Letter to the editor:

# Prenatal stress exposure is associated with increased dyspnea perception in adulthood

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**“Take home” message**

Prenatal exposure to maternal stress is associated with increased perception of dyspnea in adulthood 28 years later.

Dyspnea is the aversive cardinal symptom in various prevalent conditions such as respiratory, cardiovascular and neuromuscular diseases and is associated with great individual and socioeconomic burden [1]. Over the past years, not only several physiological, but also psychological factors have been demonstrated to impact the perception of dyspnea [1,2]. For example, high levels of anxiety in adulthood were associated with increased dyspnea perception in patients with asthma or chronic obstructive pulmonary disease (COPD), but also in healthy controls [2]. Moreover, adverse, separation-related experiences in childhood were linked to the subsequent development of increased anxiety and dyspnea [3]. However, the effects of adverse experiences in early, prenatal life on dyspnea perception remain widely unknown, although prenatal exposure to maternal stress and anxiety has convincingly been related to the development of other health- and behavioral problems later in life, including impairments of the respiratory control system and high anxiety levels [4–9]. Therefore, this study investigated the relationship between prenatal exposure to maternal stress and the perception of dyspnea in adulthood 28 years later.

Subjects were recruited from the 'Leuven Cohort', a longitudinal study that started in 1986 with 86 pregnant mothers and their firstborn children. The study examines the neurobehavioral effects of prenatal exposure to maternal stress on fetal, infant, and childhood development, continuing into adulthood [10]. At study entry, the sample of mothers consisted of healthy Belgian women without history of psychiatric disorders. Maternal stress levels during pregnancy were operationalized as trait anxiety levels and assessed with the validated State-Trait-Anxiety-Inventory (STAI)[11]. In addition, the following variables with known impact on early life development were obtained: duration of pregnancy (days), birth weight (g), maternal smoking during pregnancy (no. cigarettes/day), maternal caffeine consumption during pregnancy (mg/day) and maternal alcohol consumption during pregnancy (mg/day).

From the original cohort, 40 healthy adults could be included. After obtaining written informed consent and an anamnestic interview, spirometric lung function was measured. Additionally, levels of state and trait anxiety, dyspnea-specific anxiety and somatic symptom burden were assessed with validated questionnaires [11–13].

Subsequently, their perception of dyspnea was examined in two magnitude estimation tasks (MET), during which four inspiratory threshold loads (Respironics, Parsippany, US) with different resistances (0, 5, 20 and 40 cmH2O/L/s) were repeatedly being presented. Subjects wore a nose clip and breathed through an antibacterial filter being connected to a two-way, non-rebreathing valve (Hans Rudolph Inc., Shawnee, US). The inspiratory port was connected to a tube (diameter: 2cm; length: 150cm) where threshold loads were introduced. In the first MET, subjects breathed through the loads for one inspiration and rated the intensity of dyspnea on a Borg-scale [14]. Each load was presented four times in random order. In the second MET, subjects breathed for five subsequent inspirations through the loads and rated both the intensity and unpleasantness of dyspnea on a Borg-scale [14]. Each load was presented twice in random order.

For the analyses, subjects were grouped into a low prenatal stress group (LS) and a high prenatal stress group (HS) as in previous studies [10]. Grouping was based on trait anxiety ratings [11] of their mothers during the $12^{th}$ to $22^{nd}$ week of pregnancy (low: $<75^{th}$ vs. high:=/>$75^{th}$ percentile). Perceptual sensitivity for dyspnea was calculated with individual regression slopes (Borg scores against load resistance) [15]. Groups were compared with independent samples *t*-tests or Mann-Whitney-U-tests, respectively. Additional Spearman correlations were calculated for dyspnea sensitivity slopes. Data are presented as group means

(±SD) and were analyzed using SPSS 24 software (SPSS Inc., Chicago, US) using a statistical significance threshold of $\alpha<0.05$.

Group characteristics including data of the mothers during pregnancy are presented in figure 1a. As expected, trait anxiety ratings of the mothers during the 12$^{th}$ to 22$^{nd}$ week of pregnancy were significantly different between groups ($p<0.001$). No significant group differences were observed in other characteristics of the tested subjects or their mothers ($p's>0.23$).

No significant group differences were observed in the slopes for dyspnea intensity in the first, single-breath MET (HS: 0.17 ± 0.06; LS: 0.15 ± 0.07; $p=0.53$; figure 1b) and in the second, five-breath MET (HS: 0.20 ± 0.03; LS: 0.16 ± 0.08; $p=0.30$; figure 1c). However, the HS group demonstrated significantly higher slopes for dyspnea unpleasantness than the LS group (HS: 0.20 ± 0.03; LS: 0.15 ± 0.08; $p<0.01$; figure 1d). In addition, the slopes for dyspnea unpleasantness showed a significant positive correlation with maternal stress levels ($rho=0.34$, $p<0.05$; figure 1e), but not with other variables of the subjects or their mothers ($rho's<0.30$, $p's>0.06$).

The present results suggest that prenatal exposure to maternal stress is associated with increased perception of dyspnea, especially its affective unpleasantness, in adulthood 28 years later. This is in line with previous human and animal studies demonstrating that adverse early life experiences such as being exposed as a fetus to maternal stress, is related to the development of health- and behavioral problems later in life [4–9]. However, the specific underlying mechanism for the association between prenatal stress exposure and dyspnea perception in adulthood observed in the present study remains unclear.

Several potentially contributing factors pertaining to current characteristics of the tested subjects [1,2] including lung function, age, weight, height, gender, general and dyspnea-specific anxiety levels as well as somatic symptom burden were unrelated to the present findings. Similarly, potential factors related to pregnancy [5,7] such as duration of pregnancy, birth weight and maternal consumption of cigarette smoke, caffeine and alcohol during pregnancy were not related to the present findings. Therefore, future studies are required to test further potential mechanisms that might underlie the observed association between early life adversity and perception of dyspnea later in life. These studies might include measures of the autonomic nervous system, the hypothalamic–pituitary–adrenal (HPA)-axis, the endogenous opioidergic and chemosensitive systems as well as functional and structural measures of the brain, which have not only been suggested to be impacted by prenatal stress exposure [5–8], but are also involved in the processing of dyspnea [2,3,9].

Future studies should also address the limitations of the present study such as the rather small sample size, which is partly related to the relatively small original cohort. Moreover, the use of inspiratory threshold loads for the experimental induction of transient dyspnea sensations only mirrors some facets of dyspnea (ie, ‘increased work and effort of breathing’) [1,2], and might not be fully comparable to other, more sustained dyspnea experiences outside the lab. Finally, our findings in healthy, younger adults might not be generalizable to patients that frequently experience dyspnea, especially when paralleled by older age such as commonly observed in COPD. Therefore, studies are needed that examine the role of early life adversity on dyspnea perception later in life in dyspneic patients with respiratory, cardiovascular and neuromuscular diseases. If the present findings replicate in these future studies, it would not only improve our knowledge on potential mechanisms involved in dyspnea perception, but also warrant interventions to reduce maternal stress in pregnancy in order to decrease

symptom burden in future patients with dyspnea.

In summary, prenatal exposure to maternal stress is associated with increased perception of dyspnea in adulthood in healthy subjects. Future studies are needed to examine the underlying mechanism for this association and the respective effects of early life adversity in patients suffering from dyspnea.

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**Figure legends**

**Figure 1.**

a) Characteristics of subjects with exposure to low prenatal stress and high prenatal stress including data of their mothers during pregnancy. Whereas trait anxiety ratings of the mothers during the $12^{th}$ to $22^{nd}$ week of pregnancy are significantly different between groups, there are no significant group differences in other characteristics.

Perceptual sensitivity for dyspnea expressed as group means (SE) for individual regression slopes (Borg scores against load resistance) for b) dyspnea intensity during the single breath MET, c) dyspnea intensity during the five-breath MET and d) dyspnea unpleasantness during the five-breath MET. e) Significant correlation between perceptual sensitivity for dyspnea unpleasantness during the five-breath MET (Borg scores against load resistance) and maternal stress levels (STAI) during the $12^{th}$ to $22^{nd}$ week of pregnancy.

$FEV_1$ = forced expiratory volume in 1s;

[#]analyzed with $\chi^2$-test;

[a]measured with STAI (State-Trait-Anxiety-Inventory);

[b]measured with BCS (Breathlessness Catastrophizing Scale);

[c]measured with PHQ-15 (Patient Health Questionnaire);

**$p < 0.01$.