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Environmental factors influencing the link between childhood ADHD and risk of adult coronary artery disease

A B S T R A C T

Yorbik et al. reported novel findings regarding a hypothesized relationship between childhood attention-deficit hyperactivity disorder (ADHD) and later risk for coronary heart disease in adulthood. The authors found that mean platelet volume (MPV), a marker of platelet reactivity and a presumable biomarker in patients with cardiovascular disease, was significantly elevated in children with ADHD compared to healthy controls. The mechanistic importance of this novel discovery remains unknown and warrants clarification. We have made the novel proposition that environmental exposure to the agricultural and combustion air pollutant, nitrous oxide (N_2O), may be an etiological contributor to neurodevelopmental disorders. Clinical studies suggest that N_2O may enhance platelet hyperaggregation, possibly via its biphasic role as an MAO inhibitor especially at trace levels of exposure or via the generation of oxidative stress. Therefore, this correspondence briefly details the hypothesis that altered biochemical profiles in neurodevelopmental disorders, derived from chronic environmental exposure to the agricultural and combustion air pollutant, N_2O, may promote coronary artery disease in adulthood.

To the editor

Yorbik et al. [1] reported novel findings regarding a hypothesized relationship between childhood attention-deficit hyperactivity disorder (ADHD) and later risk for coronary heart disease in adulthood. The authors found that mean platelet volume (MPV), a marker of platelet size and a presumable biomarker in patients with cardiovascular disease, was significantly elevated in children with ADHD compared to healthy controls. The mechanistic importance of this novel discovery remains unknown and warrants clarification. We have made the novel proposition that environmental exposure to the agricultural and combustion air pollutant, nitrous oxide (N_2O), may be a leading etiological factor in the onset of ADHD and related neurodevelopmental disorders [2–4]. This correspondence proposes that this etiological factor may modulate biochemical variables implicated in both ADHD and coronary artery disease.

Through a series of epidemiological investigations, we first demonstrated that the use of the herbicide, glyphosate, in agriculture may increase hospitalizations for ADHD (representing a severe phenotype). However, the relationship appeared to be dependent on the level of land urbanization and glyphosate's county-specific association with the use of nitrogen fertilizers [2]. A subsequent epidemiological analysis confirmed the exploratory association we found between glyphosate and a severe ADHD phenotype, suggesting that the use of anthropogenic nitrogen fertilizers in agriculture and emissions of N_2O may predispose neurodevelopmental impairment [3]. Our novel review on this hypothesis highlighted numerous physiological mechanisms that may characterize this relationship, including antagonism of N-methyl-D-aspartate receptors, central release of opioid peptides, particularly dynorphin, and activation of the kappa opioid receptor, an opioidergic receptor subtype linked to cardioprotection [4,5].

Moreover, N_2O has also been shown to induce deficits in cholinergic signaling [6,7] which may drive systemic oxidative stress in humans, including ADHD children [6], and animals via the uncoupling of nitric oxide synthase and synthesis of nitric oxide [4,8–12]. Notably, a mouse knockout model of neuronal nitric oxide synthase yields an ADHD phenotype, suggesting the importance of central nitric oxide signaling in ADHD [13]. N_2O is also known to irreversibly oxidize cobalamin and thereby inhibit methionine synthase, an enzyme responsible for the methylation of homocysteine to methionine [14]. Elevated homocysteine levels are thought to be a precursor to coronary disease [15]. Though, adult ADHD patients show reduced levels of homocysteine without any differences in vitamin B12 levels [16], suggesting other pathophysiological mechanisms may link childhood ADHD with later onset of cardiovascular disease. We propose two mechanisms worthy of consideration.

Human studies indicate that N_2O may facilitate platelet hyperaggregation [17], as occurs in chronic heart failure - a risk factor for coronary artery disease [18]. Platelet reactivity may be related to systemic oxidative burden induced by N_2O [11,12], as well as alterations in monoamine neurotransmission from trace N_2O exposure [19]. Preclinical animal studies show that trace levels of exposure for 2 weeks may significantly modulate central neurotransmission by suppressing serotonin levels in several brain regions, while 13-week exposures increased serotonin levels, reflecting what the authors thought may be a biphasic role of N_2O as a monoamine oxidase inhibitor [20]. This supposition is consistent with the finding of significantly lower platelet monoamine oxidase activity in ADHD children [21], supporting a biochemical link between environmental N_2O and risk of ADHD. Interestingly, methylphenidate use for three months may reduce elevated platelet monoamine levels, including serotonin, in boys with ADHD, which was associated with improved psychometric outcomes [22]. These data point to the efficaciousness of psychostimulants in restoring altered peripheral serotonin levels, which may be a biomarker of coronary artery disease [23].

In addition to modulation of serum monoamine levels, plasma apelin-13 levels have also been reported to be elevated in ADHD children, although the reason for this novel finding is yet fully understood [24]. We have put forward the argument that since the apelin receptor (APJ) is a G

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protein–coupled receptor that is known to heterodimerize with the kappa opioid receptor (KOR), tolerance developed over the long term to chronic N_2O-mediated dynorphinergic excess likely desensitizes or otherwise modulates the KOR and APJ, leading to increased plasma apelin-13 expression in ADHD [25,26]. Given that apelin is a peptide that may act as an anti-thrombotic factor [27] via its activation of catalase [28], the elevation of apelin in ADHD may reflect the induction of compensatory mechanisms to reverse the actions of chronic N_2O-mediated desensitization of opioidergic signaling and increased oxidative stress. Interestingly, dysregulation of the apelin/APJ system has been implicated in cardiovascular disease, with the APJ receptor density being downregulated in ischemic heart disease yet apelin peptide levels remaining unchanged in the left ventricle and increased in atherosclerotic coronary artery [29]. Since we have previously shown anthropogenic nitrogen may be linked to a severe ADHD phenotype and related co-morbidity, we utilize our prior epidemiological data design from Healthcare Cost and Utilization Project (HCUPnet) to investigate the link between farm use of anthropogenic nitrogen and coronary artery disease [2,3,30–32].

We have extracted the number of hospitalizations for coronary atherosclerosis (Clinical Classification Software Diagnostic Group: 101, including the following ICD-9 codes: 411.0, 411.1, 411.8, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.0, 414.00, 414.01, 414.06, 414.2, 414.3, 414.4, 414.8, 414.9, V458.1, V458.2) and used generalized linear Poisson models with two-way fixed effects estimation in R (packages ggplot2 and sandwich for robust standard errors) to investigate the association between coronary artery disease and statewide anthropogenic nitrogen use estimates from the United States Geological Survey, as described previously [2,3,30–32]. A random variable Y is said to have a Poisson distribution with parameter μ if it takes integer values $y = 0, 1, 2, \ldots$ with probability

$$Pr\{Y = y\} = \frac{e^{-\mu}\mu^{y}}{y!}$$

for $\mu > 0$. The mean and variance of this distribution can be shown to be $E(Y) = var(Y) = \mu$. We have a sample of n observations of discharges related to an all-listed diagnosis of coronary atherosclerosis, $y_1, y_2, \ldots, y_n$, which are treated as realizations of independent Poisson random variables, with $Y_{ij} \sim P(\mu_{ij})$, where i represents a state and j an observation year. We let the logarithm of the mean depend on a vector of time-varying explanatory variables (i.e., farm and nonfarm use of anthropogenic nitrogen, state and year fixed effects), x_{ij}, such that the log-linear model is the following: $\log(\mu_{ij}) = x_{ij}'\beta_1$. Exponentiating, we have two multiplicative models for the mean discharges for our dependent condition: $\mu_{ij} = \exp\{x_{ij}'\beta_1\}$. The exponentiated regression coefficient $\exp\{\beta_{1ijk}\}$ yields an incidence rate ratio (IRR), which represents a multiplicative effect of the kth predictor on the mean. Increasing x_k by one-log unit multiplies the mean by a factor $\exp\{\beta_{1k}\}$.

The results of the Poisson model indicate a significant reduction in the risk for coronary artery disease for every one log-unit increase in farm use of nitrogen fertilizers, when controlling for non-farm use (IRR = 0.96, 95% C.I.: 0.93–0.99, $p < .01$, N = 216 state year observations). Though, including an interaction term of time with farm use of fertilizer heightens the significance of the main effect considerably, while the interaction itself significantly increases annual hospitalization risk for coronary artery disease by 9% (IRR = 1.09, 95% C.I.: 1.07–1.10, $p < .001$). These findings support our hypothesis suggesting that exposure to anthropogenic nitrogen use in agriculture and associated N_2O emissions may be initially cardioprotective but that over time, endogenous compensatory mechanisms (i.e., prolonged KOR signaling leading to "prodepressive-like" symptoms and behaviors, KOR/APJ modulation, increased peripheral apelin-13 and monoamine neurotransmitters) may take hold, increasing platelet reactivity and susceptibility to cardiovascular disease.

The mechanisms underpinning a purported connection between early ADHD and subsequent onset of coronary artery disease, as suggested by Yorbik et al. [1], warrant further investigation. The possibility presented in this correspondence relates the link on a continuum of environmental N_2O exposure. Our prior longitudinal investigations have linked a severe ADHD phenotype with anthropogenic nitrogen fertilizers and presumable N_2O emissions. N_2O has been shown to enhance platelet aggregation and oxidative stress in humans, as well as modulate brain monoamine levels in animals from trace levels of exposure, all of which are known risk factors for development of coronary artery disease. Whether chronic tolerance to the compound downregulates cardioprotective signaling, including activation of KOR and APJ, and thereby increases apelin protein levels over time, as suggested by the present results, needs further clarification, most especially since elevated apelin levels have been reported in both ADHD and atherosclerosis.

Compliance with Ethical standards

There are no funding acknowledgments or conflicts of interest to report.
This article does not contain any studies with human participants or animals performed by the author.

Competing interests

There are no competing interests to declare.

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Originality

The content included in this correspondence is original and has not been previously published or considered elsewhere.

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Keith Fluegge[a,*], Kyle Fluegge[a,b]
[a] *Institute of Health and Environmental Research, Cleveland, OH 44118, USA*
[b] *New York City Department of Health and Mental Hygiene, New York 11101-4132 USA*
E-mail address: keithfluegge@gmail.com

* Corresponding author.