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Phenome-wide diagnostic comparison among suicide deaths and living individuals with chronic pain diagnoses

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Abstract

Background Chronic pain, regardless of its type, is a significant risk factor for suicide. However, not all individuals with chronic pain also experience suicidal thoughts and behaviors. Better characterization of clinical risk profiles and comorbidities across the medical spectrum among people with chronic pain who die by suicide is urgently needed to aid treatment and prevention strategies.

Methods This case–control study leverages population-based data from the Utah Suicide Mortality Risk Study. Specifically, we identify clinical phenotypes from diagnostic data that differentiate between individuals that died by suicide with chronic pain diagnoses ($N=1,410$) and living control individuals who also had chronic pain diagnoses ($N=4,664$). Medical diagnostic codes were aggregated via phecodes to perform a phenotype-based phenome-wide association study. Using multivariable logistic regression analysis adjusting for covariates and multiple testing, differences in 1,727 common clinical phenotypes (phecodes) were assessed between suicide deaths and controls with chronic pain diagnoses. Models were also stratified by sex.

Results Chronic pain diagnoses were nearly three times more prevalent in individuals who died by suicide compared with those who did not. Sixty-five phecodes were significantly overrepresented among suicide deaths with chronic pain diagnoses compared with controls with chronic pain diagnoses. Utah suicide deaths with chronic pain had significantly more psychiatric diagnoses (mood disorders, anxiety disorders, attention deficit hyperactivity disorder, posttraumatic stress disorder, personality disorders, schizophrenia/psychosis, substance use related traits and prior overdoses, and diagnoses related to previous suicidal thoughts and behaviors) in addition to insomnia and specific pain related diagnoses compared to Utah controls with chronic pain (odds ratios ranged from 1.40–7.10). Twenty-five phecodes were overrepresented in controls with chronic pain compared to suicides. These were related to preventative care, cancer, obesity and other conditions (odds ratios ranged from 0.16–0.73). Sex-specific analyses largely replicated the combined analyses, yet the strength of the association was stronger for women with phecodes related to prior self-harm.

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Conclusions Results identified multiple clinical comorbidities with chronic pain that differentiate suicide deaths from living control individuals with a history of diagnosed chronic pain. Our findings may help discern individuals with chronic pain who may be at greater risk for suicide death.

Keywords Chronic pain, Suicide, Chronic pain comorbidities, Case control design, Clinical phenotypes

Background

Chronic pain (CP), defined as persistent and/or recurrent pain lasting longer than 3 months, is an impairing condition that affects approximately 1 in 5 persons worldwide [1]. These estimates are likely conservative given that CP is typically assessed and diagnosed via self-report (many may never seek care and others may be too injured/impaired to report) [2, 3]. CP can have multiple sources, with leading disabilities including migraines, back pain, neck pain, and other musculoskeletal, neurological, and inflammatory disorders [4]. Yet not all sources of CP are linked to a physical illness or injury [5]. Rather, CP is a complex, person-specific, and internal experience with a combination of biological, emotional, cognitive, sociological, and cultural contributors [6].

Unfortunately, CP is associated with high economic burden, lower quality of life, poorer mental wellbeing, and impaired physical functioning [7, 8]. Those who are disabled, from lower socioeconomic status areas, earning lower annual incomes, and who are from more rural living environments appear to be disproportionately affected [4, 9–11]. In the United States, estimates gathered in 2021 indicate that 20.9% of adults, or 51.6 million individuals, experienced CP, and 6.9%, or 17.1 million persons, had experienced what is termed *high-impact chronic pain* or CP that substantially restricts daily activities [12]. Higher prevalence rates were observed among non-Hispanic indigenous persons, as well as adults who identified as bisexual and those who were divorced or separated. Other research indicates that women experience and report pain at a significantly higher rate than men [13, 14], and that CP is more prevalent among older adults being one of the main reasons this group seeks medical care [10, 11, 15]. Thus, CP is widespread, pernicious, and disproportionately affects already vulnerable populations.

CP also frequently co-occurs with, and is exacerbated by, other conditions. For example, sleep disturbances occur among an estimated 50–80% of persons with CP and these problems can reciprocally escalate one another [16]. Insomnia can increase pain intensity and sensitivity, whereas CP can further disrupt an individual's sleep. Additionally, CP conditions often coexist, with 40 to 62 percent of individuals with CP experiencing multiple pain conditions simultaneously [17]. Research also highlights that the brain structures involved in processing nociceptive, neuropathic, and nociplastic stimuli are related to the brain structures and neural processes that are relevant in common mental health illnesses such as depression and anxiety [3, 9, 18, 19].

Given the persistent and extremely debilitating nature of CP, as well as shared neural pathways with mental illness, it is perhaps unsurprising that CP is associated with elevated risk of suicide. Indeed, CP is a risk factor for each component phenotype of suicidality that is, suicidal ideation (SI), suicide attempts (SA), and suicide deaths [4]. Data indicate that the risk of death by suicide increases *two-fold* among individuals with CP [20] and that CP is uniquely associated with increased risk for suicidality *even after controlling for co-occurring psychiatric conditions* [21]. One analysis of pain related clinical diagnoses in over 4 million individuals receiving services in the Department of Veterans Affairs Healthcare System in 2005 (N=4,863,086) showed associations between pain conditions (e.g., back pain, migraine, pain related to psychological conditions) and suicide death after controlling for comorbid psychiatric conditions [22]. A recent meta-analysis of suicidal behavior in CP patients showed that the lifetime prevalence of SI and SA were 28.9% and 10.8% respectively. Furthermore, one in four (25.87%) patients with CP had experienced SI within the past two weeks at the time of clinical assessment [23]. Finally, a retrospective analysis of US suicide deaths (2003–2014) with data from the CDC's National Violent Death Reporting System showed that CP was present in 9% of the individuals who died by suicide (123,000 total). This number is likely an underestimate because of the data limitations among this sample [24].

Pain-related risk factors for suicide include pain characteristics (e.g., intensity and type of pain), sleep disturbances, opioid use, pain catastrophizing, and perceived burdensomeness [6, 20]. For example, SI is more prevalent among people with CP who report severe insomnia that results in daytime dysfunction and high pain intensity [25]. Higher prescribed opioid doses have also been associated with risk for suicide even after controlling for demographic & clinical features [26]. Broader literature connects substance use to suicide risk [27–29]. Pain catastrophizing, defined as a cognitive-affective response to pain involving negative thinking about anticipated or actual pain experiences [30], is associated with subsequent increases in SI and suicidal actions [31] and can

account for differences in pain experiences [32]. Finally, CP can cause an individual to perceive themselves as a burden to others. Perceived burdensomeness can make a person less willing to reach out for and receive support, and contribute to feelings of isolation [5, 6, 33]. This is important, as perceived burdensomeness is a major risk factor for suicide in and of itself [34] and interpersonal relationships and social responses to pain affect how an individual perceives their pain and even their responsiveness to treatment [5]. Interpersonal relationships also influence patients' ability to develop and utilize coping strategies to mitigate the effects of CP [31].

Although the literature delineates some CP-related factors that increase risk for suicidality, we do not yet have a thorough understanding of why some people with CP develop suicidal thoughts and behaviors and others do not [35]. Currently, few studies examine risk factors among people who have died by suicide and experienced CP [20, 22]. Recent work has suggested that pain comorbidity may contribute to suicidal behavior (Swedish twin sample; (N = 17,148 twins) [36]. In the present study, we use unique resources available via The Utah Suicide Mortality Risk Study (USMRS) to identify clinical risk factors and comorbidities across the medical phenome that differentiate between individuals that died by suicide with CP diagnoses and population-based control individuals (who did not die by suicide) who also had CP diagnoses. Data indicate that > 80% of people who die by suicide have had contact with a health care provider within the last year of their life [37]. Given that CP is a common reason that vulnerable persons seek out medical care, there may be important opportunities for interventions and prevention among this exceptionally vulnerable group, especially if suicide-specific comorbidities and risk factors can be identified to differentiate high risk individuals.

Methods

Data sources

This study utilized the data resources available through the Utah Suicide Mortality Risk Study (USMRS). The USMRS resource has previously been described in detail [38]. Briefly, through a 25-year collaboration with a centralized Utah Office of the Medical Examiner (OME), the USMRS has built a large population-based data resource that facilitates unique opportunities to enhance ongoing suicide prevention work. Suicide mortality incidence is high in the State of Utah where determination of suicide is made carefully by the OME following a detailed investigation of the scene and circumstances of the death. Suicide death records are securely linked to demographic data and two decades of electronic health records (EHR) data (all inpatient encounters, emergency department, and ambulatory care encounters state-wide, as well as outpatient encounters from the two largest clinical data providers in the state, University of Utah Healthcare and Intermountain Healthcare which cover ~ 85% of the state's population). Linkage is done through the Utah Population Database (UPDB) [39] by UPDB staff. All identifiers are removed and deidentified data is given to the research team to protect privacy and confidentiality. For each suicide death, records from ten living individuals in the Utah population with the same sex and birth year were matched using at-risk sampling. Only health records up to the time of matching to the index individual who died by suicide were studied in control individuals so that individuals that died by suicide and matched controls did not differ in the length of their medical records. 39 control individuals that died by suicide at a later date were removed from the control data set. Control data is also processed and deidentified by UPDB staff in the same rigorous manner as the suicide death data. This study was approved by Institutional Review Boards from the University of Utah, Intermountain Healthcare and the Utah Department of Health and Human Services.

Phecode generation from diagnostic EHR data

For the present study, suicide deaths (N = 9,969; male = 7,690; female = 2,279) and controls (N = 94,775; male = 71,661; female = 23,114) at least 18 years of age with linked demographic and EHR data in the USMRS were assessed. Phenotypes for suicide deaths and controls were generated with International Classification of Diseases (ICD versions 9 & 10) diagnostic codes. For suicide deaths, ICD codes within 2 weeks of death were removed to ensure codes from the death event were not included in the phenotyping. To broadly assess common medical conditions, diagnostic data were aggregated to PheWAS trait codes (hereby "phecode") using the PheWAS R package [40] for suicides and controls separately. Phecodes represent one validated way to define phenotypes using EHR data and reflect lifetime diagnoses of medical conditions [41]. ICD 9 Phecode Map 1.2 was used to aggregate ICD 9 codes and ICD 10 CM Phecode Map 1.2 beta was used to aggregate ICD 10 codes [42]. The presence of at least one ICD diagnostic code in any given phecode phenotype was used to define individuals as having that phenotype, including the "Chronic pain" phecode (338.2), which was used to define individuals with CP diagnoses. We also performed a secondary analysis in which individuals with CP were required to have at least 2 instances of an ICD diagnostic code in the "Chronic pain" phecode.

Phenotype-based phenome-wide association tests

We performed phenotype-based phenome-wide association analyses using phecodes as predictors to identify phenotypic correlations across the medical spectrum

with suicide decedents who experienced CP [43]. Multivariable logistic regression models controlling for the square root transformed total number of diagnostic codes, age, and sex were used to evaluate the association between phecodes and suicide death in individuals with CP. The square root transformed number of total ICD codes was included as a proxy for the total number of health encounters to account for the potential influence of informative presence bias [44]. Since some phecodes have a low frequency within groups, Firth's penalized maximum likelihood logistic regression was used to reduce bias [45, 46]. All analyses were conducted in R [47].

The mean and standard deviation of the occurrence of each phecode for each group for all individuals and by sex are summarized in Additional file 1: Table S1. 1,727 phecodes were compared between suicide deaths with chronic pain diagnoses (SUI + CP) and controls with chronic pain diagnoses (CTRL + CP). With Bonferroni correction for 1,727 tests, *p*-values below 2.9e-5 were considered significant. These tests were performed in two sets of individuals. Our main comparison was between individuals that died by suicide and controls receiving one or more ICD code in the "Chronic pain" phecode and our secondary comparison was between individuals that died by suicide and controls receiving two or more ICD codes in the "Chronic pain" phecode. We also performed within-sex analyses with multivariable logistic regression models controlling for the square root transformed total number of diagnostic codes and age. 1,648 phecodes (female) and 1,624 phecodes (male) were compared between SUI + CP vs CTRL + CP, with Bonferroni correction for multiple testing and *p*-values below 3.03e-5 were considered significant for females and 3.08e-5 for males. Numbers of phecodes tested differ between comparisons based on prevalence. If the phecode was not present in either group compared it was excluded from the analysis. Additionally, we ran a model including a sex*suicide status interaction term to examine differences in effects between the sexes.

Results

Sample characteristics

Most individuals in the USMRS are non-Hispanic White in racial/ethnic background (Table 1). Persons in the main SUI + CP (N = 1,410) were 36.4% female and had a mean age of 47.4 (Table 1). This group represented 14.2% of suicide deaths in the USMRS who were at least 18 years of age with linked demographic and EHR data. Persons in the main CTRL + CP (N = 4,664) were 29% female and had a mean age of 50.6 (Table 1). This group represented 4.9% of controls in the USMRS who were at least 18 years of age with linked demographic and EHR data. Females had more diagnostic codes in the EHR than males for both SUI + CP and CTRL + CP (SUI + CP p = 6.28e-13; CTRL + CP p = 2.20e-16). In our secondary groups where CP was defined as two or more instances of a CP diagnostic code, SUI + CP (N = 1,081) were 39% female and had a mean age of 47.1. CTRL + CP (N = 3,088) were 29.4% female and had a mean age of 50. OME information on the method of death and pain related conditions noted from the death investigation for suicide decedents in the main comparison are given in Table 2. Prevalence of phecodes for selected common pain related and other medical conditions in the cohort is given in Table 3 (see Additional file 1: Table S1 for the prevalence of all phecodes examined).

Table 1 Demographic and diagnostic characteristics of suicide deaths with chronic pain diagnoses (SUI + CP) and controls with chronic pain diagnoses (CTRL + CP) from the Utah Suicide Mortality Risk Study (USMRS) cohort. In compliance with the Utah Resource for Genetic and Epidemiologic research (RGE) standards, numbers smaller than 11 individuals cannot be reported and are indicated with an asterisk

	SUI + CP	CTRL + CP
Total #	1,410	4,664
Mean Age (SD)	47.4 (14.8)	50.6 (16.7)
Mean # total diagnostic codes in EHR (SD)	129.4 (97.9)	115.0 (90.9)
Male	897	3,312
Mean Age (SD)	47.8 (15.6)	51.4 (17.3)
Mean # total diagnostic codes in EHR (SD)	114.8 (91.3)	106.9 (86.0)
Female	513	1,352
Mean Age (SD)	46.6 (13.2)	48.7 (15.0)
Mean # total diagnostic codes in EHR (SD)	154.9 (103.6)	134.8 (99.3)
Race (%)		
White	95.9	92.2
Black	*	1.2
American Indian/Alaska Native	1.0	*
Pacific Islander	*	*
Asian	*	0.6
Multiple	*	4.7
Unknown	1.3	0.7
Ethnicity (%)		
Spanish/Hispanic	4.7	12.2
Military Service (%)		
Veteran	10.4	0.4

Phenotype-based phenome-wide associations

In the main SUI + CP vs CTRL + CP comparison where one or more ICD codes in the "Chronic pain" phecode defined the groups, 65 phecodes related to psychiatric disorders (Mood disorders, Anxiety disorders, ADHD, PTSD, Personality disorders, Schizophrenia/

Table 2 Characteristics from the Utah Office of the Medical Examiner (OME) for suicide deaths with chronic pain diagnoses (SUI + CP). The OME determined method of death and significant medical conditions noted by OME investigators from the death scene investigation are listed. Information on relevant conditions is collected from law enforcement, next of kin, and close friends/family of the decedent

Suicide Method (%)	
Firearm related	44.7
Overdose/poisoning	31.7
Asphyxiation	18.5
Violent trauma	3.7
Other	1.4
Pain related conditions noted from OME investigation (%)	
Back pain	9.0
Prior suicide attempt	7.8
Multiple high-intensity pain conditions	5.6
Pain related surgery	4.5
Cancer	3.6
Fibromyalgia	2.4
Traumatic brain injury	2.1
Accident that caused significant physical damage	2.1
Sleep problems	1.9
Migraine/headaches	1.8
Seizures	1.6

psychosis, substance use disorder related traits including prior overdoses, diagnoses related to previous suicidal thoughts and behaviors) in addition to insomnia, physical effects of substance or alcohol use disorders, epilepsy and specific pain related diagnoses (back pain, chronic pain syndrome, migraine) were significantly overrepresented in suicide deaths with CP diagnoses (see Fig. 1; Additional file 1: Table S2). Odds ratios (ORs) ranged from 1.40 to 7.10 for significant phecodes. Specific phecodes included "Suicide or self-inflicted injury" [OR 7.10 (6.06–8.32); $p = 1.92e\text{-}136$], "Suicidal ideation" [OR 5.44 (4.70–6.31); $p = 5.86e\text{-}115$], "Poisoning by psychotropic agents" [OR 4.64 (3.98–5.42); $p = 1.58e\text{-}85$], "Personality disorders" [OR 3.74 (3.00–4.66); $p = 2.42e\text{-}31$], "Depression" [OR 3.70 (3.18–4.31); $p = 9.46e\text{-}70$], "Substance addiction and disorders" [OR 3.65 (3.19–4.18); $p = 1.33e\text{-}80$], "Anxiety disorders" [OR 3.04 (2.51–3.68); $p = 3.58e\text{-}29$], "Alcohol-related disorders" [OR 2.78 (2.38–3.24); $p = 2.75e\text{-}37$], "Posttraumatic stress disorder" [OR 2.58 (2.15–3.08), $p = 3.66e\text{-}24$], "Somatoform disorder" [OR 2.45 (1.90–3.16); $p = 1.78e\text{-}11$], "Psychogenic disorder" [OR 2.23 (1.58–3.13); $p = 7.30e\text{-}6$], "Insomnia" [OR 1.88 (1.65–2.16); $p = 5.57e\text{-}20$], "Epilepsy, recurrent seizures, convulsions" [OR 1.81 (1.45–2.25); $p = 2.80e\text{-}7$], "Migraine" [OR 1.49 (1.28–1.73); $p = 3.65e\text{-}7$], and "Back pain" [OR 1.47 (1.26–1.72); $p = 7.48e\text{-}7$] (see Additional file 1: Table S2 for all phecodes).

Table 3 Prevalence of common pain and medical conditions in suicide deaths with chronic pain diagnoses (SUI + CP) and controls with chronic pain diagnoses (CTRL + CP) defined from EHR phenotyping. For prevalence of all phecodes see Additional file 1: Table S1

Phecode	SUI + CP	CTRL + CP
Pain Conditions (%)		
Back pain	82.0	73.7
Other headache syndromes (TAC)	53.6	44.1
Myalgia and myositis unspecified (Fibromyalgia)	32.1	24.8
Acute pain	31.9	27.5
Migraine	30.1	19.2
Chronic pain syndrome	18.9	9.8
Irritable bowel syndrome	11.3	7.8
Tension headache	6.2	4.4
Chronic fatigue syndrome	5.1	2.7
Rheumatoid arthritis	4.4	3.6
Complex regional/central pain syndrome	2.3	1.4
Temporomandibular joint disorder	2.1	1.7
Other Conditions (%)		
Depression (broad sense)	78.0	48.7
Anxiety disorder	72.8	45.9
Tobacco use disorder	71.7	52.8
Substance addiction and disorders	60.4	29.3
Major depressive disorder	58.9	34.3
Essential hypertension	57.0	55.9
Insomnia	45.7	29.8
Suicidal ideation	44.8	13.0
Suicide attempt or self-injury	42.8	10.0
Alcoholism	38.4	17.7
Poisoning by psychotropic agents	38.4	11.8
Posttraumatic stress disorder	20.3	7.9
Type 2 diabetes	18.6	23.2
Somatoform disorder	8.9	3.2
Chemotherapy	7.1	13.5
Psychogenic disorder	4.5	1.7

Conversely, 25 phecodes related to preventative care, cancer, obesity and other conditions (e.g. osteoarthrosis, chronic kidney disease) were significantly overrepresented in controls with CP diagnoses (see Fig. 1; Additional file 1: Table S2). Odds ratios ranged from 0.16 to 0.73 for significant phecodes. Specific phecodes included "Obesity" [OR 0.67 (0.58–0.78); $p = 9.91e\text{-}8$], "Bariatric surgery" [OR 0.61 (0.51–0.73); $p = 1.92e\text{-}8$], "Benign neoplasm of skin" [OR 0.57 (0.46–0.70); $p = 3.12e\text{-}8$], "Chemotherapy" [OR 0.42 (0.33–0.52); $p = 2.33e\text{-}15$], "Cancer of brain" [OR 0.37 (0.22–0.60);

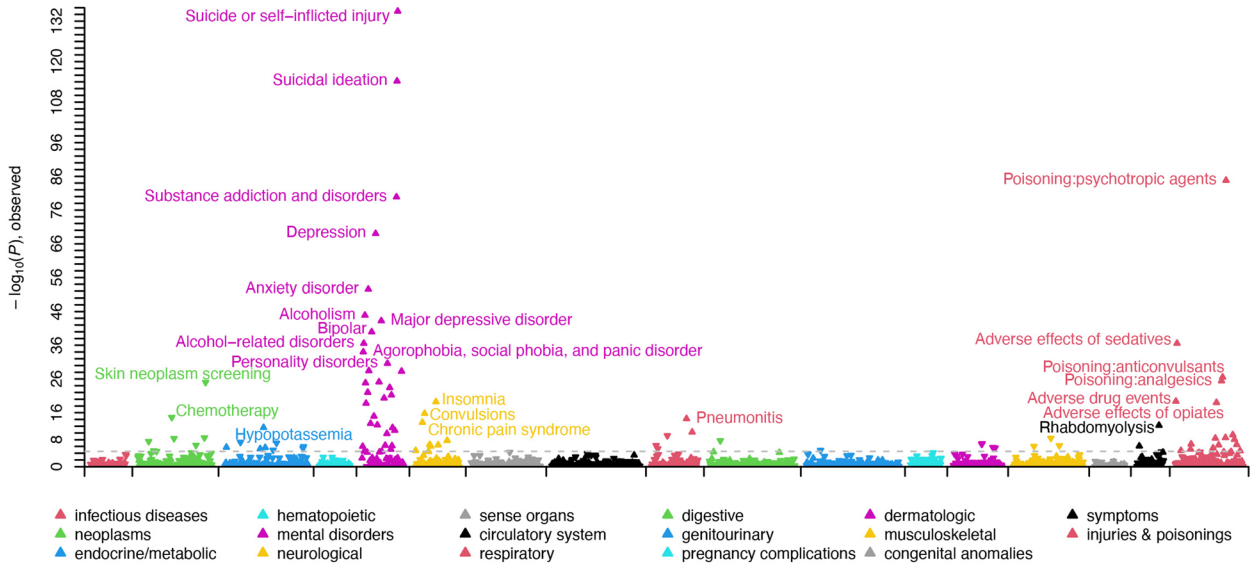

Fig. 1 Manhattan plot comparing clinical phenotypes (phecodes) across the phenome in the electronic health record (EHR) of SUI + CP vs CTRL + CP. Phenotypes are grouped into 17 color coded clinical categories along the x-axis. The y-axis represents the − log10 (*p*-value) of the association between clinical category and SUI + CP vs CTRL + CP. Arrows pointed upwards and indicate phenotypes that are elevated in SUI + CP; whereas downward arrows indicate elevated phenotypes among CTRL + CP. The dashed line indicates the significance threshold (*p*-values < 2.9e-5) with top significant clinical phenotypes (*p*-values < 2.9e-12) labeled for each category. 13 clinical phenotypes elevated in SUI + CP in the mental disorders category that meet this criteria are not labeled due to space constraints("Alteration of consciousness", "Altered mental status", "Antisocial/borderline personality disorder", "Anxiety disorders" "Attention deficit hyperactivity disorder", "Delirium due to conditions classified elsewhere" "Dysthymic disorder", "Generalized anxiety disorder", "Mood disorders", "Posttraumatic stress disorder", "Psychosis", "Schizophrenia", "Tobacco use disorder") For all significant results see Additional file 1: Table S2

p = 1.83e-5], "Type 2 diabetes with renal manifestations" [OR 0.36 (0.23–0.55); *p* = 1.04e-6], "Cancer of eye" [OR 0.28 (0.12–0.53); *p* = 2.68e-5] and "Chronic Kidney Disease, Stage IV" [OR 0.24 (0.10–0.49); *p* = 1.34e-5] (see Additional file 1: Table S2 for all phecodes).

In the secondary SUI + CP vs CTRL + CP comparison where two or more ICD codes in the "Chronic pain" phecode defined the groups, 55 phecodes related to psychiatric disorders (Mood disorders, Anxiety disorders, ADHD, PTSD, Personality disorders, Schizophrenia/psychosis, substance use disorder related traits including prior overdoses, diagnoses related to previous suicidal thoughts and behaviors) in addition to insomnia, physical effects of substance or alcohol use disorders, epilepsy and specific pain related diagnoses (chronic pain syndrome, migraine) were significantly overrepresented in suicide deaths with CP diagnoses (see Additional file 1: Table S3). Odds ratios ranged from 1.40 to 6.54 for significant phecodes. Conversely, 18 phecodes related to preventative care, cancer, obesity and other conditions (e.g. osteoarthrosis, chronic kidney disease) were significantly overrepresented in controls with CP diagnoses (see Additional file 1: Table S3). Odds ratios ranged from 0.18 to 0.68 for significant phecodes. 18 phecodes that were significantly different in the main analyses did not meet significant after correction for multiple testing in the secondary analyses.

In the female-specific analysis (SUI + CP vs CTRL + CP), 66 phecodes were significantly overrepresented in female suicide deaths with CP diagnoses (Additional file 1: Table S4). Sixty-one of these phecodes overlapped with those in the comparison of both sexes. Five phecodes related to non-specific minor injuries and fainting were significantly overrepresented only in the female SUI + CP vs CTRL + CP comparison and not in the comparison of both sexes. Four phecodes related to memory loss, abnormal movements and non-specific wounds were significant in the full analysis and not the female specific analysis. Twenty-two phecodes were statistically significantly overrepresented in female controls with CP diagnoses (Additional file 1: Table S4). Twenty of these overlapped with the comparison of both sexes with the addition of two preventative care phecodes. Five phecodes related to cancer (brain and eye), chronic kidney disease, morbid obesity and skin conditions were significant in the CTRL + CP group for full comparison but not the female-specific comparison.

In the male-specific analysis (SUI + CP vs CTRL + CP), 42 phecodes were statistically significantly overrepresented in male suicide deaths with CP diagnoses

(Additional file 1: Table S5). Forty of these phecodes overlapped with those in the comparison of both sexes and two related to open wounds were significant in the male only analysis. Twenty-five phecodes were present only in the comparison of both sexes and not the male specific analysis. These encompassed psychiatric traits (obsessive compulsive disorders, psychogenic disorder, paranoid disorders, schizoid personality disorder, alcohol and substance use disorder related traits), abnormal movement disorders and specific pain types (migraine, back pain). Thirteen phecodes were statistically significantly overrepresented in male controls with CP diagnoses (Additional file 1: Table S5). Ten of these overlapped with the comparison of both sexes with the addition of three phecodes related to dermatitis, swelling and thyroid cancer. Fifteen phecodes related to cancer (brain and eye), chronic kidney disease, obesity, type 2 diabetes, osteoarthrosis, preventative care, and skin conditions were significantly overrepresented in the CTRL + CP group for full comparison but not the male-specific comparison.

In the main SUI + CP vs CTRL + CP comparison where the model included the sex*suicide interaction term only one phecode tested ("Poisoning by psychotropic agents") had a significantly different effect sizes in males and females after correction for multiple testing. These results are shown in Additional file 1: Table S6.

Discussion

This study leveraged a unique population-based cohort to examine the complex relationship between CP and suicide death. To better understand what characterizes risk among members of a particularly vulnerable clinical population, we compared phenome-wide diagnostic records from the EHR in individuals with CP diagnoses that died by suicide to living individuals who also had CP diagnoses. Our results provide clinical risk profiles and comorbidities associated with individuals who had CP and died by suicide. These profiles highlight the need for comprehensive strategies that address not only the physical aspects of CP but also associated psychosocial implications and medical comorbidities.

Of individuals who were at least 18 years old with EHR data in the USMRS cohort, CP diagnoses were almost three times more prevalent in suicide deaths compared with 10:1 age/sex matched population controls (14.2% vs 4.9%). Also of note, 22.8% of suicide deaths in the overall cohort are female, yet 36.4% of the suicide deaths with CP are female. Additionally, there was a larger percentage of female controls with CP compared with all controls in the cohort (29.0% vs 24.3%). This is consistent with research showing that women experience and report pain at significantly higher rates compared to men [13, 14]. Since the strength of the model associations were stronger for women with CP in prior self-harm related diagnostic categories and significantly different in men and women for previous overdose events with psychotropic drugs, this work underscores the importance of proactive screening and monitoring for suicidality in individuals with CP—particularly women.

Our results highlight the significant medical complexity and multimorbidity in individuals with CP who died by suicide. The top findings and their associated odds ratios were consistent across the main and secondary analyses, which differed only in the EHR definition of CP in the assessed groups. 18 specific phecodes dropped just below significance in the more conservative EHR definition of CP, which is likely due to the reduction in sample size in the secondary analysis. Here we discuss specific comorbidities/phecodes that were significant across both analyses and discuss sample characteristics of the main analysis. Overall, results are consistent with previous studies demonstrating that CP is not an isolated issue but often coexists with other conditions across the medical spectrum, which can exacerbate each other [48]. Yet, individuals in the SUI + CP group have more diagnoses throughout their lifetime related to psychiatric traits including most major common psychiatric disorders, previous suicide and overdose attempts, insomnia, movement disorders, and physical effects of substance or alcohol use disorders, in addition to having more pain related diagnoses (chronic pain syndrome, migraine) compared with individuals in the CTRL + CP group. Clinicians may want to be aware that these types of co-occurrence are associated with increased suicide risk when seeing their patients.

Individuals in the SUI + CP group also had significantly more diagnoses in the "Substance addiction and disorders" phecode compared with controls (60.4% vs 29.3%). This phecode encompasses diagnoses related to opioid, hallucinogen, sedative, stimulant, inhalant, cannabis, and psychoactive substance use disorders. Additionally, more individuals in the SUI + CP group presented with alcohol related diagnoses compared with the CTRL + CP group (38.4% vs 17.7%). Comorbidities associated with drug and alcohol use disorders drove other primary findings (e.g. hypokalemia, pneumonitis, rhabdomyolysis, previous overdoses) in people with CP that died by suicide. Substance use disorders are common among people with CP, with prevalence ranges between 50–60% [49], and are associated with increased suicide risk, especially among women [28]. The odds of having diagnoses in the "Substance addiction and disorders" phecode are 3.70 times higher in the females and 3.00 times higher in the males who died by suicide with CP diagnoses compared to controls with CP. Our results are consistent with research

suggesting that CP, alcohol and substance use disorders, and suicidal behavior are closely linked [20, 24]. Screening, identifying and treating these conditions in an integrated manner may aid in suicide prevention efforts.

Those in the CTRL + CP group appeared more likely to present with co-occurring medical conditions that have well-established treatment strategies (e.g. those with more universally effective treatment approaches). For example, treatment strategies for type 2 diabetes and some cancers that were more prevalent in the CTRL + CP group are more well-defined, with clear guidelines and a range of effective medications available. More regular provider contact and follow-up may allow individuals to receive greater social support and validation, which could have a protective effect on mental health and mitigate suicide risk.

In contrast, the SUI + CP group appeared more likely to present with co-occurring conditions that are less clearly understood, more difficult to objectively measure, and more challenging to treat from a medical perspective. For example, substance use or alcohol disorders, insomnia and mood disorders have significant heterogeneity across various dimensions and typically require treatment plans tailored to an individual's needs and preferences [50, 51]. Perceptions of being a burden on others are common in adults experiencing functional impairment from physical conditions or psychological illness [52]. Self-perceived burden is commonly reported among people experiencing both CP and suicidal behavior [53]. Thus, it is possible that the phenome wide-medical complexity and associated treatment heterogeneity may contribute to hopelessness and perceived burdensomeness in suicidality outcomes in people experiencing CP [54].

In our analyses, rates of PTSD were also much higher in the SUI + CP group than in the CTRL + CP (20.3% vs 7.9%). There was also a relatively high prevalence of known veteran suicide decedents compared with controls (10.4% vs 0.4%). Many individuals with CP may have developed pain as a result of accidents, assaults, and other events that can result in long-term pain. These relationships are likely bi-directional, where the presence of traumatic stress can make one more likely to experience chronic pain syndromes (as seen in survivors of sexual abuse/assault) [55]. Furthermore, the high rates of depression and anxiety observed among the suicide deaths also likely include some missed cases of PTSD (given that PTSD is not routinely screened for in clinical encounters) [56]. We are unable to differentiate how many incidents of other mental health conditions observed in the suicide deaths with CP are better explained as trauma reactions. However, based on the overall outcome of suicide, it is possible that many of the anxiety/depression/other non-trauma mental health conditions were not treated adequately. This is common when trauma is not appreciated and appropriately addressed. Given the elevated rates of PTSD in the suicide group, future suicide prevention efforts among those with CP should attend to and respond to trauma and traumatic stress, even when individuals already have a non-trauma mental health diagnosis.

Overall, sleep disturbances may be a critical factor that underlies and connects many of the differences observed between the suicide and control group with CP. The major medical conditions highlighted that are more prevalent among suicide deaths with CP are directly worsened or considerably exacerbated by poor sleep. This adds support to the strong link between sleep disturbances and suicide in people with CP [16, 57]. Insomnia appears to be a key risk factor among suicide deaths with CP. Those with insomnia may use alcohol, sedatives, or other substances in an attempt to improve sleep, which can in turn worsen sleep quality [58]. Poor sleep quality is also associated with increased pain sensitivity and catastrophizing [59]. Additionally, the sleep disruption seen in conditions like PTSD, even without a physical injury, may contribute to the development of CP and further exacerbate suicide risk [60].

Our study has several limitations and implications for future work. First, the USMRS sample is predominantly composed of individuals from a Non-Hispanic White racial/ethnic background and geographically limited to Utah, USA and this limits generalizability of study results. Second, we defined common medical conditions from EHR diagnostic data. Biases in EHR data can arise for many reasons. For example, diagnostic criteria and coding policies may vary between healthcare facilities, coding errors may arise, or there may be missing data for some individuals. Third, we are unable to comprehensively characterize social determinates of health, trauma and life circumstances of suicide decedents. These are undoubtedly important risk factors in the development of CP or suicidal thoughts and behaviors. However, by focusing on clinical data derived from the healthcare system, we also highlight opportunities for treatment and prevention strategies among individuals struggling with CP and suicidality. Future research should examine diagnostic trajectories and timing of disease burden as they relate to CP and suicide death. Our findings regarding suicide death may be bi-directional in nature, and future research will need to further disentangle these complex relationships.

Conclusions

This study identified specific clinical comorbidities associated with CP that differentiate suicide deaths from living controls. Doing so highlights clinical risk profiles

that warrant future interventions tailored to address the unique challenges faced by individuals experiencing CP and suicidality. Vulnerable populations experiencing CP and suicidality may benefit from individualized medical care tailored to evaluate their level of suicide risk, to assess the influence that CP has on such risk, and to treat both CP and suicidality.

Abbreviations

ADHD	Attention deficit hyperactivity disorder
CP	Chronic pain
CTRL + CP	Control individuals with chronic pain diagnoses
EHR	Electronic health records
ICD	International Classification of Diseases
OME	Office of the Medical Examiner
OR	Odds ratio
PTSD	Post-traumatic stress disorder
RGE	Utah Resource for Genetic and Epidemiologic Research
SA	Suicide attempt
SD	Standard deviation
SI	Suicidal ideation
SUI + CP	Suicide deaths with chronic pain diagnoses
UPDB	Utah Population Database
USMRS	Utah Suicide Mortality Risk Study

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-024-03794-1.

Additional file 1: Table S1. The prevalence of phecodes by group and within each sex per group. Table S2. Model results in the main comparison of phecodes in the full analysis of SUI + CP vs CTRL + CP. Table S3. Model results in the secondary comparison of phecodes in the full analysis of SUI + CP vs CTRL + CP. Table S4. Model results in the comparison of phecodes in the female specific analysis of SUI + CP vs CTRL + CP. Table S5. Model results in the comparison of phecodes in the male specific analysis of SUI + CP vs CTRL + CP. Table S6. Model results in the comparison of phecodes in main analysis of SUI + CP vs CTRL + CP with a sex*suicide interaction term included.

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Authors' contributions
ED conceived and designed the study and analyzed the data. ED, EAK and SW wrote the first draft of the manuscript. AAS, DC and SH assisted with the study design and data analysis. SW, EEH, RJ, MS, BRK, ARD, AVB, AO, EM, and HC assisted with the methods and contributed to the interpretation of results and writing of the final manuscript. All authors read and approved the final manuscript. All authors had final responsibility for the decision to submit for publication.

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Data availability
Institutional guidelines and Institutional Review Boards from the University of Utah, Intermountain Healthcare and the Utah Department of Health and Human Services prohibit us from making individual-level data publicly available. Population-level deidentified data are availed to researchers who are interested in replicating our work upon reasonable request.

Declarations

Ethics approval and consent to participate
The Institutional Review Boards at the Utah Department of Health and Human Services (DHHS IRB #313), the University of Utah (UU IRB # 00133374) and Intermountain Health (IHC IRB # 1051740) approved this study.

Consent for publication
Individual-level data is not presented, not applicable.

Competing interests
The authors declare no competing interests.

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