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New study finds genes and air pollution multiply healthy people's risk of depression

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A genetic predisposition for depression combined with exposure to high-particulate-matter air pollution greatly elevates the risk that healthy people will experience depression, according to a first-of-its-kind study

published today in the *Proceedings of the National Academies of Sciences* (*PNAS*) from neuroscientists at the Lieber Institute for Brain Development (LIBD), on the Johns Hopkins Medical Campus, and Peking University in Beijing, China. The study involved a global partnership synthesizing scientific data on air pollution, neuroimaging, brain gene expression, and additional data gathered from an international genetic consortium from more than 40 countries.

"The bottom line of this study is that air pollution doesn't only impact climate change, it's affecting how your brain works," said Daniel R. Weinberger, M.D., Chief Executive Officer and Director of the Lieber Institute and a co-author of the study. "The effects on liability for depression may just be the tip of the iceberg where brain health is concerned. The major challenge in medicine today is a deeper understanding how genes and the environment interact with one another. This study sheds bright light on how this happens."

"The key message in this study, which has not been shown before, is that air pollution is affecting important cognitive and emotional circuitry of the brain by changing the expression of genes that are conducive to depression," said Hao Yang Tan, M.D., an investigator at the Lieber Institute, who led the research in collaboration with Peking University. "More people in high-pollution areas will become depressed because their genes and pollution in their environment exaggerate the individual effects of each."

All people have some propensity for developing depression, the researchers say, but certain people have higher risk written into their genes. This predisposition does not mean that a person will develop depression, but it elevates a person's risk above the average population. This study shows that depression is far more likely to develop in otherwise healthy humans who have these key genes and who live in environments with high levels of particulate-matter in the air.

"Our results are the first to show a direct, neurological link between air pollution and how the brain works in processing emotional and cognitive information and in risk for depression," said Zhi Li, Ph.D., a postdoctoral fellow at the Lieber Institute and lead author of the study. "What is most intriguing is that the two factors are linked in such a way that they have a multiplier effect on one's risk of depression. That is, together, risk genes and bad air raise the risk of depression much more than either factor does in isolation."

The brain circuits involved in the effects of genetic risk and air pollution control a wide range of important reasoning, problem-solving, and emotional functions, suggesting potentially widespread brain effects of air pollution.

The study recruited 352 healthy adults living in Beijing, a city with well-documented daily pollution levels. Participants first underwent genotyping from which the researchers calculated each person's polygenic depression risk score—the mathematical likelihood that a person will suffer depression based on genes alone. The researchers then collected detailed information about each participant's relative exposure to air pollution over a prior six-month period.

Next, the participants engaged in a series of simple cognitive tests while undergoing functional magnetic resonance imaging (fMRI) showing which parts of the brain were activated during the cognitive processing. While doing the tests, participants were also subjected to social stress (unexpected negative feedback about their performance), which affected how a widespread network of brain circuits operated during the tests. The researchers then showed that this brain network was disproportionately degraded by the combination of the genes for depression and the relative degree of exposure to air pollution.

To directly examine how genes for depression operated in the human

brain, the researchers examined data from a gene atlas of *postmortem* human brain tissue. They then mapped the postmortem brain networks to the very same networks in living subjects to test whether those genes underwrite the effects of air pollution.

Using that sophisticated model, the team found that people who had high genetic risk for depression and high exposure to particulate matter had brain function predicted by a tighter integration with how genes for depression operated together. The researchers also found that a subset of genes driving these associations were implicated in inflammation, as well—a finding that could provide new pharmacological insights into mitigating the effects of air pollution on brain function and depression.

Tan said that this new understanding has implications for policymakers around the world. The role of air pollution on the brain is no longer a matter of conjecture.

"Armed with this knowledge, leaders and public health officials around the globe have ample evidence that additional air pollution controls will lead to improved cognitive function and lower rates of depression —particularly in densely populated urban areas where air pollution is highest, and stress from socioeconomic and racial inequities is greater," Tan said. "Given the long-term costs of neuropsychiatric disorders, there is an urgent need for scientific and policy strategies to better identify and protect vulnerable individuals from the deleterious brain impacts of air pollution."

More information: Air pollution interacts with genetic risk to influence cortical networks implicated in depression, *Proceedings of the National Academy of Sciences* (2021). DOI: 10.1073/pnas.2109310118

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