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ORIGINAL PAPER

The iHOPE-20 study: mortality in first episode psychosis—a 20-year follow-up of the Dublin first episode cohort

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Abstract

Purpose Increased mortality rates have been found in those with a diagnosis of psychosis; studies suggest a shortened life expectancy of up to 20 years less than that of the general population. This study aimed to investigate the mortality of a first episode psychosis cohort at 20-year follow-up, compare it to that of the general Irish population, and explore whether the mortality gap has changed over time.

Methods 171 individuals diagnosed with a first episode psychosis identified between 1995 and 1999 in a community mental health service were traced. Mortality was established by matching death certificates to deceased cohort members (using name, age at date of death, and address at date of death). Date of first presentation to service was used as date of entry point and date of death or end of follow-up as the end point.

Results Of the 171 cases there were 20 deaths during follow-up. Nine deaths were attributed to natural causes; 7 to unnatural causes; and 4 were unknown. Comparing standardised mortality rates at 20-year follow-up to those at 12 year showed a reduction in rates over time.

Conclusion Findings suggest that the mortality gap in people with schizophrenia and other psychoses remains high, especially in young males.

Keywords First episode psychosis · Mortality · Epidemiological · Incidence cohort · 20-year follow-up

Introduction

It is well established that mortality rates from both natural and unnatural causes are elevated in those with a diagnosis of psychosis [1–3]. In real terms this equates to a shorter life expectancy of up to 20 years. There is little evidence that the mortality gap has narrowed in recent years, as would be expected given improvements in mental health services and the shift towards more integrated community-based services.

Studies have reported elevated standardised mortality ratios (SMRs) in this population between 1.5 and 4.2 depending on the study [1, 4, 5]. Explanations proposed to account for higher mortality rates in those with a psychotic disorder range from unhealthy lifestyle, the effects of antipsychotic medication to inadequate access to good-quality physical healthcare [6, 7]. Those with mental health difficulties may often be more vulnerable than their peers, for example often unemployed, single, marginalised, these are considered risk factors for poor health and premature mortality [8].

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Evidence as to whether excess mortality is predominantly due to unnatural or natural causes of death remains equivocal. In the 10-year follow-up of the AESOP cohort (Southeast London & Nottinghamshire, United Kingdom), Reininghaus et al. reported a twofold increase in natural-cause mortality that mirrored earlier studies [1]. This cohort showed a 13-fold increase in unnatural cause mortality and a 20-fold increase of suicide (however, there was considerable uncertainty in these estimates with wide confidence intervals). The study also found some evidence of there being a more marked excess of suicide in the London group than in Nottinghamshire. Furthermore, it is well documented in the literature that schizophrenia is associated with elevated suicide rates [9].

In summary, to date studies indicate a significant mortality gap between those with a diagnosis of Schizophrenia and the general population ranging from 10 up as high as 25 years shorter life expectancy.

Relatively few studies have examined the clinical and social factors that may impact on the increased risk of premature death in all psychosis or whether the mortality gap is changing over time within cohorts. Our study forms part of a larger 20-year follow-up of the Dublin First Episode Psychosis Cohort. While mortality has been examined in previous follow-ups at 4, 8 and 12 years, it had not been investigated whether this gap had been changing over time within this cohort.

Over the course of the 20-year study period, the Irish psychiatric system has undergone changes in organization and structure as well as treatment options. In 2006 mental health services re-orientated from a hospital and bed-based focus to community-based services in line with a national policy guideline (A Vision for Change). Secondly during the latter part of the study period there was raised awareness of the increased prevalence of cardio-metabolic disease in patients diagnosed with schizophrenia, and efforts made by services to introduce screening for cardio-metabolic risk factors. Although there is an increased relative risk of death due to unnatural causes, cardiovascular disease and other comorbid natural causes continue to be the main contributor to shorter life expectancy in those with a diagnosis of psychoses.

The aim of this study was to investigate mortality of a first episode psychosis cohort at 20-year follow-up. The objectives were to: (1) to estimate the number of additional years expected (years lost) for each death in the cohort; (2) to compare mortality of this cohort at 20-year follow-up to that of the general population; (3) to explore whether the mortality gap is changing from the 12-year follow-up to the 20-year follow-up; and (4) to examine the clinical and social factors that may impact on increased risk of premature death in psychosis. To our knowledge this is the first study examining mortality in a 20-year follow-up of a First Episode Cohort.

Method

Sample

This study forms part of a 20-year follow-up study of an epidemiological cohort of 171 individuals with a first episode psychosis (FEP), originally identified between 1995 and 1999 in a community mental health service. All patients with a first episode of psychosis, who presented to mental health services both inpatient and outpatient within a defined catchment area between the years of 1995 and 1999, were screened at baseline for inclusion in the study. This yielded a sample of 171 cases that were followed up at 4, 8, 12 and 20 years. The study received ethical approval from the relevant local ethics research committee and adhered to the STROBE guidelines for cohort studies [10]. Once ethical approval was obtained, individuals were traced by the project administrator.

Data collection

Detailed information on sociodemographic characteristics (including sex, age), clinical presentation (including diagnosis, duration of untreated psychosis), and social factors (including employment, living alone) was collected at baseline, 4, 8 and 12 years, and have been described in detail elsewhere [11].

Case-tracing procedure

We identified all occurrences of death in the cohort over a combined total of 2948 years of follow-up until July 15th 2015 by matching death certificates from the General Registry Office in Ireland to cohort members using name, sex and date of birth. For all identified deaths, principal underlying causes of death were determined as recorded on copies of death certificates. Causes of death were grouped into three broad categories: natural causes, referring to the disease which initiated the events directly leading to death; unnatural causes (or external), referring to the circumstances of the accident or violence which produced the fatality; and unknown refers to those we do not have information on cause of death (for example, died outside of Ireland and, therefore, could not be matched to Irish death certificates).

Statistical analysis

Crude mortality rates were calculated for all causes, natural causes, unnatural causes, and unknown causes of death per 100,000 person-years. The number of additional years expected (years lost) for each person who died, based on

their survival to date, sex and year of death was estimated using period life expectancy from Irish life tables (see references). Indirect standardization was used to compare mortality risk in the cohort to the risk in the general population at both the 12-year follow-up in 2008/2009 and the 20-year follow-up in 2015. SMRs and 95% confidence intervals (CIs) were calculated based on the observed number of deaths in the cohort and the expected number of deaths in the general population by age group and sex for all-cause mortality. Cox regression was used to predict survival time (time from first presentation to death with those still alive at follow-up censored at date of follow-up) using sociodemographic, clinical and social characteristics measured at baseline, i.e., age, sex, living alone or not, in full-time employment or not, duration of untreated psychosis (in months), lifetime history of alcohol misuse or dependency, lifetime history of substance misuse or dependency, diagnosis (affective, non-affective) and having any comorbidity at baseline. Hazards ratios (HR) and 95% CIs are presented. A 5% level of significance was used for all tests and analyses were conducted using Stata version 13 and SAS for Windows Version 9.2.

Results

A summary of the baseline characteristics of the cohort is given in Table 1. The majority (76%) of the cohort were male (58%), aged less than 35 at baseline, and diagnosed with a non-affective disorder (79%). Over a third of the cohort (36%) had a comorbid condition at baseline. Comorbidities at baseline included any pre-existing conditions such as diabetes, cardiac or respiratory conditions. Any history of physical trauma or brain trauma were also included as pre-existing comorbidities.

Mortality at 20-year follow-up

There was a total of 2948 years of follow-up from entry into the study to end of follow-up (July 15th, 2015) or death with a mean follow-up per person of 17.2 years (SD 4.1 years). Of the 171 cases, there were 20 deaths during follow-up (11.7%, 678 per 100,000 person-years of follow-up). There were nine deaths due to natural causes (5.3%, 305 per 100,000 person-years of follow-up); seven due to unnatural causes (4.1%, 237 per 100,000 person-years of follow-up) and four due to unknown causes (2.3%, 136 per 100,000 person-years of follow-up).

Of the 99 males in the cohort, there were 10 deaths—three from natural causes, four from unnatural causes and three from unknown causes of death. The median age of death for males who died was 29.5 years (first quartile 23, third quartile 36) and the median years lost was 47.7 years (first quartile 39.8, third quartile 52.3 years).

Table 1 Baseline characteristics of the cohort ($n = 171$)

Baseline characteristics	*n* (%)
Age group	
< 35 years	130 (76%)
≥ 35 years	41 (24%)
Sex	
Male	99 (58%)
Female	72 (42%)
Living alone[a]	
Yes	16 (9%)
No	154 (91%)
In full-time employment	
Yes	63 (37%)
No	108 (63%)
Lifetime history of alcohol misuse or dependence[a]	
Yes	39 (23%)
No	131 (77%)
Lifetime history of drug misuse or dependence[a]	
Yes	61 (36%)
No	109 (64%)
Any comorbid condition at baseline[a]	
Yes	61 (36%)
No	109 (64%)
Duration of untreated psychosis (months)[b]	5 (1, 24)
Diagnosis	
Affective	36 (21%)
Non-affective	135 (79%)

[a]Missing data for $n = 1$

[b]Median (first quartile, third quartile)

Of the 72 females in the cohort, there were 10 deaths—six from natural causes, three from unnatural causes and one cause of death was unknown. The median age of death for females who died was 55.5 years (first quartile 51, third quartile 67 years) and the median years lost was 27 years (first quartile 17.1, third quartile 33.5 years).

Mortality at 12-year and 20-year follow-up compared to the general population

SMRs are given in Table 2 for all-cause mortality. Compared with the general population, all-cause mortality was high at the 20-year follow-up (SMR 2.4, 95% CI 1.51–3.54). All-cause mortality tended to be higher in men than women (Table 2) and particularly in younger men (aged 15–34 years) with an SMR of 9.21 (95% CI 4.03–18.22).

Of the 20 deaths in the cohort at 20-year follow-up, 15 had already occurred by the 12-year follow-up (8.8%, 748 per 100,000 person-years of follow-up). At the 12-year follow-up, there were seven deaths due to natural causes (4.1%, 349 per 100,000 person-years of follow-up); five

Table 2 Standardised mortality ratios for all causes of death at the 20-year and 12-year follow-up by age and sex

	20-year follow-up			12-year follow-up		
	Observed deaths	Expected deaths	SMR (95% confidence interval)	Observed deaths	Expected deaths	SMR (95% confidence interval)
Total	20	8.32	2.40 (1.51, 3.65)	15	5.02	2.99 (1.74, 4.82)
Sex						
Male	10	3.37	2.97 (1.51, 5.29)	8	2.04	3.92 (1.82, 7.45)
Female	10	4.95	2.02 (1.03, 3.60)	7	2.98	2.35 (1.03, 4.65)
Age group (Males)						
15–34	7	0.76	9.21 (4.03, 18.22)	7	0.73	9.59 (4.19, 18.97)
≥35	3	2.61	1.15 (0.29, 3.13)	1	1.31	0.76 (0.04, 3.77)
Age group (Females)						
15–34	0	0.15	–	0	0.16	–
≥35	10	4.8	2.08 (1.06, 3.71)	7	2.82	2.48 (1.09, 4.91)

Table 3 Standardised mortality ratios for all causes of death at the 4-year and 8-year follow-up by sex

	4-year follow-up			8-year follow-up		
	Observed deaths	Expected deaths	SMR (95% confidence interval)	Observed deaths	Expected deaths	SMR (95% confidence interval)
Total	5	1.44	3.47 (1.27, 7.70)	11	2.97	3.70 (1.95, 6.44)
Sex						
Male	3	0.64	4.69 (1.19, 12.76)	6	1.26	4.76 (1.93, 9.90)
Female	2	0.8	2.49 (0.42, 8.22)	5	1.71	2.92 (1.07, 6.48)

due to unnatural causes (2.9%, 249 per 100,000 person-years of follow-up) and three due to unknown causes (1.8%, 150 per 100,000 person-years of follow-up) suggesting slightly higher mortality rates per person-years of follow-up than those at the 20-year follow-up for all three causes of death.

Comparing the SMRs at the 20-year follow-up to those at the 12-year follow-up for the same cohort showed a reduction in the estimate of the SMRs over time (Table 2) from 2.99 (95% CI 1.67 to 4.93) at the 12-year follow-up to 2.40 (95% CI 1.74, 4.82) at the 20-year follow-up. The confidence intervals are wide, however, and overlapping, reflecting the small number of deaths in the cohort. Comparison of SMRs for all causes of death at the 4-year and 8-year follow up by sex are presented (Table 3).

There were no statistically significant baseline predictors of survival time at 20-year follow-up, after adjusting for age and sex, which may reflect the relatively small number of deaths in the cohort and, therefore, a small number of events available per predictor variable.

Having a comorbid condition at baseline was associated with an increased risk of death, however, because the association was non-significant, and it would, therefore, not be defined as an association (HR 1.28, 95% CI 0.91–1.81, $p=0.15$) (Table 4). Comorbid conditions at baseline included any pre-existing conditions such as diabetes, cardiac or respiratory conditions and any history of physical trauma or brain trauma.

Table 4 Cox regression model of time to death using baseline characteristics as predictors ($n=171$)

Baseline characteristic	Hazard ratio (95% confidence interval)	*P* value
Age group		
<35 years	Reference	
≥35 years	0.99 (0.66, 1.48)	0.95
Sex		
Female	Reference	
Male	1.00 (0.71, 1.41)	0.99
Comorbid condition		
No	Reference	
Yes	1.28 (0.91, 1.81)	0.15

Discussion

This study investigated all natural and unnatural cause mortality in a large epidemiological sample of 171 individuals presenting with a first episode psychosis at 20-year follow-up. All-cause mortality in the cohort was almost 2.4

times that of the general population and more cases had died from natural causes than unnatural causes. We were unable to identify any statistically significant baseline predictors of mortality in our study and this may reflect the relatively small number of deaths in the cohort ($n = 20$).

Our findings indicated that the increased risk of mortality relative to the general population varies by age and gender. A higher risk of all-cause mortality was observed in men compared to women, particularly in the young male age group (15–34 years) with an all-cause mortality rate ninefold that of the general population. The median years lost for males who died was 47.7 years which was significantly higher than females with a median years lost of 27 years. This finding that young males with psychotic disorder are at greatest risk of premature mortality is in line with the literature [11–13].

In terms of risk time periods for mortality, the mortality in this cohort tended to be higher earlier in the follow-up period. We found excess mortality in the cohort at 12-year follow-up to be almost triple that of the general population, similar to the findings of the AESOP Cohort followed up at 10 years which found a 3.6-fold increase in all mortality. Interestingly, at 20-year follow-up our findings suggest a decrease in the point estimate for the SMR from 3 to 2.4 times that of the general population suggesting that the excess mortality in this cohort may be slowing down or decreasing over time. Although these findings must be interpreted with caution, however, due to the uncertainty in the SMR estimates and the relatively small numbers.

A recent finding in a UK-based cohort study investigating the mortality gap for people with bipolar disorder and schizophrenia from 2000–2014 [3] also found decreasing rates of all-cause mortality in both disorders since 2000 [3]. However, it was noted that mortality rates relative to the general population in those with bipolar and schizophrenia increased from the mid-2000s suggesting the improvement in health in the general population is increasing at a much faster rate than those with serious mental illness (SMI) [3]. However, an alternative explanation is that our finding of decreasing SMRs may reflect or suggest that the excess risk of mortality in this cohort compared to the general population is higher in the immediate years following diagnosis and stabilises over time. It has been shown previously in a cohort of patients diagnosed with incident and prevalent bipolar disorder that the rate of mortality was most increased initially and decreasing over time [14]. Similar findings have been found in previous studies with cohorts of those with serious mental illness or major psychiatric disorders including psychoses [15, 16]. Therefore, an alternative explanation for the decrease in SMR from 12- to 20-year follow-up in the current study may be a reduction due to survival bias.

In our study, more deaths were attributable to natural cause mortality (9 of 16 deaths with a certified cause of death) than unnatural causes. While a proportion of the excess mortality in those with psychosis and those with serious mental illness can be attributed to death due to unnatural causes, including suicide, the greater proportion of excess mortality is attributable to natural causes, often the premature onset of serious medical conditions [2, 13]. Follow-up studies of those with Schizophrenia in Swedish and Finnish cohort studies report mortality rates for diseases and medical conditions more than double that of the general population even when they controlled for lifestyle risk factors [8]. The adverse side effects associated with second-generation antipsychotic medications may be responsible for some of the excess physical health and subsequent mortality among those with psychotic illness [4, 17]. In particular, studies have shown an increased likelihood of weight-gain and metabolic syndrome for those taking second-generation medications [18]. However, a recent 13-year follow-up study of people with psychotic disorders based in Finland, found that even after adjusting for sociodemographic factors, cardio-metabolic comorbidities and lifestyle factors, the elevated mortality risk still remains higher than that of general population [19].

Despite the suggestion that further more complex factors are at play, there remains a need for investigations to identify if any of the risk factors are potentially modifiable, so that they can be directly targeted to reduce the mortality gap between those with psychotic illness and the general population. Improvements in mortality rates in various serious medical conditions have been observed in the general population. Conditions such as cancer, ischemic heart disease and acute myocardial infarctions have shown 60–80% reduction in mortality rates across Western European Countries over the past 30 years due to improvements in early detection, diagnostics and management [2, 20]. Although complex, the underlying factors associated with excess mortality are likely to be amenable to change [13].

Current data suggests that the increased risk of mortality of those with psychoses and serious mental illness is predominantly due to comorbid somatic conditions such as cardiovascular disease and cardio-metabolic disorders. A recent nationwide cohort study carried out in Denmark provides data that would support the concept of intervention for the somatic conditions in those with psychoses or serious mental illness [21]. The findings of the study suggested that some of the increased cardiac mortality among patients with schizophrenia could be partially reduced if these patients are efficiently administered combinations of secondary preventive treatments after cardiac events [21]. Careful monitoring and focused intervention in this area would potentially be a way to impact excess mortality for this vulnerable population.

Strengths and limitations

Study strengths include its epidemiological conception and its utilisation of an incidence cohort and prospective design and that cause of death were largely determined by death certificate. Limitations include the relatively small number of deaths which limited multivariable analysis of predictors of mortality, the fact that no information was available on lifestyle factors at baseline and our inability to obtain death certificates for deaths that occurred outside of Ireland.

Conclusion

The findings of our study are in line with the literature and suggest that the mortality gap in people with schizophrenia and other psychoses remains high, especially in young males and highlight the importance of early intervention both in relation to mental and physical healthcare. Those with a diagnosis of psychosis still do not appear to be benefitting from improvements in healthcare and services to the same degree as the general population.

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Compliance with ethical standards

Conflict of interest The authors declare they have no conflict of interest.

Ethical statement This study has been approved by the relevant and appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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