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HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
Genes Environment Health Behavior

Concept Paper Form

Provisional Paper Title: Neighborhood disadvantage and midlife diseases of despair
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Today's Date: 4/5/2023

Objective of the study:

Following decades of decline, mortality rates have begun to rise again among middle-aged adults in the U.S.[1] This reversal appears to be driven in large part by a dramatic rise in so-called "deaths of despair" caused by drug poisoning, alcohol-related disease, and suicide.[2-4]

Recent analyses from our research group suggest that midlife diseases of despair coalesce to form a multi-faceted, unitary syndrome consisting of suicidality, substance misuse, sleep problems, and pain.[5] This research indicated that the midlife "despair" syndrome is preceded by psychopathology during adolescence, suggesting that early-onset mental health problems are a potential risk factor for midlife diseases of despair.[5]

Although emerging research has investigated the role of individual-level factors in midlife diseases of despair, it remains unclear whether factors at the environmental level are associated with midlife diseases of despair. In particular, neighborhood disadvantage represents a potential factor to explain individuals' risk for dying a death of despair. Disadvantaged neighborhoods, by definition, are those with poorer physical, social, and economic conditions relative to other neighborhoods and wider society. Neighborhood disadvantage is typically identified through indexes of "deprivation" that rank collections of neighbors based on indicators such as low levels of employment, low income, low educational attainment, and low access to social and economic resources (e.g., cell phones, internet service, motor vehicles).

Considerable previous research has linked neighborhood disadvantage to worse health outcomes at the neighborhood level across numerous physical and mental health domains over and above individual-level risk factors, such as race, sex, and sociodemographics.[6-9] Of more relevance, a separate body of research now indicates that deaths of despair show

clear and as-yet unexplained geographic variation,[10] with regional and local differences in drug deaths, interpersonal violence, and rates of self-harm that defy ready explanation.

Research integrating the emerging construct of midlife diseases of despair with the study of neighborhood disadvantage may help identify both individuals at-risk for "despair" and entire communities that could benefit from intervention to reverse recent rises in premature mortality. No research has yet investigated whether midlife diseases of despair follow neighborhood socioeconomic gradients. The proposed study will utilize the Dunedin Cohort to determine whether neighborhood disadvantage is associated with midlife diseases of despair and, if so, test a number of potential explanatory hypotheses.

We have two primary aims:

Aim 1 (main effects): To test whether participants with a more severe syndrome of midlife diseases of despair also tend to live in more deprived neighborhoods, above and beyond individual-level social class. If main effects are found, follow-up tests will investigate whether Study Members' histories and trajectories of living in more deprived neighborhoods across adulthood are associated with a more severe syndrome of midlife diseases of despair. To this end, we will examine whether midlife diseases of despair are more strongly associated with contemporaneous (i.e., age 45) or cumulative (i.e., averaged across ages 26 to 45) neighborhood deprivation, and whether trajectories (stable, upward, or downward neighborhood mobility) show differential associations with despair. We will also test whether participants' history of living in more deprived neighborhoods helps explain variance in midlife diseases of despair, above and beyond participants' contemporaneous level of exposure to neighborhood deprivation.

Aim 2 (explanatory hypotheses): If main effects are found, secondary tests following Aim 1 will investigate potential explanatory hypotheses, including:

1) **Self-selection:** To test whether Study Members' individual-level potential risks for midlife despair (e.g., family history of mental illness, more deprived socioeconomic origins, lower childhood IQ, worse childhood physical health, adolescent psychopathology, lower educational attainment) account for associations between neighborhood disadvantage and midlife diseases of despair. If they do, it would suggest that any identified neighborhood gradients in despair (Aim 1) may reflect an underlying tendency of individuals at-risk for despair to self-select into disadvantaged neighborhoods. This would, in turn, identify disadvantaged neighborhoods as ideal targets for intervention but leave open questions about when and how interventions should be targeted.

2) **Psycho-social and physical mechanisms:** To test potential mechanisms that may mediate associations of neighborhood deprivation with midlife diseases of despair, we will investigate whether individuals living in disadvantaged neighborhoods report greater levels of poor social (e.g., loneliness), occupational (e.g., unemployment), and physical health (e.g., chronic illness, disability) and, if so, whether these factors mediate neighborhood-despair associations.

Data analysis methods:

We will use multiple regression to predict midlife diseases of despair from neighborhood disadvantage.

As part of Aim 1, we will ask whether participants' trajectories of neighborhood disadvantage across adulthood (ages 26-45) relate to midlife diseases of despair. We will create groups of participants based on their trajectories of exposure to neighborhood disadvantage across adulthood. We expect to create the following groups: (1) stable low neighborhood disadvantage, (2) stable high neighborhood disadvantage, (3) increasing neighborhood disadvantage, and (4) decreasing neighborhood disadvantage.

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

Category	Variable Description	Variable Name
Diseases of despair variables from Brennan et al. (under review)		
	Factor scores for midlife despair factor and subfactors	
	Individual indicators that make up the midlife despair factor and subfactors	
Neighborhood deprivation		
	Neighborhood disadvantage, age 26	
	Neighborhood disadvantage, age 32	
	Neighborhood disadvantage, age 38	
	Neighborhood disadvantage, age 45	
	Average neighborhood disadvantage, ages 26-45	
Background and control variables		
	Participant ID number	SNUM
	Participant sex	SEX
	Childhood SES	SESchildhd
	Childhood IQ	ChildIQ_chstd
	Adolescent psychopathology variables (ADHD, depression, anxiety disorder, conduct disorder)	dxANX1115, etc
	Childhood physical health	zChildPoorHlth
	Family history of mental illness	prMDE, etc
	Educational attainment	NewEduc45
Potential mechanisms		
	Social isolation	InfIsol45

	Loneliness	LonelyUCLA45
	Unemployment	MthUnem3845
	Disability (i.e., receiving government support due to accident, unemployment, or illness)	Govben45
	Poor physical health index	PoorPhyHlth45

*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):

Extending healthspan in the context of an aging population is a major public health challenge.[11,12] If neighborhood deprivation is associated with midlife diseases of despair, above and beyond individual-level social class and background risk factors (e.g., early-onset mental health problems, lower educational attainment), it would suggest that neighborhood disadvantage may play an important and unique role in the development of midlife diseases of despair. Thus, improving neighborhood characteristics (e.g., increasing access to local resources) might bolster the health and wellbeing of midlife adults[13] and potentially even decrease risk for diseases (and deaths) of despair.

Furthermore, elucidating associations between trajectories of neighborhood disadvantage across adulthood and midlife diseases of despair will have important implications for prevention and intervention strategies. If early and cumulative exposure to neighborhood disadvantage is most strongly associated with midlife diseases of despair, it would suggest that neighborhood-level interventions (e.g., mobility voucher programs) should be administered as early as possible to reduce risk for diseases of despair. Conversely, if contemporaneous levels of and recent increases in exposure to neighborhood disadvantage are most strongly associated with midlife diseases of despair, it would suggest that neighborhood improvements that occur as late as midlife are not too late to alleviate diseases of despair.

References cited:

1. National Academies of Sciences, Engineering, and Medicine. High and rising mortality rates among working-age adults. The National Academies Press; 2021. https://doi.org/10.17226/25976

2. Case A, Deaton A. Deaths of despair and the future of capitalism. Princeton University Press; 2021.

3. Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. *P Natl Acad Sci USA*. 2015;112(49):15078-15083. https://doi.org/10.1073/pnas.1518393112

4. Harris KM, Majmundar MK, Becker T, et al. High and rising mortality rates among working-age adults. A Consensus Study Report of the National Academies of Sciences, Engineering, and Medicine. The National Academies Press; 2021.

5. Brennan GM, Moffitt TE, Ambler, A, et al. Tracing the origins of midlife despair: Association of psychopathology during adolescence with a syndrome of despair-related maladies at midlife. *Psych Med*. Revised and resubmitted.

6. Fone D, White J, Farewell D, et al. Effect of neighbourhood deprivation and social cohesion on mental health inequality: A multilevel population-based longitudinal study. *Psychol Med*. 2014;44(11):2449-2460. doi:10.1017/s0033291713003255

7. Fuentes M, Hart-Johnson T, Green CR. The association among neighborhood socioeconomic status, race and chronic pain in black and white older adults. *Journal of the National Medical Association*. 2007;99(10):1160-9.

8. Jivraj S, Murray ET, Norman P, Nicholas O. The impact of life course exposures to neighbourhood deprivation on health and well-being: A review of the long-term neighbourhood effects literature. *Eur J Public Health*. 2019;30(5):922-928. doi:10.1093/eurpub/ckz153

9. Ulirsch JC, Weaver MA, Bortsov AV, et al. No man is an island: Living in a disadvantaged neighborhood influences chronic pain development after motor vehicle collision, and this effect is moderated by common genetic variation influencing HPA axis function. PAIN. 2014/10/01/ 2014;155(10):2116-2123. doi:10.1016/j.pain.2014.07.025

10. Dwyer-Lindgren L, Bertozzi-Villa A, Stubbs RW, et al. Trends and patterns of geographic variation in mortality from substance use disorders and intentional injuries among US counties, 1980-2014. *JAMA*. 2018;319(10):1013-1023. doi:10.1001/jama.2018.0900

11. Burch JB, Augustine AD, Frieden LA, et al. Advances in geroscience: impact on healthspan and chronic disease. *J Gerontol*. 2014;69:S1-S3.

12. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380:2163-2196.

13. White J, Greene G, Farewell D, et al. Improving mental health through the regeneration of deprived neighborhoods: A natural experiment. American Journal of Epidemiology. 2017;186(4):473-480. doi:10.1093/aje/kwx086

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: