Air Pollution and Suicide Risk: Another Adverse Effect of Air Pollution?

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Ambient and household air pollution are leading contributors to the global burden of disease; suicide is not among the causes of morbidity and mortality included in the burden estimates for air pollution, but a paper in this issue suggests that perhaps it should be if the answer to the following question were affirmative: *Does air pollution trigger suicide?* In their so-titled paper, Casas and colleagues [1] addressed this question in a population-based case-crossover study of suicide mortality carried out in Belgium, a nation with a high suicide rate in comparison with its European neighbors. They were motivated to conduct this study by the mixed findings from previous epidemiological studies of short-term and long-term air pollution exposures and various outcome measures clinically related to suicide. A biological rationale for their hypothesis was based in animal studies showing multi-organ effects of exposure to particulate matter (PM) and ozone (O_3) on gene expression, extending to the brain, and also on behavioral responses and neurotransmitters.

In their analysis, Casas and colleagues assessed patterns of association of suicide mortality with estimated daily concentrations of PM and O_3, exploring various lag structures and potential modification of risks associated with the air pollutants by age, sex, season, and mode of death. The results show significant associations in the summer for both pollutants and greater effects for PM in the youngest and oldest age groups. Their findings mirror past studies, which provide a mixed picture of associations for a variety of outcomes relevant to depression and suicide. In interpreting these findings, type 1 error merits consideration, particularly given the large sample size of more than 20,000 suicide deaths and the multiple stratified analyses reported. We note, however, that the observation of significant associations during the summer is plausible, given that personal exposures to outdoor air pollutants are likely to be greater during warm seasons. The time-stratified case-crossover design is appropriate for dealing with short-term temporal confounding and the authors explore a reasonably justified set of potential modifying factors.

This new study adds to an emerging literature suggesting that air pollution may have detrimental effects on the human brain across the life course, beginning with potential links to delayed neuropsychological development and increased risks for neurodevelopmental disorders including autism in early childhood and extending to possible influences on "brain

aging" in late life. Is there a unifying biological basis for adverse effects of air pollution exposure on the brain and, most critically, what could be the underlying pathways of injuries? We do know that very small, engineered ultrafine particles can reach the brain, either by traveling from the nose along the olfactory nerve and by the systemic circulation following translocation across the alveolar-capillary layer in the lung.

Does biological understanding support the authors' notably strong conclusion: "…high concentrations of common outdoor air pollutants such as PM_{10} or O_3 can trigger suicide, particularly during warm seasons." We argue for a better understanding of the psychological pathways and neurobiological mechanisms linking air pollution to suicidal behaviors. We draw on the stress-diathesis model of suicidal behaviors [2], because of its well-tested validity in psychopathology and neurobiology. The development of suicidal behaviors requires a diathesis – a dynamic state of vulnerability – which predisposes individuals to such behaviors when confronted with stressors. Psychosocial crises and acute states of psychiatric diseases (including a major depressive episode) are common stressors that may trigger suicide. Approximately 90% of people who die by suicide have prior histories of psychiatric disorders, notably mood, substance-related, anxiety, psychotic, and personality disorders, commonly with comorbid conditions [3]. In the elderly, multiple physical illnesses (e.g., terminal cancers and cerebrovascular disease with disabilities) also significantly increase suicide risk. While others (e.g., Kim et al.[4]) have hypothesized that air pollution could exacerbate these comorbid conditions and thus increasing suicide risk, Casas et al. suggest that ambient air pollution may act as a novel environmental trigger. But could air pollution exposure affect neuropsychological stressors or perhaps increase the diathesis for suicidal behaviors by effects at various points across the life course?

A few birth cohort studies have examined the putative effects of early-life PM exposure on symptoms of anxiety and depression in school-aged children, but the reported findings were inconsistent [5–9]. Overall, the available epidemiologic evidence does not provide a strong support for the hypothesis that that ambient air pollution exacerbates the acute stress state of major neuropsychiatric diseases and triggers suicidal behaviors in affected children and adolescents through this psychological pathway. However, emerging neurotoxicological data suggest that ambient air pollution may contribute to the psychopathological state (e.g., increased impulsivity; loss of cognitive control; emotional dysregulation) leading to suicidal behaviors in children and adolescents. For instance, behavioral phenotypes consistent with impulsivity were increased in mice with early-life exposures to concentrated ambient ultrafine particles (postnatal [10]) or diesel exhaust (prenatal [11]). Of three cross-sectional studies [12–14] that examined early-life exposure to PM and impulsivity in school-aged children and adolescents, two reported significant associations [12, 14]. Although these observations support the possibility that ambient air pollution may be a determinant of diathesis, future studies need to prospectively assess whether air pollution exposure leads to acute exacerbations of psychopathologies that trigger suicidal behaviors in children and adolescents.

Casas et al. also reported an increased risk of death from suicide associated with PM_{10} exposure in the people aged 85 years. Older people, compared to other segments of the population, are at a greater risk for suicide [3]. While mixed results have been reported for

long-term air pollution exposure effects on mood disorders in adults [15–18], more consistent associations have been observed for increased emergency visits for depressive episodes [19, 20], self-reported depressive symptoms [21, 22], and hospitalization for neuropsychiatric diseases [23] with exposures to ambient air pollutants over lags of several days up to one month. Higher levels of perceived stress were also associated with short-term exposures in older men [24]. Thus, airborne particle exposure could be another neuropsychological stressors that triggers suicide.

Cognitive impairment is a major contributor to suicide diathesis in the elderly [2]. Previous studies comparing suicide attempters to controls have shown increased risk linked with cognitive deficits, notably decision-making impairment and reduced cognitive inhibition. Particulate matter exposure has emerged as a novel determinant of cognitive aging, but the extant data primarily relate to deficits in global cognitive function and episodic memory associated with long-term exposure. Little is known about possible short-term exposure effects on the higher cortical functions involved in suicide.

Casas et al. also showed a modest but statistically significant increase in risk for suicidal death associated with O_3 exposure in adolescence and adulthood. However, we found no published data showing adverse O_3 effects on depressive symptoms, mood disorders, or other psychiatric diseases in youth. Mixed results were reported from two epidemiological studies addressing relevant endpoints, i.e., symptoms and depression, in adults [16, 25]. Epidemiologic data are not available on the possible link between O_3 exposure and increased diathesis for suicidal behaviors.

We also note that the neurobiological mechanisms linking air pollution to suicide have not been investigated directly in humans, but the neurotoxicological findings point to the need for epidemiologic studies to examine the abnormalities in the hypothalamic–pituitary–adrenal (HPA) axis stress response and the serotonergic neurotransmission, both playing a significant role in determining the diathesis for suicide. In depressed people, hyperactivity of the HPA axis increases mood instability and future risk for suicide. Deficient serotonergic function and altered HPA axis responses also contribute to increased aggression and impulsivity [2]. In experimental animal models, activation of the HPA axis has been demonstrated with inhalation exposures to concentrated ambient particles [26] and with relatively low levels of O_3 [27]. Prenatal exposure to diesel exhaust particles decrease the serotonin levels in multiple brain regions of socially-isolated male mice [28]. Regional brain serotonin levels were also suppressed in a stress-sensitive rat model of depression following chronic ozone exposure [29]. Lower levels of serotonin metabolites were found in adults with occupational exposure to urban air pollutants [30], but epidemiological research has not addressed potential adverse effects of ambient air pollution on serotonergic systems in community-based samples.

Epidemiologic evidence for an increased suicidal risk triggered by air pollution could be further advanced by research linking exposure with biological predictors of suicidal attempt. Accumulating evidence indicates that both peripheral and central inflammation contribute to the pathophysiology of suicidality. Although exposures to airborne particles and ozone are known to cause wide-spread inflammatory responses in humans and animal models, we lack

direct evidence for dysregulated immune response or neuroinflammation shown with air pollution exposure in high-risk populations. Another potential biomarker is brain-derived neurotrophic factor (BDNF), briefly discussed in Casas et. al. for its potential role in neurodevelopment. More importantly, because BDNF is involved in many neurophysiological functions in the brain (including synaptic and structural plasticity), this neurotrophic protein has been implicated in the pathogenesis of suicide. BDNF expression is decreased in the brains of people who committed suicide and in the peripheral blood of those who attempted to commit suicide or had suicidal ideation. However, two published studies examining the effect of traffic-related air pollution on BDNF yielded conflicting results. An experiment in mice [31] found decreased BDNF expression in the olfactory bulb in mice after exposure to traffic emissions in a highway tunnel. One recent report [32] from a double-blinded crossover trial on 27 healthy adults showed no significant difference in serum BDNF concentration after a 2h-controlled exposure to diesel exhaust particles (300 μg $PM_{2.5}/m^3$).

Neuroimaging studies may offer important insights on whether and how air pollution exposures affect the specific brain regions, neural structures, or functional networks related to suicidal thoughts and behaviors. Smaller gray matter volumes (GMV), primarily in prefrontal and temporal cortical sub-regions and insula, were found in most MRI studies comparing suicide attempters with controls, independent of depressed mood [33]. One recent study reported that older women residing in locations with higher long-term exposure to $PM_{2.5}$ had smaller GMV, primarily in the dorsolateral and medial prefrontal cortices [34]. Because the dorsolateral prefrontal cortex is known for its involvement in executive functions and higher cortical control processes including cognitive inhibition, this observed neurotoxic effect on GMV may be relevant to the increased biological diathesis of suicide risk associated with PM exposure in the elderly. Since lower serotonin transporter binding in suicide victims is highly localized to the ventromedial prefrontal cortex [2], molecular neuroimaging studies examining whether ambient air pollution exposure is associated with the neuroanatomical distribution of serotonin transporter binding in high-risk individuals could be informative. Depressed suicide attempters, compared to depressed non-attempters, had smaller white matter (WM) volumes in the frontal, parietal, and temporal regions [35]. Suicidal behavior is associated with atrophy of corpus callosum, the largest WM structure in human brain. Emerging data from human neuroimaging studies [36, 37] and animal experiments [38, 39] suggest that WM architecture may represent a novel target of particle-induced neurotoxicity. For instance, widespread WM loss associated with $PM_{2.5}$ exposure has been suggested in school-age children [36] and older women [37] without overt neuropsychiatric diseases.

In this commentary, we identify a few critical knowledge gaps to be addressed in future studies that may help better understand the neuropsychological processes and neurobiological mechanisms linking exposures to ambient air pollution with an increased risk for suicide. From our perspective, the new report by Casas et al. does not definitively answer the question raised by its title. Their findings, however, do add to the already strong rationale for understanding how air pollution exposure affects the health of the brain across the life course.

References

1. Casas L, Cox B, Bauwelinck M, Nemery B, Deboosere P, Nawrot TS. Does air pollution trigger suicide? A case-crossover analysis of suicide deaths over the life span. European journal of epidemiology. 2017; doi: 10.1007/s10654-017-0273-8

2. Mann JJ. Neurobiology of suicidal behaviour. Nature reviews Neuroscience. 2003; 4(10):819–28. DOI: 10.1038/nrn1220 [PubMed: 14523381]

3. Hawton K, van Heeringen K. Suicide. Lancet (London, England). 2009; 373(9672):1372–81. DOI: 10.1016/s0140-6736(09)60372-x

4. Kim C, Jung SH, Kang DR, et al. Ambient particulate matter as a risk factor for suicide. Am J Psychiatry. 2010; 167(9):1100–7. DOI: 10.1176/appi.ajp.2010.09050706 [PubMed: 20634364]

5. Genkinger JM, Stigter L, Jedrychowski W, et al. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure, antioxidant levels and behavioral development of children ages 6–9. Environ Res. 2015; 140:136–44. DOI: 10.1016/j.envres.2015.03.017 [PubMed: 25863187]

6. Perera FP, Rauh V, Whyatt RM, et al. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. Environ Health Perspect. 2006; 114(8):1287–92. [PubMed: 16882541]

7. Perera FP, Tang D, Wang S, et al. Prenatal polycyclic aromatic hydrocarbon (PAH) exposure and child behavior at age 6–7 years. Environ Health Perspect. 2012; 120(6):921–6. DOI: 10.1289/ehp. 1104315 [PubMed: 22440811]

8. Perera FP, Wang S, Rauh V, et al. Prenatal exposure to air pollution, maternal psychological distress, and child behavior. Pediatrics. 2013; 132(5):e1284–94. DOI: 10.1542/peds.2012-3844 [PubMed: 24101766]

9. Perera FP, Wang S, Vishnevetsky J, et al. Polycyclic aromatic hydrocarbons-aromatic DNA adducts in cord blood and behavior scores in New York city children. Environ Health Perspect. 2011; 119(8):1176–81. DOI: 10.1289/ehp.1002705 [PubMed: 21486719]

10. Allen JL, Liu X, Weston D, et al. Developmental exposure to concentrated ambient ultrafine particulate matter air pollution in mice results in persistent and sex-dependent behavioral neurotoxicity and glial activation. Toxicological sciences: an official journal of the Society of Toxicology. 2014; 140(1):160–78. doi:kfu059 [pii] 10.1093/toxsci/kfu059. [PubMed: 24690596]

11. Yokota S, Moriya N, Iwata M, Umezawa M, Oshio S, Takeda K. Exposure to diesel exhaust during fetal period affects behavior and neurotransmitters in male offspring mice. J Toxicol Sci. 2013; 38(1):13–23. [PubMed: 23358136]

12. Chiu YH, Bellinger DC, Coull BA, et al. Associations between traffic-related black carbon exposure and attention in a prospective birth cohort of urban children. Environ Health Perspect. 2013; 121(7):859–64. DOI: 10.1289/ehp.1205940 [PubMed: 23665743]

13. Chiu YH, Hsu HH, Coull BA, et al. Prenatal particulate air pollution and neurodevelopment in urban children: Examining sensitive windows and sex-specific associations. Environ Int. 2016; 87:56–65. DOI: 10.1016/j.envint.2015.11.010 [PubMed: 26641520]

14. Yorifuji T, Kashima S, Higa Diez M, Kado Y, Sanada S, Doi H. Prenatal Exposure to Traffic-related Air Pollution and Child Behavioral Development Milestone Delays in Japan. Epidemiology. 2016; 27(1):57–65. DOI: 10.1097/EDE.0000000000000361 [PubMed: 26247490]

15. Kim KN, Lim YH, Bae HJ, Kim M, Jung K, Hong YC. Long-Term Fine Particulate Matter Exposure and Major Depressive Disorder in a Community-Based Urban Cohort. Environmental health perspectives. 2016; 124(10):1547–53. DOI: 10.1289/ehp192 [PubMed: 27129131]

16. Kioumourtzoglou MA, Power MC, Hart JE, et al. The Association Between Air Pollution and Onset of Depression Among Middle-Aged and Older Women. American journal of epidemiology. 2017; 185(9):801–9. DOI: 10.1093/aje/kww163 [PubMed: 28369173]

17. Zijlema WL, Wolf K, Emeny R, et al. The association of air pollution and depressed mood in 70,928 individuals from four European cohorts. International journal of hygiene and environmental health. 2016; 219(2):212–9. DOI: 10.1016/j.ijheh.2015.11.006 [PubMed: 26682644]

18. Vert C, Sanchez-Benavides G, Martinez D, et al. Effect of long-term exposure to air pollution on anxiety and depression in adults: A cross-sectional study. International journal of hygiene and

environmental health. 2017; 220(6):1074–80. DOI: 10.1016/j.ijheh.2017.06.009 [PubMed: 28705430]

19. Szyszkowicz M. Air pollution and emergency department visits for depression in Edmonton, Canada. International journal of occupational medicine and environmental health. 2007; 20(3): 241–5. DOI: 10.2478/v10001-007-0024-2 [PubMed: 17932013]

20. Szyszkowicz M, Rowe BH, Colman I. Air pollution and daily emergency department visits for depression. International journal of occupational medicine and environmental health. 2009; 22(4): 355–62. DOI: 10.2478/v10001-009-0031-6 [PubMed: 20197262]

21. Lim YH, Kim H, Kim JH, Bae S, Park HY, Hong YC. Air pollution and symptoms of depression in elderly adults. Environmental health perspectives. 2012; 120(7):1023–8. DOI: 10.1289/ehp. 1104100 [PubMed: 22514209]

22. Pun VC, Manjourides J, Suh H. Association of Ambient Air Pollution with Depressive and Anxiety Symptoms in Older Adults: Results from the NSHAP Study. Environmental health perspectives. 2017; 125(3):342–8. DOI: 10.1289/ehp494 [PubMed: 27517877]

23. Gao Q, Xu Q, Guo X, Fan H, Zhu H. Particulate matter air pollution associated with hospital admissions for mental disorders: A time-series study in Beijing, China. European psychiatry: the journal of the Association of European Psychiatrists. 2017; 44:68–75. DOI: 10.1016/j.eurpsy. 2017.02.492 [PubMed: 28545011]

24. Mehta AJ, Kubzansky LD, Coull BA, et al. Associations between air pollution and perceived stress: the Veterans Administration Normative Aging Study. Environmental health: a global access science source. 2015; 14:10.doi: 10.1186/1476-069X-14-10 [PubMed: 25627872]

25. Evans GW, Colome SD, Shearer DF. Psychological reactions to air pollution. Environmental research. 1988; 45(1):1–15. [PubMed: 3338428]

26. Sirivelu MP, MohanKumar SM, Wagner JG, Harkema JR, MohanKumar PS. Activation of the stress axis and neurochemical alterations in specific brain areas by concentrated ambient particle exposure with concomitant allergic airway disease. Environ Health Perspect. 2006; 114(6):870–4. [PubMed: 16759987]

27. Thomson EM, Pal S, Guenette J, et al. Ozone Inhalation Provokes Glucocorticoid-Dependent and -Independent Effects on Inflammatory and Metabolic Pathways. Toxicological sciences: an official journal of the Society of Toxicology. 2016; 152(1):17–28. DOI: 10.1093/toxsci/kfw061 [PubMed: 27037194]

28. Yokota S, Oshio S, Moriya N, Takeda K. Social Isolation-Induced Territorial Aggression in Male Offspring Is Enhanced by Exposure to Diesel Exhaust during Pregnancy. PLoS One. 2016; 11(2):e0149737.doi: 10.1371/journal.pone.0149737 [PubMed: 26919122]

29. Mokoena ML, Harvey BH, Viljoen F, Ellis SM, Brink CB. Ozone exposure of Flinders Sensitive Line rats is a rodent translational model of neurobiological oxidative stress with relevance for depression and antidepressant response. Psychopharmacology. 2015; 232(16):2921–38. DOI: 10.1007/s00213-015-3928-8 [PubMed: 25877744]

30. Tomei F, Rosati MV, Ciarrocca M, Baccolo TP, Caciari T, Tomao E. Occupational exposure to urban pollutants and urinary 5-hydroxy-3-indoleacetic acid. Journal of environmental health. 2004; 66(6):38–42. 4. [PubMed: 14768281]

31. Bos I, De Boever P, Emmerechts J, et al. Changed gene expression in brains of mice exposed to traffic in a highway tunnel. Inhalation toxicology. 2012; 24(10):676–86. DOI: 10.3109/08958378.2012.714004 [PubMed: 22906174]

32. Cliff R, Curran J, Hirota JA, Brauer M, Feldman H, Carlsten C. Effect of diesel exhaust inhalation on blood markers of inflammation and neurotoxicity: a controlled, blinded crossover study. Inhalation toxicology. 2016; 28(3):145–53. DOI: 10.3109/08958378.2016.1145770 [PubMed: 26915823]

33. Sudol K, Mann JJ. Biomarkers of Suicide Attempt Behavior: Towards a Biological Model of Risk. Curr Psychiatry Rep. 2017; 19(6):31.doi: 10.1007/s11920-017-0781-y [PubMed: 28470485]

34. Casanova R, Wang X, Reyes J, et al. A Voxel-Based Morphometry Study Reveals Local Brain Structural Alterations Associated with Ambient Fine Particles in Older Women. Frontiers in human neuroscience. 2016; 10:495.doi: 10.3389/fnhum.2016.00495 [PubMed: 27790103]

35. Hwang JP, Lee TW, Tsai SJ, et al. Cortical and subcortical abnormalities in late-onset depression with history of suicide attempts investigated with MRI and voxel-based morphometry. Journal of geriatric psychiatry and neurology. 2010; 23(3):171–84. DOI: 10.1177/0891988710363713 [PubMed: 20430976]

36. Peterson BS, Rauh VA, Bansal R, et al. Effects of prenatal exposure to air pollutants (polycyclic aromatic hydrocarbons) on the development of brain white matter, cognition, and behavior in later childhood. JAMA Psychiatry. 2015; 72(6):531–40. DOI: 10.1001/jamapsychiatry.2015.57 [PubMed: 25807066]

37. Chen JC, Wang X, Wellenius GA, et al. Ambient air pollution and neurotoxicity on brain structure: Evidence from women's health initiative memory study. Annals of neurology. 2015; 78(3):466–76. DOI: 10.1002/ana.24460 [PubMed: 26075655]

38. Woodward NC, Pakbin P, Saffari A, et al. Traffic-related air pollution impact on mouse brain accelerates myelin and neuritic aging changes with specificity for CA1 neurons. Neurobiology of aging. 2017; 53:48–58. DOI: 10.1016/j.neurobiolaging.2017.01.007 [PubMed: 28212893]

39. Allen JL, Oberdorster G, Morris-Schaffer K, et al. Developmental neurotoxicity of inhaled ambient ultrafine particle air pollution: Parallels with neuropathological and behavioral features of autism and other neurodevelopmental disorders. Neurotoxicology. 2017; 59:140–54. DOI: 10.1016/j.neuro.2015.12.014 [PubMed: 26721665]