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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.

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3 84 **Strengths and limitations of this study:**
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- 5 85
- 6 86 • Increasing mortality due to deaths of despair is well documented in extant research. To
7 87 our knowledge, this study is the first to provide large-scale insights into the clinical
8 88 recognition of the morbidities that can ultimately culminate in those deaths. This clinical
9 89 perspective highlights potential opportunities to intervene in the progression of morbidity
10 90 toward mortality.
 - 11 91
 - 12 92 • The study uses a large and inclusive sample. As a result, we are able to identify
13 93 differential patterns in the diagnosis of substance-, alcohol-, and suicide-related diagnoses
14 94 across age and gender lines, which can improve targeted prevention efforts.
 - 15 95
 - 16 96 • The long administrative surveillance period of 10 years allows us to track changes in the
17 97 identification of diseases of despair over time, and to compare long-term trends between
18 98 documented morbidity and mortality.
 - 19 99
 - 20 100 • While trends in deaths of despair appear to vary by race/ethnicity, details on
21 101 race/ethnicity were not available for our sample.
 - 22 102
 - 23 103 • We were unable to directly link disease of despair incidence/prevalence to mortality on
24 104 an individual level; rather, we compare trends in morbidity and mortality in more general
25 105 terms.
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3 129 From 2015-2017, there has been an annual downward trend in life expectancy in the
4
5 130 United States, the longest sustained decline since 1915-1918.^{1,2} Relatedly, researchers have
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8 131 observed a longer, more marked increase in the all-cause mortality of middle-aged white non-
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10 132 Hispanic men and women in the US between 1999 and 2015, with premature deaths largely
11
12 133 associated with “deaths of despair,” including suicides, accidental poisonings (e.g. opiate
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14 134 overdose), and alcohol-related liver disease (e.g. cirrhosis).^{3,4}

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16
17 135 This troubling observation has coincided with decades of economic decline for less
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19 136 educated and unskilled workers, stagnant or falling real median wages and family incomes,^{5,6}
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21 137 lower marriage rates,⁷ increases in single-parent households,⁸ and disengagement from the labor
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23 138 force.⁹ It is theorized that these changes have fostered growing feelings of despair, i.e.,
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25 139 disillusionment, precariousness, and resignation.^{3,4,10-12} Despair may in turn trigger emotional,
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27 140 cognitive, behavioral, and even biological changes,¹³⁻¹⁷ increasing the likelihood of diseases that
28
29 141 can progress and ultimately culminate in these deaths of despair.
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33 142 While this pathway may unfold over years or decades, to date, most studies in this
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35 143 domain have primarily focused on the endpoint of mortality. Limited extant research suggests a
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37 144 parallel rise in associated morbidities,^{3,4} but specific estimates of “disease of despair” morbidity
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39 145 (i.e., substance-related disorders, alcohol-related disorders, and suicide ideation and attempts) are
40
41 146 lacking. Moreover, little is known about trends in the recognition and documentation of these
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43 147 diseases in the clinical setting. This represents an important gap in the literature; indeed, while
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45 148 primary prevention efforts to address the root causes of societal despair are needed, it may be
46
47 149 possible to intervene upon the pathway from morbidity to mortality in the clinical setting. An
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49 150 understanding of diagnostic patterns and the association between documented morbidity and
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51 151 mortality is necessary to guide these secondary and tertiary prevention efforts. Thus, the
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3 152 objectives of the present study were to use a large administrative database of healthcare claims to
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5 153 1) characterize the incidence and prevalence of diseases of despair diagnoses over the last
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8 154 decade; 2) identify individual sociodemographic factors associated with disease of despair
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10 155 diagnosis; and 3) discuss patterns in morbidity and mortality.

12 156 **Methods**

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15 157 This retrospective cohort study used claims data extracted from the administrative
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17 158 databases of Highmark Inc., a large US-based health insurance company. Highmark members are
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19 159 concentrated in states that have been disproportionately affected by deaths of despair, including
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21 160 Pennsylvania, West Virginia, and Delaware.^{18,19} The database contains clinical information such
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23
24 161 as services used and diagnoses assigned, and sociodemographic characteristics including gender,
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26 162 age, home address, and insurance coverage details. The study cohort included 12 million
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28 163 individuals who were enrolled in a Highmark health insurance plan between 2007 and 2018, and
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31 164 who had a valid age, gender, and home address on file. Over 98.5% of enrolled individuals met
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33 165 inclusion criteria and were included in the final analytic cohort.

35 166 *Study Variables*

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38 167 Diseases of despair were defined as diagnoses related to alcohol use, substance use, and
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40 168 suicide ideation/behaviors. International Classification of Diseases (ICD) codes were extracted
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42 169 from claims and classified into variables indicating the presence or absence of a diagnosis within
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44
45 170 each of the three diagnostic categories of interest. Classifications were adapted from the
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47 171 Healthcare Cost and Utilization Project Clinical Classification Software (HCUP-CCS).²⁰ Code
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49 172 mappings were used for HCUP categories alcohol-related disorders (5.11), substance-related
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51 173 disorders (5.12), and suicide and intentional self-inflicted injury (5.13). Diagnoses related to
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54 174 substance use considered outside the focus of the present study were excluded, specifically,

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3 175 codes related to the use of tobacco and cannabis, and certain non-psychoactive substances (i.e.,
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5 176 ICD-10 codes F550, F551, F552, F554). Additional indicators were created for overall disease of
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8 177 despair status (diagnosis of any type), and co-occurring diseases of despair status (diagnoses in
9
10 178 multiple categories). A two-year lookback period was used to identify incident diagnoses. If no
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12 179 record of the given diagnosis type was found during the lookback period, the diagnosis was
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14 180 recorded as an incident case. Annual and all-time incidence and prevalence estimates were
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16
17 181 computed.

182 *Insurance Coverage*

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

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

192 **Data Analysis**

193 *Incidence and Prevalence of Diseases of Despair*

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

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3 198 incidence and prevalence rates of disease of despair diagnosis were computed for years 2009
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5 199 through 2018, allowing for an initial lookback period beginning in 2007. Rates were calculated
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7 200 by dividing the number of newly identified cases by the number of members enrolled and with
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9 201 no previous diagnosis in the past two years (incidence), and the number of current year cases by
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11 202 number of members enrolled (prevalence).
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14 203 The partially overlapping samples z-test²¹ was used to statistically test if and the degree
15
16 204 to which rates of diseases of despair changed over the last decade. The partially overlapping test
17
18 205 is designed for the statistical comparison of proportions when data include a combination of
19
20 206 paired and unpaired samples, as is often the case in dynamic cohorts extracted from clinical
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22 207 databases.
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26 208 *Predicting Individual-level Risk for Diseases of Despair*

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28 209 To identify factors associated with individual-level risk for disease of despair diagnosis
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30 210 during the most recent year of follow-up (2018), logistic regression was used to estimate risk for
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32 211 diagnosis as a function of demographic and enrollment characteristics. Odds ratios and their 95%
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34 212 confidence intervals were computed for all estimates. Analyses were performed using R, version
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36 213 3.5.2²² within Highmark's secure computing environment.
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40 214 *Patient and Public Involvement*

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42 215 Patients or the public were not involved in the design, conduct, reporting, or
43
44 216 dissemination plans of this research. The study was approved by the Institutional Review Boards
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46 217 of [blinded]. Informed consent was waived, as no study participants were contacted. Due to
47
48 218 privacy laws, data cannot be made publicly available.
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51 219

54 220 **Results**

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

[TABLE 1]

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

[FIGURE 1, TABLES 1 AND 2]

232 *Any Disease of Despair Diagnosis*

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

238 *Alcohol-related Diagnosis*

239 The overall incidence and prevalence of alcohol-related diagnosis increased by 23% and
240 37%, respectively. Significant increases were seen for men and women ages 18 and above, but
241 significant decreases were seen for those ages 1-17. The most dramatic increases were seen
242 among those ages 55-74; their prevalence increased by .5% percentage points (59% relative
243 increase).

244 *Substance-related Diagnosis*

245 The overall incidence and prevalence of substance-related diagnosis increased by 48%
246 and 94%, respectively. As with the trends observed for alcohol-related diagnoses, the incidence
247 and prevalence of substance-related diagnoses increased for all groups except for those ages 1-
248 17; for this group, rates significantly decreased. Relative increases were again highest for those
249 ages 55-57 (prevalence 172% higher; .5% percentage point increase), and for infants (prevalence
250 114% higher; .25% percentage point increase).

251 *Suicide Ideation / Behaviors Diagnosis*

252 The incidence and prevalence of suicide-related diagnosis increased for all relevant age
253 groups (infants were excluded) by 149% and 170%, respectively. While the absolute rates of
254 suicide-related diagnosis were lower than other types of disease of despair diagnoses, the relative
255 increases were dramatic. Among those ages 1-17, the prevalence increased by 287%. Among
256 those ages 18-34, it increased by 210%. All other age groups saw a relative increase of at least
257 70%.

258 *Logistic Regression Results*

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

261 [TABLE 4]

262 Men had higher odds than women of having any type of disease of despair diagnosis, alcohol-
263 related diagnosis, and substance-related diagnosis (AOR [adjusted odds ratio] = 1.49, 2.35, and
264 1.23, respectively), but lower odds than women for suicide ideation/behaviors (AOR = 0.72).
265 Age was also significantly associated with risk for all four disease of despair outcomes. After
266 adjusting for gender and insurance type, individuals ages 18-35 had the highest risk for any

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3 267 disease of despair, substance-related diagnosis, and suicide-related diagnosis. For alcohol-related
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5 268 disorders, those ages 35-74 were at slightly higher risk than those ages 18-34, and much higher
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8 269 risk than any other group. Finally, type of enrollment was also significantly related to risk.
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10 270 Compared to commercial insurance plans, Affordable Care Act (ACA) plans were associated
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12 271 with approximately 1.3 times higher odds for any diagnosis, alcohol-related diagnosis, and
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14 272 substance-related diagnosis, but similar risk for suicide-related diagnoses. Medicare plans were
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17 273 associated with 1.5 times higher odds for any disease of despair and each of the three diagnostic
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19 274 subtypes (AOR range was 1.3 – 2.2).

21 275 **Discussion**

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24 276 Nearly one in twenty individuals in our sample were clinically diagnosed with a disease
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26 277 of despair between 2007 and 2018. Similar to observed despair-related mortality, diseases of
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28 278 despair have significantly increased as morbidities over the past decade. Tracking with the
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31 279 original finding that deaths of despair have disproportionately affected middle-aged men,³ our
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33 280 data showed the largest absolute increases in overall prevalence for men ages 35-74, followed by
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35 281 women ages 55-74 and 18-34. These findings reinforce the notion that while the opioid crisis
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38 282 remains a top public health priority, parallel rises in alcohol-related diagnoses and suicidality
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40 283 must be concurrently addressed.

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42 284 The relative increases in specific diagnoses seen in infants, youth, and young adults were
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44 285 also striking. Among infants, the prevalence of substance-related diagnoses doubled over the
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47 286 course of follow-up. This increase was entirely attributable to neonatal abstinence syndrome and
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49 287 corresponds closely with increases in substance-related disorders among women of childbearing
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51 288 age. Neonatal abstinence syndrome could be argued to be the direct result of a disease of despair
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54 289 among mothers, and therefore, was included. In addition, the prevalence of suicide ideation and
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3 290 behaviors among youth and young adults at least tripled over the course of follow-up. These
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5 291 findings underscore the importance of targeting vulnerable subpopulations in tailored prevention
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7 292 and early intervention services. A recent study by Gaydos et al. used nationally representative
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9 293 longitudinal data to examine diseases of despair and their age patterns from adolescence through
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11 294 the late-30s from 1994-2017.²³ This study demonstrated increases as the cohort aged into their
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13 295 late 30s, across racial and ethnic groups as well as geographic locales. In addition to broadening
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15 296 original views beyond impacting whites in rural locales, the generalized increases in despair
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17 297 documented among this younger cohort forewarn further likely increases in mid-life mortality in
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19 298 the coming decades.

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24 299 The concept of despair, itself, remains largely unstudied, with manifestations in
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26 300 cognitive, emotional, behavioral, and biological domains as well as in social and political-
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28 301 economic contexts.¹⁷ For example, Gleit et al characterized despair by social and psychological
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30 302 dysfunction such as a lack of purpose in life, a sense of worthlessness, little hope or goals for the
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32 303 future, and perceived social rejection by broader society.⁵ Shanahan et. al provided a roadmap
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34 304 for studying the social contexts that can further strengthen or weaken pathways to despair.
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36 305 Ultimately, improving the ability to measure and clinically screen for despair, as opposed to
37
38 306 resultant diseases or deaths, will allow us to best intervene. Definitively addressing despair
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40 307 requires tackling the root causes (i.e. deep structural forces that perpetuate socioeconomic
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42 308 disadvantage) for which there are no quick fixes.²⁴

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47 309 By definition, diagnoses of diseases of despair and health insurance enrollment imply
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49 310 access to health care, although it is clear additional barriers to treatment exist. Insurance type is
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51 311 an important predictor of disease diagnoses, and diseases of despair are no exception. Individuals
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53 312 with Medicare, for example, have 1.5 times higher odds of having a diagnosis of a disease of

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3 313 despair, followed by those with ACA (1.3 times higher odds). Insurance status is frequently used
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5 314 as a surrogate for measures of socioeconomic status, which are essential to describing health
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7 315 inequalities. Unfortunately, this is an imperfect proxy.²⁵
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10 316 A limitation of the current study is the incomplete nature of social determinants of health
11
12 317 data in administrative health records. Despite the significant influence of these factors on health
13
14 318 outcomes, few sources provide data that includes both clinical and social and behavioral factors.
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16 319 To address this gap in clinical records, the Institute of Medicine Committee on Recommended
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18 320 Social and Behavioral Domains and Measures for Electronic Health Records describes a concise
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20 321 panel of standard measures in every patient's electronic health record.²⁶ These measures include
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22 322 items evaluating depression, alcohol use, and social connection or isolation which would help
23
24 323 capture diagnoses of despair. Future research might consider combining clinical records with
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26 324 data originating outside of claims and electronic health records, including direct and indirect
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28 325 measures of social determinants. Due to the large size of the sample, this study had considerable
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30 326 statistical power and tests were able to detect small but statistically significant effects. Thus, it is
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32 327 important that consideration is given to the practical significance of effects, including the
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34 328 absolute differences in risks over time and between groups.
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40 329 A significant strength of the current study is the investigation of the upstream diagnoses
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42 330 for deaths of despair in a large cohort with representation of some of the most impacted states,
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44 331 including West Virginia and Pennsylvania. Further, the use of a large claims-based dataset
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46 332 provides insight into health insurance type as a consideration in the development of future
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48 333 potential healthcare interventions. Finally, these data provide information on current diagnosis
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50 334 rates in the context of long-term trends. Continued improvements to the monitoring and
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3 335 identification of substance use and abuse, suicidality, and mental health more broadly are critical
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5 336 next steps to address diseases of despair and ultimately, decrease mortality.
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8 337 Future inquiry could benefit from similar “big data” approaches to understand and model
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10 338 patterns of despair in human populations. For instance, it would be useful to identify “hot-spots”
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12 339 of high prevalence/incidence of diseases of despair diagnoses (and deaths of despair) and
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14 340 examine the socioeconomic conditions in these areas over time. While mortality increases are
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16 341 generally—if inscrutably—understood to be due to prolonged declining socioeconomic
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18 342 conditions that exacerbate despair, others argue that the phenomenon is more attributable to other
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20 343 contextual factors such as: a worsening drug environment;²⁷⁻²⁹ the collapse of social institutions
21
22 344 and weakening of traditional social bonds (e.g. reduced church attendance,³⁰ union membership,
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24 345 etc.);³¹ a generalized cultural rise in loneliness, depression, alienation, and anxiety;³² higher
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26 346 relative gun ownership in rural areas;³³ and a “loss of virtue”.³⁴ Using big data to build predictive
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28 347 models of neighborhoods or census tracts where people may be at greatest risk would not only
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30 348 clarify current debates about past causation but also offer a future tool of clinical and public
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32 349 health importance.
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38 350 Researchers might also undertake qualitative and/or mixed methods inquiry to examine
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40 351 subjective perceptions of despair in high prevalence communities. There may be particular value
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42 352 in engaging leaders of community and social service organizations (libraries, emergency rooms,
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44 353 methadone treatment centers, suicide prevention organizations, homeless shelters, Women,
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46 354 Infants, and Children (WIC) clinics, legal services organizations, state police, churches, centers,
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48 355 county health services, and places of worship, etc.) who interface with high-risk communities, as
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50 356 well as affected persons and family members. It would be especially useful to better understand
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52 357 general awareness of the diseases of despair concept, local beliefs about causation, perceptions
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358 of effective policy solutions at the local, state, and national levels, and strategies hospitals can
359 use to most effectively intervene. Given the complexity of societal despair, combining
360 quantitative and qualitative approaches may be particularly useful.

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For peer review only

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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%)	<i>p</i> -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.

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460 *Figure 1. Age and Gender-Specific Diagnostic Prevalence Rates of Diseases of Despair, 2009 –*
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463 [attached separately]

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

Age Cohort	Men				Women			
	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.

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

Age Cohort	Men				Women			
	2009	2018	<i>p</i> -value	Ratio	2009	2018	<i>p</i> -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.

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

Variable	Any Disease of Despair		Alcohol-Related Diagnosis		Substance-Related Diagnosis		Suicide-Related Diagnosis	
	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, $p < .05$.

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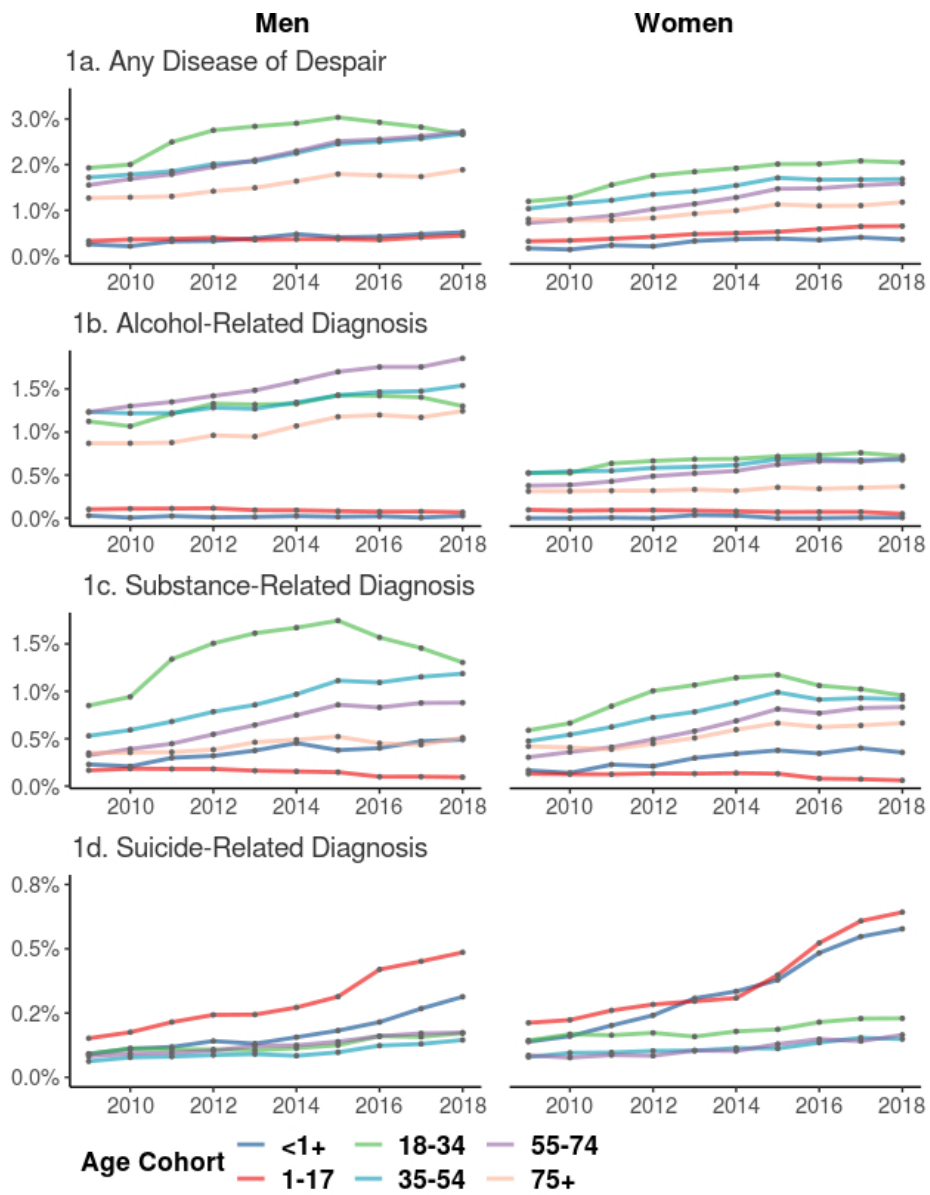


Figure 1

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4 2 **Trends in the Diagnosis of Diseases of Despair in the United States, 2009 – 2018: A**
5 3 **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.

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45 87 **Strengths and limitations of this study:**
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- 8 88 • Increasing mortality due to deaths of despair is well documented in extant research. To
9 89 our knowledge, this study is the first to provide large-scale insights into the clinical
10 90 recognition of the morbidities that can ultimately culminate in those deaths. This clinical
11 91 perspective highlights potential opportunities to intervene in the progression of morbidity
12 92 toward mortality.
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- 14 94 • The study uses a large and inclusive sample. As a result, we are able to identify
15 95 differential patterns in the diagnosis of substance-, alcohol-, and suicide-related diagnoses
16 96 across age and gender lines, which can improve targeted prevention efforts.
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- 18 98 • The long administrative surveillance period of 10 years allows us to track changes in the
19 99 identification of diseases of despair over time, and to compare long-term trends between
20 100 documented morbidity and mortality.
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- 22 102 • While trends in deaths of despair appear to vary by race/ethnicity, details on
23 103 race/ethnicity were not available for our sample.
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- 25 105 • We were unable to directly link disease of despair incidence/prevalence to mortality on
26 106 an individual level; rather, we compare trends in morbidity and mortality in more general
27 107 terms.
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3 129 From 2015-2017, there was an annual downward trend in life expectancy in the United
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5 130 States, the longest sustained decline since 1915-1918.^{1,2} Relatedly, researchers have observed a
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8 131 longer, more marked increase in the all-cause mortality of middle-aged white non-Hispanic men
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10 132 and women in the US between 1999 and 2015, with premature deaths largely associated with
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12 133 “deaths of despair,” including suicides, accidental poisonings (e.g. opiate overdose), and alcohol-
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14 134 related liver disease (e.g. cirrhosis).^{3,4}

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17 135 This troubling observation has coincided with decades of economic decline for less
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19 136 educated and unskilled workers, stagnant or falling real median wages and family incomes,^{5,6}
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21 137 lower marriage rates,⁷ increases in single-parent households,⁸ and disengagement from the labor
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23 138 force.⁹ It is theorized that these changes have fostered growing feelings of despair, i.e.,
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25 139 disillusionment, precariousness, and resignation.^{3,4,10-12} Despair may in turn trigger emotional,
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27 140 cognitive, behavioral, and even biological changes,¹³⁻¹⁷ increasing the likelihood of diseases that
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29 141 can progress and ultimately culminate in these deaths of despair.
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33 142 While this pathway may unfold over years or decades, to date, most studies in this
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35 143 domain have primarily focused on the endpoint of mortality. Limited extant research suggests a
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37 144 parallel rise in associated morbidities,^{3,4} but specific estimates of “disease of despair” morbidity
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39 145 (i.e., substance-related disorders, alcohol-related disorders, and suicide ideation and attempts) are
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41 146 lacking. Moreover, little is known about trends in the recognition and documentation of these
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43 147 diseases in the clinical setting. This represents an important gap in the literature; indeed, while
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45 148 primary prevention efforts to address the root causes of societal despair are needed, it may be
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47 149 possible to intervene upon the pathway from morbidity to mortality in the clinical setting. An
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49 150 understanding of diagnostic patterns and the association between documented morbidity and
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51 151 mortality is necessary to guide these secondary and tertiary prevention efforts. Thus, the
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3 152 objectives of the present study were to use a large administrative database of healthcare claims to
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5 153 1) characterize the incidence and prevalence of diseases of despair diagnoses over the last decade
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7 154 and 2) identify individual sociodemographic factors and patterns of comorbidity associated with
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10 155 disease of despair diagnosis. Finally, patterns in morbidity and mortality are discussed.

12 156 **Methods**

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15 157 This retrospective cohort study used claims data extracted from the administrative
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17 158 databases of Highmark Inc., a large US-based health insurance company. Highmark members are
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19 159 concentrated in states that have been disproportionately affected by deaths of despair, including
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21 160 Pennsylvania, West Virginia, and Delaware.^{18,19} The database contains clinical information such
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24 161 as services used and diagnoses assigned, and sociodemographic characteristics including gender,
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26 162 age, home address, and insurance coverage details. The study cohort included 12 million
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28 163 individuals who were enrolled in a Highmark health insurance plan between 2007 and 2018, and
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31 164 who had a valid age, gender, and home address on file. Over 98.5% of enrolled individuals met
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33 165 inclusion criteria and were included in the final analytic cohort.

35 166 *Study Variables*

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38 167 Diseases of despair were defined as diagnoses related to alcohol use, substance use, and
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40 168 suicide ideation/behaviors. International Classification of Diseases (ICD) codes were extracted
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42 169 from claims and classified into variables indicating the presence or absence of a diagnosis within
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44 170 each of the three diagnostic categories of interest. Classifications were adapted from the
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46 171 Healthcare Cost and Utilization Project Clinical Classification Software (HCUP-CCS).²⁰ Code
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48 172 mappings were used for HCUP categories alcohol-related disorders (5.11), substance-related
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50 173 disorders (5.12), and suicide and intentional self-inflicted injury (5.13). Diagnoses related to
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53 174 substance use considered outside the focus of the present study were excluded, specifically,

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3 175 codes related to the use of tobacco and cannabis, and certain non-psychoactive substances (i.e.,
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5 176 ICD-10 codes F550, F551, F552, F554). Additional indicators were created for overall disease of
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8 177 despair status (diagnosis of any type), and co-occurring diseases of despair status (diagnoses in
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10 178 multiple categories). A two-year lookback period was used to identify incident diagnoses. If no
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12 179 record of the given diagnosis type was found during the lookback period, the diagnosis was
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14 180 recorded as an incident case. Annual and all-time incidence and prevalence estimates were
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17 181 computed.

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19 182 Additional clinical comorbidities were calculated for the final year of follow-up (2018).
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21 183 Physical health comorbidities were measured using weighted Charlson Comorbidity Index
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23 184 Scores.²¹ Psychiatric comorbidities were defined using additional HCUP-CCS classifications,
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26 185 and included indicators for adjustment/anxiety disorders (5.1 and 5.2), mood disorders (5.8), and
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28 186 schizophrenia and other psychotic disorders (5.10).

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31 187 Existing research points to particular age groups as having uniquely high risk for deaths
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33 188 of despair overall and by particular subtype. Thus, individuals in the sample were stratified into
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35 189 age groups to allow for comparison between morbidity and mortality trends. Infants less than 1-
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37 190 year-old were analyzed separately included in order to capture the effects of maternal substance
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40 191 use. The remaining age groups included 1-17 years, 18-34 years, 35-54 years, 55-75 years, and
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42 192 75+-years-old.

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44 193 Insurance product information was recoded into the following categories: Employer
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46 194 sponsored; individual market Affordable Care Act (ACA) plans; Medicare, and Other. Product
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48 195 information was captured on an annual basis. If multiple products were found on file during a
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51 196 single year, the product covering the larger number of months was recorded.

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3 197 To determine whether cohort members were at-risk for being diagnosed with a disease of
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5 198 despair at any given point, the months enrolled during each year of follow-up were recorded for
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8 199 all cohort members. Except for newborns, members were considered “enrolled” for a given year
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10 200 if they were covered for at least 10 months out of the year. Newborns were considered enrolled if
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12 201 coverage was identified within the first 90 days of life.

14 202 **Data Analysis**

16 203 *Incidence and Prevalence of Diseases of Despair*

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19 204 Descriptive statistics were computed for all study variables both overall and stratified by
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21 205 diagnostic status (“any” versus “no” disease of despair diagnosis recorded over the course of
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23 206 follow-up). Differences were statistically compared using chi-square tests for categorical
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25 207 variables, and t-tests for continuous variables. Next, overall and gender- and age-specific
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27 208 incidence and prevalence rates of disease of despair diagnosis were computed for years 2009
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29 209 through 2018, allowing for an initial lookback period beginning in 2007. Rates were calculated
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31 210 by dividing the number of newly identified cases by the number of members enrolled and with
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33 211 no previous diagnosis in the past two years (incidence), and the number of current year cases by
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35 212 number of members enrolled (prevalence). For the final year of follow-up, descriptive statistics
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37 213 were also computed for weighted Charlson comorbidity scores and additional psychiatric
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39 214 comorbidities.

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42 215 The partially overlapping samples z-test²² was used to statistically test if and the degree
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44 216 to which rates of diseases of despair changed over the last decade. The partially overlapping test
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46 217 is designed for the statistical comparison of proportions when data include a combination of
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48 218 paired and unpaired samples, as is often the case in dynamic cohorts extracted from clinical
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51 219 databases.

220 *Predicting Individual-level Risk for Diseases of Despair*

221 To identify factors associated with individual-level risk for disease of despair diagnosis
222 during the most recent year of follow-up (2018), logistic regression was used to estimate risk for
223 diagnosis as a function of demographic and enrollment characteristics. Odds ratios and their 95%
224 confidence intervals were computed for all estimates. Analyses were performed using R, version
225 3.5.2²³ within Highmark's secure computing environment.

226 *Patient and Public Involvement*

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

232 **Results**

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

237 Additional cohort description is presented in **Table 1**.

238 [TABLE 1]

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

243 [FIGURE 1, TABLES 1 AND 2]

244 *Any Disease of Despair Diagnosis*

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

253 *Alcohol-related Diagnosis*

254 The overall incidence and prevalence of alcohol-related diagnosis increased by 23% and
255 37%, respectively. Significant increases were seen for men and women ages 18 and above, but
256 significant decreases were seen for those ages 1-17. The most dramatic increases were seen
257 among those ages 55-74; their prevalence increased by .5% percentage points (59% relative
258 increase).

259 *Substance-related Diagnosis*

260 The overall incidence and prevalence of substance-related diagnosis increased by 48%
261 and 94%, respectively. As with the trends observed for alcohol-related diagnoses, the incidence
262 and prevalence of substance-related diagnoses increased for all groups except for those ages 1-
263 17; for this group, rates significantly decreased. Relative increases were again highest for those
264 ages 55-57 (prevalence 172% higher; .5% percentage point increase), and for infants (prevalence
265 114% higher; .25% percentage point increase).

266 *Suicide Ideation / Behaviors Diagnosis*

267 The incidence and prevalence of suicide-related diagnosis increased for all relevant age
268 groups (infants were excluded) by 149% and 170%, respectively. While the absolute rates of
269 suicide-related diagnosis were lower than other types of disease of despair diagnoses, the relative
270 increases were dramatic. Among those ages 1-17, the prevalence increased by 287%. Among
271 those ages 18-34, it increased by 210%. All other age groups saw a relative increase of at least
272 70%.

273 *Logistic Regression Results*

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

276 [TABLE 4]

277 Men had higher odds than women for having any type of disease of despair diagnosis,
278 alcohol-related diagnosis, and substance-related diagnosis (AOR [adjusted odds ratio] = 1.49,
279 2.35, and 1.23, respectively), but lower odds than women for suicide ideation/behaviors (AOR =
280 0.72). Age was also significantly associated with risk for all four disease of despair outcomes.
281 After adjusting for gender and insurance type, individuals ages 18-35 had the highest risk for any
282 disease of despair, substance-related diagnosis, and suicide-related diagnosis. For alcohol-related
283 disorders, those ages 35-74 were at slightly higher risk than those ages 18-34, and much higher
284 risk than any other group. Finally, type of enrollment was also significantly related to risk.
285 Compared to commercial insurance plans, Affordable Care Act (ACA) plans were associated
286 with approximately 1.3 times higher odds for any diagnosis, alcohol-related diagnosis, and
287 substance-related diagnosis, but similar risk for suicide-related diagnoses. Medicare plans were

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3 288 associated with 1.5 times higher odds for any disease of despair and each of the three diagnostic
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5 289 subtypes (AOR range was 1.3-2.2).
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7 290 *Clinical Comorbidities*

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10 291 Table 5 includes average weighted Charlson comorbidity scores and diagnostic
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12 292 prevalence rates for adjustment/anxiety disorders, mood disorders, and schizophrenia and other
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14 293 psychotic disorders in 2018, stratified by age, gender, and the presence of a disease of despair
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16 294 diagnosis during the same year.
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19 295 [TABLE 5]
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21 296 Disease of despair diagnosis was associated with significantly higher mean comorbidity
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23 297 scores and significantly higher prevalence of each psychiatric comorbidity for both men and
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25 298 women across every age group. As expected, chronic health conditions were rare among younger
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27 299 cohort members, yet compared to those without disease of despair diagnoses, the average
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29 300 Charlson score among those with disease of despair diagnoses was at least two times higher for
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31 301 every age group up to 74 years. The range of the diagnostic prevalence of adjustment/anxiety
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33 302 disorders was 6.3% to 21.2% among those without disease of despair diagnoses, and 31.0% to
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35 303 84.2% among those with diagnoses. Similarly, the diagnostic prevalence of mood disorders
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37 304 ranged from 2.0% to 15.6% among those without disease of despair diagnoses, and 31.2% to
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39 305 78.7% among those with a diagnosis. Finally, while diagnoses of schizophrenia and other
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41 306 psychotic disorders were very rare among those without disease of despair diagnoses, their
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43 307 diagnostic prevalence ranged from 2.1% to 10.3% among those with diagnoses.
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49 308 **Discussion**

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51 309 Nearly one in twenty individuals in our sample were clinically diagnosed with a disease
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53 310 of despair between 2007 and 2018. Similar to observed despair-related mortality, diseases of
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3 311 despair have significantly increased as morbidities over the past decade.²⁴ Tracking with the
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5 312 original finding that deaths of despair have disproportionately affected middle-aged men,³ our
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7 313 data showed the largest absolute increases in overall prevalence for men ages 35-74, followed by
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9 314 women ages 55-74 and 18-34. These findings reinforce the notion that while the opioid crisis
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11 315 remains a top public health priority, parallel rises in alcohol-related diagnoses and suicidality
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13 316 must be concurrently addressed.²⁵ Relatedly, the association between diseases of despair and
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15 317 chronic health conditions at all ages along with very high rates of co-occurring psychiatric
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17 318 conditions underscore the interconnectedness of diseases of despair with overall well-being, and
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19 319 the importance of considering reciprocal interrelationships among these conditions in prevention
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21 320 and intervention efforts.

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26 321 The relative increases in specific diagnoses seen in infants, youth, and young adults were
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28 322 also striking. Among infants, the prevalence of substance-related diagnoses doubled over the
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30 323 course of follow-up. This increase was entirely attributable to neonatal abstinence syndrome and
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32 324 corresponds closely with increases in substance-related disorders among women of childbearing
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34 325 age. Neonatal abstinence syndrome could be argued to be the direct result of a disease of despair
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36 326 among mothers, and was therefore included. In addition, the prevalence of suicide ideation and
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38 327 behaviors among youth and young adults at least tripled over the course of follow-up. These
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40 328 findings underscore the importance of targeting vulnerable subpopulations in tailored prevention
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42 329 and early intervention services.

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46 330 A recent study by Gaydos et al. used nationally representative longitudinal data to
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48 331 examine diseases of despair and their age patterns from adolescence through the late-30s from
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50 332 1994-2017.²⁶ This study demonstrated increases as the cohort aged into their late 30s, across
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52 333 racial and ethnic groups as well as geographic locales. In addition to broadening original views
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3 334 beyond impacting whites in rural locales, the generalized increases in despair documented
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5 335 among this younger cohort forewarn further likely increases in mid-life mortality in the coming
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7 336 decades. Such trends are already beginning to be observed at the population level in the U.S.
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10 337 Researchers examining declining life expectancy using data from the US Mortality Database and
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12 338 CDC WONDER have recently established that increased death rates among people in midlife are
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14 339 in fact extending beyond the original demographic characterized by Case & Deaton to all racial
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16 340 and ethnic groups, as well as to suburbs and cities (with the largest relative increases occurring in
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18 341 the Ohio Valley and New England).²⁷ As these and other findings expand the original deaths of
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20 342 despair phenomenon across demographic and geographic boundaries it strengthens the
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22 343 aforementioned hypothesis that the crisis is systemically linked to material changes in the US
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24 344 political-economy that have broadly affected the working class over the last several decades.
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26 345 Thus, while a better understanding of the clinical manifestation of diseases of despair may
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28 346 inform efforts at intervention and mitigation, it must be acknowledged that the ultimate public
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30 347 health goal must be addressing structural root causes of despair.

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33 348 The concept of despair remains largely unstudied, with manifestations in cognitive,
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35 349 emotional, behavioral, and biological domains as well as in social and political-economic
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37 350 contexts.¹⁷ For example, Gleib et al characterized despair by social and psychological dysfunction
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39 351 such as a lack of purpose in life, a sense of worthlessness, little hope or goals for the future, and
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41 352 perceived social rejection by broader society.⁵ Shanahan et. al provided a roadmap for studying
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43 353 the social contexts that can further strengthen or weaken pathways to despair. Ultimately, as
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45 354 influencing the root causes of the crisis (i.e. societal structures that perpetuate socioeconomic
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47 355 disadvantage) will be a politically-daunting endeavor, there may be shorter-term benefit in
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49 356 improving the healthcare system's ability to measure and clinically screen for despair, as
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3 357 opposed to resultant diseases or deaths. Better processes for systemically identifying and
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5 358 tracking despair may allow for clinical interventions to help mitigate progression to despair-
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7 359 related mortality.²⁸
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10 360 *Strengths and Limitations*

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12 361 A significant strength of the current study is the investigation of the upstream diagnoses
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14 362 for deaths of despair in a large cohort with representation of some of the most impacted states,
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16 363 including West Virginia and Pennsylvania. Further, the use of a large claims-based dataset
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18 364 provides insight into health insurance type as a consideration in the development of future
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20 365 potential healthcare interventions. Finally, these data provide information on current diagnosis
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22 366 rates in the context of long-term trends. A limitation of the current study is the incomplete nature
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24 367 of social determinants of health data in administrative health records. Despite the significant
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26 368 influence of these factors on health outcomes, few sources provide data that includes both
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28 369 clinical and social and behavioral factors. To address this gap in clinical records, the Institute of
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30 370 Medicine Committee on Recommended Social and Behavioral Domains and Measures for
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32 371 Electronic Health Records describes a concise panel of standard measures in every patient's
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34 372 electronic health record.²⁹ These measures include items evaluating depression, alcohol use, and
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36 373 social connection or isolation which would help capture diagnoses of despair. Future research
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38 374 might consider combining clinical records with data originating outside of claims and electronic
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40 375 health records, including direct and indirect measures of social determinants.
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46 376 By definition, diagnoses of diseases of despair and health insurance enrollment imply
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48 377 access to health care, although it is clear additional barriers to treatment exist. Insurance type is
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50 378 an important predictor of disease diagnoses, and diseases of despair are no exception. Individuals
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52 379 with Medicare, for example, have 1.5 times higher odds of having a diagnosis of a disease of
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3 380 despair, followed by those with ACA (1.3 times higher odds). Insurance status is frequently used
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5 381 as a surrogate for measures of socioeconomic status, which are essential to describing health
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7 382 inequalities. Unfortunately, this is an imperfect proxy.³⁰ Employer-sponsored insurance suggests
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9 383 the presence of stable household income, yet the nature of coverage and cost sharing
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11 384 responsibilities of patients vary widely across insurance plans. Further, while expanded
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13 385 insurance coverage under the Affordable Care Act has reduced socioeconomic disparities in
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15 386 healthcare access,³¹ significant barriers remain. Ultimately, that an estimated 87 million working
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17 387 adults in the US are uninsured or underinsured³² remains a major structural challenge for both
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19 388 understanding the true scope of the diseases of despair crisis and mounting clinical programs to
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21 389 ensure effective treatment.
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26 390 *Directions for future research*

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28 391 Identifying diseases of despair is critical for interrupting their progression towards deaths
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30 392 of despair, but diagnoses do not necessarily guarantee the provision of appropriate and adequate
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32 393 care for acute problems or general wellbeing. Thus, future research may build upon these
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34 394 findings by quantifying treatment following disease identification, and linking this treatment to
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36 395 longer-term morbidity and mortality. Relatedly, while results from the present study suggest
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38 396 strong associations between diseases of despair and both physical and mental health
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40 397 comorbidities, additional research may build on these exploratory findings in multiple ways.
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42 398 First, identifying the clinical correlates of diseases of despair may present opportunities to
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44 399 improve their timely detection through targeted screening. In addition, integrated approaches to
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46 400 treatment that holistically target a range of physical and mental health symptoms may have
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48 401 improved efficacy. It is likely that health systems that work with vulnerable populations (e.g.
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50 402 residents of rural and remote regions, low-income adolescents, etc.) may need to co-design
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3 403 primary, secondary, and tertiary interventions aimed at addressing diseases of despair. Such
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5 404 interventions may require a wider array of community partners than are typically included in
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8 405 conventional health services. Developing and evaluating effective organizational partnerships
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10 406 and best practices in integrated care of patients with diseases of despair would be a valuable
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12 407 contribution.

14 408 Future inquiry could benefit from similar “big data” approaches to understand and model
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16 409 patterns of despair in human populations. For instance, it would be useful to identify “hot-spots”
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19 410 of high prevalence/incidence of diseases of despair diagnoses (and deaths of despair) and
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21 411 examine the socioeconomic conditions in these areas over time. As mentioned, research is
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23 412 increasingly—if somewhat inscrutably—linking mortality with prolonged stagnant or declining
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25 413 socioeconomic conditions. These conditions are associated with decades of globalization, rising
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27 414 automation, and austerity policies (i.e. cuts in social spending) that have exacerbated economic
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29 415 precariousness and despair. Notably, researchers have recently established a direct association
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31 416 between automotive assembly plant closures in 112 manufacturing counties located primarily in
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33 417 the US South and Midwest and an 85% surge in opioid overdose mortality rates among working-
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35 418 age adults five years later.³³ Others have, for instance, linked rising rates of death of despair with
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37 419 stagnant minimum wage).³⁴⁻³⁶

42 420 However, others argue that the phenomenon is more attributable to other contextual
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44 421 factors such as: a worsening drug environment;³⁷⁻³⁹ the collapse of social institutions and
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46 422 weakening of traditional social bonds (e.g. reduced church attendance,^{40,41} union membership,⁴²
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48 423 etc.);⁴³ hospital closures and shortages (particularly in rural areas)⁴⁴; a generalized cultural rise in
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50 424 loneliness, depression, alienation, and anxiety;⁴⁵ higher relative gun ownership in rural areas;⁴⁶
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53 425 racial resentment and a growing sense of social status loss⁴⁷ among poor whites; and moral

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3 426 decadence (i.e. a “loss of virtue” in ethnically white rural communities).⁴⁸ Using big data to build
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5 427 predictive models of neighborhoods or census tracts where people may be at greatest risk would
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8 428 not only help clarify current debates about past causation and identify zones of resilience, but
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10 429 also offer a future tool of clinical and public health import.

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12 430 Researchers might also undertake qualitative and/or mixed methods inquiry to examine
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14 431 subjective perceptions of despair in high prevalence communities. There may be particular value
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16 432 in engaging leaders of community and social service organizations (e.g., libraries, emergency
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18 433 rooms, methadone treatment centers, suicide prevention organizations, homeless shelters,
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20 434 Women, Infants, and Children (WIC) clinics, legal services organizations, state police,
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22 435 community centers, county health services, and places of worship, etc.) who interface with high-
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24 436 risk populations, as well as affected persons and family members. It would be especially useful
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26 437 to better understand general awareness of the diseases of despair concept, local beliefs about
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28 438 causation, perceptions of effective policy solutions at the local, state, and national levels, and
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30 439 strategies hospitals can use to most effectively intervene. Moreover, as the COVID-19 pandemic
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32 440 contracts domestic and global economies and requires the implementation of social/physical
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34 441 distancing regimes, it will be important for researchers to examine how and in what ways
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36 442 diseases of despair are affected by prolonged isolation, loss of jobs/benefits, diminution of social
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38 443 protections, lack of mental health care, drug abuse, increased domestic abuse, and other societal
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40 444 consequences of the virus. Given the complexity of despair, combining quantitative and
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42 445 qualitative approaches may be particularly useful.
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4 450 Study concept and design: All authors

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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%)	<i>p</i> -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.

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609 *Figure 1. Age and Gender-Specific Diagnostic Prevalence Rates of Diseases of Despair, 2009 –*
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Table 2. Comparison of Age and Gender Specific Annual Incidence of Disease of Despair Diagnoses, 2009 – 2018.

Age Cohort	Men				Women			
	2009	2018	<i>p</i> -value	Ratio	2009	2018	<i>p</i> -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.

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

Age Cohort	Men				Women			
	2009	2018	<i>p</i> -value	Ratio	2009	2018	<i>p</i> -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.

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

Variable	Any Disease of Despair		Alcohol-Related Diagnosis		Substance-Related Diagnosis		Suicide-Related Diagnosis	
	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, $p < .05$.

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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	<i>p</i>	No DoD	DoD	<i>p</i>	No DoD	DoD	<i>p</i>	No DoD	DoD	<i>p</i>
	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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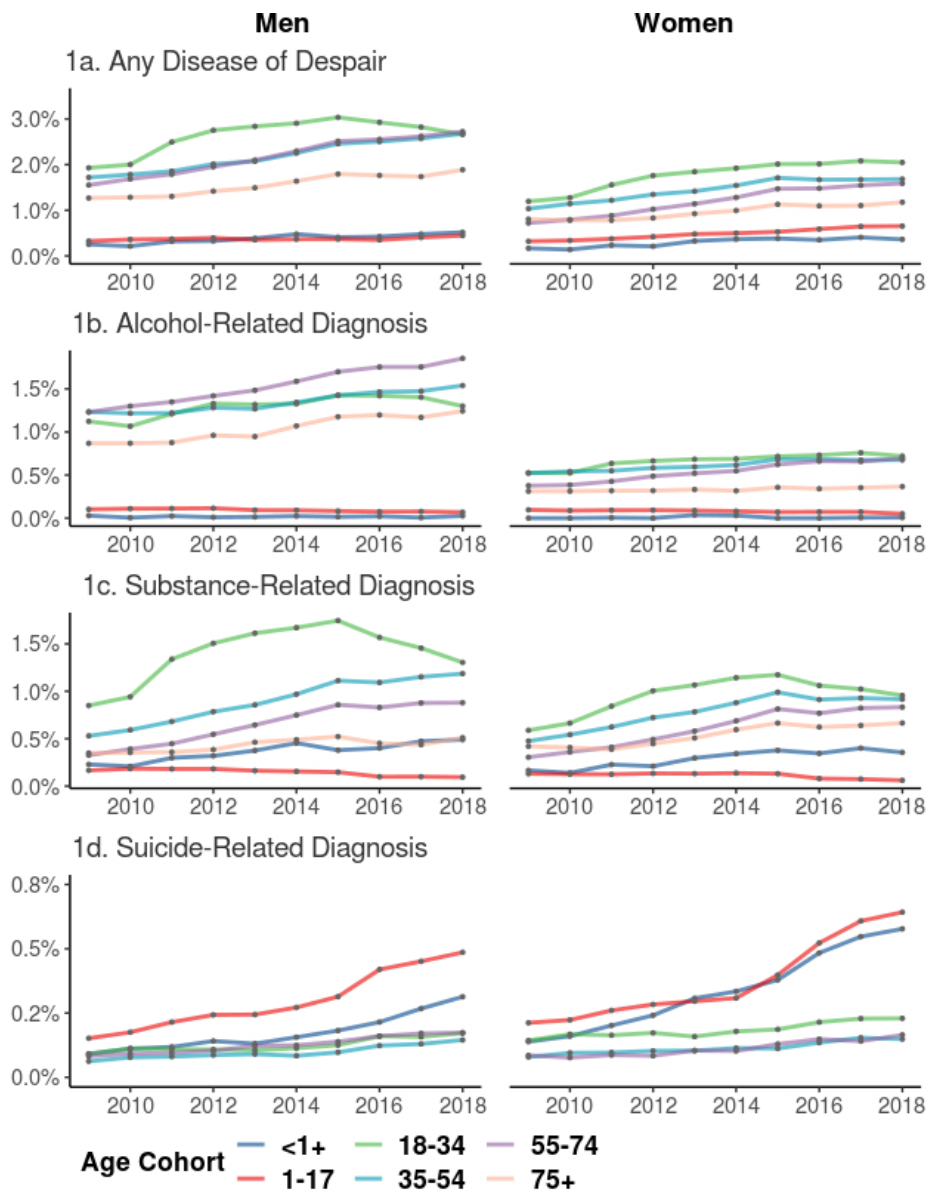


Figure 1

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

<p>1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27</p> <p>Participants</p>	<p>6</p>	<p>(a) <i>Cohort study</i> - Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> - 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 <i>Cross-sectional study</i> - Give the eligibility criteria, and the sources and methods of selection of participants</p> <p>(b) <i>Cohort study</i> - For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> - For matched studies, give matching criteria and the number of controls per case</p>	<p>A: Lines 157 – 219 B: NA</p>	<p>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.</p> <p>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.</p> <p>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.</p>	<p>6.1: Lines 157 – 181</p> <p>6.3: References 20 and 21</p> <p>6.3: NA</p>
<p>28 29 30 31 32 33 34</p> <p>Variables</p>	<p>7</p>	<p>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.</p>	<p>Lines 166 – 196; References 20 and 21</p>	<p>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.</p>	<p>7.1: Lines 166 – 196; References 20 and 21</p>
<p>35 36 37 38 39 40 41 42</p> <p>Data sources/ measurement</p>	<p>8</p>	<p>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</p>	<p>Lines 157 - 219</p>		

1 2 3 4 5 6 7 8 9 10	Bias	9	Describe any efforts to address potential sources of bias	Lines 157 - 219		
11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33 34	Study size	10	Explain how the study size was arrived at	Lines 157 - 165		
35 36 37 38 39 40 41 42 43 44	Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Lines 167 - 225		
45 46 47	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) <i>Cohort study</i> - If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> - If applicable, explain how matching of cases and controls was addressed <i>Cross-sectional study</i> - 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 (<i>e.g.</i> , 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>i.e.</i> , 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 (<i>e.g.</i> , 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) <i>Cohort study</i> - summarise follow-up time (<i>e.g.</i> , average and total amount)	A: Table 1 B: Lines 164 – 165, Table 1 C: Table 1		
Outcome data	15	<i>Cohort study</i> - Report numbers of outcome events or summary measures over time <i>Case-control study</i> - Report numbers in each exposure	Figure 1, Tables 2 and 3		

		category, or summary measures of exposure <i>Cross-sectional study</i> - 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	Lines 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, Guttman 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.

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