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# Long-term mortality and associated factors in first episode psychosis: a 25-year follow-up study

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## Original Article

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## Abstract

**Background.** Individuals with first-episode psychosis (FEP) face markedly increased excess mortality, yet the long-term trends and key contributing factors remain insufficiently characterized. This study aimed to examine long-term mortality patterns, standardized mortality ratios (SMRs), and associated factors in a FEP cohort.

**Methods.** This population-based cohort study included 1,389 individuals diagnosed with FEP, followed for up to 25 years. Mortality outcomes were obtained from Hong Kong's centralized hospital database (CMS) and coroner's court reports, with SMRs calculated. Baseline socio-demographic and clinical, as well as long-term treatment-related factors of all-cause, natural, and unnatural mortality were analyzed.

**Results.** Among 1,389 participants, 137 deaths (9.86%) occurred during the follow-up period with the overall SMR of 6.56 (95% CI, 5.50–7.71). The cumulative incidence rate of unnatural mortality increased sharply over the first 10 years and that of the natural cause of death started to increase after the first decade of the illness. Male gender and poorer social functioning were associated with increased all-cause mortality risk, while male gender, lower education, and baseline hospitalization raised unnatural mortality risk. Greater monthly antipsychotic variability during the first 10 years increased all-cause mortality risk in the period after the initial 10 years.

**Conclusions.** This 25-year follow-up study of FEP highlighted the changes in the long-term mortality pattern of FEP and thus the phase-specific needs of individuals with FEP. Therefore, it is important to integrate physical care into mental health services, as well as stage-specific and individualized care for patients with psychotic disorders to reduce long-term excess mortality.

## Introduction

Individuals with first episode psychosis (FEP) have a reduced life expectancy of 15–20 years (Kallio et al., 2022; Plana-Ripoll et al., 2019; Wahlbeck et al., 2011) with high mortality risks even decades after illness onset. A meta-analysis reported that nearly 13% of individuals with psychosis deceased within 10 years of diagnosis, and this mortality rate continues to rise over time (Chesney, Goodwin, & Fazel, 2014). Two nationwide studies from Denmark and Finland (Lomholt et al., 2019; Tanskanen, Tiihonen, & Taipale, 2018) suggested that the substantial mortality gap between individuals with schizophrenia and the general population remained over decades. Understanding the multifactorial contributors of excess mortality in individuals with psychosis, both unnatural and natural causes would be crucial for interventions aiming to narrow this gap (Laursen, Nordentoft, & Mortensen, 2014; Nordentoft et al., 2013).

Many studies have investigated excess mortality in individuals with FEP, but few have had longer-term follow-ups. One study (Doyle et al., 2019) in Ireland, tracking FEP patients for over 20 years revealed a persistently high mortality gap, particularly among young males, with mortality risk being highest during the first 8-year follow-up. Another study (Yuen et al., 2014) focusing on the FEP population aged 14–30 years over a similar period, found that a significant portion of excess mortality was initially attributed to non-suicide unnatural causes, followed by an increase in natural deaths over time. These temporal variation in causes of death and mortality rates over time highlights the need for longer-term studies to provide a comprehensive and life-course perspective. Some longer-term follow-up studies (Cheng et al., 2023; Crump, Winkleby, Sundquist, & Sundquist, 2013; Dickerson et al., 2024; Starzer et al., 2023) focusing on individuals with schizophrenia-spectrum disorder (SSD), including a 20-year follow-up study of individuals with SSD in Denmark, which demonstrates a rising proportion of deaths attributable to physical illnesses, particularly cardiovascular and metabolic diseases

(Starzer et al., 2023). Studies of individuals with narrower diagnostic categories provide a more homogenous and focused understanding. However, given the longitudinal diagnostic instability of psychosis (Bromet et al., 2011; Peralta et al., 2024) and the provision of specialized services to individuals with FEP in many parts of the world, exploring the longitudinal mortality pattern of FEPs in general may provide a more comprehensive understanding.

Excess mortality patterns in individuals with FEP are likely to be shaped by sociodemographic, clinical, and behavioral factors. Sociodemographic determinants, including unemployment (Koutsouleris et al., 2016), living alone (Starzer et al., 2023), male gender (Lieslehto et al., 2024), and ethnic minority status (Morgan et al., 2017) have been suggested to be associated with increased mortality risk. Clinical factors such as hospitalization at illness onset (Lieslehto et al., 2024), prolonged duration of untreated psychosis (DUP), poor premorbid functioning (Stephens, Richard, & McHugh, 1999), and low cognitive functioning (Doyle et al., 2019) have all been demonstrated to be risk factors of mortality. Mental health comorbidities, particularly suicidality (Simon et al., 2018) and substance use (Correll et al., 2022; Lieslehto et al., 2024), further amplify the risk of mortality. Another important clinical factor is the use of antipsychotics, with its relationship with mortality remains a subject of ongoing debate. Continuous use of antipsychotics has been shown to be associated with decreased all-cause mortality (Taipale et al., 2020; Tiihonen et al., 2012) with a recent review highlighting the protective effects of any antipsychotics against all-cause and natural-cause mortality (Correll et al., 2022). However, a systematic review has suggested that long-term antipsychotic medication may increase mortality risk, primarily due to adverse effects on physical health (Weinmann, Read, & Aderhold, 2009). Antipsychotic medications have been implicated in weight gain (Dayabandara et al., 2017), metabolic syndrome (De Hert et al., 2011), and an increased risk of cardiovascular disease (De Hert et al., 2011), which are major contributors to natural deaths. The long-term influence of antipsychotics on survival outcomes is further complicated by findings that symptom remission without antipsychotic medication and recovery during the follow-up period can lower mortality risk (Harrow, Jobe, Faull, & Yang, 2017). Therefore, understanding the nuanced impact of antipsychotic treatment on long-term mortality remains critical for optimizing treatment strategies for individuals with FEP over time.

Apart from these sociodemographic and clinical determinants, healthcare and social welfare systems might be important contextual factors that contribute to the varied mortality rates. Therefore, studies from different regions other than Western countries may provide valuable information to understand the longitudinal excess mortality pattern in individuals with psychosis. Hong Kong has a population of 7.5 million with a life expectancy of 85.6 in 2024, the third-highest life expectancy in the world (*Life Expectancy by Country 2025*, 2025). Most of the mental health services in Hong Kong, particularly for people with severe mental illness, are provided by the public health care system. The current study aims to explore long-term mortality patterns and associated factors among individuals with FEP over 20 years in Hong Kong. The specific objectives are: (1) to characterize changing patterns of mortality of individuals with FEP over 20 years; (2) to evaluate the associations between baseline sociodemographic and clinical characteristics and subsequent mortality; and (3) to assess the impact of antipsychotic medication use during the first 10 years following FEP onset on subsequent mortality outcomes. By identifying risk factors of long-term mortality, this research seeks to inform clinical and public health strategies to improve long-term survival and outcomes in individuals with FEP.

## Methods

### Study design and sample

This is a 25-year follow-up study of FEPs, which was originally established for a territory-wide historical control comparison study exploring outcomes of early intervention service (EIS) for FEPs in Hong Kong (Chen, 2004; Chen et al., 2011; Wong et al., 2024). Participants were those with FEP and received the EIS (the Easy Assessment Service for Young People with Psychosis service [EASY]) for the first time between 1 July 2001 to 30 June 2003 with an age range of 15–25 ($N$ = 700), and age, gender, and diagnosis matched FEPs received standard care services (SCS) for the first time between 1st July 1998 and 30th June 2001 ($N$ = 700). The inclusion and exclusion criteria of this cohort were comprehensively reported in the previous study (Chan et al., 2015) and summarized in the Supplemental methods. All clinical information was obtained from the medical records and electronic health records from all the public psychiatric units provided by the Hospital Authority of Hong Kong, including the Clinical Management System (CMS) and Clinical Data Analysis and Reporting System (CDARS). The CMS is a real-time, front-end system for recording patient information and clinical activities, while CDARS is a centralized, back-end system for retrospective analysis, providing anonymous data on hospitalizations, medication use, investigation results, and other healthcare service utilization, covering approximately 90% of secondary and tertiary care services (Sek et al., 2007). The reliability of clinical information from CMS and CDARS has been verified (Zhou, Tang, Chan, & Luo, 2025). Participants were excluded from the study if their identification information was invalid or unmatched between the CMS and CDARS datasets. A total of 1,389 participants (99.2%) with FEPs were included (Figure 1).

All procedures conducted in this study adhered to the Declaration of Helsinki (1975, as amended in 2008) and were approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster (HKU/HA HKW IRB) (IRB reference number: UW 22-613). The requirement for informed consent was waived by the institutional review boards and ethics committees. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (von Elm et al., 2007).

### Data collection

#### Mortality information

All mortality information, including cause and date of death, till the end date of this study of 23 November 2023, was obtained from the CMS and verified with the coroner's court report. Deaths that were due to accidents, suicide, and actions with unclear intentions were considered as unnatural deaths, whereas deaths due to documented medical conditions were considered as natural deaths (Harrow et al., 2017). The sex- and age-standardized death rates of all-cause mortality of the general population in Hong Kong from 1998 to 2022 were obtained from the Census and Statistics Department of the Government of the Hong Kong Special Administrative Region (The Mortality Trend in Hong Kong, 1991 to 2022, 2024) for the calculation of the standardized mortality ratios.

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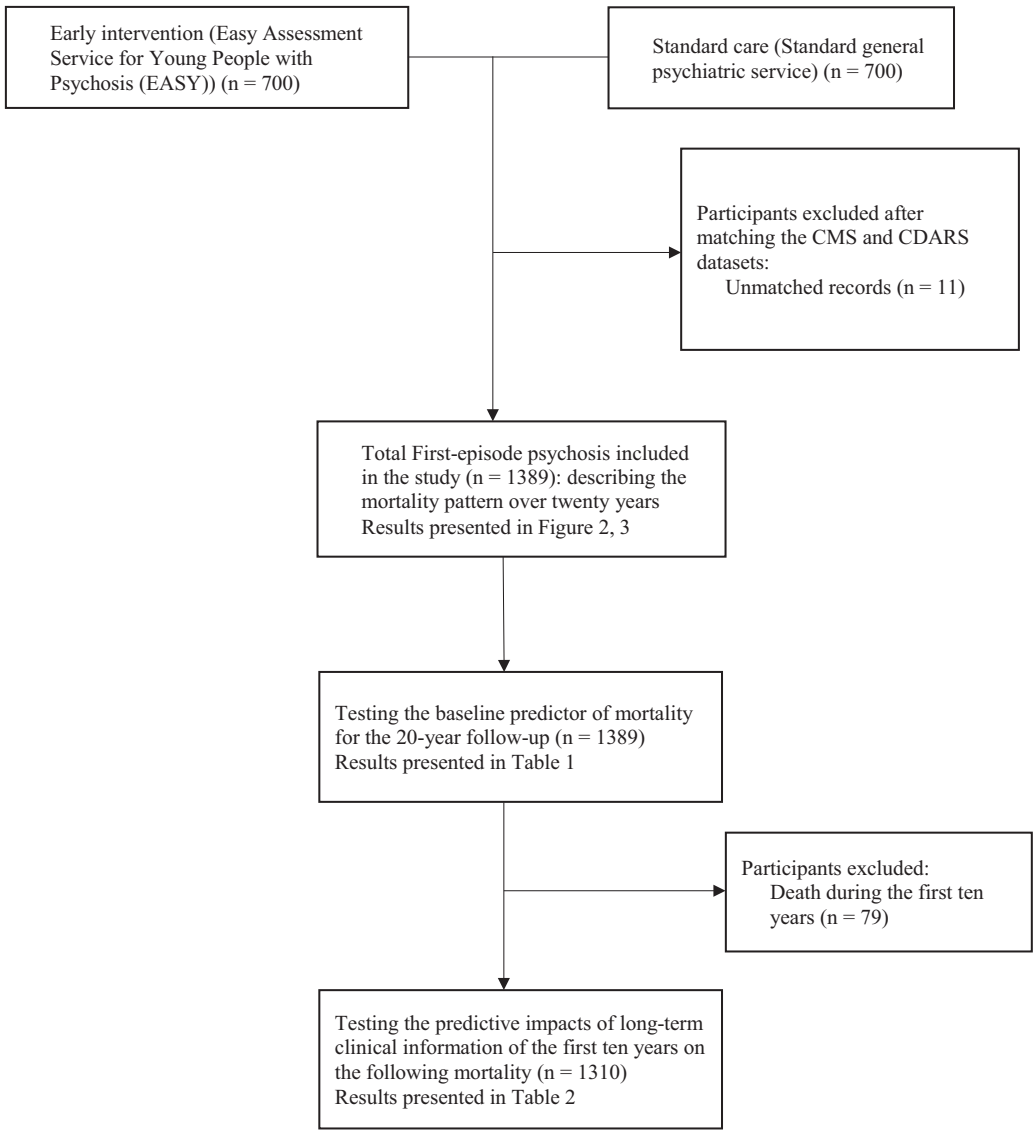


**Figure 1.** Flowchart of the study (participants' collection and sample size of included participants for each step).

### *Baseline and long-term sociodemographic and clinical information*

Baseline sociodemographic and clinical information was systematically extracted by trained researchers from the CMS and written medical records. Sociodemographic variables included sex and educational attainment. Clinical information included diagnosis, age at illness onset, DUP, social functioning, admission and discharge dates of psychiatric hospitalization, and symptom severity at onset, which included positive, negative, and affective symptoms assessed with the Clinical Global Impressions–Schizophrenia (CGI-SCH) scale (Haro et al., 2003). DUP was defined as the duration (in days) between the first manifestation of psychotic symptoms and the initiation of effective psychiatric treatment, as determined by clinicians. Participants who were hospitalized within the first month of presentation to the psychiatric services were considered hospitalized at baseline. Social functioning was evaluated using the Social and Occupational Functioning Assessment Scale (SOFAS) (Goldman, Skodol, & Lave, 1992). Biweekly consensus meetings were held for quality assurance during data collection. An experienced clinician and two researchers reviewed 12 medical records to validate the data collection process. Satisfactory validity and inter-rater reliability of key factors, including DUP, functioning, and symptom severity, were reported in a previous study (Chan et al., 2018) and briefly summarized in the Supplement methods.

Clinical information over the first 10 years of those who survived was extracted from the CDARS by trained researchers. These include dose, types, and duration of antipsychotic medications prescribed, psychiatric and non-psychiatric hospitalization durations, and physical comorbidities. The proportion of psychiatric and non-psychiatric hospitalization duration was calculated as the total duration of psychiatric or non-psychiatric hospitalization divided by the whole follow-up period within the first 10 years. The Charlson Comorbidity Index (Charlson, Carrozzino, Guidi, & Patierno, 2022) was used to assess the physical comorbidities of the participants. Polypharmacy is operationally defined as the concurrent prescription of ≥2 antipsychotics for 28 days or longer. Mean square successive difference (MSSD) (von Neumann, Kent, Bellinson, & Hart, 1941), and mean of monthly defined daily dose (DDD) (Nosè et al., 2008) of antipsychotics and monthly treatment duration of antipsychotics were calculated. MSSD estimates variability

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by calculating the mean of the squared differences between consecutive data points. Details on the definitions and calculations of clinical factors for the first 10 years are summarized in Supplementary Table 1.

### Statistical analysis

For the objective of the study, standard mortality ratios (SMRs) of all-cause were calculated by dividing the observed number of deaths in each gender and age group of the study sample by the expected number of deaths based on the population mortality rates in the Hong Kong census survey (Tsai, Hardy, & Wen, 1992). As the age group was categorized in 5-year increments in the Hong Kong census, the consecutive 5-year average SMRs with 95% confidence intervals (CIs) were calculated and plotted for this study from 1998 to 2022. The causes of mortality over the follow-up period were described. The Aalen–Johansen estimator, a standard nonparametric method for estimating cumulative incidence functions in competing risks, was used to compare trends in natural and unnatural deaths over the study period (Aalen & Johansen, 1978; Andersen, Borgan, Gill, & Keiding, 2012). As a sensitivity analysis, SMR trends and causes of mortality over the follow-up period were examined in the subgroup of individuals diagnosed with SSD at baseline.

To examine the second objective of the study, multivariable Cox proportional hazards regression models were employed to explore associations between sociodemographic and clinical characteristics at baseline and all-cause, natural, and unnatural mortality, with Bonferroni correction applied for multiple comparisons. Group differences in baseline characteristics between deceased and surviving individuals over the entire follow-up period were assessed, with continuous variables analyzed using the Monte Carlo simulation for *t*-test, to account for skewed distributions and small sample sizes (Sokal, 1992).

To study the impact of antipsychotic medication usage during the first 10 years on later mortality in our objective three, the analysis excluded participants who deceased within the first 10 years. Group differences in clinical data, including antipsychotic medication, were analyzed between individuals who later deceased and those who survived until the study's endpoint. Continuous variables were again assessed using the Monte Carlo simulation for *t*-test. To address potential non-linear relationships among dependent variables and validate the significance of antipsychotic medication patterns, distance correlation tests (Gábor, Maria, & Nail, 2007) were employed to examine associations with psychiatric and non-psychiatric hospitalizations, as well as comorbidities, over the first 10 years. Multivariate Cox regression was conducted in two steps: (1) assessing the associations of monthly antipsychotic treatment duration and DDD with all-cause, natural, and unnatural mortality, adjusting for baseline education, gender, and psychiatric diagnosis, (2) reanalyzing these associations with adjustment for identified baseline risk factors. As a sensitivity analysis, a multivariate Cox regression was applied to examine the association between antipsychotic medication patterns and mortality within the SSD subgroup. Bonferroni correction was applied to Cox regression analyses for multiple comparisons across all-cause, unnatural, and natural mortality outcomes. A two-sided *P*-value <0.05 was considered statistically significant. All statistical analyses were performed using R, version 4.3.2 (The R Foundation).

## Results

The study sample consisted of 1389 FEPs at baseline, with 967 (69.6%) participants having a diagnosis of SSD and a median observation period of 22 years. The baseline median age was 21.6 (interquartile range, IQR = 5.42) and 51.4% of the sample were male. To preliminarily validate our antipsychotic medication pattern metrics (mean and MSSD of monthly DDD and treatment duration, and proportion of polypharmacy duration), we evaluated their associations with hospitalization and comorbidity outcomes during the first 10 years (Supplementary Figure 1), highlighting links between antipsychotic patterns and psychiatric hospitalizations.

### Mortality patterns over 20 years

Among the 137 (9.86%) deceased individuals during the follow-up period, 102 of them were due to unnatural causes and 35 were due to natural causes, with details of cause of death shown in Supplementary Table 2. The overall SMR was 6.56 (95% CI, 5.50–7.71). The highest all-cause SMR was 11.82 (95% CI, 7.73–15.92) in the first 5 years, which dropped continuously to 3.33 (95% CI, 2.00–4.66) in the last five years (22 years on average after the initial onset) (Figure 2). The cumulative incidence rate of natural deaths increased after 10 years, while that of unnatural deaths rose sharply during the first decade before stabilizing (Figure 3). Similar SMR trends were observed (Supplementary Figure 2) among the individuals with SSD, yielding an overall SMR of 6.98 (95% CI, 5.82–8.25) with similar patterns of SMRs over time. The cumulative incidence patterns for natural and unnatural deaths of SSD were reported in Supplementary Figure 3.

### Baseline factors associated with long-term mortality

Compared with those survived at the end of the study, individuals with FEP deceased during the follow-up period were more likely to be male (alive vs death: 50.16% vs 65.69%, $p < 0.01$), with a high proportion of low educational level (alive vs death: 73.65% vs 84.56%, $p = 0.01$), having hospitalization in the first month (alive vs death: 67.41% vs 79.56%, $p < 0.01$), and low SOFAS scores (alive vs death: 84.83% vs 96.35%, $p < 0.01$) at baseline (Supplementary Table 3). Multivariate Cox regression analyses found male participants (hazard ratio, HR: 1.72, 95% CI, 1.20–2.45) and low SOFAS scores at baseline (HR: 3.26, 95% CI, 1.29–8.23) were associated with increased risks of all-cause mortality; male participants (HR: 1.91, 95% CI, 1.26–2.90), participants with a low educational level (HR: 2.07, 95% CI, 1.17–3.67), and hospitalization in the first month had increased risks of unnatural mortality after Bonferroni correction (Table 1).

### Association of antipsychotic medication use patterns of the first 10 years and mortality after first 10 years

After excluding those who had deceased within the first 10 years, 1,310 participants were eligible for examining the associations between long-term antipsychotic medication and the risk of later mortality (Figure 1). A total of 74 participants deceased during the follow-up period beyond the first 10 years. Among participants who survived the first 10 years, those who later deceased had a higher average monthly antipsychotics duration (alive vs deaths: 19.88 vs 21.18, $p = 0.01$, Cohen's $d = 0.29$) during the first 10 years, and those deceased from natural causes had a significantly higher average monthly DDD of antipsychotics during the first 10 years (unnatural deaths vs natural deaths: 0.44 vs 0.79, $p = 0.04$, Cohen's $d = 0.57$) than those who deceased from unnatural causes (Supplementary Table 4). Multivariate Cox regression analyses revealed that higher MSSD of

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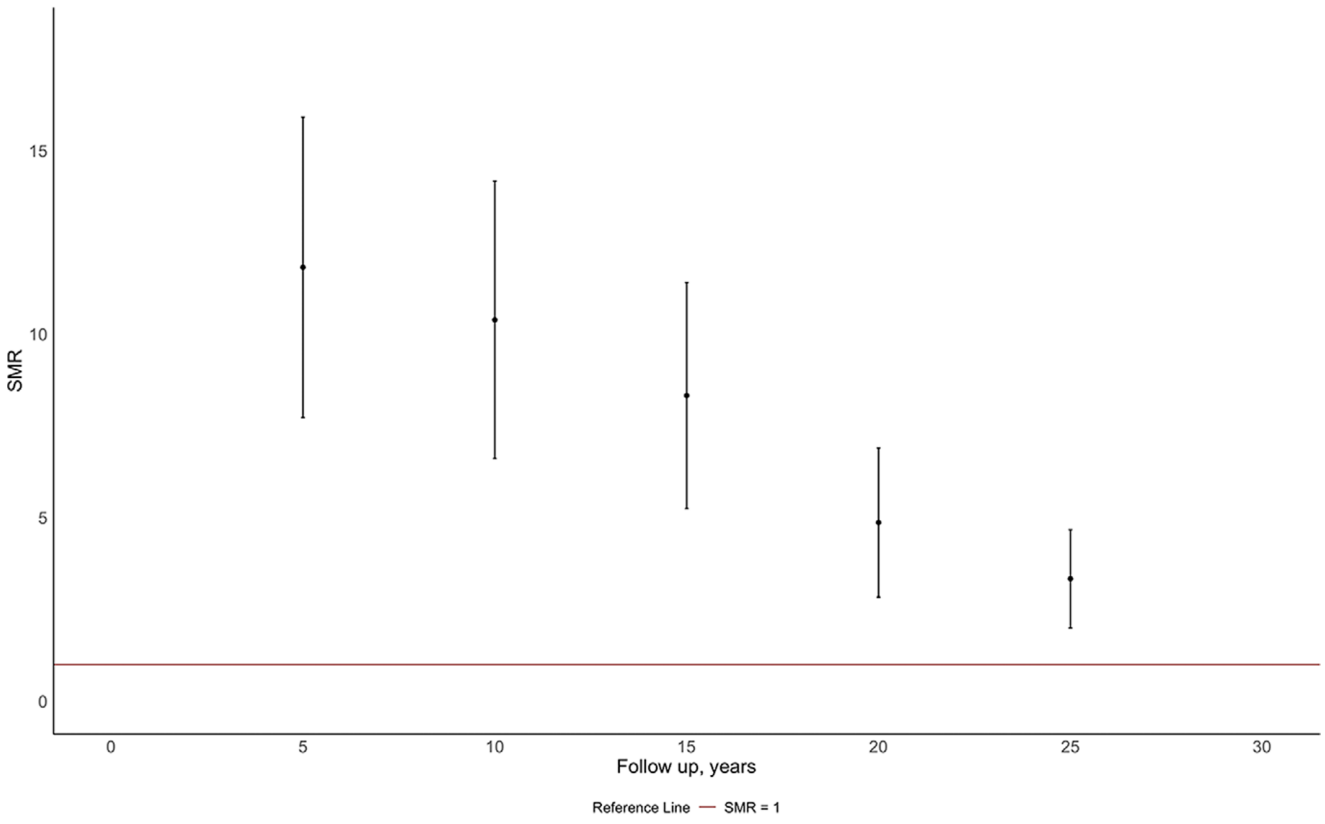
A




B

Table. Five-year average standardized mortality ratio (SMR) of all-cause mortality

| Follow-up period | SMR (95% CI) |
|---|---|
| 1 - 5 year follow ups | 11.82 (7.73, 15.92) |
| 6 - 10 year follow ups | 10.39 (6.61, 14.17) |
| 11 - 15 year follow ups | 8.33 (5.24, 11.41) |
| 16 - 20 year follow ups | 4.86 (2.83, 6.90) |
| 21 – 25 year follow ups | 3.33 (2.00, 4.66) |

**Figure 2.** The trend for standardized mortality rates over the years.
(a) This figure indicates the trend of the 5-year average standardized mortality ratio (SMR) of all-cause mortality over twenty-five years. Since the whole cohort started in 1998, the first 5-year average SMR was calculated by using the general Hong Kong population in the matched age-gender specific groups in 2002, and the following 5-year average SMRs were calculated using the mortality rates of the general Hong Kong population in the matched specific age-gender groups in 2007, 2012, 2017, and 2022. (b) This table shows the exact SMR values for each calculated period.

monthly antipsychotic treatment duration in the first 10 years was associated with an increased risk of later all-cause mortality (HR 1.01, 95% CI, 1.00–1.03, Bonferroni-corrected; Table 2). These findings persisted after additional adjustment for baseline risk factors, including sex, education level, hospitalization status, SOFAS score categories, and baseline psychiatric diagnosis (Supplementary Table 5). Similar patterns were observed among participants with SSD (Supplementary Table 6). In this subsample, greater MSSD of monthly antipsychotic duration was linked to increased all-cause mortality (HR 1.01, 95% CI, 1.00–1.03) after Bonferroni correction.

## Discussion

This study investigated the mortality patterns of 1,389 individuals with FEP followed for up to 25 years (median of 22 years), with about 70% of the study population having an SSD diagnosis at baseline. Throughout the follow-up period, 137 participants (9.86%) deceased, giving an overall SMR of 6.56. The cumulative incidence rate of natural deaths increased after the first decade of the illness, while that of unnatural deaths rose sharply during the first decade and stabilized in the second decade of the illness. Males with lower educational levels, poorer social functioning, and being hospitalized at baseline were associated with increased risk of mortality over 20 years. Greater fluctuations in monthly antipsychotic medication duration during the first 10 years were linked to an increased risk of subsequent all-cause mortality.

The all-cause long-term mortality rate observed in our study was 9.86%, consistent with findings from prior longitudinal studies, which reported mortality rates ranging between 10% and 14% among individuals with psychotic disorders (Crump et al., 2013;

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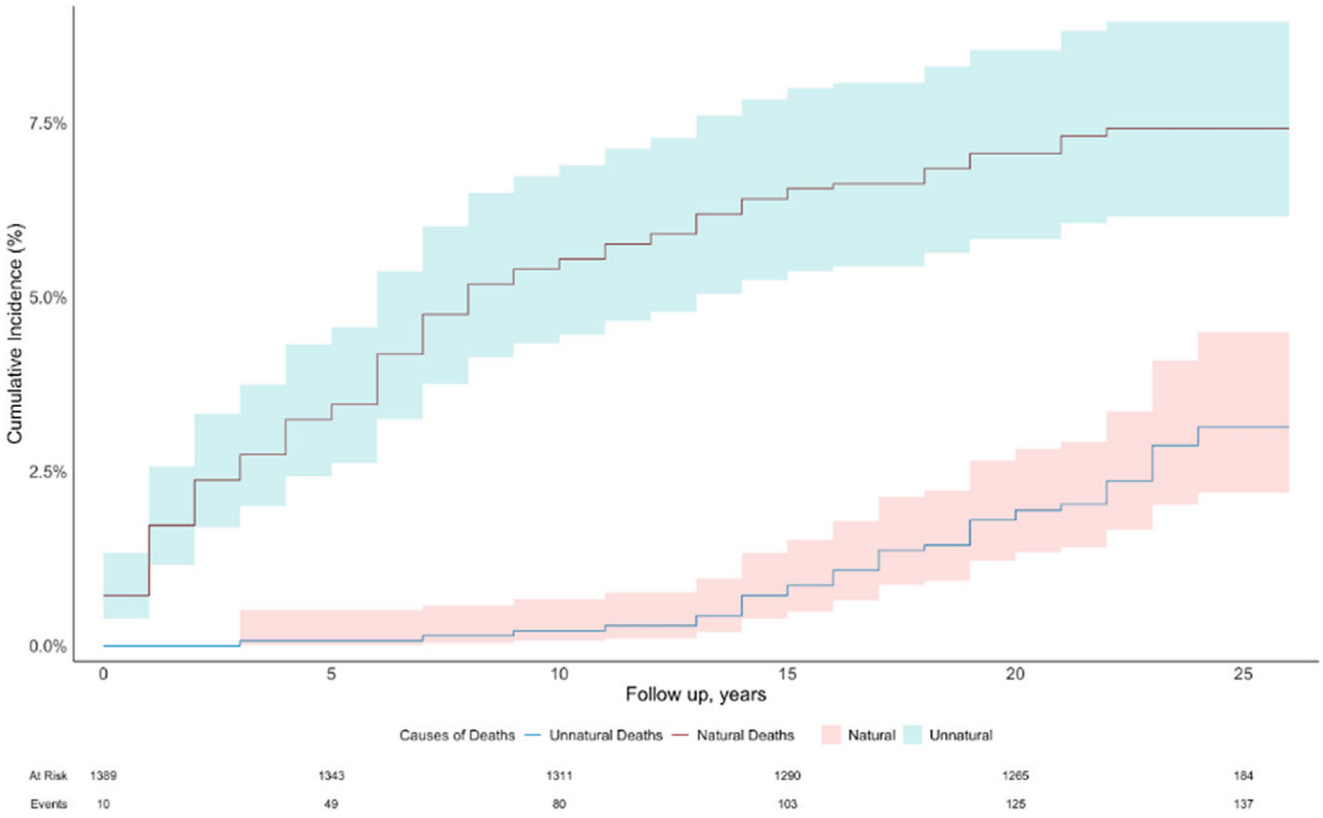


**Figure 3.** The cumulative incidence of natural and unnatural deaths over the follow-up period.

Dickerson et al., 2024; Hor & Taylor, 2010; Starzer et al., 2023). However, the overall SMR of all-cause mortality (6.56) and even the lowest SMR of all-cause mortality during the last 5 years of follow-up period (3.33) of this study population, as well as the subsample of SSD (overall all-cause SMR = 6.98, lowest all-cause SMR = 3.62), were higher than the median SMR of all-cause mortality of schizophrenia reported in a systematic review (2.56) (Saha, Chant, & McGrath, 2007). The relatively young study population at the start of the study might be a possible reason. The high life expectancy of Hong Kong might also explain this bigger excess mortality gap found in the study, reflecting more prominent health inequalities in people with psychotic disorders. Similar to the 20-year follow-up of OPUS study (Starzer et al., 2023), our study found that suicide is the leading cause of death in the FEP population (70.8%), particularly during the first 10 years of illness onset. The significantly higher risk of suicide death during the early stage of the illness reported in this study, as well as previous studies (Brown, 1997; Melle et al., 2017), highlights the crucial need to establish and implement effective interventions to reduce suicide during the early stage of the psychotic illness. Even though EIS for psychosis has been reported to be effective in reducing suicide death (Chai et al., 2024; Chan et al., 2018) and many countries and regions have already implemented the EIS (Correll et al., 2017), the excess mortality due to suicide of psychosis is still prominent. Therefore, establishing further effective intervention strategies to reduce suicide within the EIS context for people with FEP is still crucial. Identifying risk populations, possibly with algorithm-based approaches (Lieslehto et al., 2024; Wong et al., 2024), to provide targeted monitoring and intervention might be one possible strategy.

The current study revealed a change in the mortality pattern over the follow-up period. There was a gradual decline of SMR of all-cause mortality in the first 15 years of illness onset, with a plateau of incidence rate of unnatural cause of death (mostly suicide), and then a sharp reduction of SMR of all-cause mortality with an increase of natural death between 15 and 25 years of follow-up. This mortality pattern was also seen in previous long-term follow-up studies in Australia (Yuen et al., 2014) and Denmark (Starzer et al., 2023). About one quarter of the natural deaths in this study were due to cardiovascular conditions. This highlighted the importance of physical health care among individuals with FEP to reduce risk factors related to cardiovascular conditions, particularly after the initial few years of illness (Correll et al., 2017). One of which is preventing the development of metabolic syndrome during the early stage of psychosis in the young population. Using a well-validated risk calculator for the development of metabolic syndrome in the young FEP population (Perry et al., 2021; Tse et al., 2024) may be an important strategy to reduce the risk of long-term mortality. Another important reason for the excess mortality and morbidities due to physical health has been suggested to be the disparities in physical health access, utilization, and provision (Lawrence & Kisely, 2010; Nasrallah et al., 2006; Osborn, King, & Nazareth, 2003). Therefore, integrating physical health care within the mental health service provision to allow streamlined service delivery should be considered.

Our study identified male gender, low educational attainment, poor social functioning, and hospitalization at baseline as significant factors associated with long-term all-cause and unnatural mortality in individuals with FEP. Given that most of the unnatural causes of mortality in this study were suicide (95%), and the same set of factors were found to be significantly different between the natural and unnatural deaths, indicating these factors are likely to be risk factors of suicide in this population. These factors are similar

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**Table 1.** Multivariate Cox regression analysis of baseline predictors of mortality ($N$ = 1389)

| | All-cause mortality ($n$ = 137) | | Unnatural death ($n$ = 102) | | Natural death ($n$ = 35) | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | $P$ | HR (95%CI) | $P$ | HR (95%CI) | $P$ |
| Sex | | | | | | |
| Female | 1 | | 1 | | 1 | |
| Male | **1.72 (1.20, 2.45)** | **<0.01*** | **1.91 (1.26, 2.90)** | **<0.01*** | 1.29 (0.65, 2.53) | 0.47 |
| Educational levels[a] | | | | | | |
| High educational level | 1 | | 1 | | 1 | |
| Low educational level | 1.73 (1.07, 2.79) | 0.03 | **2.07 (1.17, 3.68)** | **0.01*** | 1.04 (0.42, 2.57) | 0.93 |
| Age of onset | 1.02 (0.97, 1.07) | 0.45 | 1.04 (0.98, 1.10) | 0.19 | 0.96 (0.87, 1.06) | 0.42 |
| Log DUP (days) | 1.09 (0.82, 1.46) | 0.55 | 1.01 (0.72, 1.42) | 0.94 | 1.36 (0.78, 2.36) | 0.28 |
| Onset mode | | | | | | |
| Gradual | 1 | | 1 | | 1 | |
| Acute | 0.98 (0.62, 1.55) | 0.94 | 0.96 (0.58, 1.60) | 0.88 | 1.06 (0.38, 2.93) | 0.91 |
| Substance use disorder at baseline | | | | | | |
| No | 1 | | 1 | | 1 | |
| Yes | 0.90 (0.42, 1.95) | 0.79 | 0.73 (0.28, 1.91) | 0.52 | 1.50 (0.41, 5.55) | 0.54 |
| Hospitalization status in Month one | | | | | | |
| No | 1 | | 1 | | 1 | |
| Yes | 1.66 (1.03, 2.67) | 0.04 | **2.21 (1.23, 3.98)** | **0.01*** | 0.79 (0.33, 1.91) | 0.60 |
| CGI Affective in Month one | 1.02 (0.89, 1.17) | 0.80 | 1.01 (0.85, 1.19) | 0.92 | 1.05 (0.81, 1.37) | 0.72 |
| CGI Positive in Month one | 0.83 (0.70, 0.99) | 0.04 | 0.84 (0.68, 1.04) | 0.10 | 0.83 (0.60, 1.14) | 0.24 |
| CGI Negative in Month one | 1.00 (0.87, 1.15) | 0.98 | 0.92 (0.79, 1.07) | 0.27 | 1.28 (0.95, 1.72) | 0.11 |
| SOFAS category in Month one[b] | | | | | | |
| High scores | 1 | | 1 | | 1 | |
| Low scores | **3.26 (1.29, 8.23)** | **0.01*** | 3.43 (1.07, 11.02) | 0.04 | 3.02 (0.65, 14.10) | 0.16 |
| Diagnosis at baseline[c] | | | | | | |
| Affective psychosis | 1 | | 1 | | 1 | |
| Schizophrenia spectrum disorder | 2.07 (0.95, 4.53) | 0.07 | 2.57 (0.99, 6.67) | 0.05 | 1.24 (0.33, 4.68) | 0.75 |
| Other psychotic disorders | 2.00 (0.91, 4.41) | 0.09 | 2.23 (0.87, 5.71) | 0.10 | 1.50 (0.35, 6.44) | 0.59 |
| Physical disease history at baseline[d] | | | | | | |
| No | 1 | | 1 | | 1 | |
| Yes | 1.29 (0.91, 1.83) | 0.15 | 1.12 (0.75, 1.68) | 0.58 | 1.88 (0.93, 3.78) | 0.08 |

*Note:* Bold indicates significant associations after Bonferroni correction, *denotes $P < 0.017$ (the $P$-value threshold after Bonferroni correction).
Abbreviations: CGI, Clinical Global Impressions Scale; DUP, Duration of untreated psychosis.
[a]Educational levels at baseline were categorized based on years of education: low educational level (<12 years) and high educational level (≥12 years).
[b]The Social and Occupational Functioning Assessment Scale (SOFAS) category at Month 1 was classified based on SOFAS scores: low scores (0–55) = 1, high scores (>55) = 2 (assessed using the SOFAS scale).
[c]Diagnoses at baseline were categorized as follows: "Schizophrenia spectrum disorder" included schizophrenia and schizoaffective disorder; "Other psychotic disorders" encompassed acute and transient psychotic disorder (ATPD) and psychosis not otherwise specified (NOS); "Affective psychosis" included bipolar affective disorder (BAD)/mania with psychotic symptoms and severe depression with psychotic symptoms.
[d]Physical disease history at baseline was determined from hospital records predating the baseline, excluding psychiatric diagnoses (ICD-9 codes 219–319).

to findings of previous studies (Björkenstam et al., 2014; Hawton et al., 2005; Robinson et al., 2010), including the OPUS 20-year follow-up study (Starzer et al., 2023). In fact, male gender, low educational attainment, and poorer baseline social functioning have generally been considered as risk factors for poorer outcomes of people with psychosis (Santesteban-Echarri et al., 2017). Hospitalization at baseline likely reflects higher illness severity at initial presentation. A machine learning-based model in the Swedish and Finnish population has identified hospitalization as a key risk factor of mortality in first-episode psychosis (FEP) (Lieslehto et al., 2024). Substance use disorders (SUD) at baseline were not identified as a significant risk factor for later mortality during the follow-up period in this study. This may be attributed to the low prevalence of SUD in this FEP population, which reflects the low general SUD in the Hong Kong population (Lau, Kim, & Tsui, 2005).

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**Table 2.** Multivariate Cox regression analysis of the impact of antipsychotic patterns of the first 10 years of follow-ups on the mortality for the following period

| | All-cause mortality ($n$ = 58) | | Unnatural death ($n$ = 26) | | Natural death ($n$ = 32) | |
|---|---|---|---|---|---|---|
| | HR (95%CI) | $P$ | HR (95%CI) | $P$ | HR (95%CI) | $P$ |
| Mean monthly antipsychotic DDD | 0.94 (0.46, 1.93) | 0.87 | 0.67 (0.15, 2.90) | 0.59 | 1.16 (0.54, 2.48) | 0.70 |
| MSSD of monthly antipsychotic DDD | 0.82 (0.21, 3.15) | 0.77 | 0.43 (0.01, 12.82) | 0.63 | 1.01 (0.32, 3.17) | 0.99 |
| Mean monthly duration of antipsychotic medication (days) | 1.03 (0.99, 1.07) | 0.08 | 1.02 (0.96, 1.07) | 0.58 | 1.05 (1.00, 1.10) | <0.05 |
| MSSD of monthly duration of antipsychotic medication | **1.01 (1.00, 1.03)** | **0.01*** | 1.02 (1.00, 1.03) | 0.04 | 1.01 (1.00, 1.02) | <0.05 |
| Proportion of polypharmacy duration[a] | 2.22 (0.77, 6.39) | 0.14 | 1.90 (0.37, 9.71) | 0.44 | 2.47 (0.61, 9.99) | 0.20 |

*Note*: A total of 1310 participants were included in this analysis; models were adjusted with gender, educational levels, and diagnosis at baseline. Bold indicates significant associations after Bonferroni correction, * denotes $P < 0.017$ (the $P$-value threshold after Bonferroni correction.

Abbreviations: DDD, defined daily dose; MSSD, Mean square successive difference.

[a]Polypharmacy was defined as the concurrent use of two or more antipsychotics for more than 28 days. The proportion of polypharmacy duration represents the total time a patient spent on multiple antipsychotics divided by their total duration of antipsychotic treatment.

Some risk factors that contribute to the excess mortality and morbidity due to physical illness in the psychosis population may be modifiable, including unhealthy lifestyle and the use of antipsychotics (Correll et al., 2017; Saha et al., 2007). Our study found that greater fluctuations of antipsychotic usage in the first 10 years were associated with higher subsequent mortality risks, with half of them due to physical causes. Inconsistent use of antipsychotics may reflect a course of recurring illness, which will increase vulnerability to adverse events such as suicide and accidents, and poor functioning, which then contributes to an unhealthy lifestyle (Haddad, Brain, & Scott, 2014; Tiihonen et al., 2009). Furthermore, fluctuations in antipsychotics intensify cardiovascular risks, including metabolic syndrome, QT-interval abnormalities, and diabetes-related complications, contributing to natural mortality (De Hert et al., 2011; Henderson et al., 2015; Ray et al., 2009). Additionally, irregular treatment elevates respiratory and infectious deaths through immune dysfunction and smoking-related health deterioration (Miller et al., 2011). Though the reason for unstable use of antipsychotics could not be specified, our cross-sectional analysis on the relationship between antipsychotic patterns and psychiatric hospitalization over the first 10 years revealed that fluctuation of the duration of antipsychotic usage was significantly related to both psychiatric and nonpsychiatric hospitalization. These results highlighted the importance of consistency of antipsychotic usage and thus illness stability in relation to long-term mortality.

Several limitations of the study should be considered in interpreting our findings. First, the relatively small sample size might limit the power to identify specific risk factors for some causes of death, such as suicide. Second, interpreting longitudinal SMR trends may be limited by this cohort's fixed design, which lacks new entrants over time, and this may cause survivor bias that could attenuate SMR estimates as the remaining population reflects stronger survivors. Third, the associations observed between baseline risk factors, antipsychotic treatment, and mortality may be confounded by unmeasured individual biopsychosocial variables, such as genetic predispositions, childhood trauma, and family history of self-harm (Hor & Taylor, 2010). Meanwhile, all the information of the study was obtained from the clinical records of the public mental health services. Information on participants who had emigrated or stopped receiving care from the public health services during the follow-up period will not be available, leading to bias. The quality of the information obtained depends on the quality of clinical documentation. Furthermore, only baseline diagnoses were considered without examining diagnostic transitions during follow-up. This may underestimate or obscure the distinct mortality risks of types of psychotic disorders. Finally, the cohort was drawn from a specific geographic and healthcare context, which may limit the generalizability of the results.

## Conclusions

This study highlights the persistent excess mortality among individuals with FEP despite advances in healthcare, revealing a distinct temporal shift: natural deaths increase significantly after 10 years, while unnatural deaths peak during the first decade and stabilize thereafter. Male gender, low educational attainment, poor social functioning, and hospitalization at baseline were significantly associated factors of mortality. High fluctuations in antipsychotic medication in the first 10 years increased subsequent mortality risk among FEP. Results underscore the need for individualized and integrated mental and physical health care services to reduce long-term mortality in patients with FEP.

**Supplementary material.** The supplementary material for this article can be found at http://doi.org/10.1017/S0033291725102286.

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## References

Aalen, O. O., & Johansen, S. (1978). An empirical transition matrix for non-homogeneous Markov chains based on censored observations. *Scandinavian Journal of Statistics*, **5**(3), 141–150. http://www.jstor.org/stable/4615704.

Andersen, P. K., Borgan, O., Gill, R. D., & Keiding, N. (2012). *Statistical models based on counting processes*. Springer.

Björkenstam, C., Björkenstam, E., Hjern, A., Bodén, R., & Reutfors, J. (2014). Suicide in first episode psychosis: A nationwide cohort study. *Schizophrenia Research*, **157**(1–3), 1–7. https://doi.org/10.1016/j.schres.2014.05.010.

Bromet, E. J., Kotov, R., Fochtmann, L. J., Carlson, G. A., Tanenberg-Karant, M., Ruggero, C., & Chang, S. W. (2011). Diagnostic shifts during the decade following first admission for psychosis. *The American Journal of Psychiatry*, **168**(11), 1186–1194. https://doi.org/10.1176/appi.ajp.2011.11010048.

Brown, S. (1997). Excess mortality of schizophrenia. A meta-analysis. *The British Journal of Psychiatry*, **171**, 502–508. https://doi.org/10.1192/bjp.171.6.502.

Census and Statistics Department. (2024). *The mortality trend in Hong Kong, 1991 to 2022*. Hong Kong: Census and Statistics Department. https://www.censtatd.gov.hk/en/data/stat_report/product/FA100094/att/B72401FA2024XXXXB0100.pdf

Chai, Y., Tang, J. Y., Ma, D. C. F., Luo, H., & Chan, S. K. W. (2024). Self-harm and suicide rates before and after an early intervention program for patients with first-episode schizophrenia. *JAMA Network Open*, **7**(8), e2426795. https://doi.org/10.1001/jamanetworkopen.2024.26795.

Chan, S. K., So, H. C., Hui, C. L., Chang, W. C., Lee, E. H., Chung, D. W., Tso, S., Hung, S. F., Yip, K. C., Dunn, E., & Chen, E. Y. (2015). 10-year outcome study of an early intervention program for psychosis compared with standard care service. *Psychological Medicine*, **45**(6), 1181–1193. https://doi.org/10.1017/s0033291714002220.

Chan, S. K. W., Chan, S. W. Y., Pang, H. H., Yan, K. K., Hui, C. L. M., Chang, W. C., Lee, E. H. M., & Chen, E. Y. H. (2018). Association of an early intervention service for psychosis with suicide rate among patients with first-episode schizophrenia-spectrum disorders. *JAMA Psychiatry*, **75**(5), 458–464. https://doi.org/10.1001/jamapsychiatry.2018.0185.

Charlson, M. E., Carrozzino, D., Guidi, J., & Patierno, C. (2022). Charlson comorbidity index: A critical review of Clinimetric properties. *Psychotherapy and Psychosomatics*, **91**(1), 8–35. https://doi.org/10.1159/000521288.

Chen, E. (2004). Developing an early intervention service in Hong Kong. In *Best Care in Early Psychosis Intervention: Global Perspectives* (pp. 125–130). Taylor & Francis

Chen, E. Y., Tang, J. Y., Hui, C. L., Chiu, C. P., Lam, M. M., Law, C. W., Yew, C. W., Wong, G. H., Chung, D. W., Tso, S., Chan, K. P., Yip, K. C., Hung, S. F., & Honer, W. G. (2011). Three-year outcome of phase-specific early intervention for first-episode psychosis: A cohort study in Hong Kong. *Early Intervention in Psychiatry*, **5**(4), 315–323. https://doi.org/10.1111/j.1751-7893.2011.00279.x.

Cheng, C. M., Chang, W. H., Tsai, S. J., Li, C. T., Tsai, C. F., Bai, Y. M., Lin, W. C., Su, T. P., Chen, T. J., & Chen, M. H. (2023). Risk of all-cause and suicide death in patients with schizophrenia: An entire-population longitudinal study in Taiwan. *The Journal of Clinical Psychiatry*, **84**(6). https://doi.org/10.4088/JCP.22m14747.

Chesney, E., Goodwin, G. M., & Fazel, S. (2014). Risks of all-cause and suicide mortality in mental disorders: A meta-review. *World Psychiatry*, **13**(2), 153–160. https://doi.org/10.1002/wps.20128.

Correll, C. U., Solmi, M., Croatto, G., Schneider, L. K., Rohani-Montez, S. C., Fairley, L., Smith, N., Bitter, I., Gorwood, P., Taipale, H., & Tiihonen, J. (2022). Mortality in people with schizophrenia: A systematic review and meta-analysis of relative risk and aggravating or attenuating factors. *World Psychiatry*, **21**(2), 248–271. https://doi.org/10.1002/wps.20994.

Correll, C. U., Solmi, M., Veronese, N., Bortolato, B., Rosson, S., Santonastaso, P., Thapa-Chhetri, N., Fornaro, M., Gallicchio, D., Collantoni, E., Pigato, G., Favaro, A., Monaco, F., Kohler, C., Vancampfort, D., Ward, P. B., Gaughran, F., Carvalho, A. F., & Stubbs, B. (2017). Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: A large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. *World Psychiatry*, **16**(2), 163–180. https://doi.org/10.1002/wps.20420.

Crump, C., Winkleby, M. A., Sundquist, K., & Sundquist, J. (2013). Comorbidities and mortality in persons with schizophrenia: A Swedish national cohort study. *The American Journal of Psychiatry*, **170**(3), 324–333. https://doi.org/10.1176/appi.ajp.2012.12050599.

Dayabandara, M., Hanwella, R., Ratnatunga, S., Seneviratne, S., Suraweera, C., & de Silva, V. A. (2017). Antipsychotic-associated weight gain: Management strategies and impact on treatment adherence. *Neuropsychiatric Disease and Treatment*, **13**, 2231–2241. https://doi.org/10.2147/ndt.S113099.

De Hert, M., Detraux, J., van Winkel, R., Yu, W., & Correll, C. U. (2011). Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nature Reviews. Endocrinology*, **8**(2), 114–126. https://doi.org/10.1038/nrendo.2011.156.

Dickerson, F., Khan, S., Origoni, A., Rowe, K., Katsafanas, E., Harvin, A., Yang, S., & Yolken, R. (2024). Risk factors for natural cause mortality in schizophrenia. *JAMA Network Open*, **7**(9), e2432401. https://doi.org/10.1001/jamanetworkopen.2024.32401.

Doyle, R., O'Keeffe, D., Hannigan, A., Kinsella, A., Behan, C., Kelly, A., Sheridan, A., Madigan, K., Lawlor, E., & Clarke, M. (2019). The iHOPE-20 study: Mortality in first episode psychosis-a 20-year follow-up of the Dublin first episode cohort. *Social Psychiatry and Psychiatric Epidemiology*, **54**(11), 1337–1342. https://doi.org/10.1007/s00127-019-01721-x.

Gábor, J. S., Maria, L. R., & Nail, K. B. (2007). Measuring and testing dependence by correlation of distances. *The Annals of Statistics*, **35**(6), 2769–2794. https://doi.org/10.1214/009053607000000505.

Goldman, H. H., Skodol, A. E., & Lave, T. R. (1992). Revising axis V for DSM-IV: A review of measures of social functioning. *The American Journal of Psychiatry*, **149**(9), 1148–1156. https://doi.org/10.1176/ajp.149.9.1148.

Haddad, P. M., Brain, C., & Scott, J. (2014). Nonadherence with antipsychotic medication in schizophrenia: Challenges and management strategies. *Patient Relat Outcome Meas*, **5**, 43–62. https://doi.org/10.2147/prom.S42735.

Haro, J. M., Kamath, S. A., Ochoa, S., Novick, D., Rele, K., Fargas, A., Rodríguez, M. J., Rele, R., Orta, J., Kharbeng, A., Araya, S., Gervin, M., Alonso, J., Mavreas, V., Lavrentzou, E., Liontos, N., Gregor, K., & Jones, P. B. (2003). The clinical global impression-schizophrenia scale: A simple instrument to measure the diversity of symptoms present in schizophrenia. *Acta psychiatrica Scandinavica. Supplementum* (416), 16–23. https://doi.org/10.1034/j.1600-0447.107.s416.5.x

Harrow, M., Jobe, T. H., Faull, R. N., & Yang, J. (2017). A 20-year multi-followup longitudinal study assessing whether antipsychotic medications contribute to work functioning in schizophrenia. *Psychiatry Research*, **256**, 267–274. https://doi.org/10.1016/j.psychres.2017.06.069.

Hawton, K., Sutton, L., Haw, C., Sinclair, J., & Deeks, J. J. (2005). Schizophrenia and suicide: Systematic review of risk factors. *The British Journal of Psychiatry*, **187**, 9–20. https://doi.org/10.1192/bjp.187.1.9.

Henderson, D. C., Vincenzi, B., Andrea, N. V., Ulloa, M., & Copeland, P. M. (2015). Pathophysiological mechanisms of increased cardiometabolic risk in people with schizophrenia and other severe mental illnesses. *Lancet Psychiatry*, **2**(5), 452–464. https://doi.org/10.1016/s2215-0366(15)00115-7.

Hor, K., & Taylor, M. (2010). Suicide and schizophrenia: A systematic review of rates and risk factors. *Journal of Psychopharmacology*, **24**(4 Suppl), 81–90. https://doi.org/10.1177/1359786810385490

Kallio, M., Korkeila, J., Malmberg, M., Gunn, J., Rautava, P., Korhonen, P., & Kytö, V. (2022). Impaired long-term outcomes of patients with schizophrenia spectrum disorder after coronary artery bypass surgery: Nationwide case-control study. *BJPsych Open*, **8**(2), e48. https://doi.org/10.1192/bjo.2022.10.

Koutsouleris, N., Kahn, R. S., Chekroud, A. M., Leucht, S., Falkai, P., Wobrock, T., Derks, E. M., Fleischhacker, W. W., & Hasan, A. (2016). Multisite prediction of 4-week and 52-week treatment outcomes in patients with first-episode psychosis: A machine learning approach. *Lancet Psychiatry*, **3**(10), 935–946. https://doi.org/10.1016/s2215-0366(16)30171-7.

Lau, J. T., Kim, J. H., & Tsui, H. Y. (2005). Prevalence, health outcomes, and patterns of psychotropic substance use in a Chinese population in Hong Kong: A population-based study. *Substance Use & Misuse*, **40**(2), 187–209. https://doi.org/10.1081/ja-200048454.

Laursen, T. M., Nordentoft, M., & Mortensen, P. B. (2014). Excess early mortality in schizophrenia. *Annual Review of Clinical Psychology*, **10**, 425–448. https://doi.org/10.1146/annurev-clinpsy-032813-153657.

Lawrence, D., & Kisely, S. (2010). Inequalities in healthcare provision for people with severe mental illness. *Journal of Psychopharmacology*, **24**(4 Suppl), 61–68. https://doi.org/10.1177/1359786810382058

Lieslehto, J., Tiihonen, J., Lähteenvuo, M., Leucht, S., Correll, C. U., Mittendorfer-Rutz, E., Tanskanen, A., & Taipale, H. (2024). Development and validation of a machine learning-based model of mortality risk in first-episode psychosis. *JAMA Network Open*, **7**(3), e240640. https://doi.org/10.1001/jamanetworkopen.2024.0640.

*Life Expectancy by Country 2025*. (2025). W. P. Review. https://worldpopulationreview.com/country-rankings/life-expectancy-by-country

Lomholt, L. H., Andersen, D. V., Sejrsgaard-Jacobsen, C., Øzdemir, C. M., Graff, C., Schjerning, O., Jensen, S. E., Straszek, S. P. V., Licht, R. W., Grøntved, S., & Nielsen, R. E. (2019). Mortality rate trends in patients diagnosed with schizophrenia or bipolar disorder: A nationwide study with 20 years of follow-up. *International Journal of Bipolar Disorders*, **7**(1), 6. https://doi.org/10.1186/s40345-018-0140-x.

Melle, I., Olav Johannesen, J., Haahr, U. H., Ten Velden Hegelstad, W., Joa, I., Langeveld, J., Larsen, T. K., Ilner Opjordsmoen, S., Qin, P., Ivar Røssberg, J., Rishovd Rund, B., Simonsen, E., Vaglum, P. J. W., McGlashan, T. H., & Friis,

S. (2017). Causes and predictors of premature death in first-episode schizophrenia spectrum disorders. *World Psychiatry*, **16**(2), 217–218. https://doi.org/10.1002/wps.20431.

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biological Psychiatry*, **70**(7), 663–671. https://doi.org/10.1016/j.biopsych.2011.04.013.

Morgan, C., Fearon, P., Lappin, J., Heslin, M., Donoghue, K., Lomas, B., Reininghaus, U., Onyejiaka, A., Croudace, T., Jones, P. B., Murray, R. M., Doody, G. A., & Dazzan, P. (2017). Ethnicity and long-term course and outcome of psychotic disorders in a UK sample: The ÆSOP-10 study. *The British Journal of Psychiatry*, **211**(2), 88–94. https://doi.org/10.1192/bjp.bp.116.193342.

Nasrallah, H. A., Meyer, J. M., Goff, D. C., McEvoy, J. P., Davis, S. M., Stroup, T. S., & Lieberman, J. A. (2006). Low rates of treatment for hypertension, dyslipidemia and diabetes in schizophrenia: Data from the CATIE schizophrenia trial sample at baseline. *Schizophrenia Research*, **86**(1–3), 15–22. https://doi.org/10.1016/j.schres.2006.06.026.

Nordentoft, M., Wahlbeck, K., Hällgren, J., Westman, J., Osby, U., Alinaghizadeh, H., Gissler, M., & Laursen, T. M. (2013). Excess mortality, causes of death and life expectancy in 270,770 patients with recent onset of mental disorders in Denmark, Finland and Sweden. *PLoS One*, **8**(1), e55176. https://doi.org/10.1371/journal.pone.0055176.

Nosè, M., Tansella, M., Thornicroft, G., Schene, A., Becker, T., Veronese, A., Leese, M., Koeter, M., Angermeyer, M., & Barbui, C. (2008). Is the defined daily dose system a reliable tool for standardizing antipsychotic dosages? *International Clinical Psychopharmacology*, **23**(5), 287–290. https://doi.org/10.1097/YIC.0b013e328303ac75.

Osborn, D. P., King, M. B., & Nazareth, I. (2003). Participation in screening for cardiovascular risk by people with schizophrenia or similar mental illnesses: Cross sectional study in general practice. *BMJ*, **326**(7399), 1122–1123. https://doi.org/10.1136/bmj.326.7399.1122.

Peralta, D., Janda, L., de Jalón, E., Moreno-Izco, L., Sánchez-Torres, A. M., Cuesta, M. J., & Peralta, V. (2024). Long-term diagnostic stability, predictors of diagnostic change, and time until diagnostic change of first-episode psychosis: A 21-year follow-up study. *Psychological Medicine*, **54**(7), 1329–1338. https://doi.org/10.1017/s0033291723003173.

Perry, B. I., Osimo, E. F., Upthegrove, R., Mallikarjun, P. K., Yorke, J., Stochl, J., Perez, J., Zammit, S., Howes, O., Jones, P. B., & Khandaker, G. M. (2021). Development and external validation of the psychosis metabolic risk calculator (PsyMetRiC): A cardiometabolic risk prediction algorithm for young people with psychosis. *Lancet Psychiatry*, **8**(7), 589–598. https://doi.org/10.1016/s2215-0366(21)00114-0.

Plana-Ripoll, O., Pedersen, C. B., Agerbo, E., Holtz, Y., Erlangsen, A., Canudas-Romo, V., Andersen, P. K., Charlson, F. J., Christensen, M. K., Erskine, H. E., Ferrari, A. J., Iburg, K. M., Momen, N., Mortensen, P. B., Nordentoft, M., Santomauro, D. F., Scott, J. G., Whiteford, H. A., Weye, N., & Laursen, T. M. (2019). A comprehensive analysis of mortality-related health metrics associated with mental disorders: A nationwide, register-based cohort study. *Lancet*, **394**(10211), 1827–1835. https://doi.org/10.1016/s0140-6736(19)32316-5.

Ray, W. A., Chung, C. P., Murray, K. T., Hall, K., & Stein, C. M. (2009). Atypical antipsychotic drugs and the risk of sudden cardiac death. *The New England Journal of Medicine*, **360**(3), 225–235. https://doi.org/10.1056/NEJMoa0806994.

Robinson, J., Harris, M. G., Harrigan, S. M., Henry, L. P., Farrelly, S., Prosser, A., Schwartz, O., Jackson, H., & McGorry, P. D. (2010). Suicide attempt in first-episode psychosis: A 7.4 year follow-up study. *Schizophrenia Research*, **116**(1), 1–8. https://doi.org/10.1016/j.schres.2009.10.009.

Saha, S., Chant, D., & McGrath, J. (2007). A systematic review of mortality in schizophrenia: Is the differential mortality gap worsening over time? *Archives of General Psychiatry*, **64**(10), 1123–1131. https://doi.org/10.1001/archpsyc.64.10.1123.

Santesteban-Echarri, O., Paino, M., Rice, S., González-Blanch, C., McGorry, P., Gleeson, J., & Alvarez-Jimenez, M. (2017). Predictors of functional recovery in first-episode psychosis: A systematic review and meta-analysis of longitudinal studies. *Clinical Psychology Review*, **58**, 59–75. https://doi.org/10.1016/j.cpr.2017.09.007.

Sek, A. C., Cheung, N. T., Choy, K. M., Wong, W. N., Tong, A. Y., Fung, V. H., Fung, M., & Ho, E. (2007). A territory-wide electronic health record--from concept to practicality: The Hong Kong experience. *Studies in Health Technology and Informatics*, **129**(Pt 1), 293–296.

Simon, G. E., Stewart, C., Yarborough, B. J., Lynch, F., Coleman, K. J., Beck, A., Operskalski, B. H., Penfold, R. B., & Hunkeler, E. M. (2018). Mortality rates after the first diagnosis of psychotic disorder in adolescents and young adults. *JAMA Psychiatry*, **75**(3), 254–260. https://doi.org/10.1001/jamapsychiatry.2017.4437.

Sokal, R. R. (1992). Randomization and Monte Carlo methods in biology. Bryan F. J. Manly. *The Quarterly Review of Biology*, **67**(3), 419–420. https://doi.org/10.1086/417783

Starzer, M. S. K., Hansen, H. G., Hjorthøj, C., Speyer, H., Albert, N., & Nordentoft, M. (2023). Predictors of mortality following a schizophrenia Spectrum diagnosis: Evidence from the 20-year follow-up of the OPUS randomized controlled trial. *Schizophrenia Bulletin*, **49**(5), 1256–1268. https://doi.org/10.1093/schbul/sbad111.

Stephens, J. H., Richard, P., & McHugh, P. R. (1999). Suicide in patients hospitalized for schizophrenia: 1913–1940. *The Journal of Nervous and Mental Disease*, **187**(1), 10–14. https://doi.org/10.1097/00005053-199901000-00003.

Taipale, H., Tanskanen, A., Mehtälä, J., Vattulainen, P., Correll, C. U., & Tiihonen, J. (2020). 20-year follow-up study of physical morbidity and mortality in relationship to antipsychotic treatment in a nationwide cohort of 62,250 patients with schizophrenia (FIN20). *World Psychiatry*, **19**(1), 61–68. https://doi.org/10.1002/wps.20699.

Tanskanen, A., Tiihonen, J., & Taipale, H. (2018). Mortality in schizophrenia: 30-year nationwide follow-up study. *Acta Psychiatrica Scandinavica*, **138**(6), 492–499. https://doi.org/10.1111/acps.12913.

Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., & Haukka, J. (2009). 11-year follow-up of mortality in patients with schizophrenia: A population-based cohort study (FIN11 study). *Lancet*, **374**(9690), 620–627. https://doi.org/10.1016/s0140-6736(09)60742-x.

Tiihonen, J., Suokas, J. T., Suvisaari, J. M., Haukka, J., & Korhonen, P. (2012). Polypharmacy with antipsychotics, antidepressants, or benzodiazepines and mortality in schizophrenia. *Archives of General Psychiatry*, **69**(5), 476–483. https://doi.org/10.1001/archgenpsychiatry.2011.1532.

Tsai, S. P., Hardy, R. J., & Wen, C. P. (1992). The standardized mortality ratio and life expectancy. *American Journal of Epidemiology*, **135**(7), 824–831. https://doi.org/10.1093/oxfordjournals.aje.a116369.

Tse, W., Khandaker, G. M., Zhou, H., Luo, H., Yan, W. C., Siu, M. W., Poon, L. T., Lee, E. H. M., Zhang, Q., Upthegrove, R., Osimo, E. F., Perry, B. I., & Chan, S. K. W. (2024). Assessing the generalisability of the psychosis metabolic risk calculator (PsyMetRiC) for young people with first-episode psychosis with validation in a Hong Kong Chinese Han population: A 4-year follow-up study. *The Lancet Regional Health - Western Pacific*, **47**, 101089. https://doi.org/10.1016/j.lanwpc.2024.101089.

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gøtzsche, P. C., & Vandenbroucke, J. P. (2007). Strengthening the reporting of observational studies in epidemiology (STROBE) statement: Guidelines for reporting observational studies. *BMJ*, **335**(7624), 806–808. https://doi.org/10.1136/bmj.39335.541782.AD.

von Neumann, J., Kent, R. H., Bellinson, H. R., & Hart, B. I. (1941). The mean square successive difference. *Annals of Mathematical Statistics*, **12**, 153–162.

Wahlbeck, K., Westman, J., Nordentoft, M., Gissler, M., & Laursen, T. M. (2011). Outcomes of Nordic mental health systems: Life expectancy of patients with mental disorders. *The British Journal of Psychiatry*, **199**(6), 453–458. https://doi.org/10.1192/bjp.bp.110.085100.

Weinmann, S., Read, J., & Aderhold, V. (2009). Influence of antipsychotics on mortality in schizophrenia: Systematic review. *Schizophrenia Research*, **113**(1), 1–11. https://doi.org/10.1016/j.schres.2009.05.018.

Wong, T. Y., Luo, H., Tang, J., Moore, T. M., Gur, R. C., Suen, Y. N., Hui, C. L. M., Lee, E. H. M., Chang, W. C., Yan, W. C., Chui, E., Poon, L. T., Lo, A., Cheung, K. M., Kan, C. K., Chen, E. Y. H., & Chan, S. K. W. (2024). Development of an individualized risk calculator of treatment resistance in patients with first-episode psychosis (TRipCal) using automated machine learning: A 12-year follow-up study with clozapine prescription as a proxy indicator. *Translational Psychiatry*, **14**(1), 50. https://doi.org/10.1038/s41398-024-02754-w.

Yuen, K., Harrigan, S. M., Mackinnon, A. J., Harris, M. G., Yuen, H. P., Henry, L. P., Jackson, H. J., Herrman, H., & McGorry, P. D. (2014). Long-term follow-up of all-cause and unnatural death in young people with first-episode psychosis. *Schizophrenia Research*, **159**(1), 70–75. https://doi.org/10.1016/j.schres.2014.07.042.

Zhou, H., Tang, J. Y. M., Chan, S. K. W., & Luo, H. (2025). The reliability of medication and death recording in electronic health records among people with schizophrenia in Hong Kong. *Asian Journal of Psychiatry*, **103**, 104315. https://doi.org/10.1016/j.ajp.2024.104315.

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