
<td>2.3 (1.9–2.7)</td>
<td>2.0 (1.6–2.4)</td>
</tr>
<tr>
<td>In treatment</td>
<td>0.4 (0–0.8)</td>
<td>1.0 (0.8–1.3)</td>
<td>1.4 (1.2–1.6)</td>
<td>2.0 (1.6–2.4)</td>
</tr>
<tr>
<td>Male</td>
<td>0.3 (0–0.8)</td>
<td>1.1 (0.8–1.4)</td>
<td>1.4 (1.1–1.6)</td>
<td>2.0 (1.6–2.4)</td>
</tr>
<tr>
<td>Female</td>
<td>0.4 (0–1.1)</td>
<td>0.9 (0.5–1.3)</td>
<td>1.3 (1.0–1.7)</td>
<td>1.9 (1.5–2.3)</td>
</tr>
<tr>
<td>Post-treatment</td>
<td>2.1 (1.7–2.5)</td>
<td>1.3 (0.9–1.8)</td>
<td>3.4 (3.2–3.7)</td>
<td>2.4 (2.0–2.9)</td>
</tr>
<tr>
<td>Male</td>
<td>2.3 (1.9–2.8)</td>
<td>1.8 (1.3–2.3)</td>
<td>4.1 (3.8–4.4)</td>
<td>3.1 (2.6–3.8)</td>
</tr>
<tr>
<td>Female</td>
<td>1.6 (0.9–2.3)</td>
<td>0.5 (0–1.8)</td>
<td>2.1 (1.4–2.7)</td>
<td>1.8 (1.4–2.2)</td>
</tr>
</tbody>
</table>

Intention-to-treat, including the “in-treatment” and “post-treatment” groups combined.

“intention-to-treat”.

The “post-treatment” subgroup had a higher mortality rate than any other group; this particularly applied to male subjects. Female subjects using heroin or undergoing OMT had a similar mortality rate to their male counterparts, but after OMT treatment the mortality of female subjects was lower than that of males. The general tendency was that OMT particularly reduced overdose mortality.

3.4. Mortality risk reduction with OMT

A significant overall reduction in mortality risk between the pre-treatment and the “intention-to-treat” populations with a hazard ratio of 0.6, $P = 0.004$ was found (Table 4). Similarly, there was a significant overall reduction in mort-
tality risk between pre-treatment and in-treatment groups (hazard ratio 0.5, \( P = 0.001 \)). The post-treatment group as a whole was not significantly different from the pre-treatment group in regard to mortality; however, a tendency toward gender differences was observed. Following treatment, males had significantly higher mortality than those in the pre-treatment levels. The post-treatment females had a non-significant tendency toward reduced mortality. Risk for overdose death was significantly reduced with OMT, both for the in-treatment group separately and in “intention-to-treat” analysis.

4. Discussion

4.1. Discussion of main results

The core trait of this study is the approach that allows an examination of mortality reduction from a defined baseline level both within OMT and post-OMT with overall mortality separated from overdose mortality. The study confirms earlier findings of reduced mortality in treatment and points to the change in pattern with overdose mortality dominant before and after and non-overdose mortality in treatment. Further, the approach enables calculation of concrete risk reductions in relation to the pre-treatment level, demonstrating significant reductions both in overdose deaths (RR 0.2) and all-cause mortality (RR 0.5).

This presented level of mortality reduction might be influenced by particular characteristics of OMT in Norway. For example, a long-term opiate addiction history is a precondition to be eligible for OMT in Norway; the findings should nevertheless indicate a level of reductions that might be generally expected.

In addition to these findings, the study also demonstrates that a significant mortality risk reduction is found using the “intention-to-treat” perspective; meaning mortality in dropouts included. In this perspective the overall mortality reduction, as a result of our national OMT programme, is RR 0.6 compared with the pre-treatment level. The benefits of OMT are supported from the “intention-to-treat” perspective; however, the level is reduced compared with the results from the “intention-to-treat” group. Studies focusing on in-treatment results alone will therefore tend to exaggerate the positive outcomes of OMT due to selection mechanisms.

Overdose mortality was still found in treatment although reduced from the pre-treatment level. One explanation may be that overdoses were caused by polydrug intoxications, of which illicit opiate may or may not have been involved. Secondly, only some of the death certificates were supplemented with information supported on autopsy and toxicological analyses, hence the rest of the cases were based on “external” examinations with the risk of misclassification. Deaths among patients with a known history of opiate addiction may well be misclassified as overdose rather than for example suicides or sudden cardiac deaths as previously discussed by Gossop et al. (2002). However, we have no information indicating differential misclassification between the outcome groups.

The mortality pattern demonstrated in the study is on level with other studies previously reported in Amsterdam and Stockholm (Fuglestad et al., 2007; Langendam et al., 2001; van Ameijden et al., 1999). Our overdose mortality rate during treatment (0.4 per 100 person years) is similar to what has been reported by Caplehorn et al. (1996) with a mortality of 0.5 per 100 person years during treatment.

The patterns of mortality and mortality reductions are generally similar for both genders, with a couple of exceptions. Male subjects who cease OMT treatment have twice the risk of death as female subjects in the same situation. The increase in overdose mortality post-treatment was more or less confined to males. However, males in the general population also have about twice the age-adjusted mortality risk as females (SSB, 2006). The increase in mortality for the “post-treatment” group is by and large caused by an increase in the frequency of overdose deaths, corresponding with previous findings (Brugal et al., 2005; Desmond and Maddux, 2000; Digjusto et al., 2004). Our observation is that this differs for the two genders. We have no data to provide a clear explanation for this gender-related pattern.

The nature of the study population, comprising the entire OMT population in Norway is important to notice. It is likely that the group “post-treatment” includes individuals with the largest burden of psychiatric co-morbidity, and that they have a particularly severe opioid-dependence syndrome, typically with polydrug use. It is generally accepted that it is the most heavily burdened and non-compliant patients who leave OMT (Dole et al., 1969; Fischer et al., 2005; Fuglestad et al., 2007; Johanson, 1981; Skodol et al., 2002).

Another noteworthy finding is that non-overdose deaths in the in-treatment group are dominating. One explanation for this is that to be eligible for OMT, somatic health problems promote swift acceptance into the programme.

No exact figures for HIV prevalence in the study population are available in the dataset, but it is known to be relatively low in Norway (SIRUS, 2006). Estimated HIV prevalence, based on available information, is in the range of 2–5% among Norwegian OMT patients.

4.2. Methodological considerations

The “intention-to-treat” perspective in this area of research may be regarded controversial, as OMT is usually considered to be a life-long treatment. This does not, however, justify the necessity to exclude the mortality in treatment dropouts in the estimate of benefits. It is well known that leakage of OMT drugs from the programmes can reach persons outside OMT. Mortality reduction in treatment is therefore only one of several goals in an OMT programme, and has to be assessed against competing interests. This underlines the importance of knowing the potential in reducing mortality risk for an entire population of opiate addicts eligible for OMT, not only those currently in treatment.

The dataset includes no information about individual type of maintenance drug or dosage. During the observation period for this study, methadone was the most widely used medication, whereas buprenorphine introduced in 2001 was used by 23% by the end of 2003. Additionally, no information on the sub-
jects’ drug use history was available, nor whether termination of treatment was voluntary or not.

The relatively high age of the cohort may be explained by the age limit of 25 years. Additionally, age is measured at the end of the observation time, not at inclusion.

Registry-based studies are clearly dependent on the quality of the registries employed. In this study, the national OMT patient registry was based on electronic patient records information from the regional OMT centres. For patients in-treatment and for the post-treatment group, we believe that the information is up to date and of good quality, as budgets and monitoring of expenses are based on continuously updating the data.

In spite of thorough control of each case that did not enter treatment (ineligible), some subjects might wrongly have been classified in the “pre-treatment” group. As the “ineligible for treatment” group had a low crude mortality rate, misclassifications could deflate mortality rates for the pre-treatment group. As the issue has been thoroughly examined and manually checked, we find it unlikely that results are significantly affected.

The current study population represents those who were found eligible to OMT in Norway during the study period. At present this comprises between 1/3 and 1/2 of all injecting opiate dependents in Norway, being characterised by a long term and severe opiate-dependence syndrome. The Norwegian OMT programme has distinct characteristics related to high-threshold level and rehabilitation goals (Waal, 2007).

However, as OMT programmes vary internationally due to different inclusion procedures, the absolute levels of mortality reduction will vary accordingly. Nonetheless, we believe that the relative level of risk reduction of mortality as a result of OMT is more comparable across OMT populations, than the absolute mortality levels are.

The quality of the data from the death registry in Norway is viewed as good in terms of overall mortality. Still, the mortality cause is dependent on the individual practice of each doctor submitting death certificates (SSB, 2006). I.e. a misclassification of a true suicide as overdose would tend to cause overestimation of overdose as a cause of death.

Monitoring of mortality and other aspects of treatment outcome via cross-registry studies, as done here, is a rational and efficient way of evaluating OMT. However, there are to date only a few countries, mostly Scandinavian, that have the infrastructure in terms of national registries feasible for our study approach. Registry data are typically limited in terms of covariate variables available. Therefore, other observational designs providing more extensive and varied information are needed in addition. This can yield important data on differences and characteristics of subgroups within the OMT population and the programme dropouts, e.g. on co-morbidity aspects.

4.3. Conclusion

In conclusion, the present study adds systematic evidence to the notion that OMT reduces mortality. The results support earlier studies and add the finding of reduced mortality also from an established baseline level and in an “intention-to-treat” perspective, with a mortality risk reduction in the order of RR 0.6. The cross-registry strategy is favourable in terms of allowing analyses without concerns for dropouts.

The findings argue strongly for OMT programme efforts to reduce time on waiting lists, as the mortality reducing effect in treatment is so evident. Future studies should be designed to further investigate the underlying explanatory factors for the gender differences recognized.

Conflict of interest

None.

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Contributors: Thomas Clausen has taken part in the final rounds of data collection, performed the statistical analyses and drafted the first version of the paper.

Katinka Anchersen took part during the data collection and discussions leading to the paper and has taken part and edited during analyses and writing up.

Helge Waal initiated the study and took part in the discussions leading to the paper and writing up.

All authors have read and approved this final version of the paper.

References


