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Stress Test Performance by Preterm-Born Females in Adolescence and Adulthood

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A total of 70 girls (aged 12.2±1.5) who had been born preterm (34.7±1.86 weeks) were tested in 1997. Of those, after a gap of 18 years, a group of 13 as successfully re-contacted and participated in the 2015 examination as adults (then aged 27.6±2.60 years, born preterm at 34.5±2.0 weeks). Each time, an indirect HR test was performed (W150 test) while striving to maintain HR=150 bpm; the level of physical load (W) therefore depended only on physical fitness and exercise tolerance. In the group of adolescent girls, the rate of stress oxygen uptake (O_2) and the metabolic stress response were measured by using the Jaeger ErgoOxyscreen apparatus. In the adult group, the VO_2max rate was measured.

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Stress Test and Preterm-Born Females

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A total of 70 girls (aged 12.2±1.5) who had been born preterm (34.7±1.86 weeks) were tested in 1997. Of those, after a gap of 18 years, a group of 13 as successfully re-contacted and participated in the 2015 examination as adults (then aged 27.6±2.60 years, born preterm at 34.5±2.0 weeks). Each time, an indirect HR test was performed (W150 test) while striving to maintain HR=150 bpm; the level of physical load (W) therefore depended only on physical fitness and exercise tolerance. In the group of adolescent girls, the rate of stress oxygen uptake (O_2) and the metabolic stress response were measured by using the Jaeger ErgoOxyscreen apparatus. In the adult group, the VO_2max rate was measured.

In adolescence, no difference was found between the study group and the reference group. In adulthood, however, the prematurely born adults demonstrated significantly lower values of VO_2max and total work performed in relation to the reference group, pointing to a decline in physical fitness in the study group.

Conclusions: 1. During puberty, prematurely born adolescents display better aerobic metabolism and higher rates of total work performed than their peers born at term. 2. There was a significant decrease in the level of physical fitness in the adult study group. 3. It is recommended to continuously monitor the level of exercise tolerance in prematurely born individuals at different stages of life.

I. Introduction

Preterm birth, defined as birth prior to 37 completed weeks of gestation and generally associated with low birth weight, is a widespread phenomenon, accounting for 5% to 9% of all births in Europe [1], and more than 12% of all births in the United States [2], with similar high rates in Africa and southern Asia [3]. Although morbidity is still significant among very low birth weight infants, numerous technological advances, collaborative efforts between obstetricians and neonatologists, widespread use of antenatal corticosteroids, surfactant therapy, and high-frequency ventilation have all helped improve survival rates over the past two decades [4-6]. Since individuals who were born preterm are now more likely to survive into adulthood than before, a comprehensive understanding of the impact of premature birth in adulthood is therefore needed to enable earlier prevention, detection, and treatment of its long-term health sequelae. However, such information is largely lacking from the literature; most studies of the impact of premature birth have examined subjects only in childhood.

Physical fitness is always conditioned by numerous factors, and this even more so in the case of developmental disorders (such as those resulting from premature birth). For instance, respiratory and circulatory capacities depend on the maximum oxygen uptake (VO_2max) and, as such, full lung maturation is of paramount importance in determining physical fitness [7]. Premature infants generally have difficulty breathing due to a reduced number of alveoli and underdeveloped pulmonary capillaries [8]. Such pathological conditions at an early age may result in diminished lung function later in life, including in terms of lung volume, ventilation homogeneity, and the mechanics of the respiratory system, which will in turn detract from physical fitness [9-12]. Alongside the respiratory system, the circulatory system also plays a significant role in the development of the child's physical fitness. Both systems are involved in the process of gas exchange through the blood. In premature babies, the circulatory system may experience a delayed closure of the ductus arteriosus and the pulmonary vascular resistance may be diminished after birth; this condition (patent ductus arteriosus or PDA) significantly impairs the respiratory function and hemodynamic conditions of premature infants.

The literature on exercise tolerance focuses mainly on preterm-born children in the early years of their lives, generally not proceeding beyond age ten. As such, it has yet to be determined whether premature birth is also associated with reduced physical fitness

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later in life. However, despite consistent findings concerning poor lung function, few studies have addressed exercise tolerance in low birth weight populations [13-16]. Authors have reported decreased [13,14] or relatively normal [15,16] peak VO_2 values in young prematurely born children. Contrary to these finding, in another study we previously reported finding an improvement in exercise tolerance in cohorts of preterm born children in adolescence [17]. Data concerning adults who were born prematurely are scarce, as there have been few longitudinal or follow-up studies extending into adulthood. Clemm et al. [18] compared the exercise capacity of adults born at term and EP, addressing the developmental patterns from adolescence to adulthood (18 to 25 years old) and reporting that exercise capacity was slightly lower in EP-born adults; however, those values were within a normal range, positively associated with self-reported physical activity, and unrelated to neonatal factors and current airway obstruction.

The aim of the present study, therefore, was to explore the long-term effect of prematurity by examining the stress-test performance of subjects at age 12, then to re-examine a portion of the same subjects at the age of 30, using same examination setup, and to compare the results against those of a reference group. The strength of the relationship between anthropometric parameters (height and weight, BMI) and physical fitness, as well as estimated oxygen uptake were also analyzed.

II. Material and Methods

a) *Participants*

Individuals participating in the study group for both stages of our study were females who had been registered at the Premature Birth Clinic, Rehabilitation Department, Institute of Mother and Child in Warsaw, as having been born with low birth weight, i.e. below 2,500 g, or born preterm, i.e. prior to 37th week of pregnancy (though with normal birth weight). The total work performed by the subjects on an exercise test was evaluated twice: once in 1997 (puberty) and again in 2015 (adulthood). An additional criterion for inclusion of preterm-born individuals in both states of the study was a normal resting ECG.

In the first stage, in 1997, total of 70 preterm-born girls aged 10-14 years (12.22±1.52 years) took part in the examinations (the results of which have not been previously published). The mean birth weight of among this the group was 1,865.8±566.3 g (min. 1,040 g, max. 2,580 g), and they were born in the 34.5±1.92 week (min. 32 weeks, max. 36 weeks). All of the subjects who ended up selected based on the above criteria, therefore, were all under 2,500 g birthweight and all born prior to 37th week of pregnancy. Most of the study group (85%) had been fed on formulas as infants, whereas two had been fed on a combination of infant formula and breast milk. On the basis of their health records, none of the subjects had experienced BPD.

Eighteen years later, we attempted to reestablish contact with all of the 1997 participants by twice sending out a request letter to their previously recorded residence. Only 13 of the original participants responded and agreed to undergo reexamination in 2015. The study group participants in 2015 had a mean birth weight of 1,864.6±533.7 g (min. 1,040 g, max. 2,580 g) and were born at 34.5±2.0 weeks (min. 32, max. 36) of pregnancy.

Note that, in fact, both boys and girls had been examined in the 1997 stage of the study, for which all prematurely born and/or low-birth-weight children registered with the above-mentioned clinic who met the criteria for the study had been recruited. However, the 13 participants who ultimately agreed to participate in the follow-up stage later turned out to be exclusively female; as such, we were able to analyze and report long-term results exclusively for the female group. This sample size of 13 participants for the latter, follow-up stage, while admittedly quite small in absolute terms, still represents a considerable achievement given the long time-frame involved and the relative scarcity of such long-term data in the literature.

This study group was in each case compared against a reference group of their peers, consisting of 48 girls (12.4 ± 1.52 years) in the first stage, and of 27 women (28.3 ± 2.16 years) in the second, made up of girls and women from the province including Warsaw and its environs (the Mazowsze Voivodship), born at term, at ages corresponding to the test group. To compensate for social variables, the reference group was in each case recruited by asking the study participants (or their guardians) to invite their peers born at term and weighing more than 2,500g to take part in the study.

The basic parameters of the two groups are presented in Table 1. All participants were informed about the conditions and course of the study, and written informed consent was expressed for participation in the research (either from the legal guardians of the children or by the adult participants themselves). The study received the approval of the Ethics Committee at the Józef Piłsudski University of Physical Education in Warsaw (decision no. SKE 01-47/2012).

Table 1: The mean values and standard deviation for body weight, body height and BMI in 1999 and 2015

1998	Reference (n=48) Mean±SD	Preterm (n=70) Mean±SD
Body weight (kg)	42.09±9.82	42.16±11.80
Body height (cm)	149.84±9.56	149.31±9.47
2015	**Reference (n=29) Mean±SD**	**Preterm (n=13) Mean±SD**
Body weight (kg)	62.7±9.08	60.08±14.66
Body height (cm)	167.8±5.6	163.00±10.08
BMI	22.23±2.48	22.55±4.53

b) Study Methods

Two stress-test examinations were carried out at an interval of 18 years, the first stage in 1997 and the second in 2015. All measurements were performed in the early hours of the morning at a diagnostic facility of the Central Laboratory at the University of Physical Education in Warsaw. Tests were performed at least two hours after the last meal. In each case indirect HR test (W150 Test) was performed using an ERGOTEST device, based on the original W150 program [19]. Physical load values were determined by the computer using feedback (load/HR); this results in the induction of cyclometer resistance at a certain level, forcing the achievement and maintenance of physiological balance at HR=150 bpm (control level) to evaluate aerobic metabolism. The test uses a linear relationship between the frequency of the heart rate and oxygen uptake. The effort was dispensed on a bicycle ergometer Pro Med Medical Systems with a foot drive, heart rate were recorded and measured electronically using precordial electrodes (transmitter BMI- USBD1- EU- S/N 054BM/S300). One of the criteria for qualifying was a normal resting ECG. As the test was underway, for the study group individuals (preterm-born) their ECG was monitored by a physician (Nõrava S-stress, Oxford Poland).

Before undergoing the exercise test, participants were subjected to a preliminary assessment of exercise capacity using the Ruffier test, which included measuring their blood pressure and heart rate (Dura Schock Welch Allyn sphygmomanometer). Warm-up was performed on an ergometer driven by lower limbs for 10 minutes, with a load of 1W/kg of the subject's body weight. Heart rate during warm-up did not exceed HR=130 bpm. After the warm-up stage and recovery period, the proper testing began.

Tests were carried out in the presence of a physician, and were explained to the participants before they began. The period of exercise lasted 10 minutes, followed by a recovery period lasting until the participant's HR returned to pre-test level. The physical-challenge method applied (also used in the 1997) assumes the maintenance of the heart rate on control level of HR=150 bpm; load regulation is based on the individual reactions of the cardiovascular system, with the load level (W) being adjusted as necessary during the exercise and with pedal cadence ranging from 50 to 60/min. The load level therefore depended only on the subject's physical fitness and exercise tolerance.

During the exercise test the following parameters were recorded: HR, total work performed during the test, power necessary to achieve the control level (HR=150 bpm), average power for the control period (measured from the moment of attaining HR=150 bpm until the end of the test), and the time it took to achieve the control level (HR=150 bpm). At the completion of the test in the adult group the VO_2max rate was automatically calculated. In the group of adolescent girls, the rate of oxygen uptake and the metabolic stress response were measured using the Jaeger ErgoOxyscreen apparatus.

Fig. 1: Record of HR test (HR and power exerted)

The test was halted for in the event of any adverse cardio-respiratory reactions or signs of exercise intolerance, such as dizziness, shortness of breath, pallor, chest pain or imbalance.

Statistical analysis

The data was processed and all statistical calculations were made using STATISTICA 12.0 by StatSoft, according to the software instructions. The results were presented as arithmetic means ± standard deviation. The Shapiro-Wilk test was used to evaluate the normality of distributions, and the Pearson correlation coefficient was used to measure the dependency between the parameters.

The variables were compared between the groups using a non-parametric test (the Mann- Whitney U test adjusted for continuity). The ANCOVA test (from the General Linear Model) was used to exclude a covariate (weight) in group comparisons. Because the distribution was not found to be normal, the Mann-Whitney U test was used. The threshold for statistical significance was taken to be $\alpha=0.05$.

III. Results

Among the variables considered in the first study (adolescent period), no significant differences were found between the study group and the reference group in terms of the parameters indicative of exercise tolerance at the peak of oxygen uptake – i.e. O_2 [L/min] at HR=150 bpm and the total work performed W [kJ]. The total work performed, however, was found to differ significantly between the study and reference groups of adults ($p<0.001$). Similar differences were observed in the VO_2max rate, with the adult reference group presenting significantly higher levels of VO_2max than their peers born prematurely ($p<0.001$). This indicates that adult women born prematurely do have a lower exercise tolerance.

Table 2: Total work (kJ) and aerobic metabolism VO_2max rates [L/kg body weight] and O_2 [L/min] in the reference and preterm groups tested in 1998 and 2015

Factor	Preterm group 1998 (n=70)	Reference group 1998 (n=48)	Preterm group 2015 (n=13)	Reference group 2015 (n=29)
Work [kJ]	26.94±9.40	25.79±8.74	46.18±6.90	56.66 ±11.12*
O_2[L/min]/	1.57±0.40	1.61±0.70		
VO_2max [L/kg body weight]			1.66±0.35	2.30±0.16

We considered that the total work value could be dependent on body weight, and so performed an ANCOVA analysis with covariate. The results indicated that the body weight did not affect the significant differences in the total work performed between the groups ($F = 8.97$; $p = 0.004749$; $\eta = 0.1869$). The test power was 0.83.

Table 3: Correlations between total work and body weight, body height, BMI and VO_2max in adult groups

Correlations	Reference group 2015 (n=29)	Preterm group 2015 (n=13)
Total work/Body weight	0.02	-0.18
Total work/Body height	0.23	0.05
Total work/BMI	-0.10	0.16
Total work/VO_2max	0.71	0.86

No strong correlation (understood as $p \geq 0.5$) was found between the total work and body weight, between the total work and body height, or between the total work and BMI. The correlation between the total work and VO_2max, on the other hand, at $p \geq 0.5$, is consistent with the exercise response of healthy individuals (the greater the work performed, the higher the VO_2max rate).

IV. Discussion

In this study, we sought to trace the long-term impact of preterm birth on physical fitness into puberty and later into adult life. Such long-term consequences of preterm birth are complex and notoriously problematic to study, particularly in maintaining the same group of subjects over a prolonged period of time. A major strength of our study, therefore, was its longitudinal design.

However, maintaining the participation of test subjects from childhood through adulthood is indeed challenging, and we were only able to recruit relatively few participants (13 out of 70, or 19%) to persuade them to take part in the follow-up stage of the study. The original participants who did not participate in the follow-up examination may have done so for any of a variety of reasons, including change of residence in the interim, failure to receive the request letter, unwillingness or inability to participate, lack of interest, etc. Even so, given the relative scarcity of longitudinal data of this sort, we still do consider it a success to have managed to re-examine this sizeable of a share of the original group after such a time gap, and the proportion of re-participation we achieved is nevertheless comparable to those reported in most similar studies [13,15,20]. Moreover, the magnitude of the effect we found was large (eta2>0.18), which ensured sufficient observed strength of the test (Power>0.80). This power analysis indicates that the sample size was sufficient to evaluate the phenomenon studied.

Most previous studies of children and adolescents, by contrast, have been cross-sectional [14-16, 21]. Vrijlandt et al. [16] found a mildly lower exercise capacity in a group of preterm individuals occurring in young adulthood, as compared to healthy, reference-group subjects. Moreover, their study group showed significantly lower anaerobic threshold than their healthy peers, and tended to have lower work efficiency. However, this might stem from less intensive participation in sporting activities, rather than impaired lung function or limited ventilation. Kriemler et al. [15] reported that children with and without respiratory abnormalities have some degree of pulmonary dysfunction at rest and following exercise, and a higher prevalence of exercise-induced bronchoconstriction with no reduction in maximal aerobic exercise performance. The higher oxygen uptake seen at a given mechanical power in the preterm group may cause early fatigability during prolonged exercise, even when aerobic performance is normal. Rogers et al. [14] reported significant differences between low birth weight adolescents and term-born reference subjects in terms of lower aerobic capacity, strength, endurance, flexibility, and activity level. This again could be the result of less intensive participation in physical activity and consequential physical limitations, such as neurodevelopment, sensory (visual and auditory deficits), respiratory and cardiovascular impairments, reduced muscle strength, coordination difficulties and social acceptance.

Our results, on the other hand, differed from those reported in these studies: in our study group, preterm-born subjects at puberty actually achieved better results of total work and peak oxygen uptake with heart rate maintained at 150 bpm than their peers born at term. These results indicate that, when it comes to submaximal exercise, the physical functions of the preterm children we studied were not impacted by developmental limitations in the first years of life. Of course, it could have been of more significance to study the exercise VO_2max rate in order to assess the children's physical capacity, but due to the state of health of preterm-born children and the difficulty in motivating them to engage in this type of test, maximal exercise loads were not used.

On the other hand, in our the second, follow-up testing of part of the same preterm-born subjects in adult age, we found that, to the contrary, participants performed significantly worse in terms of exercise tolerance than their peers from the reference group. This finding suggests that the evolution of physical fitness and the consequences of prematurity need to be closely monitored into later stages of life. To our knowledge, there is only one publication that addresses the developmental trajectories of exercise tolerance from adolescence to adulthood: Clemm et al. [18]. In their study of 25-year-old adults born EP, they found that exercise tolerance was 10% lower than in a reference group born at term, albeit still within a range considered normal. A decreasing trend in exercise tolerance from 18 to 25 years of age was similar in both groups, and the VO_2 peak obtained at age 18 strongly predicted the VO_2 peak at age 25. Exercise tolerance was unrelated to neonatal factors and to current airway obstruction, but was positively associated with self-reported physical activity. Our results similarly show that participants in the study group performed 22% less work than the reference group. The physical load causing the same physiological response (maintaining HR at 150 bpm) was significantly lower in the case of the study group.

In comparing our results for the study group at adulthood to those obtained during at puberty, we can conclude that the anticipated deficits in their level of exercise tolerance in comparison to healthy peers nevertheless did manifest themselves in adulthood, despite having been compensated for and even improved upon during puberty (when preterm-born subjects fared 5% better than their healthy peers). Like other authors [18], we should note that this could be attributable to a failure to maintain normal levels of physical activity after puberty due to insufficient medical supervision and reduced parental control, but at the same time we cannot rule out the late consequences of abnormal morphological and functional development in childhood due to premature birth. Overall, premature birth contributes to increased risk of cognitive, sensory, neuromotor and coordination deficits, which can interfere with the development of exercise tolerance. Less intensive physical activity may also result from real or perceived limitations and weaknesses, leading to the reinforcement of negative attitudes towards exercise, and this in turn may have adverse effects on exercise tolerance [16, 22, 23].

Baraldi and Filippone [24], however, disagree with this reasoning, arguing that early lung damage may itself have long-term consequences. Chronic lung disease cannot be considered solely as a pediatric illness because it is likely to continue into adulthood and increase the risk of acquiring chronic obstructive pulmonary disease (COPD), as well as have a negative impact on the results of pulmonary function testing. Walter et al. [25] draw similar conclusions, having found a higher risk of lung dysfunction in a group of adults born prematurely with low birth weight in relation to their peers born at term. There are few studies in the literature on the effects of cardiovascular disorders resulting from premature birth on exercise tolerance. Lewandowski et al. [26] performed an MRI on 234 individuals, and found increased left ventricular mass in young adults born prematurely, compared to the reference group. Changes in the geometry of the heart were accompanied by abnormal hemodynamic parameters. The authors argue that these disorders may consequently lead to reduced exercise tolerance, and may be associated with an increased risk of cardiac events.

In general, the long-term consequences of premature birth remain not well documented, but it is becoming clearer that its complications do not only affect individuals in childhood. As the results of our study indicate, despite the fact that subjects born prematurely had much better performance results in adolescence than their peers in the reference group, later in life their exercise tolerance decreased and the same individuals fared worse as adults than those in the reference group. Therefore, the exercise tolerance preterm-born individuals needs to be measured at different stages of life, not only during puberty. Further research in this direction may help us better understand the complex, longer-term developmental trajectories of preterm-born individuals.

V. Conclusions

1. During adolescence, prematurely born subjects displayed better aerobic metabolism and higher rates of total work performed on a stress test than their peers born at term.
2. A subset of the same group of subjects nevertheless showed a significant decrease in the level of exercise tolerance in adulthood, as compared to their peers born at term.
3. It is recommended for the level of physical fitness in prematurely born individuals to be continually monitored at different stages of life.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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