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Association between diseases of despair and atherosclerotic cardiovascular disease among insured adults in the USA: a retrospective cohort study from 2017 to 2021

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ABSTRACT

Objectives To assess associations between diseases of despair (DoD) and incident atherosclerotic cardiovascular disease (ASCVD) among insured adults in the USA.

Design Retrospective cohort study.

Setting Highmark insurance claims data in the USA from 2017 to 2021.

Participants Adults with at least 10 months of continuous insurance enrolment, no record of ASCVD in the 2016 baseline year and no missing data on study variables.

Primary and secondary outcome measures Cox proportional hazard regression was used to calculate crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) to assess risk of ASCVD (composite of ischaemic cardiomyopathy, non-fatal ischaemic stroke, peripheral arterial disease or non-fatal acute myocardial infarction) by baseline DoD overall, and by the component conditions comprising DoD (alcohol-related disorders, substance-related disorders, suicidality) individually and in combination.

Results The DoD-exposed group had an age-adjusted rate of 20.5 ASCVD events per 1000 person-years, compared with 11.7 among the unexposed. In adjusted models, overall DoD was associated with increased risk of incident ASCVD (HR 1.42, 95% CI 1.36 to 1.47). Individually and in combination, component conditions of DoD were associated with higher risk for ASCVD relative to no DoD. Substance-related disorders were associated with 50% higher risk of incident ASCVD (HR 1.5, 95% CI 1.41 to 1.59), alcohol-related disorders and suicidality/intentional self-harm were associated with 33% and 30% higher risk, respectively (HR 1.33, 95% CI 1.26 to 1.41; HR 1.30, 95% CI 1.11 to 1.52). Co-occurring DoD components conferred higher risk still. The highest risk combination was substance-related disorders+suicidality (HR 2.01, 95% CI 1.44 to 2.82).

Conclusions Among this cohort of insured adults, documented DoD was associated with increased ASCVD risk. Further research to understand and address cardiovascular disease prevention in those with DoD could reduce costs, morbidity and mortality. Further examination of overlapping structural factors that may be contributing to concurrent rises in ASCVD and DoD in the USA is needed.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used a large insurance claims database with participants concentrated in a region of the USA disproportionately affected by diseases of despair (DoD).
⇒ The claims database includes many important sociodemographic variables such as education, poverty and vehicle access, in addition to healthcare utilisation variables such as cost, inpatient, outpatient and psychotherapy services.
⇒ This study is susceptible to attrition bias as participants suffering from DoD may disproportionately be lost to follow-up due to disenrolment.
⇒ All participants in this study had health insurance which limits generalisability.
⇒ This is an observational study and therefore uncontrolled confounders may be present.

INTRODUCTION

In the USA, adult life expectancy has declined continuously in the past decade for the first time in over 50 years.[1] This concerning trend has been driven in part by an unprecedented increase in mortality among adults in midlife who are experiencing what researchers have termed 'diseases of despair' (DoD)[1 2] or 'deaths of despair'[3]—that is, morbidity and mortality resulting from drug abuse, alcoholism and suicidality.[2 4 5] While DoD were initially found to disproportionately affect white males and females in midlife with low educational attainment in rural American regions beset by long-term labour market decline, in recent years excess mortality and morbidity has been found to be increasing across diverse demographic groups.[2 6–12] Researchers have theorised[13 14]

that economic dislocation, which has disproportionately affected those lacking college degrees in a postindustrial service- and knowledge-based economy over recent decades,[15] has progressively weakened family structures, limited access to high-quality healthcare, reduced participation in social organisations and caused loneliness, isolation and loss of future-oriented hope.[3 16 17] Consequently, these phenomena may trigger biopsychosocial changes (eg, chronic pain, anxiety, depression), increasing the likelihood of self-harm and substance-use illnesses.[4] The COVID-19 pandemic has further exacerbated the DoD crisis. In 2020, 186 763 DoD-related deaths occurred in the USA—the highest in the last 30 years.[18]

Another important contributor to premature death and reduced life expectancy is largely preventable cardiometabolic diseases such as coronary heart disease, stroke, high blood pressure and diabetes. While mortality from these conditions had largely declined through much of the 20th century, progress has stalled in more recent decades consistent with the rise of DoD.[5 19] In fact, if the declining trends in atherosclerotic cardiovascular disease (ASCVD) had continued beyond 2010, prevented cardiac deaths would account for a larger share of excess mortality than the additional deaths attributable to rising DoD.[20] It has been argued that ASCVD as well as obesity should be considered a constituent part of the DoD phenomenon, as both groups of illnesses appear to be highly sensitive to economic hardship and biopsychosocial stress.[14] Similar findings have been observed in other countries during and following economic hardship. Indeed, researchers have previously noted[21] a substantial rise in mortality from DoD (suicide, alcohol and illicit drug consumption) and cardiometabolic disorders in Russia. In the 1990s, economic shocks following the fall of the Soviet Union (ie, collapse of state services, loss of pensions and healthcare access, rapid privatisation, rise of monopolies, etc) led to 7.3 million excess deaths and a dramatic loss of 6 years in mean life expectancy.[22] There is, however, a need to compare these prior findings from Russia to contemporary populations from the USA who have been subject to overlapping but different socioeconomic factors.

There are several potential indirect and direct causal links between DoD and cardiovascular disease (CVD). Consequences of despair can include behavioural inaction, or risky and unhealthy acts that reflect limited consideration of the future and negatively affect cardiometabolic health (eg, smoking, poor dietary habits, low physical activity). Biologically, despair can appear in individual stress-related physiological markers and in accumulated allostatic load, which includes various downstream physiological consequences related to cardiovascular health (eg, obesity, hypertension, high blood pressure, atherosclerosis).[23–26] Despair can also be inferred from changes in body functions like sleep, appetite, concentration and pain,[26] which may reciprocally fuel both behavioural and biological risks.

Another important consideration in this framework is the potential for differences among the component conditions that comprise DoD and differences in the degree and nature of their respective impacts on ASCVD. Recent research findings challenge the use of 'despair' as a single composite measure, and suggest distinct dimensions of despair that relate to specific health behaviours and outcomes.[27] Better understanding these associations and the biopsychosocial mechanisms linking both overall despair and its individual condition components to adverse cardiovascular outcomes is critical for developing appropriate surveillance, prevention and intervention strategies. This information could save many lives and have important public health implications including decreased morbidity and reduced healthcare costs.

We used a large national insurance claims database to investigate the association between overall DoD and the conditions comprising it during a baseline period and the subsequent incidence of ASCVD outcomes over a 5-year follow-up period. While the cohort includes individuals from across the USA, the cohort is most densely concentrated in the Appalachian region and states disproportionately affected by DoD, including Pennsylvania, West Virginia and Delaware.[28]

METHODS

Research design and population

The analytic cohort included adults insured through Highmark Health across the USA. The administrative surveillance period included 2016 as a baseline year, and follow-up during years 2017 through 2021. Individuals included in the cohort had at least 10 out of 12 months of continuous enrolment in a Highmark medical plan and no record of ASCVD in the 2016 baseline year. Individuals contributed to the follow-up period from 1 January 2017, until either their first gap in enrolment or first record of outcome diagnosis (ASCVD). Members with any missing data on model covariates were excluded from analysis (n=30 298 (1% of total exclusions)). Of Highmark's roughly 5 million members, a total of 2 323 662 were eligible for inclusion. Among these, 43 701 had a history of DoD at baseline, and 2 279 961 did not. A consort diagram is provided in figure 1. The average length of available follow-up data prior to ASCVD event or censoring was 34 months.

Measures

Incident events of ASCVD were drawn from the claims history of the analytic cohort using the International Classification of Disease (ICD)-10 for identification and classification. An ASCVD incident event was defined as the first instance in the follow-up period of a diagnosis code for atherosclerosis, ischaemic cardiomyopathy, nonfatal ischaemic stroke, peripheral arterial disease or nonfatal acute myocardial infarction at any position on the claim. See supplementary appendix for a complete list of included ICD-10 codes (online supplemental file 1).

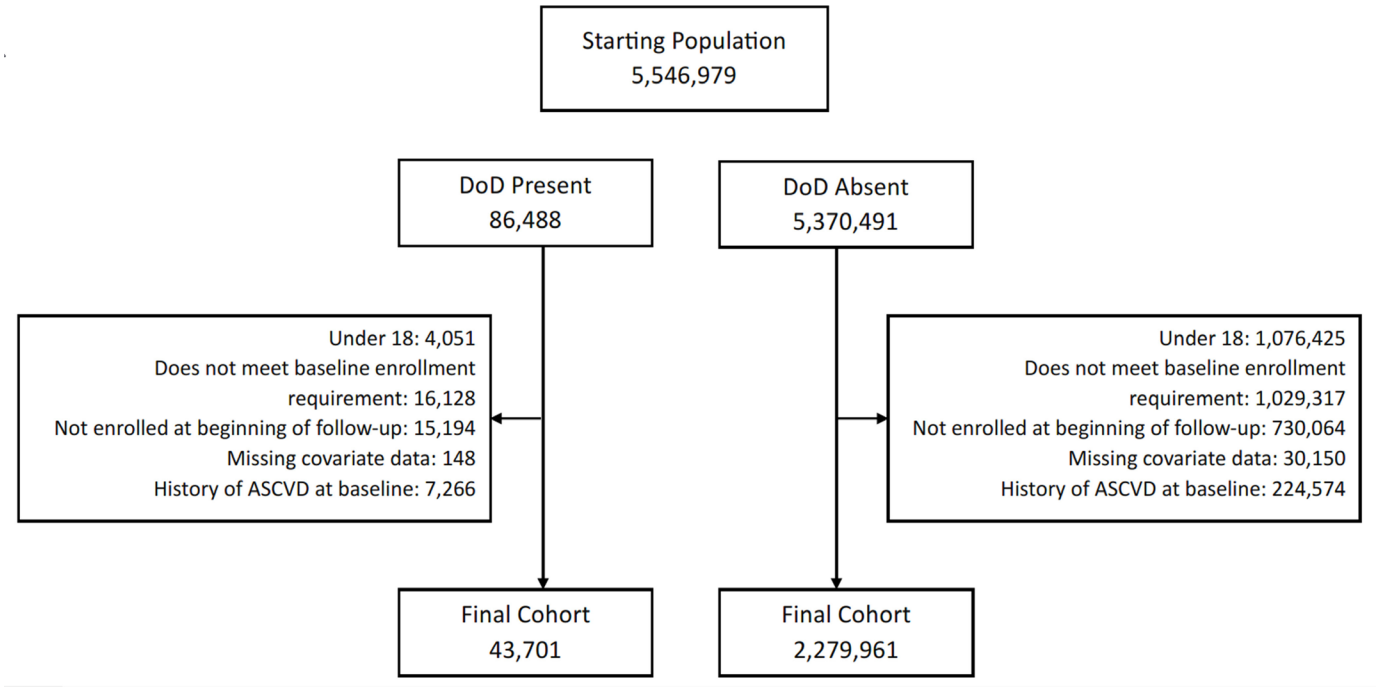

Figure 1 Consort diagram representing the number of participants in the Highmark insurance claims database stratified by diseases of despair status. Exclusions from the final analytic cohort are itemised. ASCVD, atherosclerotic cardiovascular disease; DoD, diseases of despair.

The exposure variable, DoD, was identified from the claims history of members during the baseline year. Overall exposure was defined as presence of ICD-10 codes in any position for substance-related disorders, alcohol-related disorders or suicidality/intentional self-harm. These classifications were drawn from the Healthcare Cost and Utilization Project Clinical Classification Software.[29] Diagnoses related to substance use considered outside the focus of the present study were excluded, specifically, codes related to the use of tobacco and cannabis, and certain non-psychoactive substances (ie, ICD-10 codes F550, F551, F552, F554). In addition to the composite measure of DoD, a categorical indicator was created by capturing the potential combinations of substance-related disorders, alcohol-related disorders and suicidality/intentional self-harm. The reference level for this indicator was set to 'None', that is, no substance, alcohol or suicidality diagnoses recorded.

All covariates were based on the baseline year and included sociodemographic factors, health behaviours, personal medical history and healthcare utilisation. All were sourced from publicly available census data, claims history or The Johns Hopkins ACG System, a well-established and robust software tool that provides a flexible multimorbidity framework that includes validated claims-based indicators for clinical conditions, utilisation and quality of care.[30] Sociodemographic characteristics included age and sex at the individual level as recorded in claims at baseline. Area-level social determinants of health (SDOH) characteristics were appended using geographic joining keys based on geocoding of the residential addresses that covered the longest portion of the baseline year. SDOH information included several different census tract-level measures. Rurality designations were based on census tract-level rural–urban commuting area codes. Social Vulnerability Index was extracted from the CDC's 2016 estimates.[31] Gini Index, a measure of area level income inequality, was pulled from the RAND state statistics database for 2016 and linked to the cohort using census tract to zip code tabulation area mapping.[32 33] All other SDOH covariates, poverty, educational attainment, vehicle access and marital status were drawn from the Census Bureau's American Community Survey 2016 5-year estimates.[34]

Individual smoking status and obesity were assigned based on the presence of at least one relevant ICD-10 code in any position on any baseline year claims. Frailty was based on classifications from the ACG system and identifies individuals within diagnostic clusters associated with frailty (eg, malnutrition, dementia, incontinence, difficulty in walking).

We used classifications from the ACG system to derive healthcare cost and utilisation measures. A psychotherapy service indicator identified those with at least two ambulatory psychotherapy services within 120 days during the observation period. Inpatient count reflected the total number of unique admissions unrelated to childbirth or injury. Outpatient count was defined as the total count of unique ambulatory and hospital outpatient visits. Total cost was defined as the medical plus pharmacy total cost of care during the observation period.

Statistical analysis

Baseline characteristics were compared by exposure and censoring within each cohort. Because p values offer little information on the magnitude of effects in large population-level datasets, standardised mean differences were used to assess differences. While there is no clear consensus on the effect size denoting a meaningful difference, the commonly used rule of thumb is 10%.[35 36]

Initial univariate proportional hazard models were computed against the main effect and each independent variable to understand the matrix of relationships between all the covariates and the outcome. Then, an iterative multivariate modelling process was conducted adding and removing covariates to both find the model of best fit and to understand how fitting different covariates impacted the working mechanism. We hypothesised potential effect modification by age, medical risk factors or SDOH. Several interaction terms were tested. Terms that did not meet the threshold of statistical significance or improve model fit were removed.

Following initial modelling, we posited potential bias from those individuals with greater engagement with the health system. To test for this bias, we removed individuals with cost or utilisation among the top 5% and reran the final model on the reduced sample. Additionally, E values were calculated for each cohort to provide a frame of reference for sensitivity to unmeasured confounding. E values are on the risk ratio scale and represent the relationship that an unmeasured covariate would need with both the exposure and outcome, conditional on included covariates, to nullify the main effect.[37 38] Additionally, to test for potential differences in the effect of DoD across gender and age, we conducted subgroup analyses for age and sex by fitting the models with each term interacted for age/sex. Last, to assess variability in the magnitude or direction of the component conditions that make up DoD, the multivariate model assessing the effect of overall DoD was recomputed using a categorical indicator for DoD that captures component conditions individually and in combination.

All statistical analysis was completed in SAS Enterprise Guide 8.2.

Patient and public involvement

Patients or the public were not involved in the design, reporting or dissemination of this study.

RESULTS

Cohort characteristics stratified by the presence of DoD at baseline are presented in table 1. Bivariate analysis suggested that those with a DoD diagnosis at baseline tended to be male, younger, have more medical risk factors and have greater healthcare utilisation. Among the analytic cohort, 125 312 (5%) had an incident ASCVD diagnosis. We recorded an age-adjusted rate of 20.5 ASCVD events per 1000 person-years among the DoD group and 11.7 ASCVD events per 1000 person-years among those with no baseline DoD record.

DoD exposure as a composite outcome

In unadjusted models, DoD diagnosis at baseline was associated with an increased risk of ASCVD (HR 1.42, 95% CI 1.36 to 1.47). Other univariate models suggested significant, independent relationships between baseline covariates and the outcome (see table 2). Frailty (HR 3.68, 95% CI 3.62 to 3.74) had the strongest positive effect, followed by medical costs and smoking status (HRs 2.46 and 2.29, respectively). Several area-level SDOH factors showed moderate relationships with the outcome: rurality and high school graduation rates were negatively associated with ASCVD, while Gini Index, poverty rates and percent of households without a vehicle were positively related to ASCVD.

Following best fit model selection, including testing additional adjustment for medical risk factors, health behaviours and SDOH factors, DoD maintained an independent positive association with incident ASCVD (HR 1.42, 95% CI 1.36 to 1.47). Covariates tested but ultimately removed either did not meet the threshold for significance or were significant with minimal to no impact to the main effect HR. Unadjusted and adjusted model estimates are presented in table 2. Notably, a simple model adjusted for age and sex alone resulted in an increased HR for DoD relative to the univariate effect. The subsequent addition of the full set of covariates attenuated the effect, resulting in a very similar effect for DoD in unadjusted and fully adjusted models.

Sensitivity analysis

Following the removal of individuals among the top 5% of healthcare spending and utilisation, the main effect HR was slightly attenuated (original HR 1.42, sensitivity HR 1.38, 95% CI 1.31 to 1.46, online supplemental table 2). Calculated E values suggested that an unmeasured covariate would need to have HR 2.18 to both ASCVD events and DoD conditional on other covariates to negate the relationship between DoD and ASCVD events. Subgroup analyses by age and sex suggested that while men tend to experience DoD at higher rates than women, DoD may confer slightly greater risk on women (online supplemental table 3). Additionally, while DoD exposure conferred significant risk for ASCVD across the entire life course, its effect was slightly attenuated with increasing age (online supplemental table 4). Full results of the sensitivity analyses and fitted sex- and age-models are available in online supplemental materials.

DoD exposure as separate components

When best-fitting models were refit using the categorical DoD component variable in place of the overall DoD variable, every component of DoD both individually and in combination was significantly associated with higher risk for ASCVD relative to the reference level of no DoD (HR range: 1.3–2.0), despite smaller cell sizes for some

Table 1 Characteristics of analytic cohort, stratified by diseases of despair status at baseline

	Disease of despair diagnosis at baseline Mean±SD/N (%)		
	Present (n=43 701)	Absent (n=2 279 961)	Absolute standard difference (%)
	Baseline characteristics		
Gender male	25 333 (58.0%)	1 066 992 (46.8%)	22.3
Age	44.6±17.0	48.5±18.1	22.2
Smoking	4714 (10.8%)	75 773 (3.3%)	29.5
Obesity	5305 (12.1%)	184 106 (8.1%)	13.5
Below poverty line*	12.4%±8.7%	12.1%±8.6%	3.3
High school diploma*	89.5%±6.5%	89.5%±6.7%	0.0
Households with no vehicle*	7.3%±7.4%	7.0%±7.3%	4.5
% rural	8068 (18.5%)	439 099 (19.3%)	2.2
SVI	6.6±1.8	6.5±1.8	4.1
% with frailty	4671 (10.7%)	103 329 (4.5%)	23.5
% with psychotherapy service	15 496 (35.5%)	95 260 (4.2%)	85.1
Inpatient count	0.5±1.0	0.1±0.3	53.4
Outpatient count	7.2±14.5	2.5±6.8	40.8
Total cost	$17,083.05±$35,565,50	$5,568.3±$16 900.26	41.2
Diabetes diagnosis	4623 (10.6%)	204 531 (9.0%)	5.5
	ASCVD outcomes		
Overall events	2284 (6.6%)	123 028 (5.4%)	
Age-adjusted incidence†	20.46±0.74	11.67±0.7	

*Mean and SD reported for percentage-based area-level metrics because they are averaged over the population.
†Per 1000 person-years.
ASCVD, atherosclerotic cardiovascular disease; SVI, Social Vulnerability Index.

Table 2 Results of univariate and multivariate models estimating risk for incident atherosclerotic cardiovascular disease based on overall disease of despair status at baseline

	HR (95% CI)	
	Unadjusted	Adjusted
Disease of despair diagnosis at baseline	1.42 (1.36 to 1.47)	1.42 (1.36 to 1.47)
Frailty indicator	3.68 (3.62 to 3.74)	1.38 (1.36 to 1.41)
Area educational attainment*	0.97 (0.95 to 0.98)	0.85 (0.84 to 0.87)
Obesity	1.37 (1.34 to 1.39)	1.21 (1.18 to 1.23)
Smoking	2.29 (2.24 to 2.34)	1.20 (1.17 to 1.21)
Rurality (reference=rural)	0.90 (0.88 to 0.91)	0.96 (0.95 to 0.98)
Gender (reference=male)	0.97 (0.96 to 0.98)	1.28 (1.26 to 1.29)
Area marital status†	0.85 (0.84 to 0.87)	0.89 (0.88 to 0.90)
Health costs	2.46 (2.43 to 2.48)	1.58 (1.56 to 1.59)
Psychotherapy service	0.99 (0.96 to 1.02)	1.16 (1.13 to 1.19)
Age at baseline‡	1.37 (1.36 to 1.37)	
Age at baseline squared†		

*Dichotomous indicator for tract-level graduation rate over 85%.
†Dichotomous indicator for tract-level marriage rate over 60%.
‡Estimates omitted due to their interdependent nature; age is scaled to 5 years.

Table 3 Diseases of despair component condition frequencies and results of multivariate models estimating risk for incident atherosclerotic cardiovascular disease based on disease of despair component conditions at baseline

Diseases of despair diagnoses at baseline	Incident ASCVD event			Adjusted HR (95% CI)
	Yes	No	Total	
Substance-related only	1133	16233	17366	1.50 (1.41 to 1.59)
SI/SB only	154	2837	2991	1.30 (1.11 to 1.52)
Alcohol-related only	1378	17092	18470	1.33 (1.26 to 1.41)
Substance-related+SI/SB	34	712	746	2.01 (1.44 to 2.82)
Substance-related+alcohol-related	118	2539	2657	1.64 (1.37 to 1.96)
Alcohol-related+SI/SB	828	43	871	1.65 (1.22 to 2.23)
Substance-related+SI/SB+alcohol-related	24	576	600	1.71 (1.14 to 2.55)
None (reference)	123028	2156933	2279961	

Estimates are adjusted for covariates shown in table 2.
SI/SB, suicidal ideation/behaviours.

combinations. Among components appearing in isolation (ie, only one category of DoD diagnosis present), substance-related disorders were associated with 50% higher risk of incident ASCVD (HR 1.5, 95% CI 1.41 to 1.59), alcohol-related disorders and suicidality/intentional self-harm were associated with 33% and 30% higher risk, respectively (HR 1.33, 95% CI 1.26 to 1.41; HR 1.3, 95% CI 1.11 to 1.52). Co-occurring DoD components were associated with higher risk still. The highest risk combination was substance-related disorders+suicidality/intentional self-harm where the risk was more than double (HR 2.01, 95% CI 1.44 to 2.82). All other combinations ranged from HR 1.64 to 1.71 (see table 3).

DISCUSSION

The main findings of our study demonstrate an association between a history of DoD during a baseline year and incident ASCVD over a 5-year period. This effect was found both for DoD as a composite measure, and for each of the separate components of DoD. While all components conferred risk for ASCVD, the magnitude of that relationship varied, with substance-related disorders having the strongest singular relationship with the outcome. Findings also suggested a potential dose–response relationship, where those with multiple exposures bear the most risk. Notably, the co-occurrence of suicidality with substance- or alcohol-related disorder conferred markedly higher ASCVD risk than substance- or alcohol-related disorders alone (aHR=2.01 and 1.65 with co-occurring suicidality; 1.50 and 1.33 for sole diagnosis).

The association between DoD and incident ASCVD was robust to a variety of tested confounders, and subgroup analyses demonstrated that it applied to both men and women across all age groups and was only slightly attenuated in older age as multimorbidity and associated competing risk factors became more prevalent. Although average age among those with a history of DoD was several years younger than those without, at baseline, this group had higher rates of smoking, obesity and frailty, more outpatient and inpatient encounters, and higher overall healthcare costs, suggesting the need for holistic approaches to intervention that address the complex biopsychosocial needs of this vulnerable population.

Studies linking cardiometabolic disease to all components of DoD are rare, as extant research has largely focused on CVD as it relates to the individual conditions that comprise DoD (suicidality, accidental poisoning and alcoholism). For example, excess deaths in Russia due to alcohol use, suicide and illicit drug use in coinciding with the socioeconomic crisis that followed the fall of the Soviet Union are well documented.[39] Notably, in middle-aged Russian men, death due to CVD increased in areas of high alcohol consumption versus those regions of lower alcohol consumption.[22] In a case–control study of 48557 adults deaths in Russia, alcohol contributed to more than half of deaths among those aged 15–54 years. In this study, consumption of alcohol was similarly associated with an increased risk of dying from ischaemic heart disease (relative risk 3.04, 95% CI 2.73 to 3.39).[40] Another study among 17642 Danish participants seeking outpatient treatment for drug use (mostly opioid use) from 2001 to 2006 found an increased risk of incident CVD after a mean follow-up of 7.5 years among those participants that used intravenous drugs sub-HR (SHR 1.41, 95% CI 1.22 to 1.63), methadone (SHR 1.32, 95% CI 1.15 to 1.51) and benzodiazepines (SHR 1.21, 95% CI 1.06 to 1.38).[41] Another study in 7641 adults in the USA aged 17–39 years from the Third National Health and Nutrition Examination Survey found that depression and history of a suicide attempt increased the risk of ischaemic heart disease death (HR 3.7, 95% CI 1.32 to 10.35 and HR 7.12, 95% CI 2.67 to 18.98, respectively) after a median of 14.9 years of follow-up.[42] Our findings extend this work by examining the role of these three groups of conditions in ASCVD through the composite 'despair' conceptual

framework, and as separate conditions that may appear in isolation or combination.

There are strengths and limitations to this analysis that warrant discussion. Highmark's insurance claims database has over 12 million members with longitudinal data spanning up to 15 years. Membership is concentrated in disproportionately DoD-affected regions including Pennsylvania, West Virginia and Delaware. This database also includes healthcare utilisation variables such as cost, inpatient, outpatient and psychotherapy services, as well as area-level sociodemographic variables such as education, poverty and vehicle access.

This is an observational study and therefore uncontrolled confounders could be present. While the Highmark database is a rich source of information, we lack individual level SDOH metrics for previously established key predictors of despair related illness like educational attainment.[12] However, sensitivity analyses suggest that an unmeasured confounder would need to have an effect that is quite large in this study context (HR=2.18). Many potential confounders such as sociodemographic characteristics and health behaviours are interrelated, and a potential unmeasured confounder would need to be reach this effect size independent of all measured covariates in the fully adjusted model to negate the effect of DoD on ASCVD. Notably, the adjusted effects for area-level educational attainment and marriage rates were consistent with the framework posited by DoD, with higher levels of each significantly predicting lower risk for ASCVD.

A common limitation of administrative data in research is attrition due to insufficient surveillance data. Individuals with more precarious living situations may be disproportionately lost to follow-up due to disenrolment, which could cause risk factor magnitude and prevalence of associated adverse health outcomes to be underestimated. For this reason, we instituted right censoring rather than studying more restrictive fixed-length cohorts, which is a strength in our design. Relatedly, this population was made up individuals enrolled in health insurance, which suggests some degree of stability and is often used as a proxy for socioeconomic status. This is an important consideration for generalisability. Notably, our previous work suggests that although base rates of DoD vary by insurance coverage type, there is relative consistency in the relationship between DoD and other outcomes.[28]

ICD-10 codes were used as the method for adjudication of cardiometabolic events, DoD and clinical covariates. This method could be susceptible to bias. Obesity and tobacco use may not be reliably documented in insurance claims data, and these factors are likely under-reported in the study cohort.[43] Similarly, it is possible that existing ASCVD events could be recorded as incident events if they were not documented within our surveillance period, and clinical documentation does not necessarily reflect the true chronicity of disease development. Also, given that those with DoD have higher healthcare utilisation, this may have led to more opportunity for medical diagnoses. However, in sensitivity analyses removing the highest utilisers from the sample, conclusions remained consistent, suggesting that detection was not strongly influenced by very high utilisation.

The specific casual mechanisms linking DoD and cardiometabolic disease remain poorly established, and further work is needed in this area. It has been previously proposed that obesity is the main shared driver between DoD and cardiometabolic disease, as the same mechanisms at the neurotransmitter level in the brain that contribute to addiction of opioids and alcohol may contribute to unhealthy food addictions, all in the service of numbing pain/despair or making life more bearable.[44] However, rates of obesity were only slightly higher among those with DoD in our study, and in multivariate models, DoD was independently associated with ASCVD after adjusting for clinically documented obesity. DoD may also increase the risk of cardiometabolic diseases through depression, medication adherence and poor lifestyle choices.

From a policy perspective, it is necessary to ask what measures should be undertaken to reduce ASCVD in this high-risk population. The question remains regarding whether screening for ASCVD should be intensified with frequent cardiac risk assessments, lipid profiles, blood pressure assessments and measurements of haemoglobin A1C in populations at high risk of DoD given the robust association with an increased risk of ASCVD. Ideally, ASCVD prevention strategies in populations at risk of DoD should be tested in a randomised trial. Lastly, given the apparent role of economic dislocation and precariousness as a possible key determinant of risk for DoD and cardiometabolic disease, researchers could use big data approaches to examine long-term socioeconomic indicators and their correlation with disease patterns in regions affected by long- and short-term economic decline. Establishing the predictive value of such associations could help guide directed public health efforts to the neighbourhood level.

CONCLUSION

Baseline diagnosis of DoD was associated with an increased risk of developing ASCVD. This increased risk of ASCVD was present for each of the individual components of DoD, with higher risk still in the presence of co-occurring component conditions, suggesting a dose–response relationship. Subgroup analysis showed that DoD is associated with increased risk of ASCVD in both men and women and across various age groups. Those with DoD are more likely to have increased healthcare costs and healthcare utilisation including outpatient, inpatient and psychotherapy services compared with those without DoD at baseline. Clinicians treating patients with DoD should be aware of the increased risk of ASCVD and encourage appropriate cardiovascular screening measures. It has been more recently argued that ASCVD (as well as obesity) should be considered a constituent part of the DoD phenomenon. These

findings shed an important light on the intersection between DoD and CVD and may help establish an empirical basis for integrating ASCVD into future clinical and public health and policy approaches to the growing crisis of despair-related illnesses in the USA.

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Patient consent for publication Not applicable.

Ethics approval This research protocol was reviewed by the Institutional Review Board (IRB) and Office of Research Protection at the Penn State College of Medicine (STUDY00021826) and the Allegheny Health Network Research Institute (acting IRB for Highmark Health) and was determined to meet criteria for 'Not Human Subject Research'. Informed consent was waived, as no study participants were contacted.

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