

Twenty-five year mortality of a community cohort with schizophrenia

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Background

People with schizophrenia have significantly raised mortality but we do not know how these mortality patterns in the UK have changed since the 1990s.

Aims

To measure the 25-year mortality of people with schizophrenia with particular focus on changes over time.

Method

Prospective record linkage study of the mortality of a community cohort of 370 people with schizophrenia.

Results

The cohort had an all-cause standardised mortality ratio of 289 (95% CI 247–337). Most deaths were from the common causes seen in the general population. Unnatural deaths

were concentrated in the first 5 years of follow-up. There was an indication that cardiovascular mortality may have increased relative to the general population ($P=0.053$) over the course of the study.

Conclusions

People with schizophrenia have a mortality risk that is two to three times that of the general population. Most of the extra deaths are from natural causes. The apparent increase in cardiovascular mortality relative to the general population should be of concern to anyone with an interest in mental health.

Declaration of interest

None.

Mortality is the most robust outcome measure of medical disease and hence a gold standard of clinical performance. It is an important outcome indicator in respect of mental health, where policies and services are judged, among other things, by their effectiveness in reducing suicide rates. Unnatural deaths, however, give only a partial picture of the life expectancy of a vulnerable population. Natural deaths are less dramatic but every bit as final. The excess mortality of people with schizophrenia is a consistent finding in studies of different populations, different continents and different eras.^{1–3} The pattern of mortality suggests that the excess unnatural deaths are intrinsic to the disease and the excess natural deaths best explained by altered exposure to environmental risk factors.⁴ Service planners will hope that changes in treatment such as the move from asylum to community-based services and the introduction of atypical antipsychotic drugs will improve the mortality of people with schizophrenia. Evidence from Scandinavia^{5–7} however suggests that the mortality of people with schizophrenia, especially the mortality from cardiovascular disease, increased between the 1970s and the mid-1990s. We do not know if the same trend occurred in the UK. This paper describes the 25-year follow-up of an English community cohort with schizophrenia, recruited in 1981–1982. It examines overall mortality, and mortality from particular categories and causes of disease as well as changes in mortality over that period.

Method

The cohort comprised all Southampton residents aged 16–65 with schizophrenia and living outside hospital, who had contact with the local National Health Service (NHS) psychiatric services between 1 January 1981 and 31 January 1982 ($n=370$).⁸ Potential participants were included if they had: a ‘firm diagnosis of schizophrenia’ made by the responsible consultant; case-note evidence of first-rank symptoms of schizophrenia or persistent non-affective delusions or auditory hallucinations, in the absence of organic brain disease; and misuse of alcohol or other substance.

An analysis of the cohort up to 31 December 1994 has been reported.⁹ Using identical methodology, we now present an analysis of the follow-up to 31 August 2006, the midpoint of the twenty-fifth year following recruitment. Participants were classified as alive, dead or untraced, based on the database of the Office of National Statistics.¹⁰ Vital status was then checked through Hampshire Partnership NHS Trust case notes, general practitioner or mental health worker. Participants were classified as alive if there was independent confirmation of contact since the census date. Death was confirmed by death certificate or other official document. Participants were otherwise classified as untraced and were included in the follow-up analysis until the date they were lost. The study had ethics approval from the Southampton and South West Hampshire research ethics committee.

Statistical analysis

The person-years-at-risk were calculated according to the following variables: calendar year (1981–2006), gender, age category (15–19, 20–24, 25–29, 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80–84, and ≥ 85 years). The person-years-at-risk were then multiplied by the corresponding mortality rates for England and Wales,¹⁰ thus producing the expected number of deaths for each year/gender/age-specific stratum.¹¹

The standardised mortality ratio (SMR) was obtained by dividing the number of deaths observed by the number of deaths expected, and multiplying this ratio by 100. An increased SMR is statistically significantly elevated at the 5% level of significance when the lower limit of the 95% confidence interval (CI) is greater than 100.¹²

Standardised mortality ratio were calculated for all causes, for particular ICD^{13,14} categories of disease and for specific diseases where more than two deaths were observed. The change in SMR over the study period was analysed by computing SMRs for each 5 years of follow-up. Comparisons between SMRs and tests for

trend were performed using Poisson regression. Poisson regression was also used to explore internal relationships in the data independent of the national population rates.

Results

All-cause mortality (ICD-9 001-999, ICD-10 A01-Y99)

The cohort comprised 213 males and 157 females at recruitment. The vital status of 363 (98%) individuals was established on the census date (31 August 2006). A total of 193 were confirmed to be alive, 6 were recorded as alive on the Office for National Statistics database but not independently confirmed, 7 were untraced and 164 deaths were recorded. Of these deaths, 141 were from natural causes and 21 from unnatural causes. Two deaths were from unknown causes; one abroad and one where the death certificate could not be traced.

The mean age at death of males was significantly lower than that of the females (57.3 *v.* 65.5 years, $t=4.3$, *d.f.*=162, $P<0.001$). This difference remained when unnatural deaths were excluded from the analysis (males 60.4 years *v.* females 67.3 years, $t=4.2$, *d.f.*=139, $P<0.001$). The all-cause SMR was 289 (95% CI 247–337), a threefold increase in mortality compared with the population of England and Wales (Table 1). Approximately 81% of the excess mortality was from natural causes and 17% from unnatural causes (2% of deaths were undetermined). The all-cause SMR was higher in males, the unemployed, the unmarried and people from lower social classes, but none of these differences were statistically significant. The internal analysis showed that all-cause

mortality was higher in males than females, but there were no statistically significant differences when examining unemployment, marital status and social class.

Cause of death

The SMR was increased in most major disease categories (Table 1) but is only presented for disease categories where more than five deaths were reported. Individual categories showed apparent gender differences but only that for respiratory diseases was statistically significant ($P=0.03$). The most significant contributions to the overall excess mortality came from circulatory diseases (ICD-9 390–459, ICD-10 I00–I99), which accounted for 33% and respiratory diseases (ICD-9 460–519, ICD-10 J00–J99), which accounted for a further 19%.

We also examined specific causes of death where the numbers exceeded two. Of 30 cancer deaths, 13 were from lung cancer (SMR=265, 95% CI 141–453), 4 from female breast cancer (SMR=196, 95% CI 54–503), the remaining deaths attributed to various types of cancer. The SMRs for suicide, diabetes, pneumonia and chronic obstructive airways disease were strikingly elevated (Table 2).

Smoking-related mortality

A total of 73% ($n=193$) of the cohort, for whom smoking status was recorded ($n=266$), were cigarette smokers at the outset of the study. This was more than twice the contemporary general

Table 1 Mortality between 1981 and 2006 of a community cohort of 370 people with schizophrenia by category of disease (ICD-9 and ICD-10), showing observed deaths, standardised mortality ratios (SMRs) and 95% CIs, by gender, for those disease categories where there were five or more deaths

Cause of death (ICD-9, ICD-10)	Male		Female		Total	
	Observed, <i>n</i>	SMR (95% CI)	Observed, <i>n</i>	SMR (95% CI)	Observed, <i>n</i>	SMR (95% CI)
Neoplasms (140–239, C00–D48)	20	193 (118–298)	10	102 (49–188)	30	149 (100–212)
Endocrine disease (420–297, E00–E99)	2	443 (54–1601)	5	1184 (384–2763)	7	801 (322–1651)
Nervous diseases (320–389, G00–G99)	3	498 (103–1456)	2	352 (43–1270)	5	427 (139–996)
Circulatory diseases (390–459, I00–I99)	35	269 (187–374)	22	241 (151–365)	57	258 (195–334)
Respiratory disease ^a (460–519, J00–J99)	7	270 (108–556)	19	726 (437–1133)	26	499 (326–731)
Digestive diseases (520–579, K00–K99)	4	298 (81–764)	3	278 (57–812)	7	289 (116–596)
Natural deaths (0–799, A00–R99)	76	258 (203–323)	65	262 (202–334)	141	260 (219–306)
Unnatural deaths (E800–999, V00–Y99)	14	775 (424–1300)	7	1071 (431–2207)	21	854 (529–1305)
All causes (0–999, A00–Y99)	92	294 (237–361)	72	283 (221–356)	164	289 (247–337)

a. *P* for difference between SMRs for males and females 0.03.

Table 2 Mortality between 1981 and 2006 of a community cohort of 370 people with schizophrenia by cause of death (ICD-9 and ICD-10), showing observed deaths, standardised mortality ratios (SMRs) and 95% CIs, for those diseases where there were three or more deaths

Cause of death	ICD-9 ¹³	ICD-10 ¹⁴	Observed, <i>n</i>	SMR (95%)
Lung cancer	162	C33–C34	13	265 (141–453)
Breast cancer (females)	174	C50	4	196 (54–503)
Diabetes mellitus	250	E10–E14	4	614 (167–1573)
Cardiovascular disease	390–429	I00–I52	37	225 (159–311)
Cerebrovascular disease	430–438	I60–I69	13	308 (164–527)
Pneumonia	480–487	J09–J18	15	835 (467–1377)
Chronic obstructive airways disease	490–494, 496	J40–J47	11	394 (197–705)
Accident	E800–949	V01–X59	4	307 (84–786)
Suicide	E950–959	X60–X84	14	1818 (994–3051)
Undetermined	E980–989	Y10–Y34	3	928 (191–2713)

population prevalence (35%).¹⁵ The SMR among cigarette smokers was significantly higher than among non-smokers (SMR = 379, 95% CI 311–459 *v.* SMR = 194, 95% CI 125–286, $P=0.002$) and the internal analysis showed that mortality in smokers was more than double that in non-smokers (relative risk (RR) = 2.16, 95% CI 1.31–3.59). Ninety-five deaths were from diseases caused by cigarette smoking,¹⁵ an SMR of 275 (95% CI 222–336). Smoking-related diseases accounted for 70% of the excess natural mortality in the cohort.

Time trends in mortality

Table 3 and Figures 1–4 show the time trends in mortality from all causes and various major disease categories.

The all-cause SMR showed small but non-significant changes between 1981 and 2006, falling in the first 5 years then rising slightly from 264 (95% CI 174–384) in 1986–91 to 292 (95% CI 212–392) in 2001–6 ($P=0.6$). This was produced by the aggregate effect of a non-significant ($P=0.3$) increase in the natural cause SMR between 1981–6 and 2001–6 from 196 (95% CI 105–336) to 280 (95% CI 201–380), and a large and statistically significant ($P=0.001$) fall in the unnatural cause SMR from 2482 (95% CI 1357–4164) to 472 (95% CI 57–1705) over the same time period (Table 3). The excess unnatural cause SMR was largely a result of suicide (Table 2), which fell significantly ($P=0.002$) over time. The internal analysis also revealed significant negative trends with time for suicide and unnatural deaths ($P=0.002$ for both causes).

The SMR for cardiovascular diseases increased over the study period from 129 (95% CI 27–377) in 1981–6 to 350 (95% CI 186–598) in 2001–6. This trend was of borderline statistical significance ($P=0.053$). The internal analysis showed no significant trend for this cause ($P=0.3$), although using the period 1991–96 as the baseline, the relative risks rose monotonically from 0.76 (95% CI 0.19–3.12) for 1981–86 to 1.52 (95% CI 0.57–4.07) for 2001–6. There were no consistent trends in the other disease categories where more than ten deaths were observed, either examining the SMRs or using an internal analysis.

Discussion

These results support previous findings that people with schizophrenia have a mortality of between two and three times that of the general population, and that most of the excess deaths are from diseases that are the major causes of death in the general population. They indicate that the increased mortality risk is probably lifelong and suggest that the cardiovascular mortality of schizophrenia has increased over the past 25 years relative to the general population. A large part of the excess mortality can probably be attributed to the effects of cigarette smoking.

Strengths and weaknesses

The recruitment process missed people with unrecognised schizophrenia and those who avoided service contact during the index year, but was representative of Southampton residents with schizophrenia living outside hospital and known to local mental health services in 1981–82. People living in the local long-stay hospital and those with a concurrent diagnosis of substance misuse were deliberately excluded, to yield a community cohort of people with uncomplicated disease.⁸ The Southampton mental health services were typical of contemporary services, hence the cohort is probably representative of people with schizophrenia who were engaged with mental health services in the early 1980s. The use of a cohort recruited 25 years ago inevitably means that the experience described here may differ from that of people diagnosed more recently.

Ascertainment was more rigorous than in most comparable studies as status was independently checked. Loss to follow-up was small and comparable with that in similar recent studies. Death certificates were matched to NHS central records, using family and given name, date and place of birth, place of death and NHS number where known. The death certificate causes of death are probably more accurate than in the general population, because rates of post-mortem examination (54% *v.* 22%) and coroner's inquest (15% *v.* 6%) were higher than the national

Table 3 Cause of death of 164 people with schizophrenia with observed deaths (in brackets), standardised mortality ratios (SMRs) and 95% CI, for each 5-years of follow-up, for those disease categories where more than ten deaths were reported

Cause of death (ICD-9, ICD-10)	Follow-up period (calendar years)										χ^2 test for SMR time trend, P
	1981–1986		1986–1991		1991–1996		1996–2001		2001–2006		
	SMR (observed, n)	95% CI	SMR (observed, n)	95% CI	SMR (observed, n)	95% CI	SMR (observed, n)	95% CI	SMR (observed, n)	95% CI	
Neoplasms (140–239, C00–D48)	157 (4)	43–401	161 (6)	59–351	142 (6)	52–309	138 (6)	50–299	150 (8)	65–296	0.9
Circulatory diseases (390–459, I00–I99)	136 (4)	37–348	261 (11)	130–466	275 (13)	146–470	228 (11)	114–408	332 (18)	197–525	0.2
Cardiovascular disease (390–429, I00–I52)	129 (3)	27–377	183 (6)	67–398	168 (6)	62–366	256 (9)	117–485	350 (13)	186–598	0.053
Respiratory disease (460–519, J00–J99)	435 (2)	53–1571	0 (0)	0–552	491 (5)	160–1147	907 (13)	483–1552	367 (6)	135–798	0.4
Suicide (E950–959, X60–X84)	6110 (12)	3157–10 673	0 (0)	0–1981	1276 (2)	154–4608	0 (0)	0–3041	0 (0)	0–3380	0.002
Natural deaths (0–799, A00–R99)	196 (13)	105–336	259 (25)	167–382	241 (27)	159–350	289 (35)	201–402	280 (41)	201–380	0.3
Unnatural deaths (E800–999, V00–Y99)	2482 (14)	1357–4164	352 (2)	43–1270	620 (3)	128–1812	0 (0)	0–880	472 (2)	57–1705	0.001
All causes (0–999, A00–Y99)	376 (27)	248–547	264 (27)	174–384	265 (31)	180–376	279 (35)	195–388	292 (44)	212–392	0.6

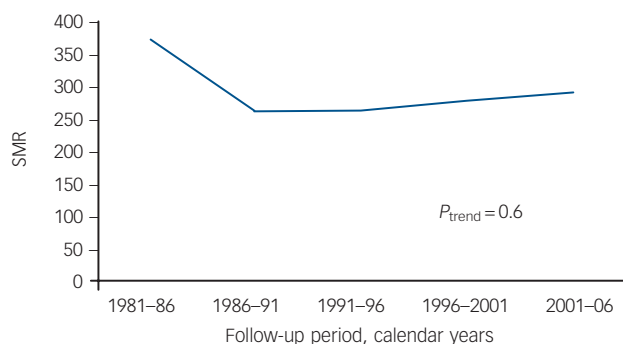


Fig. 1 Changes in all-cause standardised mortality ratios (SMRs) in 5-year periods of a community cohort of 370 people followed over 25 years.

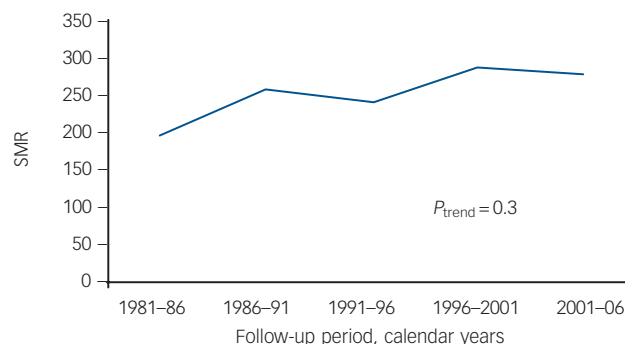


Fig. 3 Changes in natural cause standardised mortality ratios (SMRs) in 5-year periods of a community cohort of 370 people followed over 25 years.

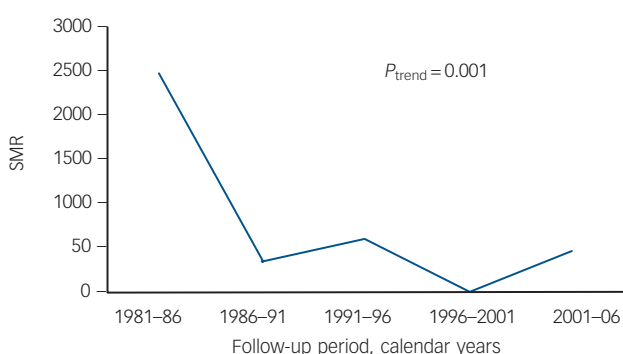


Fig. 2 Changes in unnatural cause standardised mortality ratios (SMRs) in 5-year periods of a community cohort of 370 people followed over 25 years.

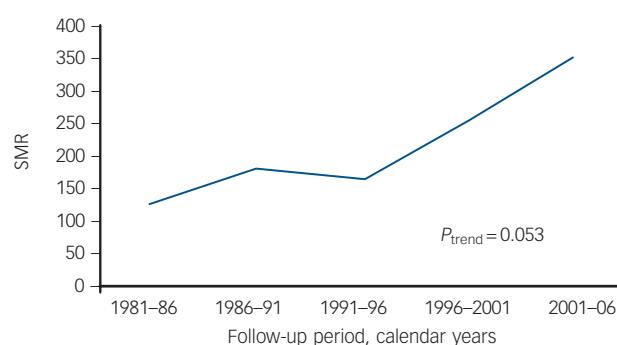


Fig. 4 Changes in cardiovascular disease standardised mortality ratios (SMRs) in 5-year periods of a community cohort of 370 people followed over 25 years.

average.¹⁶ Schizophrenia was mentioned as a contributory cause of death on nine (5%) certificates.

The strengths of this study are the longest follow-up period of recent studies on schizophrenia mortality, the completeness of follow-up and the cross-checking of status. The main weaknesses are the use of a relatively small local cohort that may limit generalisation and the use of a prevalence rather than an incidence cohort. This meant that all but 27 participants had already survived the period of greatest excess mortality at recruitment, an issue which is probably more relevant to unnatural mortality, which is concentrated early in the disease,^{17,18} than to natural mortality. The exclusion of people with comorbid substance misuse probably produced an underestimate of excess mortality.

All-cause mortality

The all-cause, natural cause and unnatural cause SMRs are broadly consistent with comparable recent studies, which suggest that schizophrenia is associated with a two- to threefold increase in mortality, with a large relative excess mortality from unnatural causes among younger people and a less dramatic but numerically greater excess mortality from natural causes among individuals in middle or older age.¹⁻³

Change in mortality with length of follow-up

Previous studies of schizophrenia mortality, both meta-analysis^{1,3} and large individual cohort studies,¹⁸ suggested with one

exception,¹⁹ that all-cause SMR falls with increasing age and with length of follow-up. A very large Scandinavian cohort study found a significant but only very slightly elevated SMR in older people with chronic schizophrenia.²⁰ This pattern is largely because the suicide SMR is highest in young people early in the disease process,^{17,18} when a small number of suicides produce a large overall SMR; probably the most significant process in shorter follow-up studies. The dramatic fall in unnatural cause SMRs over the course of the present study is consistent with these previous observations. The only study that specifically examined natural cause SMR found no clear relationship between length of follow-up and the SMR for natural causes, and an inverse relationship between length of follow-up and cardiovascular SMR.¹⁸ The present finding that natural and cardiovascular SMR increased, albeit non-significantly, with length of follow-up contradicts previous findings and gives support to the hypothesis that the cardiovascular mortality of schizophrenia is increasing.

Change in mortality in successive time periods

Evaluating apparent time changes in the mortality of a particular disease is complex. Differences in mortality in successive cohorts may be caused by confounding variables. Changes in mortality of an individual cohort may not generalise to other cohorts. Meta-analysis is susceptible to confounding by the inclusion of heterogeneous studies. One meta-analysis suggests that the all-cause mortality SMR in those with schizophrenia increased³ between the 1970s and the 1990s, a second suggests that it did

not.¹ One large Scandinavian record linkage study found dramatic increases in all-cause mortality in successive cohorts with schizophrenia,⁵ whereas another found an increase in the suicide SMR but no time trend in natural mortality.¹⁸ Other Scandinavian studies found no significant time trends in mortality over the same time period.^{21,22} The present study supports findings from Ösby *et al*'s large Swedish study that the natural cause SMR and especially the cardiovascular SMR of people with schizophrenia are increasing,⁵ a finding that should be of serious concern to mental health clinicians and service planners.

We cannot be sure whether the absolute cardiovascular mortality of people with schizophrenia increased over the study period. Changes in the SMR may be a result of increased cohort mortality, decreased general population mortality or a combination of these two trends. The absolute cardiovascular mortality of the present cohort increased over the course of the study but this would be expected as the cohort itself aged. The annual UK mortality from ischaemic heart disease fell from 36 to 19/10 000 population (males) and 16 to 9/10 000 population (females) between 1982 and 2000.²³ This was incorporated into the calculation of expected deaths but contributes to the rise in cohort cardiovascular SMR. Thus, people with schizophrenia appear to be missing out on the improved cardiovascular mortality of the general population, a situation uncomfortably reminiscent of the 1920s when public health measures reduced tuberculosis mortality in the general population a good decade earlier than among people in asylums.²⁴

Cigarette smoking

A twin study⁴ suggested that variations in the natural mortality in schizophrenia are best explained by altered patterns of exposure to environmental risk factors. The most significant cardiovascular risk factor in the general population is cigarette smoking.¹⁵ This fell in the UK general population from 39% in 1980 to 25% in 2004,¹⁵ but did not fall in people with schizophrenia; the 1996 prevalence of cigarette smoking in a subgroup ($n=102$) of the present cohort was 66%²⁵ and the prevalence in a similar 2003 Scottish cohort 70%.²⁶ Changes in the patterns of cigarette smoking are calculated to account for 36% of the fall in Scottish cardiovascular mortality between 1975 and 1994.²⁷ It is therefore likely that the continued high rate of cigarette smoking explains much of the excess cardiovascular (and indeed other) mortality of the present cohort. Reducing smoking-related mortality will require the delivery of effective anti-smoking strategies. At the present time there is evidence that individuals with schizophrenia can stop smoking with appropriate help²⁸ but no evidence that these interventions have detectable benefits for the population with schizophrenia.

Other probable aetiological factors

Other relevant risk factors include diet, exercise, obesity, relative poverty and poor healthcare,²⁶ many of which are interrelated. The present study does not address the impact of the atypical antipsychotic drugs but there are theoretical reasons for concern about their cardiovascular risk.²⁹ In this context, it is interesting (but far from conclusive) to note that the introduction of these drugs (risperidone in 1993, olanzapine in 1996 and quetiapine in 1997) coincided with the steepest rise in cardiovascular mortality in the present study.

The study suggests that the natural cause mortality of schizophrenia has been two to three times that of the general population throughout. This finding must be of concern to everyone involved with this disease. Further large-scale long-term

follow-up studies are needed to establish the reasons behind this increase and to suggest useful interventions. In the meantime the most clinically useful intervention is probably to try and help people with schizophrenia to stop smoking, to promote exercise and to facilitate effective health screening.

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Fallen Star

Mikhail Vrubel

Raymond Cavanaugh Jr

Mikhail Vrubel was born in 1856 in Omsk, Siberia. His father was a Russian army officer who supported the son's early-manifested interests in art, literature and music. Vrubel was well acquainted with the painting brush by the time he set off to St Petersburg University, where he studied law.

Though he performed adequately at his studies, Vrubel began to consider jurisprudence too straightforward a calling for one of his bohemian ilk and soon after graduating veered off the traditional career path, opting for the vicissitudes of the artistic life.

Not long after entering the St Petersburg Academy of Arts, he was recruited to assist with the revivification of holy icons at prominent area churches. It was this period that sparked the painter's long-time use of fiery and emotional colour combinations reminiscent of stained glass.

In 1889, Vrubel moved to Moscow where, while partaking in various artistic endeavours, he encountered Mikhail Lermontov's *Demon*. This poem became a lifelong obsession for Vrubel, who viewed the 'demon' as a heroic rebel, destined to remain 'tragically alone'. For the rest of his career, he would paint demons.

Vrubel's most prominent work is the *Seated Demon*, which portrays heaven's most famous exile not as the archetypal pitchfork-wielding maniac but as a contemplative-looking figure, calmly seated against an infernal background.

Though critics dismissed his *Seated Demon* as 'wild ugliness', the striking, if not entirely popular work won the ardour of art patron Savva Mamontov, who had the walls of his mansion and personal opera embellished by Vrubel's unconventional palette.

Known to be of melancholic temperament, the demon-chasing Vrubel was hospitalised for mental illness in 1902. During this time, he was observed repainting demons' faces many times over, an activity which may be construed as the artist's attempt to mask his own psychological turmoil.

One year after Vrubel's hospitalisation his son died. Following this event, the painter's added distress is manifested by his illustrated 'demons', which tend to appear increasingly tormented. Compounding Vrubel's problems was his steadily declining vision. Eventually, facing the prospect of blindness and the end of any future work, Vrubel descended into a vortex of suicidal ideation. One night in March 1910, he opened a window and, for a period of several hours, exposed his bare chest to the penetrating St Petersburg chill. One week later, he succumbed to pneumonia. However, not even death would end his misfortune, as the mysterious bronze powders he had used began to erode his painted oils and those hauntingly luminous achievements faded along with their creator's name.

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