

Are preterm-born survivors at risk of long-term respiratory disease?

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Abstract

Background: To evaluate the long-term impact of preterm birth on respiratory function in female patients born preterm, we undertook spirometric examinations twice, as they reached the age of puberty, then follow-up examinations of part of the same cohort in adulthood. We sought evidence that preterm birth is correlated with poorer spirometric results into adulthood.

Methods: A total of 70 girls (aged 12.2 ± 1.5 years in 1997) who had been born preterm (at 34.7 ± 1.86 weeks, none having experienced bronchopulmonary dysplasia) took part in spirometric examinations in 1997 and again in 1998. Of those, after a gap of 17 years, a group of 12 were successfully recontacted and participated in the 2015 examination as adults (then aged 27.6 ± 2.6 years, born at 34.5 ± 1.92 weeks). We compared spirometric results across the adolescent and adult examinations, and compared the adult results with an adult reference group.

Results: The percentage values of FEV₁ (forced expiratory volume in 1 s), FVC (forced vital capacity) and MVV (maximal voluntary ventilation) showed significant improvement between the two examinations in the early adolescent period. In adulthood, FEV₁%pred (percentage predicted forced expiratory volume in 1 s) showed no statistically significant difference. The mean values of both FVC and FVC%pred (percentage predicted forced vital capacity) for the preterm-born group were lower than for the reference group, but this was not statistically significant. The preterm-born group showed lower values of such parameters as forced expiratory flow at 25–75% of FVC, MEF₂₅ (maximal expiratory flow at 25% of forced vital capacity) and FEV₁/FVC as compared with the reference group, but again without statistical significance.

Conclusions: (1) A somewhat below-norm level of respiratory parameters among preterm-born girls entering pubescence may attest to continued negative impact on their respiratory system.

(2) A significant improvement in their spirometric results 1 year later may indicate that pubescence helps compensate for the earlier negative effect of preterm birth.

(3) No significant differences were seen in lung function in preterm-born adults as compared with a reference group of adults, although the preterm-born group did exhibit lower values of all parameters studied and more frequent obstructive disorders.

Keywords: lung physiology, preterm, pulmonary function, spirometric measurements

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Introduction

Preterm birth, defined as birth prior to 37 completed weeks of gestation and generally associated with low birth weight, is increasingly widespread, now accounting for 5–9% of all births in Europe¹ and more than 12% in the

United States.² Although morbidity is still significant among infants born preterm, numerous technological advances, collaborative efforts between obstetricians and neonatologists, widespread use of antenatal corticosteroids, surfactant therapy, and high-frequency ventilation

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have all helped improve survival rates over the past two decades.^{3,4} However, the increasing numbers of preterm infants now surviving into later life may experience a complex set of long-term negative impacts,³ including neurodevelopmental impairments and sensory deficits,⁵⁻⁷ lower weight and shorter height^{8,9} increased risk of obesity, hypertension, type-II diabetes and cardiovascular disease,¹⁰ and higher blood pressure.¹¹⁻¹⁴ Many of these studies have examined subjects in childhood, with few extending to follow up in adulthood.

One of the most important impacts of premature birth is poorer lung function.¹⁵⁻¹⁷ Lung development in preterm infants is interrupted during the sacular phase of the normal maturational process taking place *in utero*, as a result of which the respiration of preterm infants is compromised by the anatomic immaturity of the lungs, impaired or delayed surfactant synthesis, underdeveloped chest anatomy, and inefficient clearing of lung secretions. These factors may cause edema of the pulmonary interstitium, disruption of alveolar capillary membranes, damage to alveolar spaces and inadequate gas exchange immediately after birth.¹⁸ Moreover, 40% of low birth-weight survivors contract bronchopulmonary dysplasia (BPD).¹⁹ Prolonged mechanical ventilation and oxygen supplementation treatment may contribute to irreversible damage of lung parenchyma and small airways.¹⁷ These pathological changes at early age may contribute to diminished lung function: lung volume, ventilation homogeneity, and respiratory system mechanics.²⁰⁻²³

A number of studies have reported that children who were born preterm exhibit higher rates of respiratory illness, lower respiratory flow rates, reduced diffusing capacity for carbon monoxide and increased airway reactivity than peers born at term. However, little is known about any long-term consequences of respiratory impairment, as follow-up studies on lung function have been limited mainly to the childhood and sometimes adolescent period.^{24,25} The few papers that do report attempts at follow up into adulthood in this respect argue that there does exist a statistical difference in lung function between subjects born at full term and those born at less than 37 weeks' gestation.^{26,27} It is true that adults who were born preterm are more likely to report such respiratory symptoms as wheezing or recurring infection, and studies have shown an inverse proportionality

between gestational age and frequency of respiratory symptoms reported by adults who were born preterm. It has also been shown that among adults diagnosed with asthma, chronic obstructive pulmonary disease (COPD) or who experienced chronic lung disease (CLD) in childhood, a statistical majority were born preterm. In the above cases, the respiratory system changes are of an obstructive nature.^{16,17,28,29}

The goal of our study, therefore, was to evaluate the long-term impact of preterm birth on selected respiratory functions in both early adolescence and adulthood, and also (to the extent possible with just three examinations), to attempt to trace the trajectory of that impact over time. We did so by performing a follow-up examination of part of the same group of adult subjects born preterm who had previously been given two spirometric examinations, spaced 1 year apart, at our facility around the age of puberty. Specifically, we sought evidence that preterm birth was statistically correlated with poorer spirometric results into adulthood.

Material and methods

Experimental group

The individuals participating in both stages of our study were recruited among females who had been registered by the Premature Infant Clinic, Rehabilitation Department, Institute of Mother and Child in Warsaw as having been born with low birth weight, that is, below 2500 g, or born preterm, that is, prior to 37th week of pregnancy (despite correct birth weight). Their lung function was tested three times in 1997 and 1998 (around the age of puberty) and once again in a follow-up stage in 2015 (adulthood).

In the first stage of the study, a total of 70 girls aged 10–14 (12.22 ± 1.52 years in 1997) took part in the 1997 and 1998 examinations (the results of which have not been previously published). In this group, participants were born at 34.7 ± 1.86 weeks (minimum 32, maximum 36 weeks) of pregnancy.

At 17 years later, we attempted to re-establish contact with all of the 1997–1998 participants by twice sending out a request letter to their previously recorded residence. Only 13 of the original participants responded, and 12 ultimately underwent re-examination in 2015 (one

Table 1. Basic parameters for preterm-born group *versus* reference group.

	Preterm born 1997 (<i>n</i> = 70)	Preterm born 1998 (<i>n</i> = 70)	Preterm born 2015 (<i>n</i> = 12)	Reference 2015 (<i>n</i> = 27)
Height (cm)	145.32 ± 9.96	149.31 ± 9.47	162.9 ± 10.2	167.5 ± 5.6
Body weight (kg)	38.24 ± 11.98	42.16 ± 11.80	60.1 ± 14.77	61.8 ± 6.7
BMI (kg/m ²)	17.8 ± 3.79	18.6 ± 3.30	22.6 ± 4.62	22.0 ± 1.80
Chest circumference inhaled (cm)	70.92 ± 7.33	74.11 ± 6.91	82.2 ± 9.57	81.6 ± 6.14
Chest circumference exhaled (cm)	66.47 ± 8.52	69.22 ± 7.12	75.3 ± 9.11	74.1 ± 5.94

BMI, body mass index.

individual responded and agreed to participate but was unable to perform the 2015 spirometric examination). In this group, participants were born at 34.5 ± 1.92 weeks (minimum 32, maximum 36 weeks) of pregnancy.

Note that in fact, both boys and girls had been examined in the 1997–1998 stage of the study that recruited all prematurely born children registered with the above-mentioned clinic who met the criteria for the study. However, the 12 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. The sample size of 12 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.

Interviews indicated that most of the preterm-born adults (85%) had not been breastfed as infants; two further individuals had been fed a mixture of breastmilk and formula. The medical history of none of these individuals indicated they had undergone BPD as infants (bronchopulmonary dysplasia, defined as the need for oxygen or respiratory support at 28 days after birth).

This preterm-born group of adult women was then compared against a reference group consisting of 28 adult women of similar age to the preterm-born group (28.3 ± 2.16 years in 2015) likewise born in the province of Warsaw and its environs, but born at term and with birth weight greater than 2500 g. Members of the reference group were recruited by asking participants in the preterm-born group to suggest acquaintances who met the above criteria for inclusion. None of

the women recruited for the reference group reported any chronic respiratory condition.

The basic parameters for the two groups are presented in Table 1. The subjects were informed about the examination and about the purpose of the study, and provided written confirmation of their consent to take part. The study was approved by the Ethics Committee of the Academy of Physical Education, Warsaw (decision no. SKE 01-47/2012). Written consent for participation was expressed either by the legal guardians of the children (1997–1998) or by the adult participants themselves (in 2015).

Research method

The examinations of lung function and thoracic mobility reported here were carried out in two stages. The first stage involved an examination session in 1997 coupled with another in 1998, while the second stage involved one examination session in 2015. All measurements were taken in the morning hours at a diagnostic center in the Central Laboratory of the Academy of Physical Education, Warsaw. Each session consisted of two exams: free spirometry and expiratory flow-volume curve. All measurements were taken in accordance with the guidelines of the European Respiratory Society and American Thoracic Society.³⁰

For the first and second sessions, spirometric measurements were taken using a Lungtest 1000/MES spirometer (MES LLC, Cracow, Poland), whereas for the third a portable Lungtest Handy (MES LLC, Cracow, Poland) was used. The first and second examinations recorded the following parameters: VC (vital capacity), FEV₁ (forced expiratory volume in 1 s) and MVV (maximal voluntary ventilation). The third recorded the parameters: VC, FEV₁, FVC (forced vital capacity), MMEF (maximal

mid-expiratory flow) and forced expiratory flow at 25–75% of forced vital capacity (FEF_{25–75}), MEF₇₅ (maximal expiratory flow at 75% of forced vital capacity), MEF₅₀ (maximal expiratory flow at 50% of forced vital capacity), MEF₂₅ (maximal expiratory flow at 25% of forced vital capacity). After completion of the examination, the results in the form of absolute parameters FEV₁, FVC, FEF_{25–75}, MEF₂₅ and data on race, sex, age, and height of the participant were entered into the ECSC (European Coal and Steel Community) calculator (for 1997 and 1998 data) or GLI 2012 (Global Lung Function Initiative, Berlin, Germany) calculator (for 2015 data), yielding a percentage of the norm for healthy children.³¹ On this basis, the following parameters were calculated: FEV₁pred, FEV₁LLN, FEV₁Z, FEV₁%pred, FEV₁%tile, FVCpred, FVC-LLN, FVC Z, FVC%pred, FEV₁%tile, FEF_{25–75}pred, FEF_{25–75}LLN, FEF_{25–75}Z, FEF_{25–75}%pred, FEF_{25–75}%tile, FEV₁/FVC, FEV₁/FVCpred, FEV₁/FVC-LLN, FEV₁/FVC Z, FEV₁/FVC%pred, FEV₁/FVC%tile, MEF₂₅, MEF₂₅pred, MEF₂₅LLN, MEF₂₅Z, MEF₂₅%pred, MEF₂₅%tile, and MVV%pred (where ‘pred’ stands for predicted value, ‘%pred’ for percentage of predicted value, ‘%tile’ for percentile, and LLN for lower limit of normal, and ‘Z’ for Z score, the number of standard deviations the measured value differs from the predicted value). An obstructive spirometric condition was defined as FEV₁/FVC < LLN, a restrictive condition as FVC < LLN and FEV₁/FVC > LLN. Also measured for each subject were the anthropometric parameters of the chest after deep inhalation and exhalation.

Statistical analysis

The data were processed and all statistical calculations were made using STATISTICA 12.0 by StatSoft (Cracow, Poland), in keeping with the instructions for the software. For both the preterm-born and reference groups, the values of each spirometric parameter, the percentage of the benchmark value and the percentile were analyzed. The results of the examinations from 1997 and 1998 were compared with the population norms. The preterm-born group from 2015, in turn, was compared with a reference group in terms of age, height, chest mobility and spirometric parameters. The results were presented as arithmetic means ± standard deviation. The Shapiro–Wilk test was used to measure the normality of distributions, and the Pearson correlation coefficient was used to measure the dependency between the parameters.

The quantitative variables were compared between the groups using parametric tests. When the distribution of a parameter was normal in each of the groups compared, Student’s *t* test was used when the variances were equal, and the Cochran–Cox test when they were not. When the distribution was not normal, the Mann–Whitney *U* test was used. The threshold for statistical significance was taken to be $p < 0.05$.

Results

Results from puberty (exams in 1997 and 1998)

The results of the two examination sessions, 1 year apart for the preterm-born group at adolescence are shown in Table 2.

FVC, expressed as a percentage of the norm for healthy children (FVC%pred), was 95.4% in the first examination but 102.0% 1 year later; the difference proved to be statistically significant ($p < 0.001$).

Analyzing the FEV₁ among this group, a slight increase of 0.2 l/s was noted between the first and second examinations, while the maximal results varied from 3.7 to 4.0 l/s. The percentage values for this parameter (FEV₁pred) put the mean at 93.8% of the norm for the first examination, but at 100.70% for the second. The percentage values for FEV₁ improved between the two examinations, at a statistically significant level ($p < 0.001$).

Maximal voluntary ventilation (MVV) was also found to rise in the study group, with a statistically significant increase rise of 13.40 l/min in mean MVV between the first and second examination sessions. The percentage values for this parameter, which indirectly gauges the predisposition for maximal exercise, increased from 138.5 l/min. to 155.5 l/min. No correlation was found within the study group between anthropometric parameters and either birth weight or gestation week of birth.

Results from adulthood (in 2015)

The results of the much later, third examination session involving one part of the same preterm-born group and an appropriately selected reference group are shown in Table 3. As for anthropometric parameters, no significant differences were found between the preterm-born and

Table 2. Anthropometric and spirometric results from examination sessions one and two for the preterm-born group (in adolescence).

	Examination one <i>n</i> = 70					Examination two <i>n</i> = 70					<i>p</i>
	Mean	SD	Med	Min	Max	Mean	SD	Med	Min	Max	
Age	12.5	1.52	13.0	10.0	14.0	13.5	1.52	14.0	11.0	15.0	0.001
Height	145.3	9.95	148.0	127.0	166.0	149.3	9.47	148.0	134.0	168.0	0.001
Weight	38.2	11.98	33.8	26.0	84.0	42.2	11.8	38.5	29.0	84.0	0.001
Chest mobility	4.83	1.79	5.00	2.00	8.5	4.89	1.47	5.00	2.00	8.50	0.66
Chest circumference exhaled	71.1	7.46	70.0	59.0	91.0	74.1	6.91	72.0	61.0	94.0	0.001
Chest circumference inhaled	66.3	8.30	64.5	54.0	89.0	69.2	7.12	67.8	58.0	91.5	0.001
FEV ₁ %	93.8	21.1	96.9	38.0	131.9	100.7	23.6	98.0	40.0	142.1	0.001
FVC%	95.4	18.24	96.5	62.0	130.8	102.0	18.38	106.6	70.0	143.4	0.001
MVV%	138.5	29.7	137.0	72.0	216.1	155.5	32.3	153.0	78.0	218.0	0.001

FEV₁%, percentage of predicted value for forced expiratory volume at 1 s; FVC%, percentage of forced vital capacity; MVV%, percentage of maximal voluntary ventilation; SD, standard deviation; Med, median; Min, minimum, Max, maximum.

Table 3. Anthropometric and spirometric results from examination session three for the adult groups (preterm born *versus* reference groups).

	Control group (<i>n</i> = 27)					Experimental group (<i>n</i> = 12)					<i>p</i>
	Mean	SD	Med	Min	Max	Mean	SD	Med	Min	Max	
Age	28.32	2.13	28.5	23.00	32.00	28.08	2.43	29.00	23.00	30.00	0.88
Height	168.04	5.60	167.00	155.00	182.30	161.96	9.96	165.25	142.00	172.00	0.07
Weight	63.14	9.24	62.95	48.90	96.50	56.61	8.25	55.80	46.90	76.70	0.02
Chest mobility	7.43	1.88	7.5	3.00	11.00	6.83	1.84	7.00	3.00	9.5	0.40
FEV ₁ pred	3.48	0.26	3.43	2.94	4.15	3.23	0.42	3.35	2.41	3.67	0.08
FEV ₁ LLN	2.79	0.21	2.76	2.36	3.33	2.59	0.34	2.69	1.94	2.95	0.08
FEV ₁ % pred	102.75	12.70	101.70	79.70	125.40	95.54	14.75	101.90	64.70	110.70	0.33
FEV ₁ Z	0.24	1.08	0.15	-1.70	2.19	-0.36	1.23	0.17	-2.90	0.92	0.33
FVC pred	4.11	0.31	4.04	3.42	4.94	3.79	0.51	3.95	2.80	4.32	0.07
FVC LLN	3.28	0.25	3.23	2.73	3.95	3.03	0.41	3.16	2.24	3.45	0.07
FVC% pred	103.79	12.54	104.50	80.30	124.50	98.63	14.40	100.20	69.60	121.30	0.26
FVC Z	0.29	1.01	0.37	-1.61	1.93	-0.13	1.17	0.02	-2.52	1.68	0.26
FEV ₁ /FVC pred	0.85	0.01	0.85	0.84	0.87	0.86	0.01	0.86	0.85	0.87	0.16
FEV ₁ /FVC LLN	0.74	0.01	0.74	0.73	0.75	0.74	0.01	0.74	0.73	0.75	0.11
FEV ₁ /FVC Z	-0.14	0.82	0.11	-2.48	1.18	-0.39	1.02	-0.21	-2.39	1.49	0.42
FEF ₂₅₋₇₅ pred	3.83	0.22	3.79	3.46	4.35	3.65	0.36	3.68	2.96	4.11	0.13
FEF ₂₅₋₇₅ LLN	2.49	0.16	2.47	2.21	2.84	2.37	0.25	2.38	1.91	2.72	0.08
FEF ₂₅₋₇₅ Z	0.66	1.11	0.86	-1.84	2.67	0.11	1.33	0.15	-2.55	2.04	0.19
MEF ₂₅ pred	1.75	0.17	1.73	1.46	2.16	1.64	0.25	1.62	1.19	2.04	0.12
MEF ₂₅ LLN	0.92	0.10	0.92	0.75	1.17	0.87	0.14	0.85	0.62	1.11	0.18
MEF ₂₅ Z	0.79	0.95	0.77	-1.74	2.39	0.48	0.90	0.72	-1.26	1.86	0.34

SD, standard deviation; FEV₁, forced expiratory volume at 1 s; LLN, lower limit of normal; pred, predicted value; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow at 25-75% of forced vital capacity; Z, Z score; MEF₂₅, maximal expiratory flow at 25% of forced vital capacity; Med, median; Min, minimum, Max, maximum.

Table 4. Spirometry results for three subjects with obstruction.

Group	FEV ₁ /FVC	FEV ₁ /FVC LLN	Z	FEV ₁	FEV ₁ pred	FEV ₂₅₋₇₅	FEV ₂₅₋₇₅ LLN	Z
1 B	0.68	0.75	-2.39	1.56	65%	1.41	1.91	-2.55
2 B	0.75	0.75	-1.67	3.56	98%	3.52	2.72	-0.67
3 K	0.66	0.74	-2.48	3.11	87%	2.43	2.58	-1.84

FEV₁, forced expiratory volume at 1 s; LLN, lower limit of normal; Z, Z score; pred, predicted value; FVC, forced vital capacity; FEV₂₅₋₇₅, forced expiratory flow between 25% and 75% of forced vital capacity.

reference groups in terms of age or height, but the mean body weight of preterm-born subjects was found to be significantly lower than that of those born at term ($p = 0.02$). The mean chest mobility in preterm-born subjects was 6.83 ± 1.84 cm, compared with 7.43 ± 1.88 cm for those born at term, but this difference between the groups was not statistically significant. As for the previous examination sessions, no correlation was found within the study group between anthropometric parameters and either birth weight or weeks' gestation at birth.

As for the spirometric results, no significant differences were found between the average FEV₁ expressed as a percentage of the expected norm (FEV₁%pred). No statistically significant differences were found between the two groups for FVC%pred.

The preterm-born group exhibited a trend for lower values of such parameters as FEF₂₅₋₇₅, MEF₂₅ and FEV₁/FVC as compared with the reference group, but those differences were not found to be statistically significant.

An obstructive condition (FEV₁/FVC < LLN) was identified in two subjects from the premature-born group and one in the reference group. Two of these three cases coexisted with significant deficits in FEF₂₅₋₇₅. The parameters for these women with obstruction are shown in Table 4.

A restrictive condition (FEV₁/FVC > LLN), in turn, was observed in one case in the preterm-born group but not in any case in the reference group. The absolute values for this case were FVC 2.06 l, LLN 2.37 l and Z -2.52.

No correlation was found within the study group between spirometric parameters and either birth weight or weeks' gestation at birth.

Discussion

In this study, we sought to trace the long-term impact of preterm birth on lung function 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 until the end of the project.^{16,32} In our study, we ultimately succeeded in recruiting only 12 (17%) of the 70 original preterm-born female subjects who had been examined twice around the age of puberty to participate in the third stage of examination in adulthood, 18 years after the first examination. This was largely due to the major difficulty of re-establishing contact with individuals previously tested after the passage of so much time. The individuals who did not participate in the follow-up examination may therefore have done so for any of a variety of reasons, including change of residence in the interim, failure to receive the 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 a share of the original group after such a time gap.

Such long-term research poses a number of other difficulties as well, as noted in the literature. One of these lies in assaying the original perinatal condition of adolescent and adult subjects who were born preterm. A large percentage of individuals do not have well-kept medical records from their birth or early childhood, which can have an impact on research results.³³ Another major problem in evaluating the consequences of preterm birth lies in attempting to account for the large number of post-birth factors; the most important of the many such factors mentioned in the literature include: duration of hospitalization after birth, respiratory symptoms experienced, the need for mechanical ventilation or oxygen

therapy, and the mother's pre- and post-partum smoking habits.¹⁸ At present, increasing attention is also being paid to various factors present in adulthood which may likewise affect the current status of the respiratory system, and controlling for these could make research results into the impact of preterm birth significantly more reliable – these include respiratory infections experienced in childhood and adulthood, especially chronic cough or diagnosed asthma, active or passive cigarette smoking, diet, physical activity, and alcohol consumption.²⁹

A correct spirometric reading for a given subject should fall within the 5th and 95th percentile of the values obtained for the healthy reference population in terms of race, sex, age, and height. The most frequently used reference values at present are those of the Global Lungs Initiative (GLI 2012); being the most up to date and universal, created for the largest population studied to date, they have opened the way for the long-awaited ability to introduce universal spirometric reference values for people from the whole world.³⁴ Their use in research is supported by numerous lung disease associations in the world.¹⁷ However, although the GLI 2012 reference values are universal norms, they unfortunately cannot be applied to a group of subjects examined two decades ago, as the reference groups for the ECSC and GLI 2012 differed. We therefore adopted the ECSC reference values to calculate the expected spirometric parameters for the examination results from 1997 and 1998, whereas for the third and final stage of examination, we adopted the GLI 2012 calculator. Quanjer *et al.*³⁵ evaluated the diagnostic consequences and differences between reference values taken from GLI 2012, the ECSC values used in Europe in the 20th century, as well as the NHANES III (National Health And Nutrition Examination Survey) values used in the United States,³⁶ finding that the average predicted values according to GLI 2012 for spirometric parameters were significantly higher ($p < 0.0001$) than those set by ECSC and NHANES III.

Because pubescence is a time characterized by dynamic physical development, we initially carried out lung function exams twice during the period, spaced 1 year apart. In the first examination session, the preterm-born group showed somewhat poorer lung function results than their peers born at term. In the first examination, the

mean FVC%pred for the group was 95.4% and FEV₁%pred was 93.8%. This somewhat below-norm result could be seen as confirming the unfavorable influence of premature birth on the respiratory system. Just 1 year later, however, the FVC and FEV₁ results had significantly improved and were even slightly higher than the expected normative values: FVC%pred increased to 102.0% and FEV₁%pred to 100.7%. A similar tendency was observed by Kotecha *et al.*³⁷ who compared lung function in subjects born at 33–34 weeks' gestation *versus* born at term, studying them twice, once at the age of 8–9 and again at the age of 14–17. They reported that children born preterm showed reduced measures of lung function in childhood, but showed no significant difference in FEV₁ and FVC compared with the reference group at 14–17 years. Similar results were also presented by Doyle *et al.*,³⁸ reporting significant improvements in predicted values of lung function between 8 and 14 years in children whose birth weight had been <1501 g. Both of these studies carried out their first examination of children in mid childhood, whereas the second examination came after pubescence. The improvement in lung function they identified in the second examination could therefore attest to a positive effect of puberty in counterbalancing and compensating for the earlier impact of preterm birth on FVC values (the main parameter identifying the air capacity of the lungs), with the increase in the dynamic parameter of forced expiratory volume potentially being ascribable to the positive influence of increased bodily development in the pubescent period.

Only a few papers have analyzed the impact of preterm birth on respiratory functions into adulthood. Vollsæter *et al.*³⁹ studied a group of 46 individuals born extremely preterm compared with 39 individuals born at term. Because their groups differed significantly in terms of height ($p < 0.01$), only the mean values of the parameter FEV₁%pred were compared: the value for the study group (88.3%) was found to be significantly lower ($p < 0.001$) than for the reference group (100.4%). On the other hand, the authors did not find any statistically significant differences in terms of mean FVC%pred (100.9% and 96.2%). Clemm *et al.*,⁴⁰ in turn, studied 34 individuals born preterm compared with 33 born at term. Like Vollsæter *et al.*,³⁹ they reported a statistically significant difference ($p < 0.001$) in FEV₁%pred (92.5% for the study group, 101.5% for the reference group), but they

did not find significant differences in mean FVC%pred values (99.6% for the preterm-born group, 102.0% for the reference group).

The occurrence of obstruction is associated with disturbances in FEF_{25-75} .³⁵ In obstructive lung conditions, after the peak exhalation flow is achieved, the flow–volume curve shows an abnormal downward shift, taking on a distinctive low, extended, concave shape. Flows exhibit low values while volume is close to normal. Our study group showed lower FEF_{25-75} values as compared with the reference group. In restrictive-type conditions the flows reach normal values, whereas volume is significantly reduced, and consequently, the flow–volume curve is high and narrow. An obstructive model of spirometry result was identified in two women, in one case accompanied by significant disturbances of FEF_{25-75} . The restrictive model was identified in just one case from the study group, and did not occur at all in the reference group. Clemm *et al.*⁴⁰ did not calculate FEV_1/FVC but noted that the preterm-born group had a significantly lower MMEF ($p < 0.001$). The mean FEF_{25-75} % value for the study group was 78.8% of norm, but 102.9% for the reference group. Vollsæter *et al.*,³⁹ analyzing the parameter FEF_{25-75} , found that 27% of their study group, but 5% of the control group exhibited a result below LLN. This difference was not statistically different. Obstruction was identified in 8 of the 45 individuals in their study group, but 1 of the 39 individuals in their control group.

Gough *et al.*⁴¹ reported that FEV_1/FVC %pred was 94% in a group of preterm-born subjects who had BPD, 98% in preterm subjects without BPD, and 102% in a control group. Significantly lower values of FEV_1/FVC were noted in both groups of preterm subjects as compared with the control group. At the same time, the mean FEF_{25-75} value was 61% of norm in the group with BPD, 74% in the group without BPD, and 90% in the control group. Their study concludes that the mean values of this parameter are significantly lower ($p < 0.01$) in the group with BPD than in the group without BPD. Moreover, both the group with BPD ($p < 0.001$) and the group without BPD ($p < 0.05$) both show significantly lower values for this parameter than the control group. Our study did not consider the past history of BPD. The literature indicates that BPD develops most often in children with very low birth weight and born extremely preterm (below 32 weeks), with white race, male sex, and genetic factors as additional

predispositions. It most often presents in children who required oxygen therapy for at least 28 days. Researchers stress that experiencing BPD has a significant impact on subsequent lung development and therefore on the spirometric parameters attained in childhood and in adulthood.^{42,43}

Severely preterm children (<32 weeks of gestation) are born with severely underdeveloped respiratory systems, but even children born just before the 37th week of gestation are at elevated risk of lung disease in childhood. Certainly, the introduction of corticosteroids, surfactant therapy, and mechanical ventilation have improved survival rates, especially in children with advanced BPD, and most likely also helped improve FEV_1 %pred in later examination. A poor degree of lung function in adolescence may lead to quicker degeneration of lung function in adulthood, through the influence of such external factors as tobacco smoking or air pollution. It is suspected that chronic obstructive lung disease may begin already in childhood.⁴⁴ Moreover, preterm-born subjects, both with and without a history of BPD, may present more respiratory symptoms such as wheeziness, apnea, shortness of breath and more frequent diagnosis with asthma.⁴⁵ Recent years have seen an improvement in lung function in individuals born preterm. Vollsæter *et al.*³² studied a set of children born extremely preterm (<28 weeks) and with extremely low birth weight (<1000 g) over the course of 20 years. Subjects who had experienced BPD showed significantly higher values in terms of FEV_1 %pred ($p < 0.05$), FVC%pred ($p < 0.0001$), and FEF_{25-75} ($p < 0.05$) than a comparable group born in the same region, but 10 years earlier. The assumption is that children born in subsequent years will have better respiratory function than initially presumed. Baraldi and Filippone¹⁵ concluded that BPD cannot be treated exclusively as a childhood illness: the obstruction of respiratory pathways identified in youth continues in subsequent decades of life. This type of impairment may lead to greater risk of chronic obstructive lung disease in later life.

In our study of women born preterm, we did not find any significant correlation between spirometric parameters and either birth weight or weeks' gestation at birth. However, the group studied may have been too small and included too few individuals born highly preterm for important correlations to be visible in this regard.

Baumann *et al.*,³³ who studied more than 4000 adults divided into 4 subgroups based on their birth weight (<2500 g, 2500–3000 g, 3000–3500 g, >3500 g), found that the lower the birth weight, the lower the mean FEV₁%pred ($p < 0.001$) and FVC%pred ($p < 0.002$), but did not find any statistical differences in FEV₁/FVC%pred. A second spirometric examination carried out 5 years later did not find significant differences in terms of FEV₁ or FVC, but found a statistically significant reduction in FEV₁/FVC ($p < 0.01$) as compared with the first examination and noted a correlation between FEV₁/FVC and birth weight. A 1 kg higher birth weight implied a FEV₁/FVC decline that was smaller by 0.2% per year. Lower birth weight is related to poorer lung function in adulthood, a dependency related to factors from the perinatal period, childhood, and adulthood. Other researchers have also confirmed the above correlations.^{27,46} It has been hypothesized that low birth weight is a consequence of fetal undernutrition and is postnatally related to respiratory, circulatory, and metabolic disorders in adulthood.^{47,48} However, it is important to note that the term ‘low birth weight’ applies both to children whose birth weight was low but nonetheless appropriate for the early week of gestation in which they were born, and whose psychomotor development is therefore delayed, as well as to children whose birth weight is low but have developed normally. For this reason, ‘low birth weight’ children should be considered as two distinct groups in future research.

The major methodological strengths of our study are the long follow-up period examined, the use of the latest reference values from GLI 2012, and the fact that we admitted only nonsmokers, thereby excluding one factor that could otherwise be causing lower spirometric values in adulthood.

As for limitations, one major limitation of our study was the relatively small number of participants in the follow-up examination. However, as we have noted, this results from the logistical difficulty of such long-term research and is indeed comparable with most similar studies.^{36,49} To our knowledge, very little is known about longitudinal consequences on respiratory function from adolescence to adulthood after preterm birth. The follow-up studies on lung function have been limited mainly to the childhood and sometimes the adolescent period.^{24,25} The few papers that do report attempts at follow up into adulthood in this respect argue that there does exist a statistical difference in

lung function between subjects born at full term and those born at less than 37 weeks’ gestation.^{26,27} It is true that adults who were born preterm are more likely to report such respiratory symptoms as wheezing or recurring infection, and studies have shown an inverse proportionality between gestational age and frequency of respiratory symptoms reported by adults who were born preterm. A second significant weakness of this study is its restricted focus on female participants; as we have explained, the study was configured solely on the fact that all the participants who were successfully recontacted and agreed to take part in the follow-up session happened to be female. Lastly, the average birth weight of the participants was over 1800 g and of the infants who had had BPD, so the results can only be extrapolated to relatively more mature infants without pulmonary sequelae.

Overall, our analysis did not find significant impairment in respiratory function in preterm-born individuals given spirometric examinations twice during the pubescent period and once in adulthood (two decades later), as compared with a reference group born at term. It would therefore seem that the limitations in lung function in preterm-born individuals reported by other authors based on their spirometric parameters could be related not with the fact of preterm birth itself, but rather with specific perinatal conditions, a history of bronchopulmonary dysplasia (BPD) in infancy, the occurrence of other respiratory disorders in childhood, and external factors such as cigarette smoking.

Conclusions

- (1) We identified a somewhat decreased level of respiratory parameters among preterm-born girls entering the age of pubescence, as compared with norms, which may attest to the continued negative impact of prematurity on their respiratory system.
- (2) We found a statistically significant improvement in spirometric results upon re-examination 1 year later, which may attest to a positive impact of pubescence in compensating for the earlier negative effect of preterm birth on respiratory function.
- (3) No statistically significant differences were seen in lung function in prematurely born adults as compared with a reference group, although the preterm-born group did exhibit lower values of all parameters studied and more frequent obstructive disorders.

- (4) Prematurely born infants require careful follow up to monitor their respiratory development and hence whether they are likely to suffer long-term morbidity.

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Conflict of interest statement

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

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