Premature death among primary care patients with a history of self-harm

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Abstract (Word count: 254)

Purpose: To examine premature mortality in a nationally representative cohort of primary care patients who have harmed themselves.

Methods: During 2001-2013, 385 general practices in England contributed data to the Clinical Practice Research Datalink (CPRD) with linkage to Office for National Statistics (ONS) mortality records. We identified 30,017 persons aged 15-64 years with a recorded self-harm episode. We estimated the relative risks of all-cause and cause-specific natural and unnatural mortality using a comparison cohort, matched on age, gender and general practice.

Results: We found elevated risk of dying prematurely from any cause among the self-harm cohort, particularly during the first follow-up year: adjusted hazard ratio (HR) 3.6, 95% confidence interval (CI) 3.1-4.2. The elevation in suicide risk within a year was especially great: adjusted HR 54.4, CI 34.4-86.3. Beyond the first year, suicide risk declined sharply but remained much higher than in the comparison cohort. Large risk elevations throughout the follow-up period were also observed for accidental, alcohol-related and drug poisoning deaths. At 10 years of follow up, cumulative incidence values were 6.5% (CI 6.0-7.1) for all-cause mortality and 1.3% (CI 1.2-1.5) for suicide.

Conclusions: Primary care patients who have harmed themselves are at greatly increased risk of dying prematurely by natural and unnatural causes, and especially so within a year of a first episode. These individuals consult at a relatively high frequency, which presents a clear opportunity for preventive action. Primary care patients with myriad co-morbidities, including self-harming behavior, mental disorder, addictions, and physical illnesses, will require concerted, multi-pronged, multidisciplinary collaborative care approaches.

Keywords

Self-harm; General Practice; Mortality; Suicide

Introduction

Self-harm is a major public health problem. Deprived populations have higher incidence of self-harm,[1] and national incidence rates have risen in the wake of the economic downturn and subsequent austerity era.[2] Greatly reduced life expectancy and elevated risk of early death has been reported among people who present to hospital following self-harm in Australia,[3] Canada,[4] Denmark,[5] England,[6] Finland,[7] New Zealand,[8] Norway,[9] Sweden,[10] and Taiwan.[11] However, very little is known about mortality risk among primary care patients who have harmed themselves. A better understanding of mortality risk in this population is required, because national clinical guidelines in England, issued by the National Institute for Health and Clinical Excellence (NICE), have emphasized the important role of general practitioners (GPs) and primary healthcare teams in managing and monitoring risk in these patients over both short-[12] and long-term[13] follow-up. We have previously examined clinical management after a recent self-harm episode in the same primary care patient cohort.[14] We found an unexpectedly low rate of referral to mental health services, and suboptimal levels of adherence to a specific NICE recommendation against prescribing of tricyclic antidepressant medication following self-harm,[13 14] illustrating the clinical importance of examining premature morality risk in this population.

For the study reported in this paper we utilized electronic health data linked to national mortality records to investigate risk of dying prematurely after self-harm in a large primary care cohort in England. By examining mortality outcomes from both unnatural and natural causes, our intention was to highlight the potential clinical and public health benefits of addressing the physical health as well as the psychosocial needs of these patients. We currently know very little about long-term mortality risk among these individuals, because researchers have traditionally tended to examine risk in the immediate post-harm period.[4]

Methods

Data source

The study was conducted using electronic health data extracted from the Clinical Practice Research Datalink (CPRD) obtained under licence from the UK Medicines and Healthcare products Regulatory Agency.[15] The CPRD is one of the world's largest population-based, longitudinal, primary care databases containing anonymised patient information provided by general practices participating in the CPRD. In the UK National Health Service (NHS) over 98% of the population is registered with a GP with practices providing healthcare free at the point the access. In December 2013,

data were available for 684 general practices and more than 13 million patients with distributions of age and gender comparable to those reported in the UK national population census.[15] [16] Validation studies on the CPRD have demonstrated that it contains consistent, high-quality data.[17] Diagnoses are coded using the Read system that is in standard usage in UK general practice.[18] An explanation of Read coding, and how diagnostic information is routinely recorded in the CPRD, is provided in Appendix 1.

Self-harm definition

We used the definition "any act of self-poisoning or self-injury, irrespective of the apparent purpose" from NICE clinical guideline number 16.[12] Using this broad conceptualisation we developed a list of Read codes to delineate all self-harm cases across the spectrum from milder forms of non-suicidal behavior through to near-fatal suicide attempts. The Read code list is available online at: https://clinicalcodes.rss.mhs.man.ac.uk/[19] 'Self-harm' is a commonly used term in the UK, referring to all episodes irrespective of purpose; cases of attempted suicide with clear intent to die represent a subset among all persons who have harmed themselves. Appendix 2 gives a detailed description of the psychiatric and co-morbid physical illness diagnostic categories that we examined.

Self-harm cohort and matched comparison cohort

The cohort consisted of a nationally representative sample of patients who were coded for an incident presentation of self-harm to primary care during 2001-2013 at ages 15-64 years. The rationale for imposing these age restrictions was that the determinants and implications of self-harm in children and older adults are quite distinct from those of the rest of the population, and therefore warrant separate consideration. Among older persons who harm themselves, specific mechanisms such as bereavement, loneliness and social isolation[20,21] and physical illness, multi-morbidity and impairment[21] play a greater role; children aged below 15 years who harm themselves may have less suicidal intent and a relatively low long-term risk of dying by suicide.[22] Our intention was to preclude prevalent-cohort bias by delineating an incident cohort,[23,24] and we therefore required patients to have been registered with a contributing practice for at least one full year prior to their index episode. Each 'exposed' self-harm patient was matched with up to 20 'unexposed' patients with no record of self-harm in the CPRD at index episode date by gender, age (year of birth) and registered practice. We applied the same eligibility criteria for entry into both the self-harm cohort and the sampling frame for the matched comparison cohort.

Linked mortality data

We obtained linked cause-specific mortality records and examined the underlying cause of death coded at the Office for National Statistics (ONS) using the International Classification of Disease 10th revision (ICD-10).[25] The death registration records were available for patients registered with 385 practices, around 60% of all CPRD practices; i.e. those in England that participate in the CPRD scheme linking all patients with a valid National Health Service (NHS) identifier. We examined both natural and unnatural causes, with the latter defined as "… external causes, e.g. injury or poisoning, which includes death due to intentional injury, such as homicide or suicide, and death caused by unintentional injury in an accidental manner."[26] Unnatural deaths were classified according to all codes listed in ICD-10 Chapter XX 'External Causes of Morbidity and Mortality' (V01-Y98).[25] As is accepted practice for UK-based epidemiological research, our suicide definition included 'open verdicts'.[27] We examined natural causes because a significant proportion of people who harm themselves have a higher prevalence of lifestyle risk factors including smoking[28] and excessive drinking[29] that predict certain types of natural death, such as deaths from digestive diseases, respiratory diseases and lung cancer. To examine alcohol-related deaths, which are mostly from natural causes but also include acute alcohol poisonings, we used a standard ONS-endorsed coding range,[30,31] and likewise for classification of drug poisoning deaths, which includes all fatal poisonings or overdoses with prescribed medication, medication purchased legally 'over-the-counter', or illicit drugs.[32] The ICD-10 classifications for alcohol-related death and drug poisoning death are shown in Box 1 in Appendix 3.

Area-level deprivation

Based on patients' residential postcodes, Index of Multiple Deprivation (IMD) quintiles were extracted from the CPRD.[33] The IMD measures area-level deprivation on the basis of several domains including income, employment, health, education, barriers to services (including housing), crime, and general living environment. It is derived for geographical areas designated as Lower-layer Super Output Areas (LSOA's)[34] that contain 1000-3000 people and are Census-derived. The IMD provides a means of ranking and assessing whether an area is more or less deprived than others.

Statistical analyses

All analyses were performed using Stata software version 13.[35] For all individuals in a matched set, we defined the study entry point as the date of the index self-harm episode. We conducted Cox regression survival analysis[36] stratified by matched set. We generated both unadjusted hazard ratios and those adjusted for the following potential time-dependent confounders: calendar year, frequency of contact with a GP in past 12 months, mental illness diagnoses, psychotropic medication prescribed in past 12 months, clinically significant alcohol misuse, and current smoking status. The methods

used to generate these time-dependent covariates are described in Appendix 4. Right-censoring was applied at the end of the study period, and also to account for 'migration' from the database for reasons other than death, including geographical relocation or withdrawal of the patient's practice from the CPRD, and death from other causes than the specific cause being examined.

Results

Descriptive analyses

Table 1 presents socio-demographic indices for the 30,017 persons in the self-harm cohort versus the 600,258 individuals in the matched comparison cohort at index episode date. Because we matched patients on gender, age and registered practice, the proportional breakdown in the table was identical for both groups with respect to gender, age and practice-level deprivation. Females, younger people and those registered at practices in deprived localities were overrepresented. Table 2 compares clinical characteristics at baseline, indicating that the self-harm and comparison cohorts differed markedly in terms of their patterns of clinical consultation, with the former tending to attend their practice much more frequently. The self-harm cohort had much higher prevalence of psychiatric history, referral to mental health services and psychotropic medication, and alcohol misuse, smoking and physical illness co-morbidity were also considerably more prevalent.

Hazard ratios stratified by individual follow-up year

A key consideration when fitting a Cox model is the proportional hazards assumption,[34] which requires the hazard ratio to be consistent throughout follow-up. Figure 1 shows plots of hazard ratios and their 95% confidence intervals stratified by individual follow-up year. For all-cause mortality (Fig. 1a), suicide (Fig. 1b), natural death (Fig. 1c) and unnatural death (Fig. 1d), by far the greatest elevations in risk occurred during the first follow-up year. For natural death, the magnitude of the observed hazard ratio declined gradually in annual increments from first to the fourth follow-up year, whereas for suicide and for all unnatural deaths combined, risk was markedly higher for the first year than it was during the ensuing 9 years of follow-up. Because mortality risk was found to be elevated to a greater degree during the first follow-up year than for subsequent years in all four of these plots, we accounted for non-proportionality in risk[34] over time for all the hazard ratios presented in Tables 3 and 4. Thus, for these tabulations we estimated two-stage hazard ratios separately for: (i) the first year of follow-up; (ii) follow-up thereafter.

Relative risk of dying within a year of the index self-harm episode vs. long-term follow-up

Two-stage hazard ratio estimates for all-cause mortality, all natural causes and all unnatural causes are presented in Table 3. Two consistent patterns were found across these three broad mortality categories: 1) much greater risk during the first year versus subsequent follow-up years; 2) attenuated but still significant elevations in risk with covariate adjustment. Although a greater number of natural deaths were observed, the hazard ratios for unnatural death were considerably larger. Smaller effect sizes were observed for natural death, although, even with this outcome, an independent statistically significant elevation in risk persisted following adjustment. In Table 4 we present hazard ratios for the following specific causes of death: suicide, accident, alcohol-related, drug poisoning, respiratory disease and lung cancer. Self-harm was a strong and significant predictor for each of these outcomes, and the greatest risk elevations were for suicide. The increase in risk was more pronounced in the first year versus subsequent follow-up years, especially so for suicide. We did not observe any notable gender differences in the observed hazard ratios: likelihood ratio tests on gender interactions were not statistically significant for all causes of death (P=0.09), all natural causes (P=0.55), all unnatural causes (P=0.18), or suicide (P=0.14).

Cumulative incidence of premature death at 1, 5 and 10 years after index self-harm episode

Absolute risks are shown in Table 5. The numbers of deaths are summarized at varying lengths of follow-up for the self-harm and comparison cohorts along with cumulative incidence values (presented as percentages). At 10 years of follow up, the cumulative incidence values in this predominantly younger aged cohort of people who had harmed themselves were 6.5% (CI 6.0-7.1) for all-cause mortality and 1.3% (CI 1.2-1.5) for suicide.

Discussion

Summary of findings

Compared with a matched cohort of unaffected individuals, the self-harm cohort had markedly elevated risk of unnatural death during the first follow-up year. Beyond the first year, risk remained raised versus the comparison cohort, but to a considerably lesser degree. The largest elevation in risk within a year of the index self-harm episode and over longer term follow-up was for suicide. Risk of dying prematurely from a natural cause was elevated for both follow-up periods, albeit to a much lower degree than for dying by unnatural causes. Risks were raised across a broad array of cause-specific premature mortality outcomes, including suicide, accident, alcohol-related, drug poisoning, respiratory disease and lung cancer.

Comparison with existing evidence

For the first time we report short- and long-term mortality risk in UK primary care patients whose episodes of self-harming behavior may or may not be known to hospital services. Our findings also confirm those from earlier investigations that have reported elevated risk of unnatural and natural mortality following self-harm.[3-11,37-41] However, it is important to highlight that almost all previously published studies ascertained index self-harm episodes via secondary care data sources, mostly through emergency department contacts, although a small number of study cohorts were sampled from specialized poisoning treatment centers.[37] Virtually all previous studies have reported relative risks for cause-specific mortality without stratifying these estimates by length of follow-up. For some smaller studies, these estimates may have been coalesced across the whole observation period to maximize statistical power. Our proportional hazards assumption testing[36] revealed that such data pooling may yield invalid estimates averaged across the whole follow-up time, if the degree of risk elevation is substantially greater during the first follow-up year. Few investigations have reported relative risk restricted to the first follow-up year; two Taiwanese studies found age and gender adjusted risk elevations by a 100-fold or more, one conducted in Nantou County[41] and the other in Taipei City.[11] The Multi-centre Study of Self-harm in England, conducted in the cities of Derby, Manchester and Oxford, reported on the shared characteristics and similarity of risk factors for suicide and accidental death following self-harm.[42] It is therefore noteworthy that, in our study, risk of accidental death was also greatly elevated in the self-harm cohort.

Strengths and limitations

Our study had several major strengths. For the first time, we examined risks of all-cause and cause-specific premature death in a nationally representative primary care cohort, with complete case ascertainment via linkage to national mortality records. We used an optimal study design by comparing risks directly at individual patient level between an incident self-harm cohort and an unaffected comparison cohort sampled from the same population. This is a more robust approach than comparing risk indirectly via age and gender standardised mortality ratios calculated using nationally aggregated data, as was reported in previous studies.[5] By delineating an incident cohort design we precluded prevalent-cohort bias,[23,24] which underestimates the strength of exposure-outcome associations, and which could have influenced previous investigations of this topic.[3-11] Finally, our design was further enhanced by having up to 20 matched comparison subjects for every person in the self-harm cohort to enable examination of mortality outcomes that are particularly rare in the general population, such as suicide.

The study also had some limitations. First, we lacked the ability to examine confounding or effect modification by ethnicity and individual-level socioeconomic status (beyond a score allocated at the patient-postcode level). Second, the mortality record linkage scheme implemented for most CPRD practices in England did not yet exist for CPRD practices in Scotland, Wales or Northern Ireland when the study was conducted. Thus, our findings may not be generalizable to the entire UK population.

Interpretation and implications

These findings should dispel any notion that a primary care patient cohort with recorded history of self-harm would have an appreciably lower risk of dying prematurely by suicide and other unnatural and natural causes of death than individuals ascertained via hospital emergency department contacts. This indicates that secondary care study cohorts, which are the prevailing setting for research conducted in the field, do not capture a population of higher-risk individuals compared with all registered primary care patients who have harmed themselves. From this information we can infer a strong and clinically important message for primary healthcare teams: that these patients have greatly elevated risk of suicide and other causes of premature death, especially within a year of a known self-harm episode. National guidelines could provide more specific recommendations and training on how primary healthcare teams can intervene, manage and monitor risk in these patients more effectively.[43] Some of the risk factors identified, particularly alcohol misuse and smoking, are potentially modifiable. Furthermore, people who have harmed themselves consult much more frequently than their age and gender matched peers, which presents a clear opportunity for preventive action. Primary care patients with myriad co-morbidities, including self-harming behavior, mental disorder, addictions, and physical illnesses, will require a concerted, multi-pronged, multidisciplinary collaborative care model approach to enhance management of their complex health needs.[44]

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Conflict of interest: Nav Kapur was Chair of the Guideline Development Group for NICE clinical guideline 133 (*Self-harm: longer-term management* (2011), and was Chair of the NICE *Self-harm, Quality Standard Topic Expert Group* (2013). He is currently Chair of the Guideline Development Group for the NICE *Depression in Adults* guideline, and he sits on the National Suicide Prevention Advisory Group, England.

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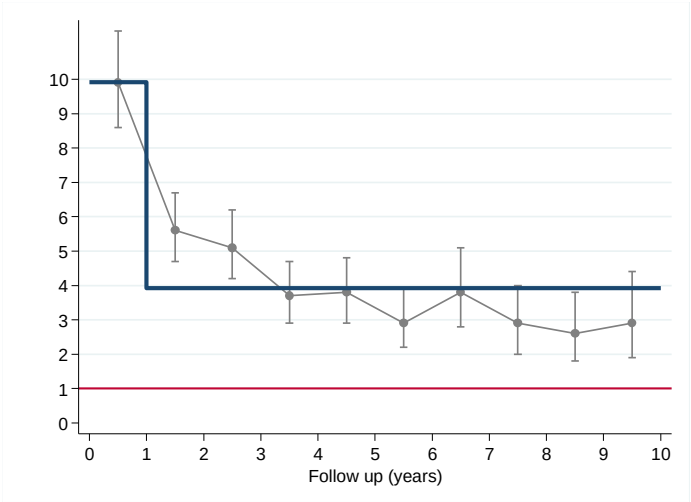
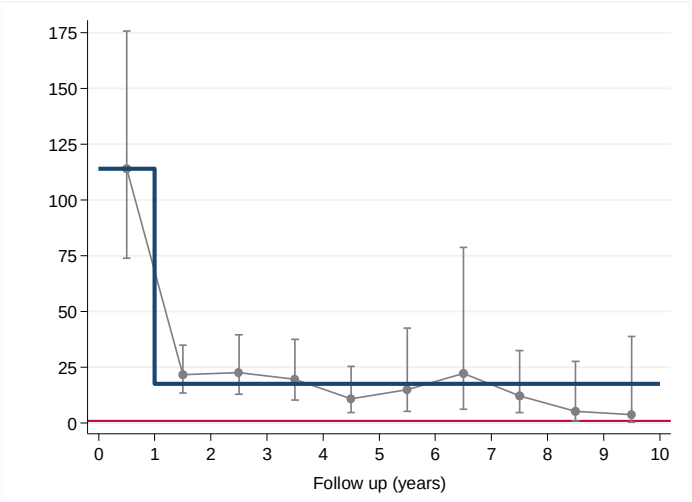
Figure 1. Hazard ratios stratified by individual follow-up year



(a) All-cause mortality



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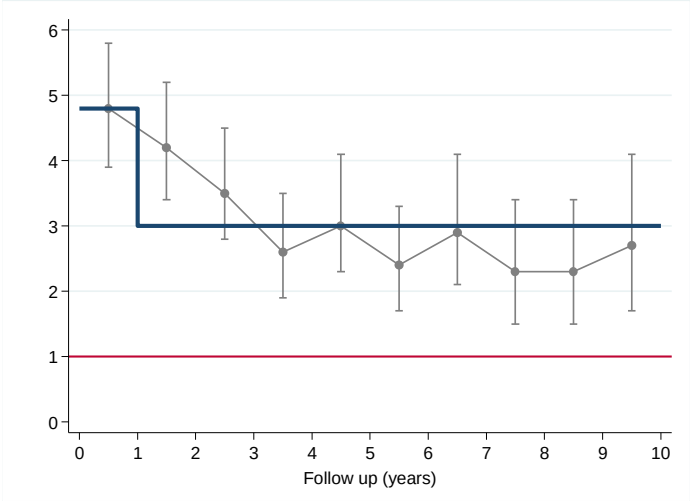
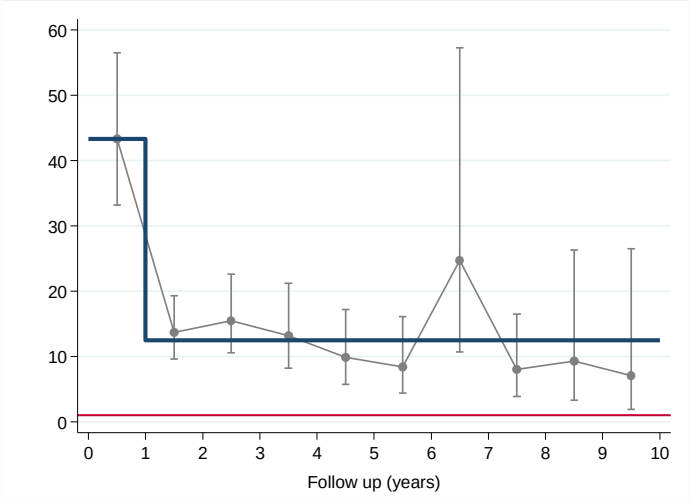


(c) Natural deaths



(d) Unnatural deaths

Table 1. Socio-demographic characteristics at index self-harm episode

Socio-demographics	Self-harm cohort: N = 30,017		Comparison cohort: N = 600,258	
	n	%	n	%
Gender:				
Male	12,390	41.3	247,746	41.3
Female	17,627	58.7	352,512	58.7
Age in years:				
15-24	11,876	39.6	237,470	39.6
25-34	6,028	20.1	120,541	20.1
35-44	6,132	20.4	122,665	20.4
45-54	3,995	13.3	79,869	13.3
55-64	1,986	6.6	39,696	6.6
Index of Multiple Deprivation:				
Quintile 1 (*least deprived*)	3,359	11.2	67,174	11.2
Quintile 2	6,023	20.1	120,452	20.1
Quintile 3	5,571	18.6	111,412	18.6
Quintile 4	7,305	24.3	146,079	24.3
Quintile 5 (*most deprived*)	7,759	25.9	155,141	25.9

Table 2. Clinical characteristics at index self-harm episode

Clinical characteristics	Self-harm cohort: N = 30,017		Comparison cohort N = 600,258	
	n	%	n	%
GP consultation in past 12 months:				
0 visits	2,395	8.0	152,795	25.5
1 or 2 visits	5,217	17.4	168,467	28.1
3 to 5 visits	6,935	23.1	143,100	23.8
6+ visits	15,470	51.5	135,896	22.6
Mental health history:				
Psychiatric diagnosis	16,513	55.0	126,301	21.0
Referral to mental health services	8,506	28.3	39,653	6.6
Psychotropic drug prescribed	20,377	67.9	191,874	32.0
Alcohol misuse	2,069	6.9	4,352	0.7
Physical health history:				
Asthma	5,860	19.5	91,830	15.3
Cancer	308	1.0	4,854	0.8
CHD	348	1.2	3,729	0.6
CKD	114	0.4	1,400	0.2
COPD	193	0.6	1,453	0.2
Diabetes	849	2.8	8,896	1.5
Hypertension	1,455	4.8	23,653	3.9
Stroke	202	0.7	1,400	0.2
Smoking status:				
Never smoked	9,545	36.7	286,547	58.9
Current smoker	13,507	52.0	134,538	27.7
Ex-smoker	2,936	11.3	65,306	13.4
Unknown	4,029	-	113,867	-

CHD: coronary heart disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disorder

Table 3. Unadjusted and adjusted two-stage hazard ratios for all-cause mortality, all natural deaths and all unnatural death

Mortality type	Follow-up period	Self-harm cohort:		Hazard ratio [95% CI]	
		Deaths (n)	Rate per 1000 PYs	Unadjusted	Adjusted ¥
All-cause mortality	Within a year	301	11.1	9.92 [8.63, 11.40]	3.59 [3.08, 4.19]
	After a year	673	6.3	3.92 [3.61, 4.27]	1.70 [1.54, 1.88]
All natural deaths	Within a year	126	4.6	4.79 [3.94, 5.82]	1.51 [1.11, 1.87]
	After a year	459	4.3	2.98 [2.69, 3.29]	1.25 [1.11, 1.40]
All unnatural deaths	Within a year	175	6.4	43.31 [33.20, 56.49]	21.11 [15.83, 28.15]
	After a year	214	2.0	12.53 [10.48, 14.99]	5.65 [4.60, 6.94]

PY = Person Year; CI = Confidence Interval.

¥ Adjusted for consultation frequency in previous 12 months, history of psychiatric diagnoses, history of mental health referral, history of psychotropic medication prescribing, history of alcohol misuse, and smoking status.

All natural versus unnatural deaths delineated using the following ICD-10 codes: **Unnatural death**: V01-Y98; **Natural death**: any code other than V01-Y98

Table 4. Unadjusted and adjusted two-stage hazard ratios for specific causes of death

Cause of death	Follow-up period	Self-harm cohort:		Hazard ratio [95% CI]	
		Deaths (n)	Rate per 1000 PYs	Unadjusted	Adjusted ¥
Suicide	Within a year	140	5.1	113.90 [73.87,175.63]	54.43 [34.32,86.32]
	After a year	122	1.1	17.45 [13.50,22.54]	7.62 [5.67,10.25]
Accident	Within a year	35	1.3	12.94 [8.45,19.84]	5.60 [3.45,9.08]
	After a year	90	0.8	9.32 [7.19,12.08]	4.16 [3.05,5.65]
Alcohol-related	Within a year	26	1.0	14.52 [8.74, 24.11]	2.62 [1.14, 6.02]
	After a year	106	1.0	11.16 [8.72, 14.29]	2.37 [1.50, 3.76]
Drug poisoning	Within a year	49	1.8	48.17 [28.63, 81.03]	17.62 [9.83, 31.58]
	After a year	91	0.8	28.46 [20.25, 39.98]	9.22 [6.14, 13.83]
Respiratory disease	Within a year	11	0.4	6.39 [3.24, 12.61]	2.64 [1.22, 5.70]
	After a year	53	0.5	4.94 [3.63, 6.72]	2.21 [1.55, 3.15]
Lung cancer	Within a year	9	0.3	4.55 [2.20, 9.39]	2.31 [1.00, 5.30]
	After a year	29	0.3	1.92 [1.31, 2.82]	0.88 [0.56, 1.37]

PY = Person Year; CI = Confidence Interval

¥ Adjusted for consultation frequency in previous 12 months, history of psychiatric diagnoses, history of mental health referral, history of psychotropic medication prescribing, history of alcohol misuse, and smoking status

Causes of death delineated using the following ICD-10 codes: **Suicide:** X60-X84, Y10-Y34 (excluding Y33.9), Y87.0, Y87.2; **Accident**: V01-X59, Y85-Y86, Y87.1; **Alcohol-related**: F10, G31.1, I42.6, K29.2, K70, K73, K74 (*excluding K74.3-K74.5*), K86.0, X45, X65, Y15; **Drug poisoning:** F11-F16, F18-F19, X40-X44, X60-X64, X85, Y10-Y14; **Respiratory disease**: J00-J99; **Lung cancer**: C33-C34.

Table 5. Cumulative incidence for all causes and specific causes of death

	Self-harm cohort: N = 30,017		**Comparison cohort: N = 600,258**	
	Number of deaths	Cumulative incidence (%)	Number of deaths	Cumulative incidence (%)
All causes:				
At 1 year	301	1.07 (0.96, 1.20)	634	0.11 (0.10, 0.12)
At 5 years	739	3.47 (3.22, 3.73)	2777	0.68 (0.66, 0.71)
At 10 years	946	6.53 (6.04, 7.06)	4455	1.79 (1.73, 1.85)
All natural causes:				
At 1 year	126	0.46 (0.38, 0.54)	551	0.10 (0.09, 0.11)
At 5 years	406	2.01 (1.82, 2.22)	2435	0.60 (0.58, 0.63)
At 10 years	563	4.43 (4.00, 4.90)	3989	1.63 (1.57, 1.69)
All unnatural causes:				
At 1 year	175	0.62 (0.53, 0.72)	83	0.01 (0.01, 0.02)
At 5 years	333	1.49 (1.33, 1.66)	342	0.08 (0.07, 0.09)
At 10 years	383	2.21 (1.95, 2.49)	466	0.16 (0.15, 0.18)
Suicide:				
At 1 year	140	0.50 (0.42, 0.58)	27	0.00 (0.00, 0.01)
At 5 years	234	1.00 (0.88, 1.14)	131	0.03 (0.03, 0.04)
At 10 years	258	1.33 (1.15, 1.53)	182	0.07 (0.06, 0.08)
Accidental:				
At 1 year	35	0.12 (0.09, 0.17)	54	0.01 (0.01, 0.01)
At 5 years	97	0.48 (0.39, 0.59)	201	0.05 (0.04, 0.05)
At 10 years	123	0.88 (0.70, 1.09)	273	0.09 (0.08, 0.11)
Alcohol-related:				
At 1 year	26	0.09 (0.06, 0.14)	40	0.01 (0.01, 0.01)
At 5 years	94	0.48 (0.39, 0.59)	165	0.04 (0.03, 0.05)
At 10 years	132	1.03 (0.84, 1.27)	260	0.10 (0.09, 0.12)
Drug poisoning:				
At 1 year	49	0.17 (0.13, 0.23)	20	0.00 (0.00, 0.01)
At 5 years	116	0.54 (0.45, 0.65)	73	0.02 (0.01, 0.02)
At 10 years	138	0.86 (0.70, 1.06)	90	0.03 (0.02, 0.03)

Appendix 1: Explanation of the Read coding system and how diagnostic information is routinely recorded in the CPRD

The Read classification was devised in the 1980s by English general practitioner (GP) James Read as a thesaurus of medical terms according to the following principles: 1) Comprehensive; 2) Hierarchical; 3) Coded; 4) Computerized; 5) Cross-referenced; 6) Dynamic. It contains a vast array of codes for the following entities: disease diagnosis, management and monitoring; history, signs and symptoms; investigative, preventive, operative and therapeutic procedures; medication and appliances; and referrals to secondary care health services. By 1990 it was claimed to be "… the most comprehensive medical coding system in the world (p1092)."[18] Read codes that denote a self-harm episode or a co-morbid physical or mental health condition are routinely entered in a patient's electronic medical record by their GP or practice nurse in the course of a clinical consultation, or by a practice administrator who has gleaned the information from a secondary healthcare provider. Thus, in some instances the patient's GP or practice nurse will have made the diagnosis whilst in others it will have been made by a clinician who had previously seen the patient in a general hospital or a mental health unit. With self-harm episodes, some patients will have self-reported the behavior at consultation (e.g. "I intentionally cut my arm today") or it will be recorded on the basis that the patient had self-poisoned or self-injured to a degree that consequently required clinical observation or treatment.

Appendix 2: Explanation of psychiatric and co-morbid physical illness diagnostic classifications

Our schizophrenia-spectrum definition included diagnoses of delusional disorders, brief psychotic disorders, schizophreniform disorders, schizoaffective disorders, and schizophrenia. The spectrum definition also included patients with psychotic symptoms that did not adequately fit the definition for any of the specified diagnostic subgroups. We identified patients with bipolar disorder via records that referred directly to bipolar or affective disorder and records describing recurrent mania, manic-depression, or depression with psychosis. We applied broad definitions for the two most common conditions: depression and anxiety. Our definition of depression included the full range of diagnoses from either single or recurrent episodes of mild to severe depression through to more persistent chronic conditions. Anxiety incorporated panic disorders, phobias, post-traumatic stress disorders, social anxiety disorders, and generalized anxiety disorder.

Defining personality disorders can be complex due to the substantial overlap with other diagnostic categories. This is particularly true when considering variants that include some form of paranoia or psychosis. For instance, some definitions place schizoid and schizotypal personality disorders in the schizophrenia spectrum whereas our definition included these conditions as personality disorders when references to delusions or hallucinations were not present in the patient's records. Our definition also incorporated erratic variants (including antisocial, borderline, histrionic, and narcissistic personality disorders) and anxiety or stress-related variants (including avoidant, dependent, and obsessive-compulsive personality disorders). The classification of eating disorders is also prone to subjectivity. Again, we applied a broad definition that covered the more common conditions (including anorexia nervosa, bulimia, and binge eating) but also included some rarer psychogenic variants.

Table 2 ('Clinical characteristics at index self-harm episode') of the manuscript presents the prevalence of physical illness conditions that are monitored in the Quality Outcomes Framework (QOF), which has been part of the General Medical Services contract for general practices in the UK National Health Service since April 1st 2004: http://www.nhsemployers.org/your-workforce/primary-care-contacts/general-medical-services/quality-and-outcomes-framework

Appendix 3: ICD-10 codes and descriptions for classifying alcohol-related death and drug poisoning death

These two categories of cause-specific mortality are routinely reported by the Office for National Statistics (ONS), England and Wales: alcohol-related death;[30] drug poisoning death.[32] Box 1 presents the lists of codes used to classify these outcomes along with their respective descriptions.

Box 1: ICD-10 classification for alcohol-related death and drug poisoning death

ICD-10 code or range	Description
Alcohol-related death:	
F10	Mental and behavioral disorders due to use of alcohol
G31.2	Degeneration of the nervous system due to alcohol
G62.1	Alcoholic polyneuropathy
I42.6	Alcohol gastritis
K70	Alcoholic liver disease
K73	Chronic hepatitis, not elsewhere classified
K74	Fibrosis and cirrhosis of liver (*excluding K74.3-K74.5 - Biliary cirrhosis*)
K86.0	Alcohol-induced chronic pancreatitis
X45	Accidental poisoning by and exposure to alcohol
X65	Intentional self-poisoning by and exposure to alcohol
Y15	Poisoning by and exposure to alcohol - undetermined intent
Drug poisoning death:	
F11-F16, F18-F19	Mental and behavioral disorders due to drug use
X40-X44	Accidental self-poisoning by drugs, medicaments and biological substances
X60-X64	Intentional self-poisoning by drugs, medicaments and biological substances
X85	Assault by drugs, medicaments and biological substances
Y10-Y14	Poisoning by drugs, medicaments and biological substances - undetermined intent

Appendix 4: Generating time-dependent covariates for multivariable modelling

We fitted time-dependent covariates to account for potential confounders of the relationship between self-harm and premature mortality risk. With cohort entry as the origin for a given patient, we derived covariates at time points $t = t_1, t_2, t_3, \ldots$ where $t > 0$.

(a) *Calendar year*. To account for any trends in the relationship between self-harm and premature mortality, we adjusted for the calendar year at each time point *t*.

(b) *Frequency of contact with a GP in past 12 months*. We applied a previously developed consultation categorization scheme to identify face-to-face patient contacts with clinical staff.[45] When a patient had more than one consulting record on the same day, we regarded it as a single consultation, or 'contact day'. At each time point *t* (for each patient), we identified all direct contacts in the interval [*t* –12 months, *t*).

(c) *Mental illness diagnoses*. We considered diagnoses of mental illness in the following six categories: the schizophrenia-spectrum, bipolar disorders, depression, anxiety disorders, personality disorders, and eating disorders. Appendix 2 contains detailed information on diagnostic category specifications; read code lists are available at: https://clinicalcodes.rss.mhs.man.ac.uk/. We constructed a binary time-dependent variable for a history of mental illness diagnoses on or prior to each time point *t*.

(d) *Referral to mental health services*. We identified relevant referrals to specialist mental health services using the family health services authority (FHSA) specialty which indicated the department to which the patient was referred; it is mandatory for GPs to enter this information upon referral. For our purposes, there was just one relevant specialty: psychiatry. Secondly, information on the National Health Service (NHS) specialty was also available. The information in this field was more granular, but completion by general practice staff is not compulsory when coding referrals. We combined the information from both fields to construct indicators for each patient's referral history.

(e) *Psychotropic medication prescribed in past 12 months*. The dataset also contained records of primary care prescribed medication for our study cohort. GPs selected and recorded prescription items using the Multilex product dictionary. Information on the Multilex coding system is available at: http://www.fdbhealth.co.uk/solutions/multilex/. Dictionary items include medicinal products, devices and appliances. We extracted all prescriptions for our cohort in the following classes of psychotropic medication: typical, atypical and depot antipsychotics; lithium and other mood stabilisers; selective

serotonin reuptake inhibitor (SSRI), tricyclic and other antidepressants; benzodiazepines; opioid analgesics; other anxiolytics and hypnotics. Our categorized lists of Multilex codes for psychotropic medication are also available at www.clinicalcodes.org. We constructed a binary indicator variable for any psychotropic prescription in the interval [t –12 months, t).

(f) *Clinically significant alcohol misuse*. We constructed binary indicator variables representing any history of clinically significant alcohol misuse prior to time *t*. The read code list is provided at:

https://clinicalcodes.rss.mhs.man.ac.uk/

(g) *Current smoking status*. Defining this covariate at each time point required a complex algorithm to address coding inconsistencies over time. We created a categorical variable for never smoked, current smoker and ex-smoker. The list of read codes for current smoking status is available at: https://clinicalcodes.rss.mhs.man.ac.uk/ Feasible one-step changes in smoking status over time were specified using the state transition matrix that is outlined here:

		Status at time t_j:		
		Never	Current	Ex
Status at time t_{j-1}:	Never	1	1	1
	Current	0	1	1
	Ex	0	1	1