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## Shorter telomere length in cord blood associated with prenatal air pollution exposure: Benefits of intervention

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### ABSTRACT

**Background:** To examine the molecular benefits of the government action to close the local coal burning power plant in Tongliang County, Chongqing Municipality, we compared biologic markers and health outcomes in two successive birth cohorts enrolled before and after the plant was shut down. In this city, polycyclic aromatic hydrocarbons (PAH) were primarily emitted by the coal burning facility. We previously reported that cord blood levels of PAH-DNA adducts (a biomarker of exposure) and various adverse health outcomes were reduced in the second cohort, whereas levels of brain-derived neurotrophic factor/BDNF (a protein involved in neuronal growth) were increased. Here we assessed telomere length (TL), which has been associated with risk of certain chronic diseases, early mortality, aging and cognitive decline in adults.

**Objectives:** The goals of the present study were to determine whether TL differed between the two cohorts and whether prenatal PAH exposure, estimated by PAH-DNA adducts in cord white blood cells of newborns in China, were predictive of shorter TL in cord blood, suggesting the potential accrual of risk of certain chronic diseases during the prenatal period. We explored relationships of TL with BDNF and neurodevelopmental outcomes, each previously associated with PAH-DNA adducts in these cohorts, as well as the potential mediating role of TL in the associations between adducts and neurodevelopmental outcomes.

**Methods:** We analyzed TL in cord blood of 255 newborns who also had data on PAH-DNA adducts, BDNF, and relevant covariates. Multiple regression analysis was carried out to test associations between adducts and TL and between TL and BDNF, adjusting for relevant covariates. In the subset with developmental quotient (DQ) scores from Gesell testing at age 2 (N = 210), we explored whether TL was a mediator of the relationship between PAH-DNA adducts and DQ scores by first examining the associations between cord adducts and DQ, cord adducts and TL, and TL and DQ, adjusting for the same covariates.

**Results:** As hypothesized, the mean TL was significantly higher in the second cohort compared to the first cohort. Overall, PAH-DNA cord adducts were significantly and inversely correlated with TL. Multiple regression analysis showed a significant association between adducts and TL, after adjusting for key covariates:  $\beta$  (effect size per standard deviation adducts) =  $-0.019$ ,  $p = .003$ . The regression coefficient of TL on (Ln) BDNF was also significant ( $\beta = 0.167$ ,  $p < .001$ ). Exploratory analysis, regressing TL on Gesell developmental scores, showed generally inverse, but not significant associations. TL was not, therefore, deemed to be a potential mediator of the association between adducts and developmental scores at age two.

**Conclusion:** This study provides the first evidence that prenatal PAH exposure from coal burning may adversely affect TL, with potential implications for future risk of chronic diseases including cardiovascular disease. The improvement in TL in the second cohort and the observed correlation between increased TL and higher levels of BDNF indicate direct benefits to the health and development of children resulting from the government's closure of the power plant.

### 1. Introduction

Coal currently supplies about two-thirds of China's overall energy use (U.S. Energy Information Administration, 2015). Although the

share from coal has declined somewhat in recent years and that from renewable energy sources has been growing, many new power plants continue to be designed to run on coal, which will contribute to unhealthy levels of air pollution. Coal burning in China is the major source

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of ambient polycyclic aromatic hydrocarbons (PAH), a constituent of respirable fine particulate matter (PM) known as PM<sub>2.5</sub>. Molecular and epidemiologic studies have shown that fetuses and infants are more susceptible to the toxic effects of PAH than adults (Perera et al., 2005). PAH are known transplacental carcinogens (Bostrom et al., 2002), reproductive (Choi et al., 2006; Tang et al., 2006), and neurodevelopmental toxicants (F Perera et al., 2008; Tang et al., 2006). PAH–DNA adducts (resulting from the covalent binding of PAH with DNA) reflect individual variation in exposure, absorption, metabolic activation, and DNA repair. They therefore provide an informative biologic dosimeter that has been associated with risk of lung cancer (Tang et al., 2001) as well as adverse reproductive and neurodevelopmental outcomes (Perera et al., 1998; Tang et al., 2006; Tang et al., 2008). PAH–DNA adduct concentrations in cord blood have been shown to increase across a gradient of ambient PAH exposure, albeit with substantial inter-individual variation (Perera et al., 2005).

In Tongliang County, Chongqing Municipality, the high pollutant concentrations in ambient air prompted the government to shut down the local coal burning power plant in May of 2004 to improve community health (Tang et al., 2014). This action, announced in advance, provided a unique opportunity to compare data on ambient PAH levels, biomarkers, and health outcomes in two successive cohorts of children, with and without prenatal exposure to emissions from the coal-fired power plant. In partnership with Chongqing Children's Hospital, the Columbia Center for Children's Environmental Health (CCCEH) carried out two prospective cohort studies between 2002 (cohort 1) and 2005 (cohort 2) of children conceived and delivered pre-plant shutdown and post-plant shutdown, respectively. Our previous studies compared cord blood levels of PAH–DNA adducts, brain-derived neurotrophic factor/BDNF (a protein involved in neuronal growth), and outcomes in the two successive birth cohorts. The findings that the second cohort had significantly lower cord blood PAH–DNA adducts and higher levels of BDNF compared to the first cohort testified to the molecular benefits of plant closure (FP Perera et al., 2008; Tang et al., 2014), documenting benefits of government action. Further, the significant inverse association between PAH–DNA adducts in cord blood and lower scores for cognitive development at age 2 seen in the first cohort was no longer observed in the second cohort.

The present analysis evaluated telomere length (TL) in cord blood white blood cells in relation to the previous findings. Telomeres are non-coding repetitive sequences of DNA (TTAGGG) bound by specialized nucleoproteins that form 'caps' at the ends of chromosomes and maintain the integrity of the genome. They allow chromosomes to be faithfully copied during cell division. However, telomeres shorten with each round of cell division, resulting in a gradual loss of genomic stability and progression toward senescence and apoptosis. Genetic instability associated with short telomeres is an early event in tumorigenesis; and short TL in peripheral blood lymphocytes (PBLs) has been linked to increased risk for certain cancers (Sun et al., 2015; Zhu et al., 2016) as well as cardiovascular disease (Brouillette et al., 2003; Haycock et al., 2014), and early mortality (Cawthon et al., 2003). TL has been associated with cognitive decline in adults (Martin-Ruiz et al., 2006); but relationships with cognitive development in children have not been explored. There has been growing interest in the role of TL as a biomarker of potential risk resulting from lifestyle or toxic environmental exposures: both as an outcome of concern in its own right and a potential mediator of health effects (Factor-Litvak et al., 2016) (Hou et al., 2012b). Recent studies suggest that TL in adults and related risk of disease may be associated with TL in newborns, reflecting the influence of environmental as well as genetic factors (Factor-Litvak et al., 2016). Further, early life alterations in TL could have important implications for health over the life course (Factor-Litvak et al., 2016).

The goal of the present study was to determine whether prenatal PAH exposure estimated by PAH–DNA adducts in cord white blood cells (CWBC) of 267 newborns in China were predictive of TL, suggesting the potential accrual of risk of cancer as well as other chronic diseases

during the prenatal period. We also sought to compare TL in cord blood of the newborns born before the closure of the coal plant (cohort 1) (N = 129) with newborns conceived and born after operation ceased (cohort 2) (N = 138). A connection exists between BDNF and TL in that BDNF has been shown to increase neuronal expression of telomerase, which mediates an augmented resistance to telomere shortening and apoptosis (Fu et al., 2002), (Nagelhus et al., 2013), (Niu and Yip, 2011). Therefore, we explored relationships of TL with BDNF and of TL with neurodevelopmental outcomes previously associated with PAH–DNA adducts in these cohorts. We also explored the potential mediating role of TL in the associations observed between PAH–DNA adducts and neurodevelopmental outcomes.

## 2. Methods

The overall approach used in this investigation and the comparison of the two cohorts with respect to adducts and developmental quotient (DQ) scores has been presented elsewhere (Tang et al., 2014).

### 2.1. Ethics statement

This study was approved by the Institutional Review Board of Columbia University and Chongqing Medical University. All subjects gave informed written consent by completing a form approved by both the Columbia University Institutional Review Board and Chongqing Medical University.

### 2.2. Study site

The city of Tongliang has a population of approximately 810,000 and is situated in a small basin approximately 3 km in diameter (Tang et al., 2014). A coal-fired power plant located south of the town center operated during the dry season from December 1st to May 31st of each year prior to 2004 in order to compensate for insufficient hydroelectric power during that time period. This plant was the principal source of local air pollution; in 1995, nearly all domestic heating and cooking units were converted to natural gas, motor vehicles were not a major pollution source, and there were no other major coal-burning sources within 20 km of the city (Tang et al., 2014). In May 2004, the power plant was closed and replaced by the national grid system of electrical energy.

### 2.3. Study subjects

As previously reported (Tang et al., 2014), the 2002 cohort comprised of 150 nonsmoking mothers and their newborns enrolled between March 4th, 2002 and June 19th, 2002 at four hospitals in Tongliang: the Tongliang County Hospital, the Traditional Chinese Medicine Hospital, the Tongliang Maternal Children's Health Hospital, and the Bachuan Hospital. The 2005 cohort included 158 mothers and their newborns delivered at the same hospitals from March 2nd, 2005 to May 23rd, 2005 who were recruited in the same way as the first cohort. The women were selected using a screening questionnaire when they checked in for delivery. Eligibility criteria included current non-smoking status,  $\geq 20$  years of age, and residence within 2.5 km of the Tongliang power plant. All but one eligible woman agreed to enter the study. As shown in Figs. 1, 270 of the newborns had sufficient cord blood samples for PAH–DNA adduct analysis; 259/270 had available data on TL measured in newborn genomic DNA; and a subset of 255 newborns also had data on BDNF and relevant covariates. The main analyses involved this subset of 255 newborns.

### 2.4. Personal interview and medical record review

A 45-min questionnaire was administered by a trained interviewer after delivery. The questionnaire elicited demographic information

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