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HUMAN DEVELOPMENT, BIRTH TO DEATH

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Genes Environment Health Behavior

Concept Paper Form

Provisional Paper Title: Diseases of despair in midlife: The role of early-life psychopathology and intervening factors
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Today's Date: 2/21/2022

Objective of the study:

Mortality rates among working-age adults in the U.S. are increasing, driven in large part by a dramatic rise in "deaths of despair" caused by drug poisoning, alcohol-related disease, and suicide.[1-3] Consistent with this trend, some evidence suggests that so-called "diseases of despair" (i.e., substance use disorders, suicide-related diagnoses) are on the rise as well.[4] In addition to putting individuals at higher risk for mortality, diseases of despair create enormous burdens at both the individual and societal level. At the individual level, diseases of despair cause significant functional impairments (e.g., inability to work, damaged social relationships). At the societal level, they incur hundreds of billions of dollars in healthcare and other costs.[5]

Although it is recognized that despair may manifest in forms other than substance misuse and suicidality,[6] research is lacking regarding the role of these other manifestations in the diseases of despair phenotype. Two candidate manifestations that likely feature prominently in diseases of despair are chronic physical pain and sleep disturbances. Paralleling the rise in deaths of despair, the prevalence of chronic pain has reached an unprecedented high among midlife adults in the U.S.[7] Based on this pattern, pain has been proposed as a key contributor to the rise in deaths of despair.[1] Similarly, sleep disturbances have a well-established link to alcohol[8] and substance use disorders[9] as well as suicidality.[10] Moreover, chronic pain and sleep disturbances commonly co-occur, in part because chronic pain presents an obstacle to obtaining high-quality sleep. Pain medications can ameliorate sleep disturbances and vice versa, and co-prescription of opioids and sedatives is relatively common despite the potential for misuse of these substances.[11] Taken together, since physical pain and sleep disturbances could serve as additional drivers of deaths of despair, their role as elements of the diseases of despair phenotype should be examined.

An additional gap in our knowledge about diseases of despair is the individual-level factors that precede the onset of these problems. Although it is well established that early-life mental health predicts adult health and wellbeing,[12-14] knowledge is limited regarding the role of psychopathology in predisposing individuals to diseases of despair later in life. The only longitudinal investigation on this topic to our knowledge indicates that despair-related cognitions in young adulthood predict diseases of despair several years later.[15] However, no studies have examined childhood predictors of diseases of despair in midlife.

Finally, the role of work-related factors and social relationships in diseases of despair is poorly understood. Economists have proposed that the underlying cause of the rise in deaths of despair is economic stagnation and its ripple effects, which include diminished job prospects, disengagement from the labor force, social isolation, and loss of hope among segments of the population.[1] Moreover, working-class adults, who are disproportionally affected by diseases of despair, are more likely to have physically demanding jobs and inconsistent work schedules; it may be that these work-related factors contribute to physical pain and sleep disturbances. Although initial support for the role of these factors in diseases of despair is provided by population-level data, direct empirical support by testing longitudinal associations within individuals is lacking.[6] We aim to fill this gap by testing whether these factors among working-age adults predict midlife diseases of despair. More specifically, we aim to examine whether these factors mediate associations between early-life psychopathology and midlife diseases of despair. Early-life psychopathology may represent an unexplored early link in the chain of events leading toward diseases of despair, since psychopathology can curtail individuals' education[16] and cut them off from opportunities and meaningful social relationships, thereby increasing risk for diseases of despair.

To fill these gaps in our understanding of diseases of despair, we have three primary aims:

Aim 1: To develop an empirically derived characterization of the "diseases of despair" phenotype in midlife, considering four domains:

- Substance misuse
- Suicidality
- Physical pain
- Sleep disturbances

Aim 2: To examine whether psychopathology in childhood and adolescence prospectively predict "diseases of despair" indicators. The forms of early-life psychopathology we will consider are ADHD, conduct disorder, depression, and anxiety disorders.

Aim 3: To identify mediators of any associations between early-life psychopathology and midlife "diseases of despair" indicators. We will consider factors in the following domains:

- Work (e.g., job characteristics, work attitudes)
- Social (i.e., loneliness/social isolation)
- Mental health (i.e., depression)

Data analysis methods:

Data preparation:

In addition to the variables that already exist in the dataset, we will prepare several new variables to use as indicators of diseases of despair. The time frame for the diseases of despair outcome variables will be age 45, or the period between age 38 and 45.

To create substance misuse indicators, we will create a variable that is the sum of the number of substance use disorder symptoms for which study members meet criteria, across alcohol, marijuana, and other substances (range: 0-30). We will also create a variable that is the sum of the informant reports of alcohol and drug problems (range: 0-4). Finally, we will create a variable that is the sum of two treatment variables, one for alcohol and one for substances (range: 0-2).

To create a pain indicator that captures medication use for pain, we will use the New Zealand pharmacy data, which indicates whether study members have been prescribed pain medication in the past 12 months. This variable only includes study members who were residents of New Zealand at phase 45 (*N*=710), so we will use self-reported medication use at phase 45 to complement the pharmacy data. Specifically, if study members reported taking any pain medications in the past two weeks at phase 45, they will be coded as having taken pain medications in the past year. Additionally, we will compute a chronic pain composite score based on study members' self-report. During phase 45 data collection, study members reported on whether they experienced chronic pain and in what area(s) of their bodies. Their pain was then coded as either regional (1) or widespread (2). If they endorsed chronic pain, they also reported whether they consulted a health professional for this pain in the past 12 months, whether they took off work for this pain in the past 12 months, and whether they applied for disability/benefits because they were unable to work due to pain in the past 12 months. These four items will be summed to create the chronic pain composite score (range: 0-5).

*Note: To be included in analyses, we will require that individuals have data available for at least 50% of the variables examined. We will use full information maximum likelihood to estimate parameters in the context of missing data.

Aim 1: What indicators characterize the "diseases of despair" phenotype in midlife?

We will conduct confirmatory factor analysis to estimate a model of diseases of despair in midlife. We will use indicators of substance misuse, suicidality, sleep, and physical pain to examine the extent to which these indicators coalescence to form a latent "diseases of despair" variable. The model will be structured such that the indicators from each domain are clustered together to form four subfactors under the broader "diseases of despair" factor. We will extract factor scores from each of these latent variables.

Aim 2: Does early-life psychopathology prospectively predict the "diseases of despair" phenotype?

We will use a series of regression analyses to examine whether psychopathology (i.e., symptoms meeting criteria for ADHD, CD, depression, or an anxiety disorder) at age 11, 13, or 15 predict the "diseases of despair" factor score and each of the component

subfactor scores (i.e., substance misuse, suicidality, physical pain, sleep disturbances). We will also examine whether specific psychiatric diagnoses, as well as the broader category of having an internalizing disorder (i.e., depression and/or anxiety disorder) or externalizing disorder (i.e., ADHD and/or conduct disorder), predict the "diseases of despair" factor and subfactor scores. Finally, we will examine whether age of onset of psychiatric diagnosis as well as the number of psychiatric diagnoses in adolescence predict the "diseases of despair" factor and subfactor scores. As a supplementary analysis, we will examine whether early-life psychopathology predicts each of the diseases of despair indicators individually. We will control for childhood IQ, childhood SES, and sex in these analyses.

Aim 3: What factors mediate associations between early-life psychopathology and midlife "diseases of despair" indicators?

We will use structural equation modeling to examine whether several putative contributors to diseases of despair (e.g., job characteristics, work attitudes, social isolation, and depression) in young adulthood mediate associations between early-life psychopathology and midlife diseases of despair.

*Note: We envision reporting on these findings in two separate manuscripts. Findings from Aims 1 and 2 will be addressed in a first manuscript, while Aim 3 will be addressed in a second manuscript.

Variables needed at which ages:
*Variable names are provided for measures currently listed in the data dictionary

Category	Variable Description	Variable Name
Putative "diseases of despair" phenotype indicators at age 45		
Substance misuse domain		
	Alcohol dependence diagnosis	DxAL45D4
	Informant report of alcohol problem	infalcprb45
	Treatment since age 38 for alcohol use	
	DIS reported Past year meds for Alcohol problems	medsAlc45
	Number of alcohol use disorder symptoms	AlcCritSc45
	Cannabis dependence diagnosis	dxMar45
	Other drug dependence OR methadone maintenance	DxDrug45m
	Informant report of drug problem	infMarprb45
	Treatment since age 38 for drug use	
	Number of cannabis use disorder symptoms	mjCritSc45
	Number of other drug use disorder	DrgCritSc45

	symptoms	
	On methadone maintenance in last year	DRG7
	Street opioid use	DRG6
	Nicotine dependence, DSM-IV, past-year, phase 45	DXTOB45
Suicidality domain		
	Any suicide attempt starting at age 26	SuicAtt2645
	Informant report “talks about suicide”	infSuic45
	Treatment since age 38 for suicidality	
Pain domain		
	Pain interference scale	PromisPain45
	Spheres with significant pain interference (work, home, etc.)	SigPainIntVar45
	Any pain meds in last year	PharmaPain_NZonly
	Work causes pain, fatigue, or need meds to work	WorkPainFatg45
	Chronic pain present	painprsnt45
	Consulted health professional regarding pain in past 12 months	PainSrv45
	Applied for ACC/disabilty because unable to work in past 12 months	PainBenefit45
	Off work for pain in past 12 months	Painoffwk45
	Migraine headaches	Migraine45
	Self-reported use of pain medication in past 2 weeks/brought pain medication to the unit	SR_Painmeds45
	Prescription opioid use	DRG5
Sleep domain		
	Takes meds/alc/cannabis as sleep aid in past month	SleepAids45
	Insomnia diagnosis at age 45	dxInsom45
	Pittsburgh Sleep Quality Index	PSQI_p45
	Social jetlag	SJL_abstrunc45
Prospective predictors at ages 11-15		
	Any psychiatric diagnosis at age 11, 13, 15	childdx
	ADD dx by age 15	ADDthru15
	dsm4 cd ge 5, limit to dis cases, ages 11 to 15	CD1115
	MDE dx at 11, 13, or 15	MDE1115
	had anxiety at age 11, 13, or 15	ANX1115
	Age of onset of MH diagnosis	ageMHDxOnset

	Number of MH diagnoses at 11, 13, 15	SumDx1115
	Any internalizing dx at 11, 13, 15	MDEANX1115
	Any externalizing dx at 11, 13, 15	CDADD1115
Mediators in adulthood		
	Depression	
	Job characteristics	
	Work attitudes	
	Social isolation/loneliness	
	Educational attainment	
	Adult social class	
Background and control variables		
	Participant ID number	SNUM
	Participant sex	SEX
	Childhood SES	SESchildhd
	Childhood IQ	ChildIQ_chstd

*Note: Described above are the pre-planned analyses. Additional analyses may be added as suggested through internal review and will be identified as secondary in the manuscript.

Significance of the Study (for theory, research methods or clinical practice):

The results of this study will refine our understanding of the "diseases of despair" phenotype, particularly the various manifestations of diseases of despair, which likely extend beyond substance misuse and suicidality. Additionally, identifying risk factors for diseases of despair at multiple stages of the life-course could provide multiple targets for early identification of individuals at risk for diseases of despair in midlife, informing strategies designed to prevent diseases of despair before they take hold. Finally, results of this study could inform life-course epidemiologic models of deaths of despair.

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Data Security Agreement

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☒	I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent)
☒	My project is covered by the Duke ethics committee OR I have /will obtain ethical approval from my home institution.
☒	I will treat all data as "restricted" and store in a secure fashion. My computer or laptop is: a) encrypted (recommended programs are FileVault2 for Macs, and Bitlocker for Windows machines) b) password-protected c) configured to lock-out after 15 minutes of inactivity AND d) has an antivirus client installed as well as being patched regularly.
☒	I will not "sync" the data to a mobile device.
☒	In the event that my laptop with data on it is lost, stolen or hacked, I will immediately contact Moffitt or Caspi.
☒	I will not share the data with anyone, including my students or other collaborators not specifically listed on this concept paper.
☒	I will not post data online or submit the data file to a journal for them to post. *Some journals are now requesting the data file as part of the manuscript submission process. Study participants have not given informed consent for unrestricted open access, so we have a managed-access process. Speak to Temi or Avshalom for strategies for achieving compliance with data-sharing policies of journals.*
☒	I will delete all data files from my computer after the project is complete. Collaborators and trainees may not take a data file away from the office. This data remains the property of the Study and cannot be used for further analyses without an approved concept paper for new analyses.
☒	I have read the Data Use Guidelines and agree to follow the instructions.

Signature: