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Ten-Year Outcomes of First-Episode Psychoses in the MRC ÆSOP-10 Study

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Abstract: It has long been held that schizophrenia and other psychotic disorders have a predominately poor course and outcome. We have synthesized information on mortality, clinical and social outcomes from the ÆSOP-10 multicenter study, a 10-year follow-up of a large epidemiologically characterized cohort of 557 people with first-episode psychosis. Symptomatic remission and recovery were more common than previously believed. Distinguishing between symptom and social recovery is important given the disparity between these; even when symptomatic recovery occurs social inclusion may remain elusive. Multiple factors were associated with an increased risk of mortality, but unnatural death was reduced by 90% when there was full family involvement at first contact compared with those without family involvement. These results suggest that researchers, clinicians and those affected by psychosis should countenance a much more optimistic view of symptomatic outcome than was assumed when these conditions were first described.

Key Words: Schizophrenia, psychosis, recovery, course and outcome, risk factors

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Symptoms and Social Function

Psychotic disorders such as schizophrenia are largely defined on the basis of abnormal mental phenomena, or symptoms; and their effect on everyday function drives much of the illness burden on sufferers. Studies investigating the long-term course and outcome of psychotic disorders have focused for many decades on cohorts of people with on-going illness, prevalent cases, and predominately those with a diagnosis of schizophrenia or non-affective psychosis (Hegarty et al., 1994). This approach systematically excludes those who recover soon after onset and suggests predominately poor outcomes, skewing our understanding of the true long-term prognosis of these disorders (Cohen & Cohen, 1984; WHO, 2007). A growing body of evidence suggests that we have been too pessimistic about outcome and so give an overly gloomy answer to the question frequently asked by family members when their relative seeks help for the first time: what will happen? Sources such as the World Health Organization (WHO) in their 2007 report "Recovery From Schizophrenia: An International Perspective" show good outcomes in over half of those with psychotic disorders followed for 12 to 26 years after diagnosis (WHO, 2007). Kraepelin's assertion of the deteriorating course of schizophrenia as its hallmark appears inconsistent with the data and a likely consequence of the individuals with chronic conditions that his samples predominantly included (Jablensky, 2010). Remission and recovery need now to be incorporated into models of schizophrenia (Barber, 2012).

Mortality Disparities

Despite the need to transform our overall perspective on the expected course of schizophrenia, profoundly negative outcomes remain a serious challenge for some within this population. Life expectancy has risen in developed countries over the last few decades (WHO, 2014) but recent estimates suggest that people with schizophrenia, as well as other psychotic disorders, die 15 to 20 years earlier than their peers (Beary et al., 2012; Crump et al., 2013; Hoang et al., 2013; Hoang et al., 2011; Laursen et al., 2014; Nielsen et al., 2013; Saha et al., 2007; Wahlbeck et al., 2011). The reasons for this disparity are unclear (Dutta et al., 2012; Hoang et al., 2013; Hoang et al., 2011; Koivisto et al., 2002; Rantanen et al., 2009; Saha et al., 2007) and it remains a major public health concern (Reininghaus et al., 2014; Tiihonen et al., 2009; van Os et al., 1997). Recent attempts to unravel clinical and social factors associated with excess mortality in this population suggest that lifestyle, side effects of antipsychotic drug treatment and factors associated

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with the conditions, themselves, may be involved (Crump et al., 2013; Joukamaa et al., 2006; O'Connor et al., 2014; Weinmann et al., 2009).

This paper synthesizes two lines of research from the ÆSOP-10 study, "Reappraising the long-term course and outcome of psychotic disorders: the ÆSOP-10 study" (Morgan et al., 2014) and "Mortality in schizophrenia and other psychoses: a 10-year follow-up of the ÆSOP first-episode cohort" (Reininghaus et al., 2014). These report the primary findings on course and outcome from a 10-year follow-up of a large epidemiologically characterized cohort of 557 individuals who experienced their first-episode psychosis a decade before. The aim of former was to provide novel insights into three domains (i.e. clinical, social, and service use/hospital admissions) of long-term outcomes and trajectories (Morgan et al., 2014). The latter reported mortality in this cohort, comparing it with that of the general population, and further investigating baseline clinical and social factors associated with an increased risk of death (Reininghaus et al., 2014).

Eco-epidemiology provides a conceptual framework within which to integrate factors spanning several layers of causation including genetic, epigenetic, individual, familial, community, and societal influences (Kirkbride and Jones, 2011; Susser and Susser, 1996). In an attempt to reach and eco-epidemiological understanding of recovery in affective and non-affective psychoses, we review and integrate findings from the ÆSOP-10 study regarding the factors involved in variation of outcomes, particularly those concerning remission, recovery, and life expectancy. This has important clinical implications for evidence-based approaches to treatment, family education (i.e. psycho education) and long-term strength based approaches to care (Kelly et al., 2009).

METHODS

Sample

ÆSOP-10 is a 10-year follow-up study of a cohort of 557 individuals with a first episode of psychosis who were initially identified in two centers (i.e. southeast London, and Nottinghamshire, UK) contributing to the ÆSOP study (Fearon et al., 2006; Kirkbride et al., 2006). At baseline the researchers screened all inpatient and outpatient mental health services (MHS) in defined catchment areas of Southeast London and Nottingham (September 1997–August 1999), and the first 9 months of this period in Bristol, to identify eligible cases of first-episode psychosis between the ages of 16 and 64 years (Kirkbride et al., 2006). Morgan et al. (2014) reported on outcomes in the 532 incident cases in the cohort; Reininghaus et al. (2014) reported on mortality in the full cohort (n = 557). Full details of the methods of the ÆSOP-10 study appear in Morgan et al. (2014).

Follow-up

At approximately 10 years after inclusion in the baseline study, we sought to trace, re-contact, and re-interview all cases. For those who were in contact with MHS, we sought to make contact and invite them to participate via their current clinical teams. For those who were not, letters were sent to their last known address inviting them to participate. Non-responders were sent a further letter 2 weeks later, and, if necessary, researchers made a maximum of up to three visits to the address (morning, afternoon, and evening) to make initial contact. For those who had moved address (and for whom general practitioner [GP] contact details were available), they sought to make contact and invite them to participate via their GP.

Mortality

We identified all occurrences of death and emigration in the cohort over a combined total of 5184 person years of follow-up until 12 December 2012 (mean length of follow-up 10.0 years, SD = 2.3) via a tracing procedure conducted on their behalf by the Office for National Statistics (ONS) for England and Wales and the General Register Office (GRO) for Scotland using name, sex, date of birth, and the last known address (Morgan et al., 2014). For all identified deaths, principal underlying causes of death were determined according to the International Classification of Diseases, 10th revision (ICD-10) (World Health Organization, 1992), as recorded on copies of death certificates obtained from ONS. These are grouped into three broad categories (using ICD-10 codes): natural causes to refer to the disease which initiated the train of events directly leading to death (A00-Q99), unnatural (or external) causes to refer to the circumstances of the accident or violence which produced the fatal injury (U50.9, V01-Y89) (World Health Organization, 1992), and unknown causes to refer to symptoms, signs and abnormal clinical and laboratory findings not elsewhere classified (R00-R99) (World Health Organization, 1992). Unnatural causes of death included accidents (V01-X59) and suicide (X60-X84, Y10-Y34). Consistent with the classification of causes of death by ONS, both intentional self-harm (X60-X84) and events of undetermined intent (Y10-Y34) were coded as suicide. The underlying cause of death recorded on copies of death certificates was further ascertained from information collated from clinical records at follow-up using an extended version of the World Health Organization (WHO) Life Chart (Morgan et al., 2014; Sartorius et al., 1996; WHO, 2014).

Detailed information on socio-demographic characteristics (including sex, age, and ethnicity), clinical presentation (including diagnosis, duration of untreated psychosis (DUP), and illicit drug use in past year), and social factors (including education, employment, involvement of family at first contact with MHS) was collected at baseline (Morgan et al., 2006a). Data on time to first remission were collected at follow-up using the extended version of the WHO Life Chart (Morgan et al., 2014; Sartorius et al., 1996). Mortality rates in the population at risk for all-, natural- and unnatural-cause and population estimates stratified by sex, age band, year, and the Census Area Statistics (CAS) wards in Lambeth and Southwark in south east London (33 CAS wards) and Nottinghamshire (95 CAS wards), in which cases were initially identified, were obtained from ONS for the duration of the follow-up period.

Symptoms (Remission and Recovery)

In line with Andreasen et al. (2005), *remission* was defined for this study as absence of overt psychotic symptoms (operationalized as a score of 2 or 3 on Rating Scale 2 in the SCAN; 0 = absence, 1 = symptom occurred, but fleeting, 2 = symptom definitely present, 3 = symptom present more or less continuously) for a period of at least 6 months. Symptom *recovery* was defined as sustained remission for 2 or more years.

Social

Information on sociodemographic markers of social function and integration across a number of domains (i.e. housing, employment, relationships, education, and social networks) during and at follow-up was collected using the Life Chart (Supplementary Table 2, http://links.lww.com/JNMD/A4 in Morgan et al., 2014). In this previous publication the researchers present illustrative data on employment and relationship status as the key markers used to assess social inclusion.

Analysis

Symptoms and Social Function

Differences in primary outcomes were compared by sex, baseline diagnosis (non-affective *vs.* affective) and study center using chi-square tests, t-tests, ANOVAs and rank sum tests as appropriate. For time to first remission Kaplan-Meier survival curves and log-rank tests were used.

Mortality

Researchers constructed Kaplan-Meier plots and used Cox regression to inspect variation in risk of death over time according to

TABLE 1. Core Sample by Baseline Demographic and Clinical Characteristics (Derived From Supplementary Table 3, http://links.lww.com/JNMD/A4 in Morgan et al., 2014)

Length of follow-up		
Mean (years)	10.7	
SD	1.17	
Administrative outcome		% of Sample
Re-interview	193	49.9%
Declined	156	40.3%
No contact (unable to trace or contact)	38	9.8%
Sex		
Men	215	55.6%
Women	172	44.4%
Baseline age		
Mean (years)	30.3	
SD	10.2	
Ethnicity		
White British	167	43.2%
Other white	25	6.5%
Black Caribbean	108	27.9%
Black African	45	11.6%
Asian (all)	22	5.7%
Other	20	5.2%
Center		
Nottingham	157	40.6%
London	230	59.4%
Baseline diagnosis		
Non-affective	277	71.6%
Affective	110	28.4%
Baseline employment (7 missing, $n = 381$)		
Employed	90	23.6%
Economically inactive	68	17.9%
Unemployed	223	58.5%

Core sample (data 8+ yrs) $n = 387$.

socio-demographic, clinical, and social characteristics. Log-rank tests were used to examine whether probability of death over time varied by socio-demographic, clinical, and social characteristics. Poisson regression was used to quantify the effect of these characteristics on risk of all-, natural-, and unnatural-cause mortality in people with first-episode psychosis. Indirect standardization was used to compare mortality risk between people with first-episode psychosis and the local general population. Full details of these methods and analysis have been reported in Reininghaus et al. (2014).

RESULTS

Of the 532 incident cases identified at baseline, 37 (7.0%) had died (see mortality analysis, below), 29 (5.5%) had emigrated and 8 (1.5%) were excluded based on information unavailable at baseline. Of the 458 remaining, 412 (90.0%) were successfully traced and 219 (53.2%) were re-interviewed. Of the remaining 193, 4 (1.0%) lacked capacity (because of dementia or head trauma), and 189 (45.8%) could not be contacted or declined re-interview. Those who had died tended to be older and were more likely to be men; those who had emigrated were more likely to be of black African ethnicity and from the London cohort. Those who were not traceable tended to be men and had a diagnosis of a non-affective psychosis (Table 1 in Morgan et al., 2014).

After removing those who had died, emigrated or been excluded, useable information on clinical course and outcome across one or more of the three domains was available on 387 cases for at least 8 years of follow-up (the core analytic sample, see Table 1), with a mean length of follow-up of 10.7 years (SD 1.2, range 8–14) (Morgan et al., 2014).

There was little evidence of selection bias in terms of those with and without follow-up information over 8 years or more (Supplementary Table 3, http://links.lww.com/JNMD/A4 in Morgan et al., 2014). Individuals who were re-interviewed were more likely to have a slightly shorter length of follow-up and were more likely to have been from the London center (Supplementary Table 4, http://links.lww.com/JNMD/A4 in Morgan et al., 2014).

Long-term Course and Outcome

There was marked variability in clinical course (Table 2; Morgan et al., 2014), ranging from the 80 (23% of 345, missing 42) cases who did not experience a remission of psychotic symptoms (6 months or more) at any point during the follow-up, to the 43 (13% of 345) cases who had a remission of symptoms within 6 months of first contact and remained symptom free for the duration of the follow-up. An additional 69 (20% of 345) did have further episodes after initial remission, but none that lasted more than 6 months. The remaining cases (153, 44% of 345) formed an intermediate group that had at least one remission and at least one episode lasting more than 6 months (i.e., neither continuous nor episodic). In total, 265 (77%) of the cases had at least one remission during the follow-up period. At follow-up, 213 (65% of 326, missing 61) were not experiencing psychotic symptoms and 140 (46% of 303 on whom complete data were available, missing 84) had been free of psychotic symptoms for the preceding 2 years or more, thus meeting criteria for symptom recovery. Among cases for which there was reliable information (228; 75% of 303 with data on recovery), 56% of those who recovered (57 of 101) had been prescribed antipsychotic medication in the 2 years before follow-up, in contrast with

TABLE 2. Core Sample by Clinical and Social Outcomes (Derived From Table 2 and Supplementary Table 5, http://links.lww.com/JNMD/A4 in Morgan et al., 2014)

Time to remission ($n = 326$)		
Median (weeks)	17.5	
IQR	5.6–425.4	
Course ($n = 345$)		% of n
No episodes	43	12.5%
Episodic	69	20%
Neither	153	44.3%
Continuous	80	23.2%
Recovered (symptoms) ($n = 303$)		
Yes	140	46.2%
No	163	53.8%
% of time employed ($n = 290$)		
>75%	34	11.7%
25–75%	48	16.6%
<25%	208	71.7%
Employed at follow-up ($n = 295$)		
Yes	66	22.4%
No	229	77.6%
Main relationship status ($n = 307$)		
In relationship	89	29%
Not in relationship	218	71%
In relationship at follow-up ($n = 300$)		
Yes	95	31.7%
No	205	68.3%

Core sample (data 8+ yrs) $n = 387$.

86% (109 of 127) of those not recovered (χ^2 24.6, *df* 1, $p < 0.001$). Note that all cases were, at some point, prescribed anti-psychotic medication (Table 2 and Supplementary Figure 1, http://links.lww.com/JNMD/A4 in Morgan et al., 2014).

Social

Relationship status and employment were used as indicators of social outcomes and compared with data from previous studies. There was strong evidence that social exclusion present among cases at baseline (28% of cases employed *vs.* 55% of controls, 29% in a relationship *vs*. 61% of controls (Morgan et al., 2008) persisted at follow-up (22% of cases employed and 32% in a relationship). Only 34 (12% of 290) cases had been in paid work for over 75% of the follow-up period. A slightly larger but still small proportion had been employed for between 25% and 75% of the follow-up (48; 17%). The majority had been employed for less than 25% of the 10-year follow-up (208, 72%). With regard to relationship status, a majority of cases were single for most of the follow-up (218, 71%) and at follow-up (205, 68%). Those with a baseline diagnosis of non-affective psychosis and those incepted in London were more likely to experience poor outcomes in these domains (Table 3 in Morgan et al. 2014). These findings suggest that social exclusion emerges either before or shortly after onset and persists over the long term. Only 15% (34 of 223) of the cases in the core sample that were unemployed at baseline were in employment at follow-up. Similarly, of those not in a relationship at baseline, only 16% (33 of 210) were in a relationship at follow-up.

Mortality

There was evidence of excess mortality over the follow-up period. Of the 557 cases with first-episode psychosis identified at baseline, 8 were excluded based on additional diagnostic information not available at baseline. Of the remaining 549 cases, 39 (7.1%) cases had died, 15 (2.7%) because of natural causes, 21 (3.8%) because of unnatural causes, and 3 (0.6%) because of unknown causes of death. Cases with a natural cause of death predominantly died of diseases of the digestive system (n = 7, 1.3%), with 3 (0.6%) of these having died of definite alcohol-related causes and 3 (0.6%, 0.05%) from probable alcohol-related causes (Supplementary Table 1, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014). The most common unnatural cause of death was suicide (n = 13, 2.4%) (Supplementary Table 1, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014). Of the 17 cases with an unnatural cause of death for whom reliable information was obtained on baseline illicit drug use (81.0% of 21 who had died of unnatural causes), 12 (70.6% of 17) had reported use of illicit drugs in the previous year (cannabis use, n = 7 (41.1%); amphetamine use, n = 1 (5.9%); multiple substance use, n = 4 (23.5%)). At follow-up, 3 cases (0.6%) had died of accidental poisoning (Supplementary Table 1, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014).

There was a decreased risk of unnatural-cause mortality in women compared with men after controlling for age at baseline (Table 2 in Reininghaus et al., 2014) and a reduced risk of all-cause and natural-cause mortality in younger cases. There were no statistically significant differences in risk of mortality by broad ethnic group (Table 2 in Reininghaus et al., 2014).

Mortality in the ÆSOP Cohort Compared with the Local General Population

SMRs (standardized mortality ratios) for all, natural, and unnatural causes of death were reported (Table 3 in Reininghaus et al., 2014). There was an almost fourfold increase in all-cause mortality in the cohort compared with that in the general population (SMR = 3.6, 95% CI 2.6–4.9). All-cause SMRs were of similar magnitude in the two study sites (London and Nottingham), slightly more pronounced in men (SMR = 4.1, 95% CI 2.8–5.9) than in women (SMR = 2.8, 95% CI 1.6–5.1), and lower for cases in higher age bands. When broken down by natural and unnatural causes of death, the increase in natural-cause mortality was approximately twofold, compared with a 13-fold increase in unnatural-cause mortality. There was no strong evidence that unnatural-cause SMRs varied by place, sex, or age and SMRs remained high for older cases (aged 60–74). On examination risk of suicide was the most common unnatural cause of death in the cohort; there was a 20-fold increase compared with that in the local general population (SMR = 20.0, 95% CI 11.7–34.5) (Table 3 in Reininghaus et al., 2014).

All-, Natural- and Unnatural-Cause Mortality by Clinical and Social Factors

The Kaplan-Meier survival curves show evidence that a long DUP (Supplementary Figure 3, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014) and a long time to first remission (Supplementary Figure 4, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014) were associated with an increased risk of all- and natural-cause death over time. Findings from Cox regression indicated that the association between time to first remission and natural-cause death over time held after adjusting for age at baseline and sex (Fig. 1; Adj. HR 6.76; p = 0.02) (Supplementary Table 4, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014). Further, illicit drug use in the year before baseline was associated with an increased risk of all- and unnatural-cause death over time, while adjusting for age and sex (Fig. 1; all-cause Adj. HR 2.30; p = 0.04 and unnatural-cause Adj. HR 3.04; p = 0.05) (Supplementary Table 4, http://links.lww.com/JNMD/A5 and Supplementary Figure 5, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014). In addition, researchers found strong evidence of reduced risk of unnatural

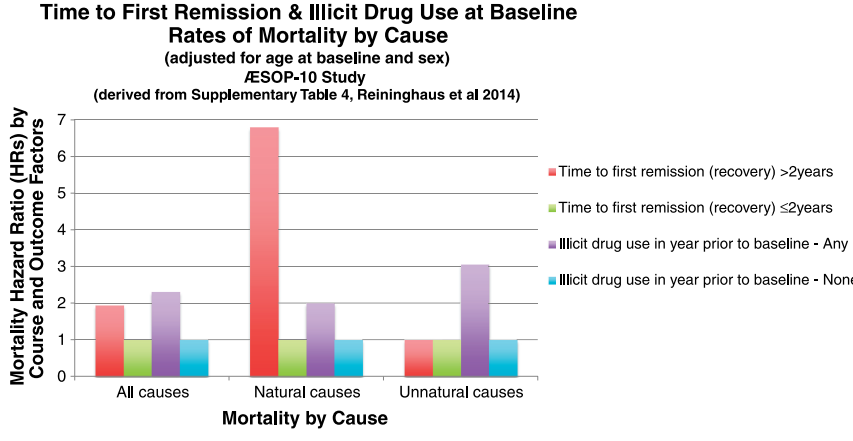

FIGURE 1. Time to first remission and illicit drug use at baseline; rates of mortality by cause.

death over time for cases with full family involvement at first contact with services (family actively sought help for individual), which remained when adjusted for age at baseline and sex, as reflected in Figure 2 (Adj. HR 0.09; $p = 0.02$) (Supplementary Table 4, http://links.lww.com/JNMD/A5 and Supplementary Figure 6, http://links.lww.com/JNMD/A5 in Reininghaus et al., 2014).

Rate ratios for all-, natural- and unnatural-cause mortality by clinical and social factors are shown in Table 4 in Reininghaus et al. (2014). Although a long DUP was associated with an increased risk of all- and natural-cause mortality in unadjusted analyses, this association was diminished and ceased to be statistically significant when adjusting for age at baseline and sex. Similarly, after adjusting for these factors, the association between a long time to first remission and increased risk of all-cause mortality was no longer significant. However, the rate ratio for a long time to first remission and increased risk of natural-cause mortality held after adjusting for age and sex (Adj. RR 6.61; $p = 0.02$) (see Table 4 in Reininghaus et al., 2014). Further, illicit drug use was associated with a twofold to almost fourfold increased risk of all- and unnatural-cause mortality, respectively, while controlling for age and sex (all-cause Adj. RR 2.31; $p = 0.04$ and unnatural-cause Adj. RR 3.78; $p = 0.03$) (see Table 4 in Reininghaus et al., 2014). However, researchers found some evidence that the association between illicit drug use and unnatural-cause mortality was confounded by lack of family involvement at first contact (LRT, $\chi^2 = 7.22$, $p = 0.03$). Although this association was attenuated, there was still some evidence of an approximately threefold increased risk of unnatural-cause mortality in cases using illicit drugs (Adj. RR 3.25; $p = 0.06$). Finally, a reduced risk of unnatural-cause mortality was found in cases with full family involvement when compared with those with no family involvement at first contact with services, while controlling for age and sex (Adj. RR 0.09; $p = 0.02$). This association held when further adjusted for illicit drug use ($\chi^2 = 2.65$, $p = 0.10$) (Table 4 in Reininghaus et al., 2014).

DISCUSSION

We have distilled the results of two contrasting aspects of the *ÆSOP*-10 follow-up, mortality and illness course, the latter in terms of symptomatic and functional measures. The most striking findings concern the high rate of symptomatic recovery at approximately 50% in contrast to the less encouraging social outcomes, with only around 15% of individuals having improved work or relationship status by follow-up. The notable points from the Reininghaus et al. (2014) paper stand in stark contrast—as two extremes. First, compared with no family involvement, there was a marked 90% reduction in risk of unnatural-cause mortality when full family involvement was present at first contact. Second, and in contrast, there was a sevenfold increase in risk of natural-cause mortality when the time to first remission was >2 years and a threefold increase in risk of unnatural-cause mortality with illicit drug use before baseline.

Methodological Considerations

ÆSOP-10 sought to minimize selection bias due to attrition by making exhaustive efforts to trace cases and by using official sources to establish deaths and emigrations. Thus, the whereabouts and/or status of over 90% of the original cohort were ascertained and there was surprisingly little evidence that selection bias through differential follow-up was a major problem.

To address the challenge of reducing information (recall) bias, researchers used multiple sources of information to complete the Life Chart, and established clinical ratings by consensus after careful consideration of all available data (Morgan et al., 2014).

Mortality

Deaths in this cohort were notably elevated when compared with the general population. In absolute terms, though, the number of deaths overall was small and consequently confidence limits were wide. However, the elevated mortality is in line with other data and continued follow-up of this cohort would be an effective approach to increasing the precision of these findings. An important factor that was not measured at baseline in this study was alcohol use. Nonetheless, by utilizing person tracing procedures (ONS and GRO), researchers were able to examine alcohol where implicated in a principal underlying cause of death. Still, insufficient data exist in this study to form a firm conclusion regarding its role as a risk factor for mortality (Reininghaus et al., 2014).

The most noteworthy strength of ÆSOP-10 is that it is a large epidemiological cohort of unselected first-episode cases of psychoses from clearly defined geographic areas. Examining factors based specifically on local population variances may lend itself to an improved understanding of not only the risk factors implicated, but also those more pronounced within specific areas. This may help better inform local intervention services on issues more specific to their area (Ezzati

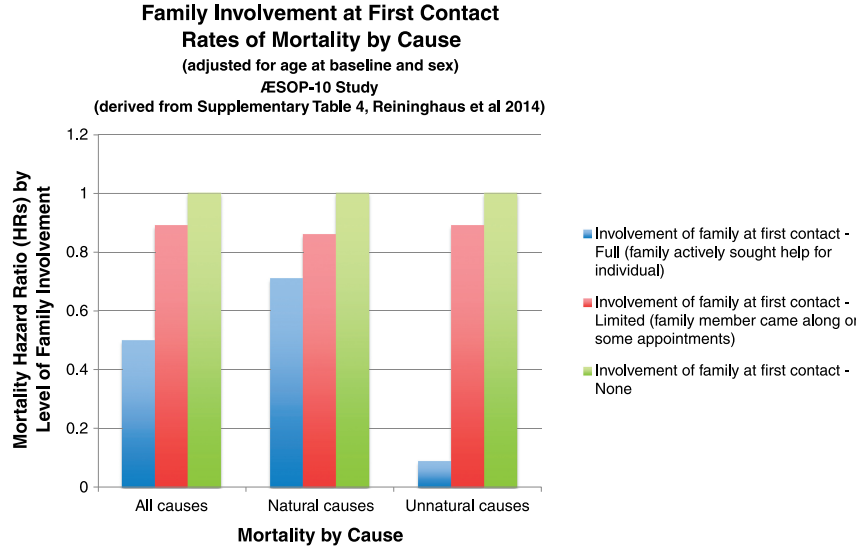

FIGURE 2. Family involvement at first contact; rates of mortality by cause.