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Trends in the Diagnosis of Diseases of Despair, 2009 - 2018

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Abstract

Objective: Increasing mortality and decreasing life expectancy in the U.S. are largely attributable to accidental overdose, alcohol-related disease, and suicide. These "deaths of despair," often follow years of morbidity, yet little is known about trends in the clinical recognition of "diseases of despair". The objective of this study is to characterize rates of clinically documented diseases of despair over the last decade and identify sociodemographic risk factors.

Design: Retrospective study using a healthcare claims database with 10 years of follow-up.

Setting: Participants resided nationwide but were concentrated in U.S. states disproportionately affected by deaths of despair, including Pennsylvania, West Virginia, and Delaware.

Participants: Cohort included 12,144,252 participants, with no restriction by age or gender.

Outcome Measures: Diseases of despair were defined as diagnoses related to alcohol misuse, substance misuse, and suicide ideation/behaviors. A lookback period was used to identify incident diagnoses. Annual and all-time incidence/prevalence estimates were computed, along with risk for current diagnosis.

Results: 515,830 participants received a disease of despair diagnosis (58.5% male, median 36 years). From 2009-2018, the prevalence of alcohol-, substance-, and suicide-related diagnoses respectively increased by 37%, 94%, and 170%. Ages 55-74 had the largest increase in alcohol/substance related diagnoses (59% and 172%). Ages <18 had the largest increase in suicide-related diagnoses (287%). Overall, odds for current-year diagnosis were higher among men (Adjusted Odds Ratio [AOR] = 1.49, 95% CI=1.47-1.51), and among those with Affordable Care Act or Medicare coverage relative to commercial coverage (AOR=1.30, 1.24-1.37; AOR=1.51, 1.46-1.55).

Conclusions: Increasing clinical rates of disease of despair diagnoses largely mirror broader societal trends in mortality. While the opioid crisis remains a top public health priority, parallel rises in alcohol-related diagnoses and suicidality must be concurrently addressed. Findings suggest opportunities for healthcare systems and providers to deploy targeted prevention to mitigate the progression of morbidities toward mortality.

Strengths and limitations of this study:

- Increasing mortality due to deaths of despair is well documented in extant research. To our knowledge, this study is the first to provide large-scale insights into the clinical recognition of the morbidities that can ultimately culminate in those deaths. This clinical perspective highlights potential opportunities to intervene in the progression of morbidity toward mortality.

- The study uses a large and inclusive sample. As a result, we are able to identify differential patterns in the diagnosis of substance-, alcohol-, and suicide-related diagnoses across age and gender lines, which can improve targeted prevention efforts.

- The long administrative surveillance period of 10 years allows us to track changes in the identification of diseases of despair over time, and to compare long-term trends between documented morbidity and mortality.

- While trends in deaths of despair appear to vary by race/ethnicity, details on race/ethnicity were not available for our sample.

- We were unable to directly link disease of despair incidence/prevalence to mortality on an individual level; rather, we compare trends in morbidity and mortality in more general terms.

From 2015-2017, there has been an annual downward trend in life expectancy in the United States, the longest sustained decline since 1915-1918.[1,2] Relatedly, researchers have observed a longer, more marked increase in the all-cause mortality of middle-aged white non-Hispanic men and women in the US between 1999 and 2015, with premature deaths largely associated with "deaths of despair," including suicides, accidental poisonings (e.g. opiate overdose), and alcohol-related liver disease (e.g. cirrhosis).[3,4]

This troubling observation has coincided with decades of economic decline for less educated and unskilled workers, stagnant or falling real median wages and family incomes,[5,6] lower marriage rates,[7] increases in single-parent households,[8] and disengagement from the labor force.[9] It is theorized that these changes have fostered growing feelings of despair, i.e., disillusionment, precariousness, and resignation.[3,4,10-12] Despair may in turn trigger emotional, cognitive, behavioral, and even biological changes,[13-17] increasing the likelihood of diseases that can progress and ultimately culminate in these deaths of despair.

While this pathway may unfold over years or decades, to date, most studies in this domain have primarily focused on the endpoint of mortality. Limited extant research suggests a parallel rise in associated morbidities,[3,4] but specific estimates of "disease of despair" morbidity (i.e., substance-related disorders, alcohol-related disorders, and suicide ideation and attempts) are lacking. Moreover, little is known about trends in the recognition and documentation of these diseases in the clinical setting. This represents an important gap in the literature; indeed, while primary prevention efforts to address the root causes of societal despair are needed, it may be possible to intervene upon the pathway from morbidity to mortality in the clinical setting. An understanding of diagnostic patterns and the association between documented morbidity and mortality is necessary to guide these secondary and tertiary prevention efforts. Thus, the

objectives of the present study were to use a large administrative database of healthcare claims to 1) characterize the incidence and prevalence of diseases of despair diagnoses over the last decade; 2) identify individual sociodemographic factors associated with disease of despair diagnosis; and 3) discuss patterns in morbidity and mortality.

Methods

This retrospective cohort study used claims data extracted from the administrative databases of Highmark Inc., a large US-based health insurance company. Highmark members are concentrated in states that have been disproportionately affected by deaths of despair, including Pennsylvania, West Virginia, and Delaware.[18,19] The database contains clinical information such as services used and diagnoses assigned, and sociodemographic characteristics including gender, age, home address, and insurance coverage details. The study cohort included 12 million individuals who were enrolled in a Highmark health insurance plan between 2007 and 2018, and who had a valid age, gender, and home address on file. Over 98.5% of enrolled individuals met inclusion criteria and were included in the final analytic cohort.

Study Variables

Diseases of despair were defined as diagnoses related to alcohol use, substance use, and suicide ideation/behaviors. International Classification of Diseases (ICD) codes were extracted from claims and classified into variables indicating the presence or absence of a diagnosis within each of the three diagnostic categories of interest. Classifications were adapted from the Healthcare Cost and Utilization Project Clinical Classification Software (HCUP-CCS).[20] Code mappings were used for HCUP categories alcohol-related disorders (5.11), substance-related disorders (5.12), and suicide and intentional self-inflicted injury (5.13). Diagnoses related to substance use considered outside the focus of the present study were excluded, specifically,

codes related to the use of tobacco and cannabis, and certain non-psychoactive substances (i.e., ICD-10 codes F550, F551, F552, F554). Additional indicators were created for overall disease of despair status (diagnosis of any type), and co-occurring diseases of despair status (diagnoses in multiple categories). A two-year lookback period was used to identify incident diagnoses. If no record of the given diagnosis type was found during the lookback period, the diagnosis was recorded as an incident case. Annual and all-time incidence and prevalence estimates were computed.

Insurance Coverage

Insurance product information was recoded into the following categories: Employer sponsored; individual market Affordable Care Act (ACA) plans; Medicare, and Other. Product information was captured on an annual basis. If multiple products were found on file during a single year, the product covering the larger number of months was recorded.

To determine whether cohort members were at-risk for being diagnosed with a disease of despair at any given point, the months enrolled during each year of follow-up were recorded for all cohort members. Except for newborns, members were considered "enrolled" for a given year if at they were covered for at least 10 months out of the year. Newborns were considered enrolled if coverage was identified within the first 90 days of life.

Data Analysis

Incidence and Prevalence of Diseases of Despair

Descriptive statistics were computed for all study variables both overall and stratified by diagnostic status ("any" versus "no" disease of despair diagnosis recorded over the course of follow-up). Differences were statistically compared using chi-square tests for categorical variables, and t-tests for continuous variables. Next, overall and gender- and age-specific

incidence and prevalence rates of disease of despair diagnosis were computed for years 2009 through 2018, allowing for an initial lookback period beginning in 2007. Rates were calculated by dividing the number of newly identified cases by the number of members enrolled and with no previous diagnosis in the past two years (incidence), and the number of current year cases by number of members enrolled (prevalence).

The partially overlapping samples z-test[21] was used to statistically test if and the degree to which rates of diseases of despair changed over the last decade. The partially overlapping test is designed for the statistical comparison of proportions when data include a combination of paired and unpaired samples, as is often the case in dynamic cohorts extracted from clinical databases.

Predicting Individual-level Risk for Diseases of Despair

To identify factors associated with individual-level risk for disease of despair diagnosis during the most recent year of follow-up (2018), logistic regression was used to estimate risk for diagnosis as a function of demographic and enrollment characteristics. Odds ratios and their 95% confidence intervals were computed for all estimates. Analyses were performed using R, version 3.5.2[22] within Highmark's secure computing environment.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. The study was approved by the Institutional Review Boards of [blinded]. Informed consent was waived, as no study participants were contacted. Due to privacy laws, data cannot be made publicly available.

Results

Overall, 4.2% of cohort members (N = 515,830) were diagnosed with at least one disease of despair at some point during follow-up. Among these, 54.0% were diagnosed with an alcohol-related disorder, 44.2% with a substance-related disorder, and 16.3% with suicide ideation/behaviors; multiple types of diseases of despair diagnoses were recorded for 12.9%. Additional cohort description is presented in **Table 1**.

[TABLE 1]

Age and gender-specific diagnostic prevalence rates from 2009 to 2018 are presented in **Figure 1.** Aggregate incidence and prevalence rates and statistical comparisons between 2009 and 2018 are discussed in the following sections. Age- and gender-stratified statistics are presented in **Tables 2 and 3**.

[FIGURE 1, TABLES 1 AND 2]

Any Disease of Despair Diagnosis

Between 2009 and 2018, the annual diagnostic incidence of diseases of despair increased by 44%, and the diagnostic prevalence increased by 68%. Significant increases were seen for both men and women across every age group, although the magnitude of increases varied along age and gender lines. While percentage point increases tended to be smaller among women compared to men, relative increases tended to be larger among women.

Alcohol-related Diagnosis

The overall incidence and prevalence of alcohol-related diagnosis increased by 23% and 37%, respectively. Significant increases were seen for men and women ages 18 and above, but significant decreases were seen for those ages 1-17. The most dramatic increases were seen among those ages 55-74; their prevalence increased by .5% percentage points (59% relative increase).

Substance-related Diagnosis

The overall incidence and prevalence of substance-related diagnosis increased by 48% and 94%, respectively. As with the trends observed for alcohol-related diagnoses, the incidence and prevalence of substance-related diagnoses increased for all groups except for those ages 1-17; for this group, rates significantly decreased. Relative increases were again highest for those ages 55-57 (prevalence 172% higher; .5% percentage point increase), and for infants (prevalence 114% higher; .25% percentage point increase).

Suicide Ideation / Behaviors Diagnosis

The incidence and prevalence of suicide-related diagnosis increased for all relevant age groups (infants were excluded) by 149% and 170%, respectively. While the absolute rates of suicide-related diagnosis were lower than other types of disease of despair diagnoses, the relative increases were dramatic. Among those ages 1-17, the prevalence increased by 287%. Among those ages 18-34, it increased by 210%. All other age groups saw a relative increase of at least 70%.

Logistic Regression Results

Results of logistic regression models predicting the odds for 2018 disease of despair diagnoses as a function of individual and enrollment characteristics are presented in **Table 4**.

[TABLE 4]

Men had higher odds than women of having any type of disease of despair diagnosis, alcohol-related diagnosis, and substance-related diagnosis (AOR [adjusted odds ratio] = 1.49, 2.35, and 1.23, respectively), but lower odds than women for suicide ideation/behaviors (AOR = 0.72). Age was also significantly associated with risk for all four disease of despair outcomes. After adjusting for gender and insurance type, individuals ages 18-35 had the highest risk for any

disease of despair, substance-related diagnosis, and suicide-related diagnosis. For alcohol-related disorders, those ages 35-74 were at slightly higher risk than those ages 18-34, and much higher risk than any other group. Finally, type of enrollment was also significantly related to risk. Compared to commercial insurance plans, Affordable Care Act (ACA) plans were associated with approximately 1.3 times higher odds for any diagnosis, alcohol-related diagnosis, and substance-related diagnosis, but similar risk for suicide-related diagnoses. Medicare plans were associated with 1.5 times higher odds for any disease of despair and each of the three diagnostic subtypes (AOR range was 1.3 – 2.2).

Discussion

Nearly one in twenty individuals in our sample were clinically diagnosed with a disease of despair between 2007 and 2018. Similar to observed despair-related mortality, diseases of despair have significantly increased as morbidities over the past decade. Tracking with the original finding that deaths of despair have disproportionately affected middle-aged men,[3] our data showed the largest absolute increases in overall prevalence for men ages 35-74, followed by women ages 55-74 and 18-34. These findings reinforce the notion that while the opioid crisis remains a top public health priority, parallel rises in alcohol-related diagnoses and suicidality must be concurrently addressed.

The relative increases in specific diagnoses seen in infants, youth, and young adults were also striking. Among infants, the prevalence of substance-related diagnoses doubled over the course of follow-up. This increase was entirely attributable to neonatal abstinence syndrome and corresponds closely with increases in substance-related disorders among women of childbearing age. Neonatal abstinence syndrome could be argued to be the direct result of a disease of despair among mothers, and therefore, was included. In addition, the prevalence of suicide ideation and

behaviors among youth and young adults at least tripled over the course of follow-up. These findings underscore the importance of targeting vulnerable subpopulations in tailored prevention and early intervention services. A recent study by Gaydosh et al. used nationally representative longitudinal data to examine diseases of despair and their age patterns from adolescence through the late-30s from 1994-2017.[23] This study demonstrated increases as the cohort aged into their late 30s, across racial and ethnic groups as well as geographic locales. In addition to broadening original views beyond impacting whites in rural locales, the generalized increases in despair documented among this younger cohort forewarn further likely increases in mid-life mortality in the coming decades.

The concept of despair, itself, remains largely unstudied, with manifestations in cognitive, emotional, behavioral, and biological domains as well as in social and political-economic contexts.[17] For example, Glei et al characterized despair by social and psychological dysfunction such as a lack of purpose in life, a sense of worthlessness, little hope or goals for the future, and perceived social rejection by broader society.[5] Shanahan et. al provided a roadmap for studying the social contexts that can further strengthen or weaken pathways to despair. Ultimately, improving the ability to measure and clinically screen for despair, as opposed to resultant diseases or deaths, will allow us to best intervene. Definitively addressing despair requires tackling the root causes (i.e. deep structural forces that perpetuate socioeconomic disadvantage) for which there are no quick fixes.[24]

By definition, diagnoses of diseases of despair and health insurance enrollment imply access to health care, although it is clear additional barriers to treatment exist. Insurance type is an important predictor of disease diagnoses, and diseases of despair are no exception. Individuals with Medicare, for example, have 1.5 times higher odds of having a diagnosis of a disease of

despair, followed by those with ACA (1.3 times higher odds). Insurance status is frequently used as a surrogate for measures of socioeconomic status, which are essential to describing health inequalities. Unfortunately, this is an imperfect proxy.[25]

A limitation of the current study is the incomplete nature of social determinants of health data in administrative health records. Despite the significant influence of these factors on health outcomes, few sources provide data that includes both clinical and social and behavioral factors. To address this gap in clinical records, the Institute of Medicine Committee on Recommended Social and Behavioral Domains and Measures for Electronic Health Records describes a concise panel of standard measures in every patient's electronic health record.[26] These measures include items evaluating depression, alcohol use, and social connection or isolation which would help capture diagnoses of despair. Future research might consider combining clinical records with data originating outside of claims and electronic health records, including direct and indirect measures of social determinants. Due to the large size of the sample, this study had considerable statistical power and tests were able to detect small but statistically significant effects. Thus, it is important that consideration is given to the practical significance of effects, including the absolute differences in risks over time and between groups.

A significant strength of the current study is the investigation of the upstream diagnoses for deaths of despair in a large cohort with representation of some of the most impacted states, including West Virginia and Pennsylvania. Further, the use of a large claims-based dataset provides insight into health insurance type as a consideration in the development of future potential healthcare interventions. Finally, these data provide information on current diagnosis rates in the context of long-term trends. Continued improvements to the monitoring and

identification of substance use and abuse, suicidality, and mental health more broadly are critical next steps to address diseases of despair and ultimately, decrease mortality.

Future inquiry could benefit from similar "big data" approaches to understand and model patterns of despair in human populations. For instance, it would be useful to identify "hot-spots" of high prevalence/incidence of diseases of despair diagnoses (and deaths of despair) and examine the socioeconomic conditions in these areas over time. While mortality increases are generally—if inscrutably—understood to be due to prolonged declining socioeconomic conditions that exacerbate despair, others argue that the phenomenon is more attributable to other contextual factors such as: a worsening drug environment;[27-29] the collapse of social institutions and weakening of traditional social bonds (e.g. reduced church attendance,[30] union membership, etc.);[31] a generalized cultural rise in loneliness, depression, alienation, and anxiety;[32] higher relative gun ownership in rural areas;[33] and a "loss of virtue".[34] Using big data to build predictive models of neighborhoods or census tracts where people may be at greatest risk would not only clarify current debates about past causation but also offer a future tool of clinical and public health importance.

Researchers might also undertake qualitative and/or mixed methods inquiry to examine subjective perceptions of despair in high prevalence communities. There may be particular value in engaging leaders of community and social service organizations (libraries, emergency rooms, methadone treatment centers, suicide prevention organizations, homeless shelters, Women, Infants, and Children (WIC) clinics, legal services organizations, state police, churches, centers, county health services, and places of worship, etc.) who interface with high-risk communities, as well as affected persons and family members. It would be especially useful to better understand general awareness of the diseases of despair concept, local beliefs about causation, perceptions

of effective policy solutions at the local, state, and national levels, and strategies hospitals can use to most effectively intervene. Given the complexity of societal despair, combining quantitative and qualitative approaches may be particularly useful.

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Table 1. Descriptive Statistics for Study Cohort, Overall and Stratified by the Presence of Disease of Despair (DoD) Diagnosis at any Point during Follow up, 2007 – 2018.

	Overall N = 12,144,252 (100.0%)	**No DoD** N = 11,628,422 (95.8%)	**DoD** N = 515,830 (4.2%)	*p*-value
	N (%) / M (SD)			
Type of DoD Diagnosis				
Alcohol-related	278,309 (2.3%)	-	278,309 (54.0%)	
Drug-related	228,227 (1.9%)	-	228,227 (44.2%)	
Suicide Ideation/Behavior	84,117 (0.7%)	-	84,117 (16.3%)	
Multiple Diagnosis Types	66,585 (0.5%)	-	66,585 (12.9%)	
Gender				<.001
Women	6,124,183 (50.4%)	5,909,902 (50.8%)	214,281 (41.5%)	
Men	6,020,069 (49.6%)	5,718,520 (49.2%)	301,549 (58.5%)	
Age at Enrollment Midpoint				<.001
0 – 17 years	2,666,135 (22%)	2,625,797 (22.6%)	40,338 (7.8%)	
18 – 25 years	1,539,995 (12.7%)	1,456,629 (12.5%)	83,366 (16.2%)	
26 – 35 years	1,752,493 (14.4%)	1,677,395 (14.4%)	75,098 (14.6%)	
36 – 45 years	1,638,938 (13.5%)	1,560,822 (13.4%)	78,116 (15.1%)	
46 – 55 years	1,754,037 (14.4%)	1,659,732 (14.3%)	94,305 (18.3%)	
56 – 65 years	1,628,179 (13.4%)	1,547,308 (13.3%)	80,871 (15.7%)	
66 – 75 years	586,303 (4.8%)	552,101 (4.7%)	34,202 (6.6%)	
76 – 85 years	366,120 (3%)	345,023 (3%)	21,097 (4.1%)	
85+ years	212,052 (1.7%)	203,615 (1.8%)	8,437 (1.6%)	
Number of Years Enrolled	4.8 (3.4)	4.7 (3.4)	6.6 (3.4)	<.001
Most Recent Enrollment				<.001
2007 – 2009	1,467,763 (12.1%)	1,440,453 (12.4%)	27,310 (5.3%)	
2010 – 2012	1,796,257 (14.8%)	1,739,269 (15%)	56,988 (11.0%)	
2013 – 2015	2,528,619 (20.8%)	2,421,676 (20.8%)	106,943 (20.7%)	
2016 – 2018	6,351,613 (52.3%)	6,027,024 (51.8%)	324,589 (62.9%)	
Medical Insurance Type				<.001
Employer Sponsored	9,516,477 (78.4%)	9,105,741 (78.3%)	410,736 (79.6%)	
ACA	354,355 (2.9%)	340,900 (2.9%)	13,455 (2.6%)	
Medicare	752,594 (6.2%)	699,619 (6%)	52,975 (10.3%)	
Other	1,520,825 (12.5%)	1,482,161 (12.7%)	38,664 (7.5%)	

Notes: If there were multiple values on file for state or type of insurance, the value covering longest period was selected. ACA plans were available 2014-2018.

Figure 1. Age and Gender-Specific Diagnostic Prevalence Rates of Diseases of Despair, 2009 – 2018.

[attached separately]

Table 2. Comparison of Age and Gender Specific Annual Incidence of Disease of Despair Diagnoses, 2009 – 2018.

	Men				Women			
Age Cohort	**2009**	**2018**	***p*-value**	**Ratio**	**2009**	**2018**	***p*-value**	**Ratio**
Any Disease of Despair Diagnosis								
> 1 Year	.25%	.52%	<.001	**2.05**	.17%	.36%	.001	**2.18**
1 - 17 Years	.28%	.38%	<.001	**1.37**	.27%	.53%	<.001	**1.96**
18 - 34 Years	1.44%	1.73%	<.001	**1.21**	.94%	1.42%	<.001	**1.51**
35-54 Years	1.21%	1.58%	<.001	**1.30**	.72%	1.01%	<.001	**1.40**
55-74 Years	1.08%	1.61%	<.001	**1.48**	.53%	.95%	<.001	**1.78**
75+ Years	.99%	1.23%	<.001	**1.25**	.69%	.85%	<.001	**1.23**
Alcohol-Related Diagnosis								
> 1 Year	.03%	.03%	1.000	.90	.00%	.01%	.951	-
1 - 17 Years	.09%	.05%	<.001	**.60**	.09%	.04%	<.001	**.49**
18 - 34 Years	.93%	.97%	.103	1.05	.45%	.56%	<.001	**1.26**
35-54 Years	.90%	1.03%	<.001	**1.15**	.36%	.44%	<.001	**1.22**
55-74 Years	.84%	1.11%	<.001	**1.32**	.26%	.42%	<.001	**1.60**
75+ Years	.63%	.76%	.003	**1.19**	.24%	.25%	.932	1.07
Substance-Related Diagnosis								
> 1 Year	.23%	.49%	<.001	**2.14**	.17%	.36%	<.001	**2.14**
1 - 17 Years	.14%	.08%	<.001	**0.58**	.11%	.05%	<.001	**0.47**
18 - 34 Years	.57%	.72%	<.001	**1.26**	.44%	.58%	<.001	**1.33**
35-54 Years	.37%	.58%	<.001	**1.59**	.34%	.50%	<.001	**1.50**
55-74 Years	.26%	.51%	<.001	**2.00**	.24%	.49%	<.001	**2.04**
75+ Years	.32%	.37%	.117	1.16	.39%	.46%	<.001	**1.20**
Suicide-Related Diagnosis								
> 1 Year	-	-	-	-	-	-	-	-
1 - 17 Years	.09%	.28%	<.001	**3.20**	.13%	.47%	<.001	**3.77**
18 - 34 Years	.14%	.42%	<.001	**2.95**	.19%	.52%	<.001	**2.69**
35-54 Years	.09%	.15%	<.001	**1.81**	.13%	.20%	<.001	**1.52**
55-74 Years	.06%	.13%	<.001	**2.23**	.07%	.13%	<.001	**1.75**
75+ Years	.08%	.16%	<.001	**2.09**	.08%	.14%	<.001	**1.83**

Notes: Ratios represent 2018 rates relative to 2009 incidence rates. Bolded ratios correspond to statistically significant differences in diagnostic incidence.

Table 3. Comparison of Age and Gender Specific Annual Prevalence of Disease of Despair Diagnoses, 2009 – 2018.

	Men				Women			
Age Cohort	**2009**	**2018**	***p*-value**	**Ratio**	**2009**	**2018**	***p*-value**	**Ratio**
Any Disease of Despair Diagnosis								
> 1 Year	.25%	.52%	<.001	**2.05**	.17%	.36%	<.001	**2.18**
1 - 17 Years	.33%	.45%	<.001	**1.37**	.32%	.65%	<.001	**2.04**
18 - 34 Years	1.93%	2.66%	<.001	**1.38**	1.19%	2.05%	<.001	**1.71**
35-54 Years	1.72%	2.68%	<.001	**1.56**	1.03%	1.68%	<.001	**1.63**
55-74 Years	1.55%	2.72%	<.001	**1.75**	.72%	1.59%	<.001	**2.21**
75+ Years	1.27%	1.89%	<.001	**1.49**	0.80%	1.18%	<.001	**1.46**
Alcohol-Related Diagnosis								
> 1 Year	.03%	.03%	1.000	0.90	.00%	.01%	0.950	**-**
1 - 17 Years	.10%	.07%	<.001	**0.67**	.10%	.05%	<.001	**0.53**
18 - 34 Years	1.12%	1.30%	<.001	**1.16**	.52%	.72%	<.001	**1.37**
35-54 Years	1.23%	1.54%	<.001	**1.25**	.52%	.68%	<.001	**1.29**
55-74 Years	1.23%	1.85%	<.001	**1.51**	.38%	.69%	<.001	**1.84**
75+ Years	0.87%	1.24%	<.001	**1.43**	.31%	.37%	0.140	1.17
Substance-Related Diagnosis								
> 1 Year	.23%	.49%	<.001	**2.14**	.17%	.36%	<.001	**2.14**
1 - 17 Years	.17%	.09%	<.001	**0.57**	.13%	.06%	<.001	**0.46**
18 - 34 Years	.85%	1.30%	<.001	**1.53**	.59%	.96%	<.001	**1.62**
35-54 Years	.53%	1.19%	<.001	**2.24**	.48%	.92%	<.001	**1.93**
55-74 Years	.33%	.88%	<.001	**2.70**	.30%	.83%	<.001	**2.73**
75+ Years	.35%	.51%	<.001	**1.47**	.42%	.67%	<.001	**1.59**
Suicide-Related Diagnosis								
> 1 Year	-	-	-	-	-	-	-	-
1 - 17 Years	.09%	.31%	<.001	**3.43**	.14%	.58%	<.001	**4.17**
18 - 34 Years	.15%	.49%	<.001	**3.20**	.21%	.64%	<.001	**3.03**
35-54 Years	.09%	.17%	<.001	**1.89**	.14%	.23%	<.001	**1.60**
55-74 Years	.06%	.15%	<.001	**2.33**	.08%	.15%	<.001	**1.88**
75+ Years	.08%	.17%	<.001	**2.11**	.09%	.17%	<.001	**1.94**

Notes: Ratios represent 2018 rates relative to 2009 prevalence rates. Bolded ratios correspond to statistically significant differences in diagnostic prevalence.

Table 4. Risk for Disease of Despair Diagnosis as a Function of Demographic and Enrollment Characteristics, 2018.

	Any Disease of Despair		Alcohol-Related Diagnosis		Substance-Related Diagnosis		Suicide-Related Diagnosis	
Variable	Adjusted Odds Ratio (95% Confidence Interval)							
Men [ref = Women]	**1.49**	**(1.47, 1.51)**	**2.35**	**(2.30, 2.41)**	**1.23**	**(1.20, 1.25)**	**0.72**	**(0.70, 0.75)**
Age [ref = 18-34]								
<1	**0.18**	**(0.15, 0.22)**	**0.02**	**(0.01, 0.04)**	**0.37**	**(0.31, 0.44)**	-	- -
1-17	**0.23**	**(0.22, 0.24)**	**0.06**	**(0.05, 0.06)**	**0.07**	**(0.06, 0.08)**	**0.79**	**(0.75, 0.83)**
35-54	**0.92**	**(0.90, 0.94)**	**1.09**	**(1.06, 1.13)**	**0.92**	**(0.90, 0.95)**	**0.35**	**(0.33, 0.37)**
55-74	**0.83**	**(0.81, 0.84)**	**1.19**	**(1.15, 1.22)**	**0.66**	**(0.64, 0.68)**	**0.21**	**(0.20, 0.23)**
75+	**0.44**	**(0.42, 0.46)**	**0.59**	**(0.55, 0.63)**	**0.34**	**(0.31, 0.36)**	**0.15**	**(0.13, 0.17)**
Insurance [ref = employer sponsored]								
ACA	**1.30**	**(1.24, 1.37)**	**1.37**	**(1.28, 1.48)**	**1.33**	**(1.24, 1.42)**	1.05	(0.91, 1.21)
Medicare	**1.51**	**(1.46, 1.55)**	**1.30**	**(1.25, 1.36)**	**1.73**	**(1.65, 1.81)**	**2.19**	**(1.98, 2.43)**
Other	**0.71**	**(0.67, 0.74)**	**0.73**	**(0.68, 0.78)**	**0.61**	**(0.57, 0.66)**	**0.84**	**(0.77, 0.92)**

Notes: Bold indicates statistical significance, $p < .05$.

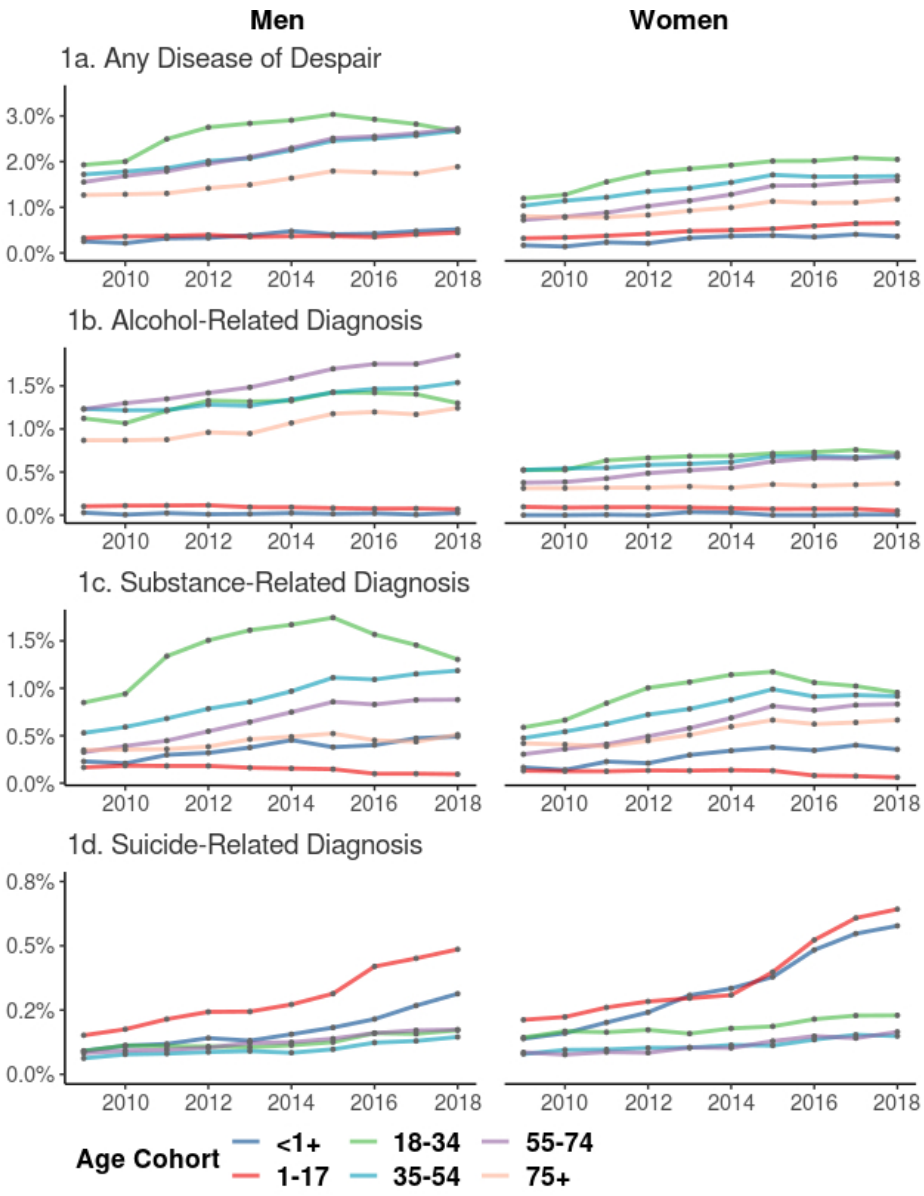
Men
Women
1a. Any Disease of Despair
3.0%
2.0%
1.0%
0.0%
2010
2012
2014
2016
2018
1b. Alcohol-Related Diagnosis
1.5%
1.0%
0.5%
0.0%
1c. Substance-Related Diagnosis
1d. Suicide-Related Diagnosis
0.8%
0.5%
0.2%
0.0%
Age Cohort
<1+
1-17
18-34
35-54
55-74
75+

Figure 1

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Trends in the Diagnosis of Diseases of Despair in the United States, 2009 – 2018: A Retrospective Cohort Study

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Abstract

Background and Objective: Increasing mortality and decreasing life expectancy in the U.S. are largely attributable to accidental overdose, alcohol-related disease, and suicide. These "deaths of despair" often follow years of morbidity, yet little is known about trends in the clinical recognition of "diseases of despair". The objective of this study is to characterize rates of clinically documented diseases of despair over the last decade and identify sociodemographic risk factors.

Design: Retrospective study using a healthcare claims database with 10 years of follow-up.

Setting: Participants resided nationwide but were concentrated in U.S. states disproportionately affected by deaths of despair, including Pennsylvania, West Virginia, and Delaware.

Participants: Cohort included 12,144,252 participants, with no restriction by age or gender.

Outcome Measures: Diseases of despair were defined as diagnoses related to alcohol misuse, substance misuse, and suicide ideation/behaviors. A lookback period was used to identify incident diagnoses. Annual and all-time incidence/prevalence estimates were computed, along with risk for current diagnosis and patterns of comorbidity.

Results: 515,830 participants received a disease of despair diagnosis (58.5% male, median 36 years). From 2009-2018, the prevalence of alcohol-, substance-, and suicide-related diagnoses respectively increased by 37%, 94%, and 170%. Ages 55-74 had the largest increase in alcohol/substance related diagnoses (59% and 172%). Ages <18 had the largest increase in suicide-related diagnoses (287%). Overall, odds for current-year diagnosis were higher among men (Adjusted Odds Ratio [AOR] = 1.49, 95% CI=1.47-1.51), and among those with Affordable Care Act or Medicare coverage relative to commercial coverage (AOR=1.30, 1.24-1.37; AOR=1.51, 1.46-1.55).

Conclusions: Increasing clinical rates of disease of despair diagnoses largely mirror broader societal trends in mortality. While the opioid crisis remains a top public health priority, parallel rises in alcohol-related diagnoses and suicidality must be concurrently addressed. Findings suggest opportunities for healthcare systems and providers to deploy targeted prevention to mitigate the progression of morbidities toward mortality.

Strengths and limitations of this study:

- Increasing mortality due to deaths of despair is well documented in extant research. To our knowledge, this study is the first to provide large-scale insights into the clinical recognition of the morbidities that can ultimately culminate in those deaths. This clinical perspective highlights potential opportunities to intervene in the progression of morbidity toward mortality.

- The study uses a large and inclusive sample. As a result, we are able to identify differential patterns in the diagnosis of substance-, alcohol-, and suicide-related diagnoses across age and gender lines, which can improve targeted prevention efforts.

- The long administrative surveillance period of 10 years allows us to track changes in the identification of diseases of despair over time, and to compare long-term trends between documented morbidity and mortality.

- While trends in deaths of despair appear to vary by race/ethnicity, details on race/ethnicity were not available for our sample.

- We were unable to directly link disease of despair incidence/prevalence to mortality on an individual level; rather, we compare trends in morbidity and mortality in more general terms.

From 2015-2017, there was an annual downward trend in life expectancy in the United States, the longest sustained decline since 1915-1918.[1,2] Relatedly, researchers have observed a longer, more marked increase in the all-cause mortality of middle-aged white non-Hispanic men and women in the US between 1999 and 2015, with premature deaths largely associated with "deaths of despair," including suicides, accidental poisonings (e.g. opiate overdose), and alcohol-related liver disease (e.g. cirrhosis).[3,4]

This troubling observation has coincided with decades of economic decline for less educated and unskilled workers, stagnant or falling real median wages and family incomes,[5,6] lower marriage rates,[7] increases in single-parent households,[8] and disengagement from the labor force.[9] It is theorized that these changes have fostered growing feelings of despair, i.e., disillusionment, precariousness, and resignation.[3,4,10-12] Despair may in turn trigger emotional, cognitive, behavioral, and even biological changes,[13-17] increasing the likelihood of diseases that can progress and ultimately culminate in these deaths of despair.

While this pathway may unfold over years or decades, to date, most studies in this domain have primarily focused on the endpoint of mortality. Limited extant research suggests a parallel rise in associated morbidities,[3,4] but specific estimates of "disease of despair" morbidity (i.e., substance-related disorders, alcohol-related disorders, and suicide ideation and attempts) are lacking. Moreover, little is known about trends in the recognition and documentation of these diseases in the clinical setting. This represents an important gap in the literature; indeed, while primary prevention efforts to address the root causes of societal despair are needed, it may be possible to intervene upon the pathway from morbidity to mortality in the clinical setting. An understanding of diagnostic patterns and the association between documented morbidity and mortality is necessary to guide these secondary and tertiary prevention efforts. Thus, the

objectives of the present study were to use a large administrative database of healthcare claims to 1) characterize the incidence and prevalence of diseases of despair diagnoses over the last decade and 2) identify individual sociodemographic factors and patterns of comorbidity associated with disease of despair diagnosis. Finally, patterns in morbidity and mortality are discussed.

Methods

This retrospective cohort study used claims data extracted from the administrative databases of Highmark Inc., a large US-based health insurance company. Highmark members are concentrated in states that have been disproportionately affected by deaths of despair, including Pennsylvania, West Virginia, and Delaware.[18,19] The database contains clinical information such as services used and diagnoses assigned, and sociodemographic characteristics including gender, age, home address, and insurance coverage details. The study cohort included 12 million individuals who were enrolled in a Highmark health insurance plan between 2007 and 2018, and who had a valid age, gender, and home address on file. Over 98.5% of enrolled individuals met inclusion criteria and were included in the final analytic cohort.

Study Variables

Diseases of despair were defined as diagnoses related to alcohol use, substance use, and suicide ideation/behaviors. International Classification of Diseases (ICD) codes were extracted from claims and classified into variables indicating the presence or absence of a diagnosis within each of the three diagnostic categories of interest. Classifications were adapted from the Healthcare Cost and Utilization Project Clinical Classification Software (HCUP-CCS).[20] Code mappings were used for HCUP categories alcohol-related disorders (5.11), substance-related disorders (5.12), and suicide and intentional self-inflicted injury (5.13). Diagnoses related to substance use considered outside the focus of the present study were excluded, specifically,

codes related to the use of tobacco and cannabis, and certain non-psychoactive substances (i.e., ICD-10 codes F550, F551, F552, F554). Additional indicators were created for overall disease of despair status (diagnosis of any type), and co-occurring diseases of despair status (diagnoses in multiple categories). A two-year lookback period was used to identify incident diagnoses. If no record of the given diagnosis type was found during the lookback period, the diagnosis was recorded as an incident case. Annual and all-time incidence and prevalence estimates were computed.

Additional clinical comorbidities were calculated for the final year of follow-up (2018). Physical health comorbidities were measured using weighted Charlson Comorbidity Index Scores.[21] Psychiatric comorbidities were defined using additional HCUP-CCS classifications, and included indicators for adjustment/anxiety disorders (5.1 and 5.2), mood disorders (5.8), and schizophrenia and other psychotic disorders (5.10).

Existing research points to particular age groups as having uniquely high risk for deaths of despair overall and by particular subtype. Thus, individuals in the sample were stratified into age groups to allow for comparison between morbidity and mortality trends. Infants less than 1-year-old were analyzed separately included in order to capture the effects of maternal substance use. The remaining age groups included 1-17 years, 18-34 years, 35-54 years, 55-75 years, and 75+-years-old.

Insurance product information was recoded into the following categories: Employer sponsored; individual market Affordable Care Act (ACA) plans; Medicare, and Other. Product information was captured on an annual basis. If multiple products were found on file during a single year, the product covering the larger number of months was recorded.

To determine whether cohort members were at-risk for being diagnosed with a disease of despair at any given point, the months enrolled during each year of follow-up were recorded for all cohort members. Except for newborns, members were considered "enrolled" for a given year if they were covered for at least 10 months out of the year. Newborns were considered enrolled if coverage was identified within the first 90 days of life.

Data Analysis

Incidence and Prevalence of Diseases of Despair

Descriptive statistics were computed for all study variables both overall and stratified by diagnostic status ("any" versus "no" disease of despair diagnosis recorded over the course of follow-up). Differences were statistically compared using chi-square tests for categorical variables, and t-tests for continuous variables. Next, overall and gender- and age-specific incidence and prevalence rates of disease of despair diagnosis were computed for years 2009 through 2018, allowing for an initial lookback period beginning in 2007. Rates were calculated by dividing the number of newly identified cases by the number of members enrolled and with no previous diagnosis in the past two years (incidence), and the number of current year cases by number of members enrolled (prevalence). For the final year of follow-up, descriptive statistics were also computed for weighted Charlson comorbidity scores and additional psychiatric comorbidities.

The partially overlapping samples z-test[22] was used to statistically test if and the degree to which rates of diseases of despair changed over the last decade. The partially overlapping test is designed for the statistical comparison of proportions when data include a combination of paired and unpaired samples, as is often the case in dynamic cohorts extracted from clinical databases.

Predicting Individual-level Risk for Diseases of Despair

To identify factors associated with individual-level risk for disease of despair diagnosis during the most recent year of follow-up (2018), logistic regression was used to estimate risk for diagnosis as a function of demographic and enrollment characteristics. Odds ratios and their 95% confidence intervals were computed for all estimates. Analyses were performed using R, version 3.5.2[23] within Highmark's secure computing environment.

Patient and Public Involvement

Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. The study was approved by the Institutional Review Boards of Penn State College of Medicine and the Allegheny Health Network Research Institute (acting IRB for Highmark Health). Informed consent was waived, as no study participants were contacted. Due to privacy laws, data cannot be made publicly available.

Results

Overall, 4.2% of cohort members (N = 515,830) were diagnosed with at least one disease of despair at some point during follow-up. Among these, 54.0% were diagnosed with an alcohol-related disorder, 44.2% with a substance-related disorder, and 16.3% with suicide ideation/behaviors; multiple types of diseases of despair diagnoses were recorded for 12.9%. Additional cohort description is presented in **Table 1**.

[TABLE 1]

Age and gender-specific diagnostic prevalence rates from 2009 to 2018 are presented in **Figure 1.** Aggregate incidence and prevalence rates and statistical comparisons between 2009 and 2018 are discussed in the following sections. Age- and gender-stratified statistics are presented in **Tables 2 and 3**.

[FIGURE 1, TABLES 1 AND 2]

Any Disease of Despair Diagnosis

Between 2009 and 2018, the annual diagnostic incidence of diseases of despair increased by 44%, and the diagnostic prevalence increased by 68%. Significant increases were seen for both men and women across every age group, although the magnitude of increases varied along age and gender lines. Due to the relatively low base rate of diseases of despair, small increases in the absolute rates (i.e., percentage point increases) often translated to large increases in the comparison of 2018 rates to 2009 rates (i.e., relative rate increases). While percentage point increases tended to be smaller among women compared to men, relative rate increases tended to be larger among women.

Alcohol-related Diagnosis

The overall incidence and prevalence of alcohol-related diagnosis increased by 23% and 37%, respectively. Significant increases were seen for men and women ages 18 and above, but significant decreases were seen for those ages 1-17. The most dramatic increases were seen among those ages 55-74; their prevalence increased by .5% percentage points (59% relative increase).

Substance-related Diagnosis

The overall incidence and prevalence of substance-related diagnosis increased by 48% and 94%, respectively. As with the trends observed for alcohol-related diagnoses, the incidence and prevalence of substance-related diagnoses increased for all groups except for those ages 1-17; for this group, rates significantly decreased. Relative increases were again highest for those ages 55-57 (prevalence 172% higher; .5% percentage point increase), and for infants (prevalence 114% higher; .25% percentage point increase).

Suicide Ideation / Behaviors Diagnosis

The incidence and prevalence of suicide-related diagnosis increased for all relevant age groups (infants were excluded) by 149% and 170%, respectively. While the absolute rates of suicide-related diagnosis were lower than other types of disease of despair diagnoses, the relative increases were dramatic. Among those ages 1-17, the prevalence increased by 287%. Among those ages 18-34, it increased by 210%. All other age groups saw a relative increase of at least 70%.

Logistic Regression Results

Results of logistic regression models predicting the odds for 2018 disease of despair diagnoses as a function of individual and enrollment characteristics are presented in **Table 4**.

[TABLE 4]

Men had higher odds than women for having any type of disease of despair diagnosis, alcohol-related diagnosis, and substance-related diagnosis (AOR [adjusted odds ratio] = 1.49, 2.35, and 1.23, respectively), but lower odds than women for suicide ideation/behaviors (AOR = 0.72). Age was also significantly associated with risk for all four disease of despair outcomes. After adjusting for gender and insurance type, individuals ages 18-35 had the highest risk for any disease of despair, substance-related diagnosis, and suicide-related diagnosis. For alcohol-related disorders, those ages 35-74 were at slightly higher risk than those ages 18-34, and much higher risk than any other group. Finally, type of enrollment was also significantly related to risk. Compared to commercial insurance plans, Affordable Care Act (ACA) plans were associated with approximately 1.3 times higher odds for any diagnosis, alcohol-related diagnosis, and substance-related diagnosis, but similar risk for suicide-related diagnoses. Medicare plans were

associated with 1.5 times higher odds for any disease of despair and each of the three diagnostic subtypes (AOR range was 1.3-2.2).

Clinical Comorbidities

Table 5 includes average weighted Charlson comorbidity scores and diagnostic prevalence rates for adjustment/anxiety disorders, mood disorders, and schizophrenia and other psychotic disorders in 2018, stratified by age, gender, and the presence of a disease of despair diagnosis during the same year.

[TABLE 5]

Disease of despair diagnosis was associated with significantly higher mean comorbidity scores and significantly higher prevalence of each psychiatric comorbidity for both men and women across every age group. As expected, chronic health conditions were rare among younger cohort members, yet compared to those without disease of despair diagnoses, the average Charlson score among those with disease of despair diagnoses was at least two times higher for every age group up to 74 years. The range of the diagnostic prevalence of adjustment/anxiety disorders was 6.3% to 21.2% among those without disease of despair diagnoses, and 31.0% to 84.2% among those with diagnoses. Similarly, the diagnostic prevalence of mood disorders ranged from 2.0% to 15.6% among those without disease of despair diagnoses, and 31.2% to 78.7% among those with a diagnosis. Finally, while diagnoses of schizophrenia and other psychotic disorders were very rare among those without disease of despair diagnoses, their diagnostic prevalence ranged from 2.1% to 10.3% among those with diagnoses.

Discussion

Nearly one in twenty individuals in our sample were clinically diagnosed with a disease of despair between 2007 and 2018. Similar to observed despair-related mortality, diseases of

despair have significantly increased as morbidities over the past decade.[24] Tracking with the original finding that deaths of despair have disproportionately affected middle-aged men,[3] our data showed the largest absolute increases in overall prevalence for men ages 35-74, followed by women ages 55-74 and 18-34. These findings reinforce the notion that while the opioid crisis remains a top public health priority, parallel rises in alcohol-related diagnoses and suicidality must be concurrently addressed.[25] Relatedly, the association between diseases of despair and chronic health conditions at all ages along with very high rates of co-occurring psychiatric conditions underscore the interconnectedness of diseases of despair with overall well-being, and the importance of considering reciprocal interrelationships among these conditions in prevention and intervention efforts.

The relative increases in specific diagnoses seen in infants, youth, and young adults were also striking. Among infants, the prevalence of substance-related diagnoses doubled over the course of follow-up. This increase was entirely attributable to neonatal abstinence syndrome and corresponds closely with increases in substance-related disorders among women of childbearing age. Neonatal abstinence syndrome could be argued to be the direct result of a disease of despair among mothers, and was therefore included. In addition, the prevalence of suicide ideation and behaviors among youth and young adults at least tripled over the course of follow-up. These findings underscore the importance of targeting vulnerable subpopulations in tailored prevention and early intervention services.

A recent study by Gaydosh et al. used nationally representative longitudinal data to examine diseases of despair and their age patterns from adolescence through the late-30s from 1994-2017.[26] This study demonstrated increases as the cohort aged into their late 30s, across racial and ethnic groups as well as geographic locales. In addition to broadening original views

beyond impacting whites in rural locales, the generalized increases in despair documented among this younger cohort forewarn further likely increases in mid-life mortality in the coming decades. Such trends are already beginning to be observed at the population level in the U.S. Researchers examining declining life expectancy using data from the US Mortality Database and CDC WONDER have recently established that increased death rates among people in midlife are in fact extending beyond the original demographic characterized by Case & Deaton to all racial and ethnic groups, as well as to suburbs and cities (with the largest relative increases occurring in the Ohio Valley and New England).[27] As these and other findings expand the original deaths of despair phenomenon across demographic and geographic boundaries it strengthens the aforementioned hypothesis that the crisis is systemically linked to material changes in the US political-economy that have broadly affected the working class over the last several decades. Thus, while a better understanding of the clinical manifestation of diseases of despair may inform efforts at intervention and mitigation, it must be acknowledged that the ultimate public health goal must be addressing structural root causes of despair.

The concept of despair remains largely unstudied, with manifestations in cognitive, emotional, behavioral, and biological domains as well as in social and political-economic contexts.[17] For example, Glei et al characterized despair by social and psychological dysfunction such as a lack of purpose in life, a sense of worthlessness, little hope or goals for the future, and perceived social rejection by broader society.[5] Shanahan et. al provided a roadmap for studying the social contexts that can further strengthen or weaken pathways to despair. Ultimately, as influencing the root causes of the crisis (i.e. societal structures that perpetuate socioeconomic disadvantage) will be a politically-daunting endeavor, there may be shorter-term benefit in improving the healthcare system's ability to measure and clinically screen for despair, as

opposed to resultant diseases or deaths. Better processes for systemically identifying and tracking despair may allow for clinical interventions to help mitigate progression to despair-related mortality.[28]

Strengths and Limitations

A significant strength of the current study is the investigation of the upstream diagnoses for deaths of despair in a large cohort with representation of some of the most impacted states, including West Virginia and Pennsylvania. Further, the use of a large claims-based dataset provides insight into health insurance type as a consideration in the development of future potential healthcare interventions. Finally, these data provide information on current diagnosis rates in the context of long-term trends. A limitation of the current study is the incomplete nature of social determinants of health data in administrative health records. Despite the significant influence of these factors on health outcomes, few sources provide data that includes both clinical and social and behavioral factors. To address this gap in clinical records, the Institute of Medicine Committee on Recommended Social and Behavioral Domains and Measures for Electronic Health Records describes a concise panel of standard measures in every patient's electronic health record.[29] These measures include items evaluating depression, alcohol use, and social connection or isolation which would help capture diagnoses of despair. Future research might consider combining clinical records with data originating outside of claims and electronic health records, including direct and indirect measures of social determinants.

By definition, diagnoses of diseases of despair and health insurance enrollment imply access to health care, although it is clear additional barriers to treatment exist. Insurance type is an important predictor of disease diagnoses, and diseases of despair are no exception. Individuals with Medicare, for example, have 1.5 times higher odds of having a diagnosis of a disease of

despair, followed by those with ACA (1.3 times higher odds). Insurance status is frequently used as a surrogate for measures of socioeconomic status, which are essential to describing health inequalities. Unfortunately, this is an imperfect proxy.[30] Employer-sponsored insurance suggests the presence of stable household income, yet the nature of coverage and cost sharing responsibilities of patients vary widely across insurance plans. Further, while expanded insurance coverage under the Affordable Care Act has reduced socioeconomic disparities in healthcare access,[31] significant barriers remain. Ultimately, that an estimated 87 million working adults in the US are uninsured or underinsured[32] remains a major structural challenge for both understanding the true scope of the diseases of despair crisis and mounting clinical programs to ensure effective treatment.

Directions for future research

Identifying diseases of despair is critical for interrupting their progression towards deaths of despair, but diagnoses do not necessarily guarantee the provision of appropriate and adequate care for acute problems or general wellbeing. Thus, future research may build upon these findings by quantifying treatment following disease identification, and linking this treatment to longer-term morbidity and mortality. Relatedly, while results from the present study suggest strong associations between diseases of despair and both physical and mental health comorbidities, additional research may build on these exploratory findings in multiple ways. First, identifying the clinical correlates of diseases of despair may present opportunities to improve their timely detection through targeted screening. In addition, integrated approaches to treatment that holistically target a range of physical and mental health symptoms may have improved efficacy. It is likely that health systems that work with vulnerable populations (e.g. residents of rural and remote regions, low-income adolescents, etc.) may need to co-design

primary, secondary, and tertiary interventions aimed at addressing diseases of despair. Such interventions may require a wider array of community partners than are typically included in conventional health services. Developing and evaluating effective organizational partnerships and best practices in integrated care of patients with diseases of despair would be a valuable contribution.

Future inquiry could benefit from similar "big data" approaches to understand and model patterns of despair in human populations. For instance, it would be useful to identify "hot-spots" of high prevalence/incidence of diseases of despair diagnoses (and deaths of despair) and examine the socioeconomic conditions in these areas over time. As mentioned, research is increasingly—if somewhat inscrutably—linking mortality with prolonged stagnant or declining socioeconomic conditions. These conditions are associated with decades of globalization, rising automation, and austerity policies (i.e. cuts in social spending) that have exacerbated economic precariousness and despair. Notably, researchers have recently established a direct association between automotive assembly plant closures in 112 manufacturing counties located primarily in the US South and Midwest and an 85% surge in opioid overdose mortality rates among working-age adults five years later.[33] Others have, for instance, linked rising rates of death of despair with stagnant minimum wage).[34-36]

However, others argue that the phenomenon is more attributable to other contextual factors such as: a worsening drug environment;[37-39] the collapse of social institutions and weakening of traditional social bonds (e.g. reduced church attendance,[40,41] union membership,[42] etc.);[43] hospital closures and shortages (particularly in rural areas)[44]; a generalized cultural rise in loneliness, depression, alienation, and anxiety;[45] higher relative gun ownership in rural areas;[46] racial resentment and a growing sense of social status loss[47] among poor whites; and moral

decadence (i.e. a "loss of virtue" in ethnically white rural communities).[48] Using big data to build predictive models of neighborhoods or census tracts where people may be at greatest risk would not only help clarify current debates about past causation and identify zones of resilience, but also offer a future tool of clinical and public health import.

Researchers might also undertake qualitative and/or mixed methods inquiry to examine subjective perceptions of despair in high prevalence communities. There may be particular value in engaging leaders of community and social service organizations (e.g., libraries, emergency rooms, methadone treatment centers, suicide prevention organizations, homeless shelters, Women, Infants, and Children (WIC) clinics, legal services organizations, state police, community centers, county health services, and places of worship, etc.) who interface with high-risk populations, as well as affected persons and family members. It would be especially useful to better understand general awareness of the diseases of despair concept, local beliefs about causation, perceptions of effective policy solutions at the local, state, and national levels, and strategies hospitals can use to most effectively intervene. Moreover, as the COVID-19 pandemic contracts domestic and global economies and requires the implementation of social/physical distancing regimes, it will be important for researchers to examine how and in what ways diseases of despair are affected by prolonged isolation, loss of jobs/benefits, diminution of social protections, lack of mental health care, drug abuse, increased domestic abuse, and other societal consequences of the virus. Given the complexity of despair, combining quantitative and qualitative approaches may be particularly useful.

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Study concept and design: All authors
Acquisition, analysis, or interpretation of data: Brignone, George, Gladden, Katz, Kraschnewski, Sinoway
Drafting of the manuscript: Brignone, George, Kraschnewski
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Brignone
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Table 1. Descriptive Statistics for Study Cohort, Overall and Stratified by the Presence of Disease of Despair (DoD) Diagnosis at any Point during Follow up, 2007 – 2018.

	Overall N = 12,144,252 (100.0%)	**No DoD** N = 11,628,422 (95.8%)	**DoD** N = 515,830 (4.2%)	*p*-value
	N (%) / M (SD)			
Type of DoD Diagnosis				
Alcohol-related	278,309 (2.3%)	-	278,309 (54.0%)	
Drug-related	228,227 (1.9%)	-	228,227 (44.2%)	
Suicide Ideation/Behavior	84,117 (0.7%)	-	84,117 (16.3%)	
Multiple Diagnosis Types	66,585 (0.5%)	-	66,585 (12.9%)	
Gender				<.001
Women	6,124,183 (50.4%)	5,909,902 (50.8%)	214,281 (41.5%)	
Men	6,020,069 (49.6%)	5,718,520 (49.2%)	301,549 (58.5%)	
Age at Enrollment Midpoint				<.001
0 – 17 years	2,666,135 (22%)	2,625,797 (22.6%)	40,338 (7.8%)	
18 – 25 years	1,539,995 (12.7%)	1,456,629 (12.5%)	83,366 (16.2%)	
26 – 35 years	1,752,493 (14.4%)	1,677,395 (14.4%)	75,098 (14.6%)	
36 – 45 years	1,638,938 (13.5%)	1,560,822 (13.4%)	78,116 (15.1%)	
46 – 55 years	1,754,037 (14.4%)	1,659,732 (14.3%)	94,305 (18.3%)	
56 – 65 years	1,628,179 (13.4%)	1,547,308 (13.3%)	80,871 (15.7%)	
66 – 75 years	586,303 (4.8%)	552,101 (4.7%)	34,202 (6.6%)	
76 – 85 years	366,120 (3%)	345,023 (3%)	21,097 (4.1%)	
85+ years	212,052 (1.7%)	203,615 (1.8%)	8,437 (1.6%)	
Number of Years Enrolled	4.8 (3.4)	4.7 (3.4)	6.6 (3.4)	<.001
Most Recent Enrollment				<.001
2007 – 2009	1,467,763 (12.1%)	1,440,453 (12.4%)	27,310 (5.3%)	
2010 – 2012	1,796,257 (14.8%)	1,739,269 (15%)	56,988 (11.0%)	
2013 – 2015	2,528,619 (20.8%)	2,421,676 (20.8%)	106,943 (20.7%)	
2016 – 2018	6,351,613 (52.3%)	6,027,024 (51.8%)	324,589 (62.9%)	
Medical Insurance Type				<.001
Employer Sponsored	9,516,477 (78.4%)	9,105,741 (78.3%)	410,736 (79.6%)	
ACA	354,355 (2.9%)	340,900 (2.9%)	13,455 (2.6%)	
Medicare	752,594 (6.2%)	699,619 (6%)	52,975 (10.3%)	
Other	1,520,825 (12.5%)	1,482,161 (12.7%)	38,664 (7.5%)	

Notes: If there were multiple values on file for state or type of insurance, the value covering longest period was selected. ACA plans were available 2014-2018.

Figure 1. Age and Gender-Specific Diagnostic Prevalence Rates of Diseases of Despair, 2009 – 2018.

[attached separately]

Table 2. Comparison of Age and Gender Specific Annual Incidence of Disease of Despair Diagnoses, 2009 – 2018.

	Men				Women			
Age Cohort	**2009**	**2018**	***p*-value**	**Ratio**	**2009**	**2018**	***p*-value**	**Ratio**
Any Disease of Despair Diagnosis								
> 1 Year	.25%	.52%	<.001	**2.05**	.17%	.36%	.001	**2.18**
1 - 17 Years	.28%	.38%	<.001	**1.37**	.27%	.53%	<.001	**1.96**
18 - 34 Years	1.44%	1.73%	<.001	**1.21**	.94%	1.42%	<.001	**1.51**
35-54 Years	1.21%	1.58%	<.001	**1.30**	.72%	1.01%	<.001	**1.40**
55-74 Years	1.08%	1.61%	<.001	**1.48**	.53%	.95%	<.001	**1.78**
75+ Years	.99%	1.23%	<.001	**1.25**	.69%	.85%	<.001	**1.23**
Alcohol-Related Diagnosis								
> 1 Year	.03%	.03%	1.000	.90	.00%	.01%	.951	-
1 - 17 Years	.09%	.05%	<.001	**.60**	.09%	.04%	<.001	**.49**
18 - 34 Years	.93%	.97%	.103	1.05	.45%	.56%	<.001	**1.26**
35-54 Years	.90%	1.03%	<.001	**1.15**	.36%	.44%	<.001	**1.22**
55-74 Years	.84%	1.11%	<.001	**1.32**	.26%	.42%	<.001	**1.60**
75+ Years	.63%	.76%	.003	**1.19**	.24%	.25%	.932	1.07
Substance-Related Diagnosis								
> 1 Year	.23%	.49%	<.001	**2.14**	.17%	.36%	<.001	**2.14**
1 - 17 Years	.14%	.08%	<.001	**0.58**	.11%	.05%	<.001	**0.47**
18 - 34 Years	.57%	.72%	<.001	**1.26**	.44%	.58%	<.001	**1.33**
35-54 Years	.37%	.58%	<.001	**1.59**	.34%	.50%	<.001	**1.50**
55-74 Years	.26%	.51%	<.001	**2.00**	.24%	.49%	<.001	**2.04**
75+ Years	.32%	.37%	.117	1.16	.39%	.46%	<.001	**1.20**
Suicide-Related Diagnosis								
> 1 Year	-	-	-	-	-	-	-	-
1 - 17 Years	.09%	.28%	<.001	**3.20**	.13%	.47%	<.001	**3.77**
18 - 34 Years	.14%	.42%	<.001	**2.95**	.19%	.52%	<.001	**2.69**
35-54 Years	.09%	.15%	<.001	**1.81**	.13%	.20%	<.001	**1.52**
55-74 Years	.06%	.13%	<.001	**2.23**	.07%	.13%	<.001	**1.75**
75+ Years	.08%	.16%	<.001	**2.09**	.08%	.14%	<.001	**1.83**

Notes: Ratios represent 2018 rates relative to 2009 incidence rates. Bolded ratios correspond to statistically significant differences in diagnostic incidence.

Table 3. Comparison of Age and Gender Specific Annual Prevalence of Disease of Despair Diagnoses, 2009 – 2018.

	Men				Women			
Age Cohort	**2009**	**2018**	***p*-value**	**Ratio**	**2009**	**2018**	***p*-value**	**Ratio**
Any Disease of Despair Diagnosis								
> 1 Year	.25%	.52%	<.001	**2.05**	.17%	.36%	<.001	**2.18**
1 - 17 Years	.33%	.45%	<.001	**1.37**	.32%	.65%	<.001	**2.04**
18 - 34 Years	1.93%	2.66%	<.001	**1.38**	1.19%	2.05%	<.001	**1.71**
35-54 Years	1.72%	2.68%	<.001	**1.56**	1.03%	1.68%	<.001	**1.63**
55-74 Years	1.55%	2.72%	<.001	**1.75**	.72%	1.59%	<.001	**2.21**
75+ Years	1.27%	1.89%	<.001	**1.49**	0.80%	1.18%	<.001	**1.46**
Alcohol-Related Diagnosis								
> 1 Year	.03%	.03%	1.000	0.90	.00%	.01%	0.950	**-**
1 - 17 Years	.10%	.07%	<.001	**0.67**	.10%	.05%	<.001	**0.53**
18 - 34 Years	1.12%	1.30%	<.001	**1.16**	.52%	.72%	<.001	**1.37**
35-54 Years	1.23%	1.54%	<.001	**1.25**	.52%	.68%	<.001	**1.29**
55-74 Years	1.23%	1.85%	<.001	**1.51**	.38%	.69%	<.001	**1.84**
75+ Years	0.87%	1.24%	<.001	**1.43**	.31%	.37%	0.140	1.17
Substance-Related Diagnosis								
> 1 Year	.23%	.49%	<.001	**2.14**	.17%	.36%	<.001	**2.14**
1 - 17 Years	.17%	.09%	<.001	**0.57**	.13%	.06%	<.001	**0.46**
18 - 34 Years	.85%	1.30%	<.001	**1.53**	.59%	.96%	<.001	**1.62**
35-54 Years	.53%	1.19%	<.001	**2.24**	.48%	.92%	<.001	**1.93**
55-74 Years	.33%	.88%	<.001	**2.70**	.30%	.83%	<.001	**2.73**
75+ Years	.35%	.51%	<.001	**1.47**	.42%	.67%	<.001	**1.59**
Suicide-Related Diagnosis								
> 1 Year	-	-	-	-	-	-	-	-
1 - 17 Years	.09%	.31%	<.001	**3.43**	.14%	.58%	<.001	**4.17**
18 - 34 Years	.15%	.49%	<.001	**3.20**	.21%	.64%	<.001	**3.03**
35-54 Years	.09%	.17%	<.001	**1.89**	.14%	.23%	<.001	**1.60**
55-74 Years	.06%	.15%	<.001	**2.33**	.08%	.15%	<.001	**1.88**
75+ Years	.08%	.17%	<.001	**2.11**	.09%	.17%	<.001	**1.94**

Notes: Ratios represent 2018 rates relative to 2009 prevalence rates. Bolded ratios correspond to statistically significant differences in diagnostic prevalence.

Table 4. Risk for Disease of Despair Diagnosis as a Function of Demographic and Enrollment Characteristics, 2018.

	Any Disease of Despair		Alcohol-Related Diagnosis		Substance-Related Diagnosis		Suicide-Related Diagnosis	
Variable	Adjusted Odds Ratio (95% Confidence Interval)							
Men [ref = Women]	**1.49**	**(1.47, 1.51)**	**2.35**	**(2.30, 2.41)**	**1.23**	**(1.20, 1.25)**	**0.72**	**(0.70, 0.75)**
Age [ref = 18-34]								
<1	**0.18**	**(0.15, 0.22)**	**0.02**	**(0.01, 0.04)**	**0.37**	**(0.31, 0.44)**	-	- -
1-17	**0.23**	**(0.22, 0.24)**	**0.06**	**(0.05, 0.06)**	**0.07**	**(0.06, 0.08)**	**0.79**	**(0.75, 0.83)**
35-54	**0.92**	**(0.90, 0.94)**	**1.09**	**(1.06, 1.13)**	**0.92**	**(0.90, 0.95)**	**0.35**	**(0.33, 0.37)**
55-74	**0.83**	**(0.81, 0.84)**	**1.19**	**(1.15, 1.22)**	**0.66**	**(0.64, 0.68)**	**0.21**	**(0.20, 0.23)**
75+	**0.44**	**(0.42, 0.46)**	**0.59**	**(0.55, 0.63)**	**0.34**	**(0.31, 0.36)**	**0.15**	**(0.13, 0.17)**
Insurance [ref = employer sponsored]								
ACA	**1.30**	**(1.24, 1.37)**	**1.37**	**(1.28, 1.48)**	**1.33**	**(1.24, 1.42)**	1.05	(0.91, 1.21)
Medicare	**1.51**	**(1.46, 1.55)**	**1.30**	**(1.25, 1.36)**	**1.73**	**(1.65, 1.81)**	**2.19**	**(1.98, 2.43)**
Other	**0.71**	**(0.67, 0.74)**	**0.73**	**(0.68, 0.78)**	**0.61**	**(0.57, 0.66)**	**0.84**	**(0.77, 0.92)**

Notes: Bold indicates statistical significance, $p < .05$.

Table 5. Physical and Mental Health Comorbidities by Disease of Despair Diagnosis, Age, and Gender, 2018

	Charlson Comorbidity Weighted Score			Adjustment / Anxiety Disorders			Mood Disorders			Schizophrenia and Other Psychotic Disorders		
	No DoD	DoD	*p*	No DoD	DoD	*p*	No DoD	DoD	*p*	No DoD	DoD	*p*
	Mean (SD)			**N (%)**								
Men												
<1	.03 (.21)	.24 (.56)	.001	-	-	-	-	-	-	-	-	-
1-17	.10 (.33)	.20 (0.62)	<.001	20,980 (6.3%)	949 (63.9%)	<.001	6,538 (2.0%)	1,022 (68.8%)	<.001	137 (0.0%)	136 (9.2%)	<.001
18-34	.09 (.42)	.24 (.78)	<.001	31,405 (8.8%)	4,340 (44.5%)	<.001	17,307 (4.9%)	3,980 (40.8%)	<.001	597 (0.2%)	618 (6.3%)	<.001
35-54	.32 (.93)	.80 (1.66)	<.001	49,603 (10.8%)	5,178 (41.1%)	<.001	26,333 (5.8%)	4,094 (32.5%)	<.001	556 (0.1%)	260 (2.1%)	<.001
55-74	1.1 (1.87)	2.5 (2.94)	<.001	39,191 (9.3%)	4,021 (34.0%)	<.001	27,685 (6.6%)	3,684 (31.2%)	<.001	1,016 (0.2%)	294 (2.5%)	<.001
75+	2.86 (2.8)	3.00 (4.57)	<.001	10,126 (10.3%)	563 (31.0%)	<.001	9,204 (9.4 %)	639 (35.2%)	<.001	672 (0.7%)	89 (4.9%)	<.001
Women												
<1	.03 (.21)	.17 (.51)	.044	-	-	-	-	-	-	-	-	-
1-17	.08 (.31)	.21 (0.50)	<.001	25,099 (7.9%)	1,640 (78.7%)	<.001	9,545 (3.0%)	1,756 (84.2%)	<.001	88 (0.0%)	214 (10.3%)	<.001
18-34	.13 (.46)	.32 (0.77)	<.001	67,210 (19.3%)	4,495 (61.7%)	<.001	38,526 (11.0%)	4,318 (59.3%)	<.001	381 (.1%)	407 (5.6%)	<.001
35-54	.36 (0.96)	.92 (1.72)	<.001	101,708 (21.2%)	5,030 (61.4%)	<.001	64,072 (13.4%)	4,475 (54.6%)	<.001	604 (.1%)	294 (3.6%)	<.001
55-74	.93 (1.69)	2.06 (2.62)	<.001	83,373 (18.4%)	4,015 (54.8%)	<.001	62,141 (13.7%)	3,728 (50.9%)	<.001	1,243 (.3%)	273 (3.7%)	<.001
75+	2.28 (2.45)	3.70 (3.0)	<.001	29,101 (19.7%)	881 (53.4%)	<.001	23,102 (15.6%)	779 (47.2%)	<.001	1,776 (1.2%)	135 (8.2%)	<.001

Notes: DoD = Diseases of Despair; p-values for Charlson scores correspond to t-tests; p-value for psychiatric comorbidities correspond to chi-square tests.

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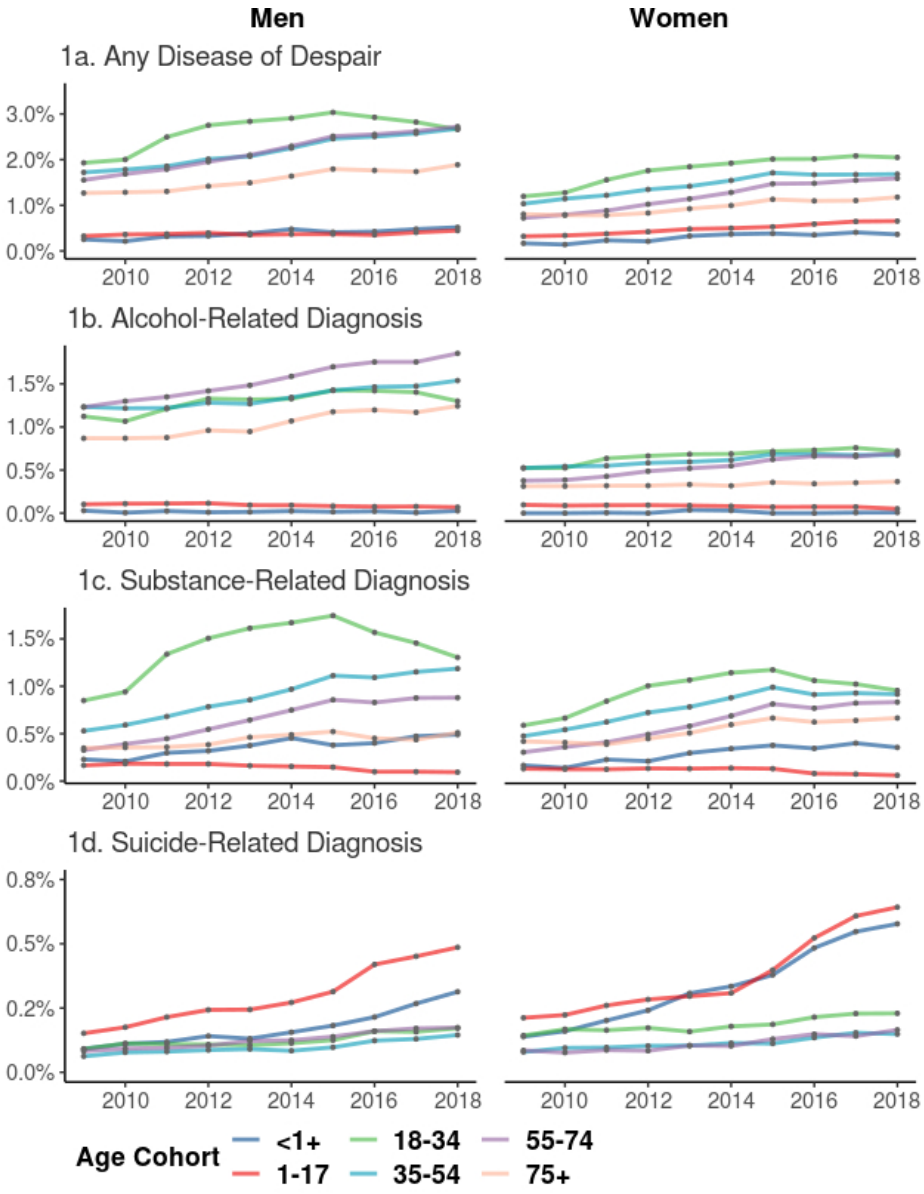
Men
Women
1a. Any Disease of Despair
3.0%
2.0%
1.0%
0.0%
2010
2012
2014
2016
2018
1b. Alcohol-Related Diagnosis
1.5%
1.0%
0.5%
0.0%
1c. Substance-Related Diagnosis
1d. Suicide-Related Diagnosis
0.8%
0.5%
0.2%
0.0%
Age Cohort
<1+
1-17
18-34
35-54
55-74
75+

Figure 1

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	A: Title and abstract B: Abstract	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1: Abstract 1.2: Abstract 1.3: NA
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported			Lines 129 – 151
Objectives	3	State specific objectives, including any prespecified hypotheses			Lines 151 - 155
Methods					
Study Design	4	Present key elements of study design early in the paper			Line 152; lines 157-165
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection			Lines 157 - 201

Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	A: Lines 157 – 219 B: NA	RECORD 6.1: The methods of study population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	6.1: Lines 157 – 181 6.3: References 20 and 21 6.3: NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Lines 166 – 196; References 20 and 21	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	7.1: Lines 166 – 196; References 20 and 21
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Lines 157 - 219		

Bias	9	Describe any efforts to address potential sources of bias	Lines 157 - 219		
Study size	10	Explain how the study size was arrived at	Lines 157 - 165		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Lines 167 - 225		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	A: Lines 203 - 225 B: NA C: Lines 164 – 165 D: Lines 203 – 219 E. NA		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	12.1: Lines 157 – 165

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.2: Lines 167 - 196
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	12.3: NA
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	A: Lines 164 – 165 B: NA C: NA	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1: Lines 157 - 165
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	A: Table 1 B: Lines 164 – 165, Table 1 C: Table 1		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure	Figure 1, Tables 2 and 3		

		category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	A: Table 4 B: Tables 1-5 C: NA		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Lines 203 - 225		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Lines 308 - 329		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Lies 359 - 388	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	19.1: Lines 359 - 388
Interpretation	20	Give a cautious overall interpretation of results considering objectives,	Lines 308 - 388		

		limitations, multiplicity of analyses, results from similar studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Lines 359 - 388		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Lines 22 - 26		
Accessibility of protocol, raw data, and programming code		..	Line 231.	RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	22.1: Line 231

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.