

Review article

Revascularisation and mortality rates following acute coronary syndromes in people with severe mental illness: comparative meta-analysis

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Background

High levels of comorbid physical illness and excess mortality rates have been previously documented in people with severe mental illness, but outcomes following myocardial infarction and other acute coronary syndromes are less clear.

Aims

To examine inequalities in the provision of invasive coronary procedures (revascularisation, angiography, angioplasty and bypass grafting) and subsequent mortality in people with mental illness and in those with schizophrenia, compared with those without mental ill health.

Method

Systematic search and random effects meta-analysis were used according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies of mental health and cardiovascular procedures following cardiac events were eligible but we required a minimum of three independent studies to warrant pooling by procedure type. We searched Medline/PubMed and EMBASE abstract databases and ScienceDirect, Ingenta Select, SpringerLink and Online Wiley Library full text databases.

Results

We identified 22 analyses of possible inequalities in coronary procedures in those with defined mental disorder, of which 10 also reported results in schizophrenia or related psychosis. All studies following acute coronary syndrome

originated in the USA. The total sample size was 825 754 individuals. Those with mental disorders received 0.86 (relative risk, RR: 95% CI 0.80–0.92, $P < 0.0001$) of comparable procedures with significantly lower receipt of coronary artery bypass graft (CABG; RR = 0.85, 95% CI 0.72–1.00), cardiac catheterisation (RR = 0.85, 95% CI 0.76–0.95) and percutaneous transluminal coronary angioplasty or percutaneous coronary intervention (PTCA/PCI; RR = 0.87, 95% CI 0.72–1.05). People with a diagnosis of schizophrenia received only 0.53 (95% CI 0.44–0.64, $P < 0.0001$) of the usual procedure rate with significantly lower receipt of CABG (RR = 0.69, 95% CI 0.55–0.85) and PTCA/PCI (RR = 0.50, 95% CI 0.34–0.75). We identified 6 related studies examining mortality following cardiac events: for those with mental illness there was a 1.11 relative risk of mortality up to 1 year (95% CI 1.00–1.24, $P = 0.05$) but there was insufficient evidence to examine mortality rates in schizophrenia alone.

Conclusions

Following cardiac events, individuals with mental illness experience a 14% lower rate of invasive coronary interventions (47% in the case of schizophrenia) and they have an 11% increased mortality rate. Further work is required to explore whether these factors are causally linked and whether improvements in medical care might improve survival in those with mental ill health.

Declaration of interest

None.

Coronary heart disease is the leading cause of death worldwide.^{1,2} Acute coronary syndrome refers to acute myocardial ischaemia caused by atherosclerotic coronary disease and includes myocardial infarction and unstable angina. Patients with ST elevation myocardial infarction are recommended for immediate reperfusion therapy using thrombolytic agents or percutaneous coronary intervention (PCI).^{3,4} From 1980 to 1990 there was a 34% decline in coronary heart disease mortality in the USA.⁵ Over the same period there was a substantial growth in the number of cardiovascular procedures performed, particularly PCI. Improvements in the quality of care are thought to be a major factor underlying declining mortality.⁵ Yet despite these improvements evidence of sociodemographic inequalities in procedural rates has been accumulating.^{6–11} Inequalities have also been documented with regard to the medical care of those with known mental health diagnoses. Medical care includes medical treatment and processes of care such as investigations and monitoring. Mitchell *et al* evaluated 27 studies that examined receipt of medical care in those with and without mental illness (including 11 studies of severe mental illness or schizophrenia and 10 of dual diagnosis or substance use disorder).¹² The majority of studies demonstrated significant inequalities in receipt of quality of care including 7 of 10 studies that examined the quality of cardiovascular care. Lord *et al* recently reviewed 25

studies that examined preventive care in individuals with or without psychiatric illness; for individuals with schizophrenia, 8 of 9 analyses suggested inferior receipt of preventive care in several areas including blood pressure monitoring, vaccinations, mammography and cholesterol monitoring.¹³ From these narrative reviews it is clear that the magnitude of the deficits in quality of care varies considerably depending on the setting and method of data collection.

There is substantial concern about the cardiovascular health of those with known mental health diagnoses, especially severe mental illness and schizophrenia.^{14,15} National guidelines from several countries are agreed that the medical care of patients with mental disorders is of paramount importance.^{16–19} However, serious concerns have been raised about the quality of medical care offered to patients with severe mental illness. People with schizophrenia have higher rates of several important conditions including the metabolic syndrome.^{20,21} Most studies,^{15,22–28} but not all,^{29,30} suggest that incidence of cardiovascular disease is higher in people with schizophrenia. Such individuals often have higher than expected rates of contributing background risk factors including smoking,³¹ obesity,³² dyslipidaemia,³³ lack of exercise,³⁴ and possibly essential hypertension.³⁵ A meta-analysis suggested a relative risk of 1.87 (95% CI 1.68–2.09) for diabetes in schizophrenia, but with no significant elevation of hypertension

or cholesterol.³⁶ Of these factors, smoking and obesity may be most critical to future cardiovascular health.³⁷ An estimated 42% of patients with schizophrenia have a body mass index above 27 kg/m² compared with 27% among the general US population;¹⁵ three-quarters are regular cigarette smokers compared with a quarter of the general population.¹⁵ It is therefore probably not surprising that people with schizophrenia have higher than expected non-suicide-related mortality; in fact, mortality from comorbid physical illness outnumbers the excess mortality from suicide.³⁸ A systematic review of 37 studies found that those with schizophrenia have a 2.6 times greater rate of mortality compared with the general population, including 1.8 times the mortality rate from cardiovascular disease.³⁹

Given these numerous concerns regarding cardiovascular health in severe mental illness and in particular in schizophrenia, we aimed to examine and quantify, first, the receipt of medical procedures following acute coronary syndrome, and second, the mortality rate following acute coronary syndrome using meta-analysis of published data. We were interested in comparative studies that examined the adequacy of appropriate procedures and subsequent mortality for people with cardiac disorders stratified into those with and without severe mental illness/schizophrenia.

Method

Search

We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, a checklist of 27 items that ensure the quality of systematic review or meta-analysis.⁴⁰ Inclusion criteria were studies of patients with acute coronary syndromes (with data on rates of subsequent invasive coronary procedures or mortality) which reported data for those with defined mental illness as well as those without mental ill health. We only included those with severe mental illness provided there was a subgroup with schizophrenia. We excluded non-comparative studies, and also those concerning depression or anxiety only. We searched Medline/PubMed and EMBASE abstract databases from inception to 20 July 2010. In these databases the keywords/MeSH terms ('ACS or REVASCULARISATION or REVASCULARIZATION or PROCEDURES or GRAFT or ANGIOPLASTY or PERCUTANEOUS or CATHETERIZATION or CARDIA* or HEART') and ('PSYCHI* or MENTAL or PSYCHOSIS or PSYCHOTIC or SCHIZOPHR* or SEVERE MENTAL ILLNESS or SMI') were used. In addition, four full text collections were searched: ScienceDirect, Ingenta Connect, SpringerLink and Wiley Online Library. In these online databases the same search terms were used as a full text search and as a citation search. The abstract databases Web of Knowledge and Scopus were searched, using the above terms as a text word search, and using key papers in a reverse citation search. Finally, a number of journals were hand-searched and several experts contacted. We excluded studies where the event rate was measured in the general population rather than in those with cardiovascular disease.⁴¹ Where 30-day and 365-day mortality rates were cited, we examined only 365-day rates. Data were extracted using a standard form (available from the authors on request) by A.J.M. and checked by D.L.

Meta-analysis

We used summary meta-analysis, pooling hazard ratios where reported. All hazard ratios were entered adjusted rather than unadjusted (where reported and except where indicated). Odds ratios were converted into relative risks (hazard ratios) using the reported control event rate.⁴² Confidence intervals were obtained from all studies or calculated from the data provided.

Heterogeneity was reduced by stratifying using type of mental illness and procedure type; despite this, heterogeneity (defined by I^2) remained high and so random effects meta-analysis was preferred. We required a minimum of three independent studies to justify pooling by procedure type. Any potential sources of bias were reported. Publication bias was assessed using the Begg–Mazumdar statistic.⁴³

Results

The initial PubMed search generated 572 hits. Of these, only 16 discussed cardiac procedures and 58 discussed mortality (online data supplement). Searches in the four full-text collections generated 1572 hits (Fig. 1). Using these strategies we identified 241 references of interest but only 74 were primary data studies. After excluding studies with no relevant outcome, no comparison group or other methodological issues, we identified 9 papers relating to cardiac procedures following acute coronary syndrome and 6 papers relating to mortality following acute coronary syndrome.

Studies examining procedure rate after acute coronary syndrome

Our search identified 9 publications relating to cardiac procedures following acute coronary syndrome and contained in these reports were 22 analyses using broadly defined mental disorder or severe mental illness and 10 using an adequate definition of schizophrenia or related psychosis (online Table DS1). There was no evidence of publication bias using the Begg–Mazumdar statistic (Fig. DS1). The total sample size was 825 754 (mean 91 750, s.d. = 120 158). Druss *et al* examined cardiovascular care following an acute myocardial infarction.⁴⁴ After adjusting for demographic, clinical, hospital and regional factors, those with mental disorders were only 41% (for schizophrenia) to 78% (for substance use) as likely to undergo cardiac catheterisation as those without mental disorder. In a further study, Druss *et al* found patients hospitalised for myocardial infarction with mental health diagnoses were less likely to have reperfusion conducted.⁴⁵ Young & Foster identified people with mental illness who had experienced a myocardial infarction: this group had significantly lower levels of all three revascularisation procedures – cardiac catheterisation, percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass graft (CABG) – compared with those without mental illness, with the lowest rates seen in those over 64 years old.⁴⁶ Petersen *et al* examined the records of 4340 male veterans discharged after a clinically confirmed myocardial infarction: those with mental illness were less likely to have undergone in-patient diagnostic angiography (age-adjusted RR = 0.90, 95% CI 0.83–0.98) but there was no difference in CABG.⁴⁷ Kisely *et al* carried out a population-based record-linkage analysis of related data from 1995 through 2001 compared with the general public for each outcome ($n = 215\ 889$): in psychiatric in-patients the adjusted rate ratios for cardiac catheterisation, PTCA and CABG were 0.41, 0.22 and 0.34 respectively.⁴⁸ However, Plomondon *et al* found no difference in cardiac procedure rates after acute coronary syndromes presenting to Veterans Health Administration (VHA) hospitals.⁴⁹ Similarly, Jones & Carney found no difference in the rates of revascularisation.⁵⁰ Laursen *et al* followed 605 649 patients admitted with heart disease in Denmark between 1994 and 2007: people with admissions for severe mental disorder had higher mortality rates from heart disease following cardiac procedures but received lower rates of cardiac revascularisation.⁵¹ Abrams *et al* examined the rate of PCI or CABG within 30 days of

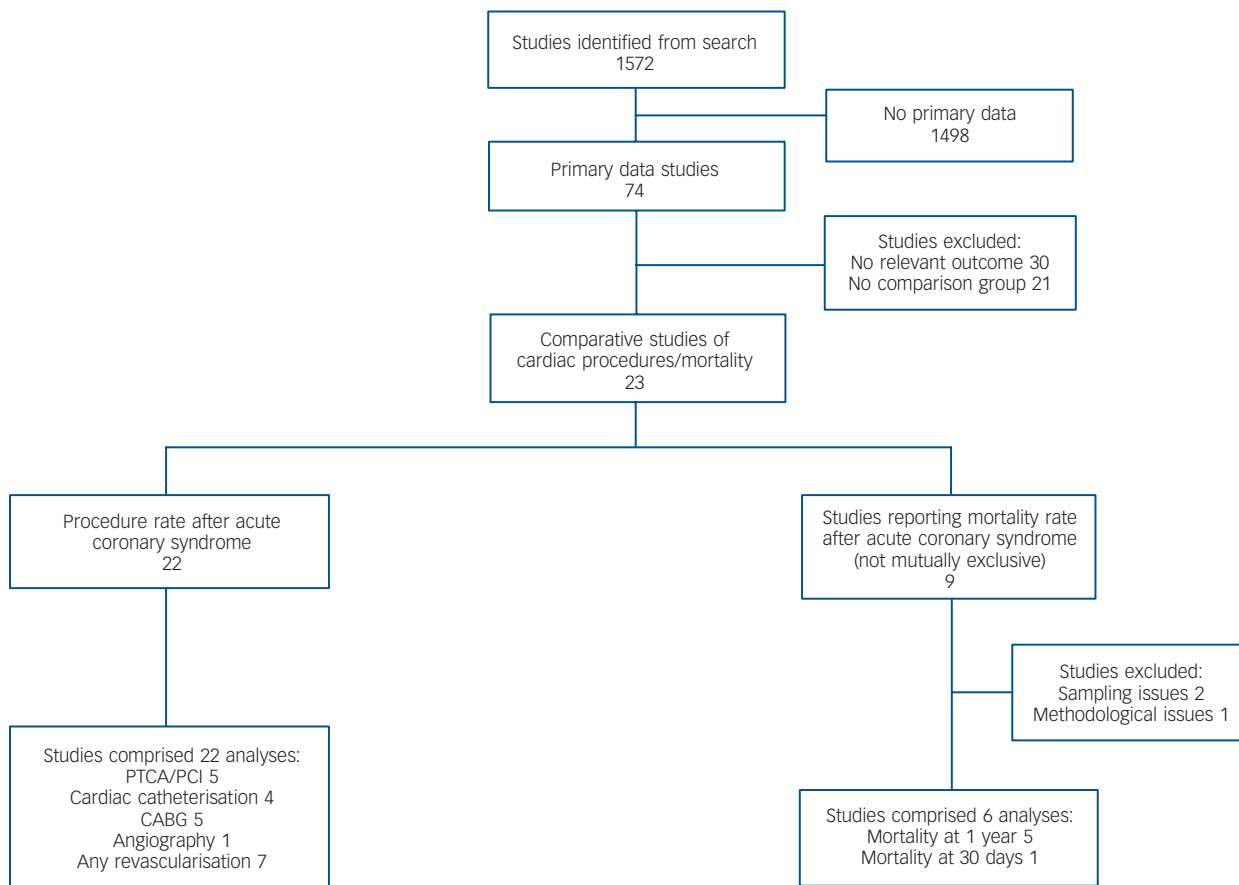


Fig. 1 Study selection. CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

admission.⁵² They examined mixed mental disorders, defined by ICD-9 codes, in 21 745 patients admitted following acute myocardial infarction. They reported results in two related samples: patients with psychiatric comorbidity had lower receipt of coronary revascularisation (hazard ratio, HR=0.92, 95% CI 0.85–0.99) in the out-patient sample but equal rates (HR=1.00, 95% CI 0.91–1.1) in the in-patient sample.⁵²

Quantitative differences in procedure rates

For those with mental illness or severe mental illness there was significant heterogeneity ($I=98.1\%$). The meta-analytic random effects size was 0.86 (95% CI 0.80–0.92, $P<0.0001$), suggesting that those with any mental illness received a 14% lower rate of cardiac procedures (Fig. 2). Looking at each procedure individually, there was significantly lower receipt of CABG (RR=0.85, 95% CI 0.72–1.00), cardiac catheterisation (RR=0.85, 95% CI 0.76–0.95) and PTCA/PCI (RR=0.87, 95% CI 0.72–1.05). For those with schizophrenia there was moderate heterogeneity ($I=77.6\%$). The meta-analytic relative risk was 0.53 (95% CI 0.44–0.64, $P<0.0001$), suggesting that those with schizophrenia received about half the comparable rate of cardiac procedures (Fig. 3). Looking at each procedure individually, there was significantly lower receipt of CABG (RR=0.69, 95% CI 0.55–0.85) and PTCA/PCI (RR=0.50, 95% CI 0.34–0.75).

Studies examining mortality after acute coronary syndrome

We identified ten studies relating to mortality following cardiac events but two reported mortality as the general population rate,

one had a significant methodological issue and one had insufficient data for analysis. The total sample size from six valid studies was 596 368 (mean 99 394, s.d. = 132 344). In Druss *et al*'s 2000 study, patients with mental disorders had a small but statistically significantly lower risk of mortality at baseline, and in unadjusted analysis 12.8% of those with schizophrenia died within 30 days compared with 10.8% in the comparator population; however, this was not significant after adjustments.⁴⁴ Yet in their replication study, Druss *et al* found that mental disorder of all types was associated with a 19% increase in mortality at 1 year.⁴⁵ Importantly, when the five quality indicators were added to the model the association was no longer significant, suggesting that elevated mortality is related to poor quality of care. Petersen *et al* examined the records of 4340 male veterans discharged after a clinically confirmed myocardial infarction and found a trend towards higher rate of death at 1 year in those with mental illness; the risk of death within 1 year was 1.25 (95% CI 1.00–1.53).⁴⁷ Plomondon *et al* studied 14 194 patients (including 18% with severe mental illness) with acute coronary syndromes presenting to VHA hospitals between October 2003 and September 2005.⁴⁹ One-year mortality was lower for patients with severe mental illness (15.8% *v.* 19.1%, $P<0.001$). However, in multivariable analysis there was no significant difference in mortality (HR=0.91, 95% CI 0.81–1.02) between patients with and without severe mental illness.⁴⁹

Four additional studies were noteworthy but could not be entered into the meta-analysis. Young & Foster found that in the older cohort (≥ 65 years old) with mental illness there was a 21% lower risk-adjusted likelihood of death ($P<0.001$) compared

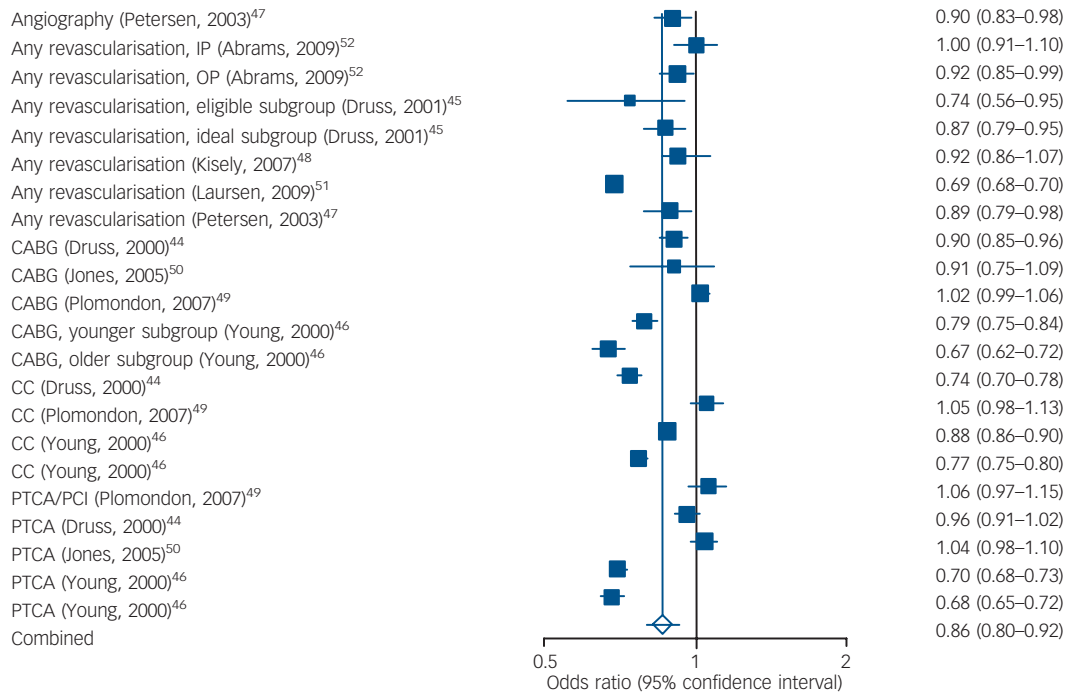


Fig. 2 Meta-analytic summary for receipt of cardiac procedures in patients with mental ill health v. those with no mental illness. CABG, coronary artery bypass graft; CC, cardiac catheterisation; IP, in-patient; OP, out-patient; PTCA, percutaneous transluminal coronary angioplasty; PCI, percutaneous coronary intervention.

with those without mental illness.⁴⁶ In the younger cohort those with schizophrenia and substance misuse had higher in-patient mortality rates (both $P < 0.001$). Unfortunately, data were inadequately reported for extraction. Kisely *et al* examined mortality and revascularisation in a general population sample.⁴⁸ They conducted a population-based record-linkage analysis of related data from 1995 through 2001 compared with the general population for each outcome ($n = 215\,889$): the age-standardised mortality rate ratio for psychiatric patients was 1.31 (95% CI

1.25–1.36). In the study from Lawrence *et al*, ischaemic heart disease was the major cause of excess mortality in psychiatric patients.⁴¹ The standardised mortality rate from ischaemic heart disease in mental health users was almost twice that in the overall population (1.91 in total ischaemic heart disease, 1.74 in acute myocardial infarction). However, in the latter two studies the risk was measured at the population level, not specifically in those with acute coronary syndrome. Recently, Blecker *et al* examined mortality in 341 individuals with heart failure and severe mental

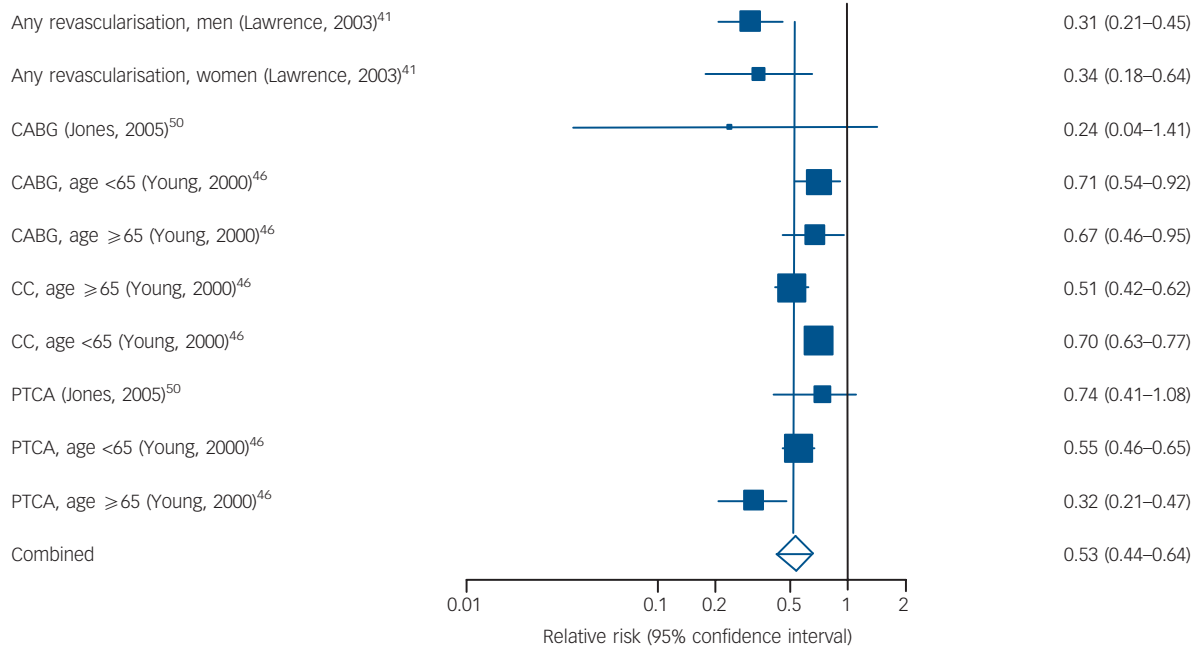


Fig. 3 Meta-analytic summary for receipt of cardiac procedures in patients with schizophrenia v. those with no mental illness. CABG, coronary artery bypass graft; CC, cardiac catheterisation; PTCA, percutaneous transluminal coronary angioplasty.

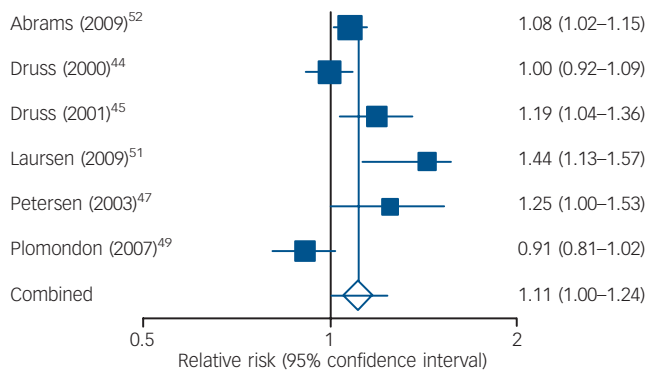


Fig. 4 Meta-analytic summary of mortality rates following acute coronary syndrome in patients with mental illness v. those with no mental illness.

illness compared with 1460 with heart failure and no severe mental illness.⁵³ Mortality was 29.9% in the severe mental illness group compared with 31.7% in those without severe mental illness. However, we excluded this study from the meta-analysis because it was not clear whether the follow-up period was identical in the two groups.

Quantitative differences in mortality following acute coronary syndrome

For those with severe mental illness there was significant heterogeneity ($I^2 = 91.6\%$), therefore random effects meta-analysis was preferred. The pooled relative risk for mortality was 1.15 (95% CI 1.02–1.29). Excluding the studies by Kisely *et al* and Lawrence *et al* which did not focus on acute coronary syndrome, the pooled relative risk for mortality was 1.11 (95% CI 1.00–1.24; $P = 0.05$), suggesting an 11% increase in mortality rates (Fig. 4).

Discussion

It is already known that people with depression have higher than expected mortality after myocardial infarction.^{54,55} We also know that background cardiovascular mortality in those with schizophrenia or severe mental illness is at least double the expected rate.^{27,39,56–60} Here, we extend these findings to a population with established acute coronary syndrome, largely myocardial infarction. Pooled results suggest an 11% increase in comparator mortality rates in those with severe mental illness. This is lower than previously documented in depression but nevertheless statistically significant. We also extend previous narrative reviews that highlighted inferior quality of medical care.^{12,16} From 22 analyses of coronary interventions following serious cardiac events, we found that those with defined mental disorder received 86% of comparable procedures with significantly lower receipt of CABG, cardiac catheterisation and PTCA/PCI. From 10 analyses, people with a diagnosis of schizophrenia or related psychosis received only 0.53 of the usual procedure rate, with significantly lower receipt of CABG and PTCA/PCI. One possible explanation is that physicians do not offer procedures to those with mental illness because they believe that such individuals are likely to have poorer uptake of care. However, findings regarding uptake of medical care are conflicting.¹² Another possibility is that the needs of those with mental illness are crowded out by the focus on mental concerns or possibly other medical factors, which may lead physicians to think that procedures are not a priority in this group. There is also a

question whether people with severe mental illness follow through with advice they are given. These questions can only be answered by good-quality studies examining physician responses to unmet medical needs in those with mental ill health as well as follow-up of patient behaviour.

Possible mechanisms underlying elevated mortality rates

In the general population prolonged QT_c interval and low heart rate variability have been associated with increased cardiovascular mortality and sudden death, particularly in people with prior cardiovascular disease and diabetes.^{61,62} Schizophrenia appears to be associated with similar QT abnormalities, possibly even in the absence of antipsychotic medication, and it is possible that these factors are influential following acute coronary syndrome.^{63–65} It is also well known that metabolic syndrome and diabetes increase the risk of mortality,^{66,67} and these conditions are often more common in those with severe mental illness. There is also a higher rate of sudden cardiac death in those taking antipsychotics;⁶⁸ that said, sudden cardiac death accounts for only a small proportion of excess mortality in schizophrenia.⁶⁹ Unfortunately none of the studies cited here examined use of psychotropic drugs. A second mechanism might be the influence of severe mental illness on the effectiveness of cardiac treatment, for example through low engagement in rehabilitation. Preliminary evidence suggests similar uptake but lower completion of physical exercise programmes in those with known mental ill health.⁷⁰ Confounding factors such as alcohol and drug use and medical comorbidities may also be influential. Most concerning is whether deficits in quality of care influence high mortality in this population. Li *et al* analysed New York's publicly released Cardiac Surgery Report of surgeons' risk-adjusted mortality rates.⁷¹ After adjustments, patients with both substance use and psychiatric disorders were more likely to receive care from surgeons in the high-mortality group (OR = 1.76, $P = 0.024$). Druss *et al* found that the excess mortality following myocardial infarction was negated when five quality measures were added to the model, suggesting that poor quality of care may be an important explanatory variable.⁴⁵ More recently, Copeland *et al* analysed whether patients' reduced primary care use over time was a significant predictor of mortality over a 4-year period among VHA patients; those with schizophrenia were likely to have low primary care use decreasing with time, and this was linked with inferior survival.⁷²

Despite the large sample size we acknowledge several limitations in this meta-analysis. Our results may not be representative of all healthcare systems as all studies following acute coronary syndrome originated in the USA. It is not clear that inequalities would exist in other healthcare systems where there are fewer barriers to care for those who are most socially disadvantaged. One limitation is that the definition of severe mental illness varied in some studies, and although most used ICD-8 or ICD-9 coding the definition employed by one group was not entirely clear.⁴⁴ A second limitation is that all studies were retrospective and none distinguished current from historical mental ill health and thus it is uncertain if risk applies to those with prior as well as current diagnoses. A third limitation in relation to mortality was that the studies by Lawrence *et al* and Kisely *et al* reported risk in population samples not specifically following acute coronary syndrome and were therefore excluded from the analysis.^{41,48} Additionally, Druss *et al* and Young & Foster did not report 1-year mortality rates,^{44,46} adding to the heterogeneity in mortality analysis. Finally, there was poor data

quality regarding hospitalisation and patient-provider factors underlying poor outcomes.

Improving inequalities in cardiac care

The disparities in cardiac care noted here are consistent with the wider literature documenting disparities in treatment of other medical domains including diabetes, general medicine and cancer care.^{12,73,74} Individuals with schizophrenia and severe mental illness receive as little as half of the monitoring offered to people without mental ill health.^{75,76} For example, in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, patients with schizophrenia had limited access to or received suboptimal medical care.⁷⁷ In a retrospective analysis of 1998–2003 Medicaid claims, fewer than 20% of people starting treatment with antipsychotic medication received baseline glucose testing and fewer than 10% received baseline lipid testing.⁷⁸ Unfortunately, professional responsibility for comorbid medical disorders is often unclear. Poor mental health status is linked with poor general practitioner accessibility and perceived barriers to medical treatment.⁷⁹ Hence medical comorbidity often is overlooked in those with severe mental illness, with up to half of all chronic conditions remaining unrecognised.^{80–84} Yet there is great interest in effective interventions that might reduce cardiovascular mortality in schizophrenia as well as in mental illness in general. Several groups have developed screening and monitoring guidelines.^{85–88} However, implementation of these has been inconsistent.^{89–93} In the general population lifestyle interventions can significantly influence mortality.⁹⁴ In diabetes glycaemic control has similar benefits. The magnitude of the effect of intensive glycaemic control in diabetes is of the same order as the excess risk documented here.⁶⁷ Interventions specifically targeting weight control and eating habits in people with chronic mental illness have shown some promising results.^{95–99} However, it is uncertain if benefits are maintained and whether there is any measurable effect on mortality. Ultimately it has been suggested that a reorganisation of mental health services would help redefine responsibility for physical health.¹⁰⁰ There is some support for a collaborative model of care, co-locating psychiatric and primary care.¹⁰¹ Yet to improve cardiac care in severe mental illness, interventions must be effective at the secondary-care level for hospital specialists with limited interest in mental illness.

In conclusion, following cardiac events individuals with mental illness appear to receive about 14% less frequent therapeutic cardiac procedures (47% in the case of schizophrenia), and they have about an 11% increased mortality rate. Further work is required to explore whether these factors are causally linked and whether improvements in medical care might improve survival in those with mental ill health.

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EXTRA
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