

Original Article



# The risk of preschool asthma at 2–4 years is not associated with leukocyte telomere length at birth or at 1 year of age

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Conflict of Interest

The authors have no financial conflicts of interest.

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## ABSTRACT

**Background:** Exposure to prenatal stress is associated with offspring allergic-disease development, and oxidative stress may mediate this relationship.

**Objective:** We aimed to evaluate whether leukocyte telomere length (LTL) shortening, a marker for exposure to oxidative stress, in early life is associated with increased risk of asthma development during the preschool period.

**Methods:** We assessed the follow-up clinical data of a subgroup from a birth cohort whose LTLs had been measured from cord-blood and 1-year peripheral-blood samples. We examined whether the LTLs would be associated with asthma development at the age of 2–4 years.

**Results:** The data of 84 subjects were analyzed. LTLs were measured from the cord-blood and 1-year peripheral blood of 75 and 79 subjects, respectively. Among them, 14 subjects (16.7%) developed bronchial asthma between 2–4 years old. Prenatally stressed subjects had marginally increased odds of developing asthma ( $p = 0.097$ ). There was no significant difference in the odds of preschool-asthma development between the groups with shorter and longer cord-blood LTLs (odds ratio [OR], 0.651; 95% confidence interval [CI], 0.184–2.306) or in the odds between the groups with shorter and longer 1-year peripheral-blood LTLs (OR, 0.448; 95% CI, 0.135–1.483). Finally, subjects with both higher prenatal stress and shorter LTLs did not have significantly higher odds of preschool-asthma development (for cord-blood: OR, 1.242; 95% CI, 0.353–4.368; for 1-year peripheral-blood: OR, 1.451; 95% CI, 0.428–4.919).

**Conclusion:** There was no significant association between early life LTLs and higher risk of bronchial-asthma development during the preschool years.

**Keywords:** Allergy; Asthma; Bronchial diseases; Child, Preschool; Oxidative stress, Telomere shortening

**Author Contributions**

Conceptualization: Dong In Suh, Soo-Jong Hong. Data curation: Dong In Suh, Youn Ho Sheen, Kyung Won Kim, Kangmo Ahn, Soo-Jong Hong. Formal analysis: Dong In Suh, So-Yeon Lee. Funding acquisition: Dong In Suh, So-Yeon Lee. Investigation: Dong In Suh, Yoon Mee Park. Project administration: Mi-Jin Kang, Yoon Mee Park, Jun-Kyu Lee, Soo-Jong Hong. Resources: Mi-Jin Kang, Yoon Mee Park, Jun-Kyu Lee, Soo-Jong Hong. Supervision: Soo-Jong Hong. Validation: Dong In Suh, Soo-Jong Hong. Writing - original draft: Dong In Suh, So-Yeon Lee, Soo-Jong Hong. Writing - review & editing: Soo-Jong Hong.

**INTRODUCTION**

Oxidative stress affects non-communicable disease development [1, 2]. In patients with metabolic syndrome, oxidative stress increases and antioxidant defenses decrease [3, 4]. Oxidative stress is increased in the asthmatic airway, and this increase is suggested to play a role in the pathogenesis of asthma [5-8]. According to birth cohort data, some adverse condition that would increase oxidative stress presented close association with later asthma and other allergic-disease development [9-12]. Therefore, oxidative stress is regarded as the key pathophysiologic mechanism through which perinatal environmental factors program later allergic-disease development [6, 8, 13].

Telomeres shorten with every cell division cycle, constituting a well-established indicator for the cellular aging process [14, 15]. As the telomeres have a high content of guanine residues, which are particularly sensitive to oxidative damage, oxidative stress accelerates telomere shortening [16]. Leukocyte telomere length (LTL) is considered a surrogate marker for exposure to oxidative stress [16, 17]. Indeed, exposure to a variety of adverse prenatal conditions such as maternal stress, suboptimal diet, obesity, and obstetric complications, is associated with shorter offspring LTL at birth and in adult life [16, 18, 19].

Wheezing is one of the most relevant symptoms of asthma. Although wheezing in toddlers is usually triggered by respiratory tract infections, recurrent wheezing in preschool children is often indicative of asthma, especially when the children are sensitized to inhalant allergens [20, 21]. In this pilot study, we aimed to evaluate whether the LTL, a marker for exposure to oxidative stress, in early life is associated with risk of preschool-asthma development, suspected by physician-diagnosed asthma or recurrent wheezing in children aged 2–4 years.

**MATERIALS AND METHODS**

This pilot study is a follow-up evaluation of a study that explored the relationship between prenatal stress, LTL at birth and at 1 year, and atopic dermatitis (AD) development at 1 year [22]. Subjects comprised a subgroup of a birth cohort (the COhort for Childhood Origin of Asthma and allergic diseases) where an epidemiologic association was observed between prenatal maternal stress and AD development in the children [23, 24]. We gathered more clinical information on the development of physician-diagnosed asthma or recurrent wheezing from this subgroup at their annual follow-up visits between the ages 2–4 years.

In the original birth cohort study, subject exposure to prenatal maternal stress was assessed using 2 self-reported questionnaires at 36 weeks' gestation, namely the Center for Epidemiological Studies-Depression (CESD) 10 and the State-Trait Anxiety Inventory-Trait subscale (STAI), which measure depression and anxiety, respectively [25, 26]. At the enrolment stage, children were not evenly distributed in terms of prenatal-stress exposure; they were either in the low-stress group pool, with both the CESD and STAI scores in the lowest tertile; the high-stress group pool, with either the CESD or STAI score being in the highest quartile or both the CESD and STAI scores in the highest tertile; or the other group that were used as the control in measuring the telomere length [22].

Subjects' AD and preschool asthma were verified from the original cohort database; during the annual follow-up, subjects were evaluated for presence of relevant episodes of AD,

physician-diagnosed asthma, or recurrent wheezing by detailed history recording and physical examination by pediatric allergy specialists. If subjects had experienced relevant episodes at least once during the age of 2–4 years, they were classified as having AD or preschool asthma.

The detailed protocol used to measure the LTLs was described in our previous study [22]. In short, DNA was extracted from the buffy coat of cord blood and 1-year-old peripheral blood using a DNA extraction kit (Qiagen, Crawley, United Kingdom), and the average terminal restriction fragment length was measured using a chemiluminescence technique according to the manufacturer's manual of a commercially available Telo-TAGGG telomere length assay kit (Roche-Applied Science, Mannheim, Germany).

The study protocol was approved by the Institutional Review Board of Seoul National University Hospital/Seoul National University College of Medicine (IRB No. 1701-118-827). As the mothers had agreed to provide their children's blood samples for secondary use in the original birth cohort, the requirement for written informed consent was waived.

Data were analyzed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA). Clinical characteristics are displayed using descriptive statistics. For nonnormally distributed variables i.e., LTLs, CESD, and STAI scores, we present the median and the interquartile ranges. Within-group comparisons of the LTLs between the cord-blood and 1-year peripheral blood were performed using the Wilcoxon signed-rank test, and the Mann-Whitney test was used for comparisons between the prenatally stressed and nonstressed groups. The rate of preschool-asthma development was compared using the chi-square test according to prenatal-stress exposure, telomere length, and both. Differences were considered statistically significant when the *p* value was lower than 0.05.

## RESULTS

The data of 84 subjects were analyzed. The sample included 68 subjects from which the LTLs were successfully measured both at birth and at the age of 1 year in the previous study to evaluate the relationship between the LTL and AD development [22]. Their characteristics are shown in **Table 1**. Cord-blood LTLs were successfully measured in 75 subjects and the 1-year LTLs in 79 subjects. Forty-three of 84 subjects (51.2%) were prenatally stressed, and 49 subjects (58.3%) developed AD during the follow-up period. At the age of 2–4 years, 14 subjects (16.7%) developed physician-diagnosed asthma or recurrent wheezing.

**Table 1.** Characteristics of the entire population (n = 84)

Characteristic	Value
Cord-blood LTLs (kbp) (n = 75)	15 (11.0–16.5)
1-year peripheral blood LTLs (kbp) (n = 79)	10 (8.6–15.0)
Prenatal maternal CESD-10	6 (2.25–13)
Prenatal maternal STAI-T	42.5 (30–52.25)
Prenatally stressed	43 (51.2)
Atopic dermatitis ever	49 (58.3)
Preschool asthma/wheezing	14 (16.7)

Values are presented as median (interquartile range) or number (%).

LTL, leukocyte telomere length; CESD-10, Center for Epidemiological Studies- Depression 10; STAI-T, State-Trait Anxiety Inventory-Trait subscale.

**Table 2.** Rate of preschool asthma/wheezing according to prenatal stress

	Preschool asthma/wheezing (n)	Preschool nonasthma/wheezing (n)	Odds ratio (95% CI)	<i>p</i> value*
Prenatal stress			2.803 (0.802–9.795)	0.097
Stressed prenatally	10	33		
Nonstressed prenatally	4	37		

CI, confidence interval.

\*Chi-square test.

**Table 2** shows the rate of physician-diagnosed asthma or recurrent wheezing according to prenatal-stress exposure at the age of 2–4 years. The rate of preschool asthma was 23.3% (10 of 43) in the prenatally stressed group, higher than the 9.8% (4 of 41) in the prenatally nonstressed group. However, the difference was not statistically significant (odds ratio [OR], 2.803; 95% confidence interval [CI], 0.802–9.795; chi-square,  $p = 0.097$ ).

The cord-blood and 1-year peripheral-blood LTLs according to prenatal-stress exposure are presented in **Table 3**. The 1-year peripheral-blood LTLs were significantly shorter than the cord-blood LTLs in both prenatally stressed (median [interquartile range], 1-year peripheral blood versus cord-blood, Wilcoxon signed-rank test; 10.0 [8.6–12.5] kbps vs. 15.0 [11.0–16.0] kbps;  $p < 0.001$ ) and prenatally nonstressed (12.5 [8.9–16.0] kbps vs. 15.0 [10.25–18.0] kbps,  $p = 0.001$ ) groups. However, the LTLs of the participants in the prenatally stressed group were significantly shorter than those of the participants in the prenatally nonstressed group only in the 1-year peripheral blood (Mann-Whitney test,  $p = 0.038$ ) and not in the cord-blood ( $p = 0.140$ ).

Subjects were classified into the shorter or longer LTL groups; as the median LTLs were 15 kbps for cord-blood and 10 kbps for 1-year peripheral blood, the longer LTL groups included subjects who had LTLs >15 kbps for cord-blood and >10 kbps for 1-year peripheral blood. The rate of physician-diagnosed asthma or recurrent wheezing at the age of 2–4 years was compared between the shorter and the longer LTL groups as shown in **Table 4**. The rate of preschool asthma was 14.0% (7 of 50) in the shorter cord-blood LTL group, which was not significantly different from the 20.0% (5 of 25) in the longer cord-blood LTL group (OR, 0.651; 95% CI, 0.184–2.306). In addition, the rate of preschool asthma was 12.2% (5 of 41) and 23.7% (9 of 38) in the longer and shorter 1-year peripheral-blood LTL groups, respectively, also showing nonsignificant differences (OR, 0.448; 95% CI, 0.135–1.483).

**Table 3.** LTLs according to prenatal stress

Parameter	Stressed prenatally (n = 43)	Nonstressed prenatally (n = 41)	<i>p</i> value*
Cord-blood LTLs (kbp)	15.0 (11.0–16.0) (n = 38)	15.0 (10.25–18.0) (n = 37)	0.140
1-Year peripheral blood LTLs (kbp)	10.0 (8.6–12.5) (n = 41)	12.5 (8.9–16.0) (n = 38)	0.038
<i>p</i> value†	< 0.001 (n = 34)	0.001 (n = 36)	

Values are presented as median (interquartile range).

LTL, leukocyte telomere length.

\*Mann-Whitney test. †Wilcoxon signed-rank test.

**Table 4.** Rate of preschool asthma/wheezing according to LTLs

	Preschool asthma/wheezing (n)	Preschool nonasthma/wheezing (n)	Odds ratio (95% CI)	<i>p</i> value*
Cord-blood LTLs			0.651 (0.184–2.306)	0.504
Shorter (n = 50)	7	43		
Longer (n = 25)	5	20		
1-Year PB LTLs			0.448 (0.135–1.483)	0.182
Shorter (n = 41)	5	36		
Longer (n = 38)	9	29		

LTL, leukocyte telomere length; CI, confidence interval; PB, peripheral blood.

\*Chi-square test.

**Table 5.** Rate of asthma/wheezing according to the prenatal stress/LTL groups

Group	Preschool asthma /wheezing	Preschool nonasthma /wheezing	Odds ratio (95% CI)	<i>p</i> value*
Shorter cord-blood LTLs and prenatal-stress	5	23	1.242 (0.353–4.368)	0.735
Longer cord-blood LTLs or prenatal nonstress	7	40		
Shorter 1-year peripheral blood LTLs and prenatal-stress	5	18	1.451 (0.428–4.919)	0.549
Longer 1-year peripheral blood LTLs or prenatal nonstress	9	47		

LTL, leukocyte telomere length; CI, confidence interval.

\*Chi-square test.

Finally, the risk of physician-diagnosed asthma or recurrent wheezing at the age of 2–4 years was assessed between the shorter LTL and prenatal-stress group, and the longer LTL or prenatal nonstress groups as displayed in **Table 5**. The risk of preschool asthma was not increased, although the subjects were exposed to high prenatal stress and had shorter LTLs (for cord-blood: OR, 1.242; 95% CI, 0.353–4.368; for 1-year peripheral-blood: OR, 1.451; 95% CI, 0.428–4.919).

## DISCUSSION

In this follow-up study of a subpopulation of a birth cohort, prenatal-stress exposure affected LTL shortening. However, neither prenatal-stress nor the shortened LTL were associated with elevated risk of preschool-asthma development. This was the first small-group analysis that explored the association between the LTLs, a marker for oxidative stress, in early life and elevated risk of preschool-asthma development.

In this analysis, asthma was suspected in 16.7% of subjects. The diagnosis of asthma is complex in toddlers and preschoolers; in the early period, wheezing is so prevalent that as many as 34% of children experience at least one wheezing episode in the first 3 years of life [21], whereas some asthma presents without wheezing [27]. Therefore, in the original cohort [23], pediatric allergists confirmed the diagnosis of preschool asthma only in subjects  $\geq 2$  years old after paying special attention to discern cases of preschool asthma from cases of viral infection-associated wheezing. Considering that the cumulative rates of preschool asthma were 9.8% in the lower prenatal-stress group and 23.3% in the higher prenatal-stress group, the actual rate of preschool asthma appears to be within this range, which is comparable to the results of previous reports [28, 29].

Although it was not statistically significant, the rate of preschool asthma tended to be higher in subjects exposed to prenatal stress. In the literature, exposure to prenatal stress is associated with pediatric asthma [30, 31], and in preschool children prenatal stress also increased the risk of developing AD [30, 32]. However, the possibility of a close relationship between prenatal stress and asthma development has not been sufficiently evaluated in preschool children.

When we confined the analysis to the subpopulation where the LTLs were successfully measured both at birth and at 1 year of age, the LTLs had significantly shortened during the 1st year of life, which did not preferentially occur in the prenatally stressed group. Conversely, when we focused on the association between LTL shortening and prenatal-stress exposure, exposure to prenatal stress was associated with shortening of the 1-year blood LTL. Although we could not justify how prenatal stress could still affect LTL shortening after birth, the observed relationship leads us to consider that it is appropriate to use LTL shortening as a surrogate marker for prenatal-stress exposure.

The risk of preschool-asthma development did not differ between the longer and the shorter LTL groups. Even when we focused on the higher-risk subgroup, which had been exposed to higher prenatal stress and presented with shorter LTLs, the association did not change; the odds for preschool-asthma development in these subjects were slightly increased compared to those of the other subjects but they were not statistically significant when we defined the groups based on cord-blood or 1-year peripheral blood LTLs. This may indicate that the association of oxidative stress with shorter LTLs is not as strong as we had initially expected or that the impact of oxidative stress in programming preschool-asthma development can be modifiable by environmental factors encountered after birth. We could not exclude the uneven distribution of possible confounders [33, 34], i.e., the rate of daycare attendance or the number of siblings, because the number of subjects in which the LTLs were initially assessed was limited.

Another study limitation pertains to the study design. Although the sample size was not small, the distributions of the degree of prenatal-stress exposure and of AD development were not normally distributed, probably because this was a follow-up of the previous study that measured the LTLs to assess the relationship between prenatal stress and AD development [22]. Therefore, caution is required when applying the present results to the general preschool population. Nonetheless, this pilot study is valuable in that we showed the limited value of LTLs in early life as a biomarker of higher risk for later preschool-asthma development.

In conclusion, this small-group pilot analysis showed the LTLs in early life were not associated with elevated risk of asthma development in the preschool period. Even when combined with history of prenatal-stress exposure, LTLs in early life are not associated with higher risk of asthma during the preschool years.

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