Lung Function in Children of Different Origins

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by

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Abstract 300 words

Background:

Differences in lung function between people of varying ethnic origins are recognised, but the underlying physiological reasons have not been widely explored.

Aims:

The overall aim was to explore the physiological basis of differences in spirometry between white and South Asian children.

Methods:

We measured spirometry and maximum inspiratory pressures (MIP and MEP) in 307 children aged five to eleven years in primary schools. Spirometry included FEV_1 and FVC. A subgroup of 37 children attended the laboratory for plethysmography and attempted measurements of distensibility of the respiratory system, made by measuring pressure and volume after brief interruptions of tidal breathing. Lung volumes were available from an additional 122 healthy children aged 7 to 16 years. Lung volume measurements were expressed as Z-scores based on predicted values for white children.

Results:

The mean(SD) FEV_1 Z-scores for white and South Asian children were 0.17(1.01)and-0.55(0.97) respectively($p<0.001$). Corresponding FVC Z-scores were 0.36(1.02) and-0.67(0.94), ($p<0.001$). We did not find significant ethnic differences in MIP or MEP. Adjusted mean(SD) MIP(kPa) was 7.51(1.99) for white and 7.02(1.91) for South Asians ($p=0.14$). Equivalent values for MEP(kPa) were 6.29(1.58) and 6.46(1.53), ($p=0.48$). Mean(SD) Z-scores for Total Lung Capacity were larger in white than south Asian children:(0.29(0.09) and -0.59(0.82) respectively, $p<0.001$). Mean(SD) Z-scores for Residual Volume were also larger in white children: (0.04(0.76) and -0.28(0.89) respectively, $p=0.039$). The measurements of distensibility yielded potentially useful data in 16/37 (43%) of children.

Conclusions:

Absolute lung volumes were lower in south Asian than white children. We did not find significant differences in respiratory muscle strength between two ethnic groups that would account for differences in spirometry. The distensibility of the respiratory system can be measured in almost half of children. Further work may show whether ethnic differences in distensibility exist, which could explain differences in spirometry.

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Statement of author's contribution to this thesis

I would like to place in record my personal contributions to this work. I was involved in planning the ethic submission, contacting schools and parents, recruiting the subjects, designing and validating the questionnaires, and collecting and analysing all the data included in this thesis. I designed all the studies in this thesis.

I planned and developed the standard operating procedures for the physiological measurements, spirometry, whole-body plethysmography, respiratory muscle strength and lung distensibility. My supervisor Dr. Caroline Beardsmore and I performed almost the measurements included in this thesis for all participants. A small number of measurements of spirometry in two primary schools were made by Mr Gregory Duncan, an intercalated BSc student being supervised by Dr Beardsmore. I took the full responsibility in managing data entry, the statistical analysis of the data, and interpretation of results.

I acknowledge the contribution of plethysmographic data from Dr Manjith Narayanan included in chapter 7.

I presented the data in several national and international meetings. The thesis is all my own work.

Nidhal Gharbawi

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1 CHAPTER 1 INTRODUCTION AND BACKGROUND

1.1 Introduction

There are abundant studies that have shown that divisions of lung volume measured by spirometry in the white population are greater than in other ethnic groups, after adjustment for age, height and gender (1) and (2). Previous studies have compared South Asian children (who have their origins in the Indian subcontinent) with their white counterparts and shown a relative reduction in lung function, measured as forced vital capacity (FVC) of 13.4% (1), 9% (3) and 13% (4), and forced expiratory volume in 1 second (FEV_1) of 10.6% (1), 8% (3) and 13% (4). Differences in lung volume (FEV_1 and FVC) according to ethnic origin were also documented in adults (5) and (6).

It is not clear why lung function differs between ethnic groups, and many studies have attempted to describe that factors that might explain this phenomenon such as chest dimension (1) and (7), socioeconomic status and respiratory disorder (2), ethnic origin (8), birth weight, breastfeeding, environmental exposure, and genetic factor and family history of disease (7), (9), (10), (11) and (12), amongst others. Factors known to affect the measurement of lung function include gender, height, and age. When white people are compared with people of Afro-Caribbean origin, differences are reduced (but not negated) when lung function is related to sitting height because Afro-Caribbean people have longer legs than their white counterparts (13). This does not appear to be the case when South Asian children are compared with their white counterparts, and neither do differences in chest dimensions appear to be important (1). The differences do not otherwise appear to be related to either socioeconomic status or body proportions (2).

Ethnic differences in lung function were evaluated in a community study of 393 children (158 blacks, 235 whites). Mean forced vital capacity was 18 % larger in non-smoking white males than in non-smoking black males, and 11 % larger in non-smoking white females than in non-smoking black females. Similar differences were observed for the forced expiratory volume in 1 second and for the maximal expiratory flow at 50 % of the forced vital capacity. However, when adjusted for lung size (based on forced vital capacity), forced expiratory volume in 1 second and maximal expiratory flow at 50 % of the forced vital capacity were larger in the black children than the white children. Equations to predict lung function based on race, sex, age, height and weight have been developed for healthy non-smoking children; these allow for the evaluation of normal lung function in both black and white children (14).

One important little-studied factor that may explain the difference in lung function between different ethnic groups is respiratory muscle strength. This is assessed using the measurements of Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP). Previous studies in adolescents and adults have shown that MIP and MEP values in healthy males are significantly larger than in healthy females (15).

A separate study has shown that in men, MIP and MEP could only be significantly correlated with age. In women, MIP and MEP were correlated only with height. A small number of children were included in this study, and in children, MIP was related only to weight, while MEP was related only to age, and the adjustment was applied as per height, age and weight (16).

A limited body of work has considered ethnic differences in respiratory muscle strength. An American study has examined the MIP of 3849 adults from four groups: non-Hispanic white, African-American, Hispanic and Asian (of Chinese origin) (17). It was found that important correlates of higher values of MIP observed through multi-ethnic groups in this study were males, those of younger age, obesity, higher FVC and those of shorter height. The differences in MIP by ethnicity were, however, small (17).

This study was limited because it addressed only one variable (MIP) and did not include measurements of MEP. It also did not include anyone of South Asian origin; the main minority group forming the population of Leicester and Leicestershire. The study seeks to address this knowledge gap.

An alternative explanation for the ethnic-related differences in spirometry might be that the elasticity of the lung (or of the chest wall) varies with ethnic group. The lungs are elastic structures that change in volume with the pressures produced through the inspiratory and expiratory muscles. There is little data available in the literature on elasticity (or compliance) of the respiratory structures, possibly because it is not easy to measure in the relaxed, awake state.

One previous study has investigated the relationship between the chest wall, pulmonary distensibility and age by studying 42 healthy males aged 24-78 (18). It was found that pulmonary volume was increased, and lung elasticity decreased, in the younger subjects compared with the older. No consideration was given to ethnicity, however. No subsequent study has attempted to confirm this hypothesis. We aimed to measure the static recoil of the respiratory system in children from different ethnic groups.

Binder et al. have attempted to explain the difference in lung function between black and white children by studying 393 children aged 9 to 17 years (14). They hypothesised that pulmonary volume in black children was decreased due to increasing elastic recoil, but there is no evidence that appears to confirm this hypothesis (14).

The measurement of ethnic differences in lung function has in the past relied almost exclusively on spirometric indices of forced vital capacity (FVC, the amount of air that can be exhaled from full inspiration to the maximal expiration) and forced expiratory volume in 1 second (FEV_1). Much less data exists regarding measurements of absolute lung volume. By measuring total lung capacity (TLC) and residual volume (RV) where possible, we aimed to determine whether the reduced vital capacity in South Asians results from a lower TLC, a raised RV, or a combination of the two. This will aid in the interpretation of other measurements.

Ethnic differences in lung function are well documented and the importance of adjusting for ethnicity has been emphasised (19), (20), (1) and (2). However, the paucity of spirometry references that take ethnicity into account, especially in children, impedes diagnosis and clinical management of lung disease, and complicates the interpretation of clinical trials where lung function is a primary outcome (21). The recently published Global Lung Function Initiative (GLI)-2012 multi-ethnic spirometry equations (22) provide a good fit for contemporary Black-African origin and white London primary schoolchildren (23) , and although the published equations did not cover all ethnic groups, a preliminary coefficient for South-Asian children based on GLI-2012 has been developed (24) and (25). Nevertheless, ascribing ethnicity is complicated in an increasingly multi-ethnic society. Most lung function prediction equations are derived from whites; thereby, those of non-white are at risk of misclassification and potentially inappropriate therapy if they are assessed using ethnically-inappropriate prediction equations.

The rationale for the proposed study is based on potential misclassification of children if they are assessed using ethnically-inappropriate prediction equations. Ethnic differences are not lessened by generation since migration to the UK (26), nor can they be explained on the basis of chest dimensions or differences in the ratio of sitting height to standing height (the cormic index) (1). In this study, we wanted to explore the physiological basis for these ethnic differences.

1.2 Lung function and ethnicity

Ethnic differences in lung function have been extensively reported and most ethnic differences can be found in FVC and FEV_1 among 17 different ethnic groups (27), (28), (29), (30), (31), (32) and (33).

Ethnic differences between children are considered an important issue that can explain the variation in lung function in childhood (8). Many published studies have investigated ethnic group differences in children of school-age (10). The findings reported therein described significantly decreased spirometric forced expiratory volumes in black African children and south Asian children when compared to white European children (10).

Whitrow et al. have reported that Black African, Black Caribbean and South Asian children had lower FEV_1 and FVC values than white children (2).

White people have a larger TLC than Asian (Chinese and Indian) people (34), (35), (36), (37), (38), (39) and (12). There is one plausible explanation for these results, namely that a large FEV_1 and FVC can be attributed to large TLC, and thereby, that a large TLC influences the chest size, strength of the inspiratory muscles, and compliance of the lung and chest wall (40) and (41). There is an acceptable agreement between researchers that there are ethnic differences in FVC and FEV_1, which are indicators that reflect TLC (42), (3), (13) and (43).

Several studies have revealed that Afro-Caribbeans consistently have lower lung function after adjustment for height than white Caucasians. The variations appear in both children and adults; figures between 13% and 19% for FVC and FEV_1 / FVC (44), (4), (28), (45), (46), (47) and (14) are frequently quoted. After adjustment for sitting height, there is a reduction in this difference (7), (13) and (43). Children who come from mixed ethnic groups tend to have lung volumes that are intermediate to those predicted for white and black people (48).

A number of researchers have attempted to investigate the ethnic differences in lung function in Singapore and Hong Kong in both children and adults (49), (50) and (51). The findings showed that the Chinese have better pulmonary function than Malay and Indians, Indians having lower lung function (49) and (51). Chinese children and adults had lower FEV_1 and FVC compared to their white counterparts of the same height (12) and (52).

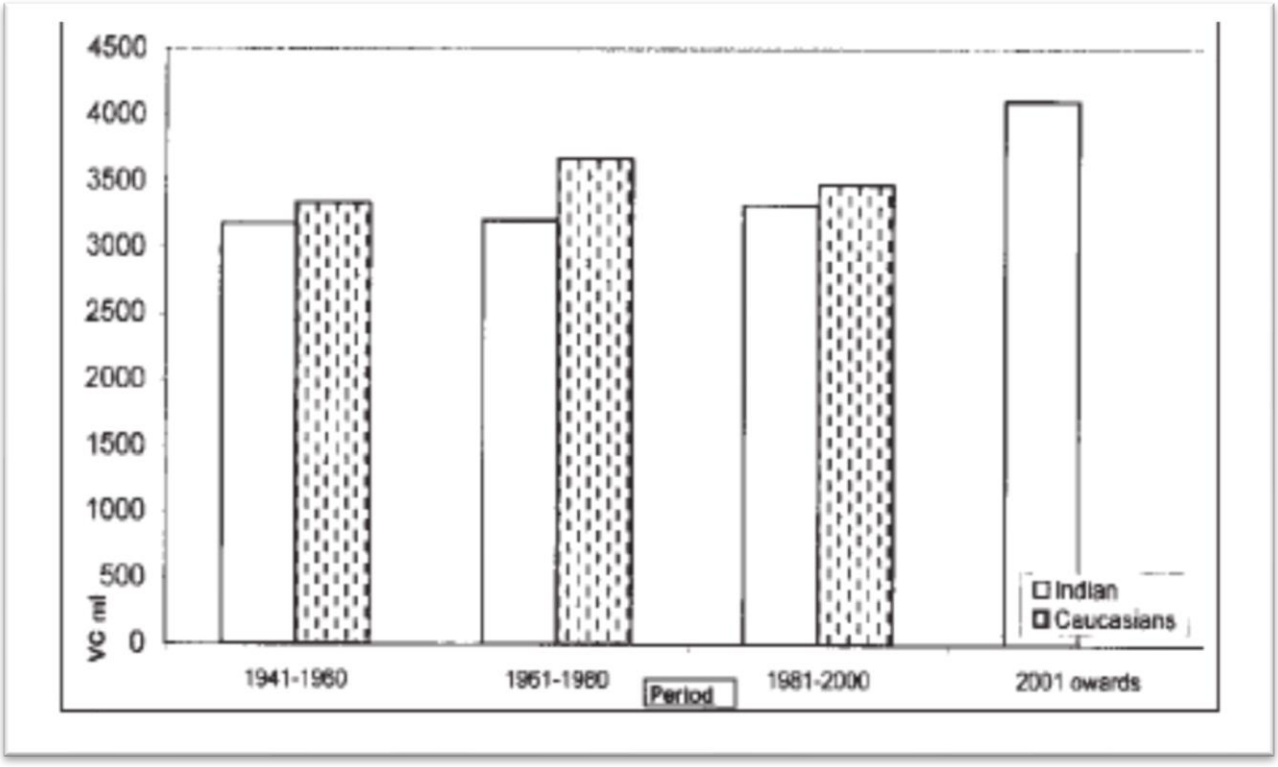
Spirometric measurements of Asian subjects residing in the Indian subcontinent or in Western countries has found decreased pulmonary function, in the region of 6 to 13%, compared to white populations (27), (4), (53), (54) and (55). Variations in pulmonary function even occur among different regions in India (27), (56) and (54). Asian males residing in India and in England have a higher pulmonary function for a given height than Asian females (27) and (56).

One study reported on 664 healthy children of European, Afro-Caribbean and Indian origin aged 5-16 years, who were living in the same environment in inner city Nottingham (4). The percentage of each group born in England was 100%, 95%, and 80%, respectively. The researchers measured FVC and FEV_1 and demonstrated clear differences between European and Indian children amounting to 13% for both indices for a given stature. The Afro-Caribbean children had values similar to those of the Indians. There were no material ethnic variations in peak expiratory flow or for FEV_1 /FVC. The differences between these groups appear to be related to constitutional, instead of environmental, effects (4).

Patrick et al. have shown that for a given stature, Europeans had a bigger trunk size when compared to black people, where these variations were calculated, giving a 13% increase in the thoracic volume of white people (4).

One study of Indian adults has revealed that VC for Indian men is lower than that of Caucasian men (57), as shown in (Fig1.1), where data have been obtained from (58), (59), (60) and (61). One suggestion might be that Caucasian men are physically fitter, and hence they have bigger lung volumes than Indian men when adjusted for ethnicity and height (57).

Figure 1-1 Vital capacity.



Legend: The Vital capacity of Indian and Caucasian males. Adopted from (57).

Kirkby et al. studied 400 healthy children from two different ethnic groups, namely black and white, aged 6-12 years (9). They used spirometry and plethysmography to explain the differences in lung function between ethnic groups. Black children had a lower lung function for a given height when compared with white children. Spirometry from these children was 100% predicted as based on the Wang equations (62). Lung volume results showed significant differences between observed and percentage predicted based on published equations derived from white children. FRC and TLC in black subjects were, on average, 14 and 6% lower than predicted, while mean RV and RV/TLC were 4 and 10% higher than predicted. In white children FRC was, on average, 9% lower than predicted, based on the equations of Rosenthal et al. (63).

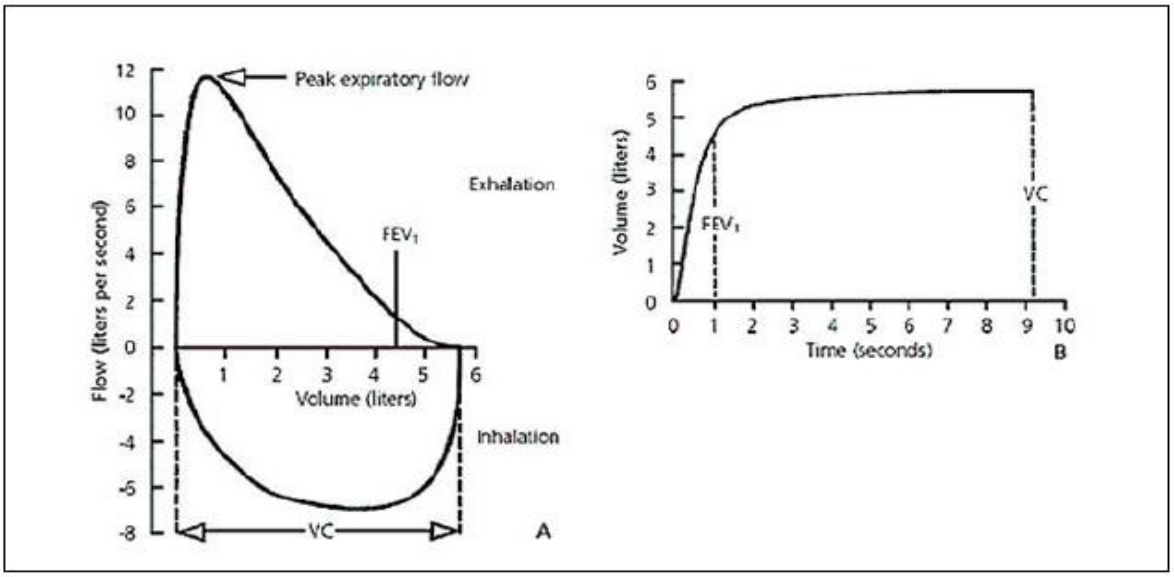
A study of 57 young children aged 4.9-8 years has been conducted to investigate the ethnic variation in respiratory function in young children (47). It has been confirmed that ethnic origin has a significant impact on pulmonary function, with children of Afro-Caribbean origin having significantly smaller lung volume than Caucasian children when adjusted for standing height (47).

1.3 Definitions of lung function parameters and lung volume

1.3.1 Parameters of lung function (FEV_1, FVC)

Forced expiratory volume in 1 second (FEV_1) is the maximum volume of air a subject can exhale in the first second of a forced expiration from a position of full inspiration, and is expressed in litres at body temperature and ambient pressure at saturated water vapour pressure (BTPS) (64). FVC (Forced vital capacity) is the maximal volume of air a subject can exhale with maximally forced effort from maximal inspiration expressed in litres at BTPS (Fig 1.2) (64).

Figure 1-2 The determination of FEV1.



Legend: The determination of FEV_1 from A. Flow-Volume Loop B. Volume-Time Curve by measuring the volume of air expired over the first second of an FVC manoeuvre. Adopted from (64).

FEV_1 and FVC are considered to be important parameters for diagnosing obstructive impairments in patients with obstructive lung diseases. FEV_1 and FVC can be measured via spirometry (20).

Generally, spirometry is considered a good way to assess lung function and diagnose lung disorders. Pulmonary diseases are classified as those with airflow limitations that are considered obstructive, those with lung volumes restrictions are referred to as restrictive, and finally there are those with a combination of obstructive and restrictive disorders. This gives three patterns of spirometry: the first pattern is normal spirometry (normal FVC and FEV_1 /FVC ratio); the second pattern, obstructive, might have a normal FVC but low FEV_1 /FVC ratio, or a low FVC with a low FEV_1 /FVC ratio; and the third pattern, restrictive may have low FVC with normal or

high FEV_1 / FVC ratio. There can also be a mixed pattern (mixed obstructive and restrictive). Generally, the diagnosis of obstruction in the airflow using spirometry is useful when made, in the face of even a normal FVC (VC) but when the FEV_1 /FVC ratio is lower than normal. However, the gold standard for diagnosing restrictive pulmonary disorders still remains the measurement of total lung capacity using helium dilution or plethysmography (57).

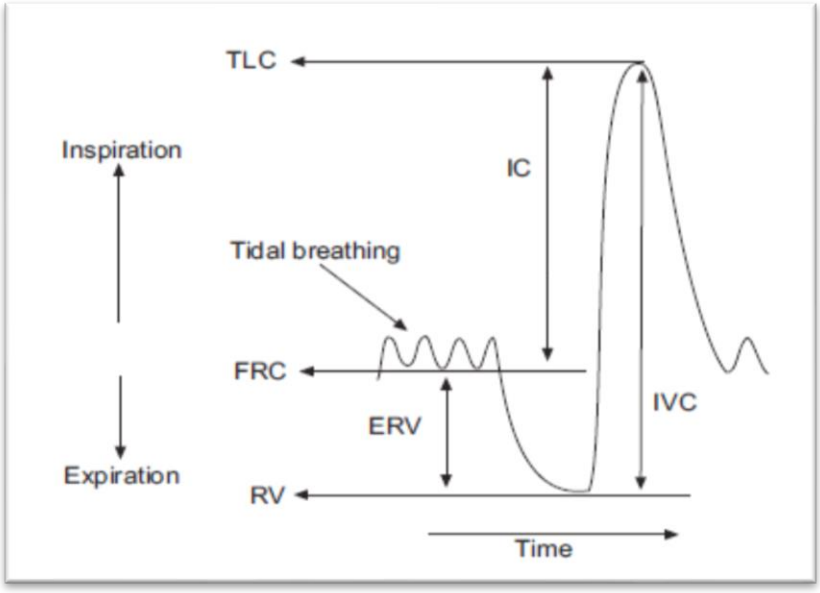
1.4 Divisions of lung volume

Pulmonary volume indicates the volume of gas within the lungs, as measured using one of the following methods: body plethysmography, gas dilution or nitrogen washout (65), (20) and (64).

The definitions below explain some of the divisions and subdivisions of lung volume, (Fig 1.3) and (Fig1.4) show divisions, and subdivision of lung volume, and lung capacities (65), (20) and (64).

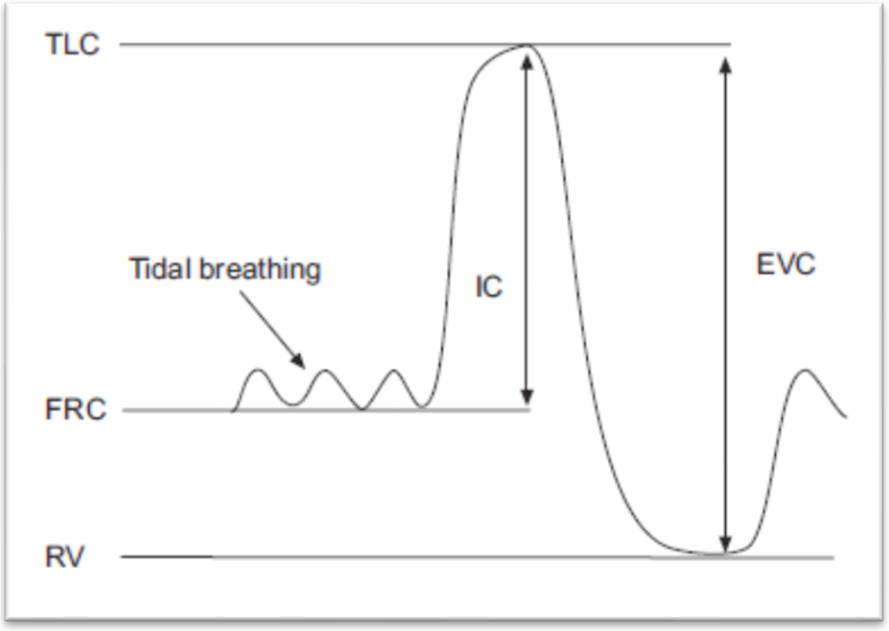
- Total lung capacity (TLC) is the volume of gas in the lungs at maximal inflation, where TLC= VC + RV. TLC is considered the most important parameter for making a diagnosis of restrictive lung diseases.
- Vital capacity (VC) is the volume of air a subject can exhale after the deepest inhalation.
- Functional residual capacity (FRC) is the volume of air present in the lungs at end of a normal, quiet expiration, and is a subdivision of TLC. FRC= ERV+RV.
- Residual volume (RV) is the volume of air remaining in the lungs after a maximal expiration, RV =TLC - VC.
- Inspiratory reserve volume (IRV) is the maximum amount of air a subject can inhale from the end-inspiratory level during tidal breathing.
- Expiratory reserve volume (ERV) is the amount of air a subject can exhale maximally from the end-expiratory level during tidal breathing.
- Inspiratory capacity (IC) is the maximum volume of air a subject can inspire from FRC, where IC= IRV + TV.
- Tidal volume (TV) is the volume of air inhaled or exhaled during the respiratory process.

Figure 1-3 The divisions and subdivision of lung volume.



Legend: Trace of tidal breathing followed by an expiratory manoeuvre to residual volume (RV), followed by a full inspiration to total lung capacity (TLC) to record inspiratory vital capacity (IVC) and inspiratory capacity (IC). FRC: functional residual capacity; ERV: expiratory reserve volume. Adopted from (64).

Figure 1-4 The divisions and subdivision of lung volume.



Legend: Trace of tidal breathing followed by an inspiratory manoeuvre to achieve total lung capacity (TLC) in order to record inspiratory capacity (IC), followed by a full expiration to residual volume (RV) to record expiratory reserve volume (EVC). FRC: functional residual capacity. Adopted from (64).

1.5 Reference variables that affect lung function

1.5.1 Height

1.5.1.1 Standing height

Standing height is usually considered to be an important factor when measuring lung function. Quanjer et al. have reported that Caucasian adult males had FEV_1 and FVC bigger than that of non-Caucasians of the same age and standing height (22). During childhood, a linear relationship can be found between most indices of pulmonary function and standing height (66).

An Indian study was conducted to derive regression equations to allow the prediction of lung function by recruiting 469 healthy South Indian children (246 boys and 223 girls) aged 7 to 19 years. This study considered three variables (height, weight, and age). Correlation of lung function was greatest with height, followed by weight and age. Thereby, height can be considered the best predictor of such (27).

A study of 5,115 white and black men and women aged 18 to 30 was conducted to investigate if race and gender variations in pulmonary function could be explained by frame size (44). They found that height explained roughly 40% of the variance of FVC and FEV_1 in whites, 30% in black women, and 20% in black men. It was found that FVC and FEV_1 were larger in whites than in blacks, and also in males than in females after adjustment for standing height (44).

South Asians and black Caribbean children were found to have smaller FEV_1 and FVC than white children after adjustment for standing height (3), (4) and (1).

Whitrow et al. studied 3,924 healthy children aged 11 to 13 years from different ethnic groups (white, black Caribbean, black African, and South Asian) to investigate ethnic differences in adolescent lung function. They observed that FEV_1 and FVC were lower in the black Caribbean, black African and South Asian children than in white children after adjusting for standing height (2).

1.5.1.2 Sitting height

Another useful reference variable is sitting height. This has been used when investigating gender and ethnic differences. The research conducted in the USA reported that differences in FEV_1 and FVC between African American and white children seem to be attributable to variations in body proportions with sitting height (SiH) being less in proportion to standing height (SH) in African Americans (19).

The adult study found the black adults have shorter sitting heights and longer legs than white adults of the same standing height (44), (7) and (14). In general, sitting height was considered to reduce, but not remove, racial differences among black and white groups (44), (13) and (7). Schwartz et al. demonstrated that inclusion of sitting height reduced the effect of race on lung function by roughly 16% (13).

However, Whittaker et al. have found no evidence that differences in the sitting height: standing height exist between Asian children and white children (1) and (2).

1.5.2 Weight

Weight has been shown to be a significant predictor of lung function (46) and (43), but when weight is added to the appropriate regression equations it has been shown to be of little importance, either for children or adults (67), (45), (49) and (68). A study of children aged 6-18 years reported that the inclusion of age and/or weight, only allowed for an interpretation of an additional 1% of the differences in the data (49).

A study of 3046 white and black healthy subjects aged 7 and over has been completed to explain the correlation between lung function and weight (46). It was found that weight impacts pulmonary function measurements, where at first lung function increases with weight due to the so-called "muscularity effect'' but then decreases when the subject is overweight in the so-called "obesity effect'' (46). This result confirmed previous work showing that VC increases with increasing weight but decreases with the extent to which an individual is overweight (69).

1.5.3 Gender

Some studies have found that is not important to have gender-specific equations (42). However, most researchers found a small, but a statistically significant difference does exist between males and females (66). Males have bigger values for FVC and FEV_1 than females (3) and (70). However, a study has been reported that girls have a higher FEV_1/ FVC than boys, reporting a relative increase in FEV_1 (4), (13) and (46) but others works have been found the biggest ratio in males by 2.4% (70).

Gender variations in flows are less certain, and several studies have been found that no differences exist (4), (13) and (70). When considered per unit lung volume, flows from girls were higher than from boys. Peak expiratory flow (PEF) does not show any significant difference before or after adjustment for lung size (48), (13) and (70).

A longitudinal study has been conducted to explain the correlation between lung function and sex by studying 281 boys and girls aged 8 to 12 years, and 287 boys and girls aged 12 to 20 (71). During childhood, MEF was larger in girls than boys, but in adulthood, by 18.5 years old, boys showed a larger MEF than girls. Lung volumes were larger in boys than girls. One possible explanation for such differences are that in childhood, girls might have wider and/or shorter airways than boys, while in adulthood boys may have bigger airways and a bigger lung size than girls (71).

Studies have shown that the VC of boys is expected to be higher than that of girls pre-puberty because boys tend to be physically more active than girls (72), (4) and (73). During adolescence, the VC of females was significantly lower than that of males, as might be expected ($P<0.001$). The cause of this variation with sex has been related to the greater respiratory muscle strength of males (72), (4) and (73).

1.5.4 Age

In childhood and adulthood, pulmonary function increases with height; peak growth in FVC and FEV_1 is at age 11 in females and 13 in males, and lags 1 year behind peak growth in height (74), (75), (71) and (76). Standing height ceases to increase at age 16 in females and beyond 17 in males, while in males FVC and FEV_1 increases up to approximately 25 years of age then plateaus before declining (67), (20), (46) and (74).

Quanjer et al. have identified that in children and adolescents, FEV_1 and FEV_1 /FVC increased, while on reaching adulthood ageing has a different effect. Some lung function measurements might be increased, such as RV, while others may decrease such as FEV_1 and FVC (22).

Puberty has been shown to influence the respiratory system in a number of ways, chiefly in that it stimulates growth in mass and size of the respiratory muscle fibres (77). The pubertal development also causes changes in the chest wall dimensions of boys and girls and leads to central nervous system maturation, influencing the contractility of the respiratory muscle fibres (77). Studies have shown that pre-pubertal children have a reduced respiratory muscle endurance compared to those of a similar age who have undergone puberty (78). A separate study has shown a sharp increase in FVC and FEV_1 for girls and boys at the average time of the onset of their pubertal growth spurt (10 and 12 years, respectively)(62).

Studies have used age as a variable in regression equations for predicting pulmonary function on the basis of height, and have found increments consistent with variation in sex and ethnic groups (12). Age is considered an important variable in both the prediction of volumes and, occasionally, flows (29). Schoenberg et al. found that a term for age in the regression equation indeed created a noticeable improvement in correlation with flow indices (46). The additional advantage to adding age in the regression equation is arguable; while Schoenberg et al. confirmed the benefit of adding age, other authors have found age to be little or no importance (44), (45) and (50).

1.6 Lung function and other factors

1.6.1 Leg length

One explanation for differences in lung functions between different ethnic group is leg length. A study of 4064 married couples aged 30-59 was conducted in an attempt to explain the relationship between height, leg length and lung function with cardiovascular risk factor (79). Taller people have better lung function, due to a positive association between height and FEV_1. The biggest FEV_1 was related to lower blood pressure, cholesterol, glucose, fibrinogen, white blood cell count and body mass index (79).

Leg length, an indicator of a pre-pubertal nutritional factor, indicates that a good nutritional status leads to an increase in leg length. Thereby, lung function and FEV_1 are better in taller people (80).

Another study considered 294 healthy children of different white and South Asian origins (1). Standing height was an important predictor of lung function, ethnicity has been considered an independent predictor for all lung function measurements except Peak Expiratory Flow, where the impact was marginal (1). Moreover, this study found that FVC in white children was 13.4% higher than in South Asian children of the same height. The FEV_1 was 10.6% larger in white children than in South Asian children. There have been no significant differences found in the ratio of leg length to trunk length for the children in this study (1).

1.6.2 Chest wall dimensions

A longitudinal study has been conducted to explain the relationship between chest wall dimensions, lung function and age by studying 42 males aged 24-78 years (18). Elderly subjects have lower VCs than younger subjects; there has been shown to be a proportionately increased RV. Thereby, TLC showed little difference with that of younger subjects (18).

Another study was conducted to investigate the relationship between chest wall dimensions and lung function for different ethnic groups (1). The data for this study were collected from 294 healthy children from Asian (Indian) and whites, with the most important predictor of lung function being found to be standing height, while an independent predictor for all spirometry measurements was ethnicity. Chest dimensions did not explain the differences in lung function between the different ethnic groups. The impact of Body Mass Index (BMI) being smaller in Asian children than in white was not apparently significant (1).

Donnelly et al. attempted to examine the association between chest wall dimensions and differences in lung function between different ethnic groups. They studied chest radiographs of 38 adults from different ethnic groups (Caucasian, Chinese, and Indian). They found that Caucasian adults had larger chest cavities than their counterparts from China and India. Caucasian adults had wider chests than other ethnic groups. The residual volume for all ethnic groups was not found to vary significantly. A larger TLC was related to a larger FVC and FEV_1; also, the TLC reflects the size of the chest cage (7).

Furthermore, Donnelly et al. have attempted to examine the possible relationship between the physical features of the lung and chest wall to differences in lung volumes of different ethnic groups. They demonstrated that Caucasians had a larger inspiratory and expiratory muscle pressure and wider chests than Chinese and Indians. Caucasians had bigger lung volumes than Chinese and Indians because of their associated number of alveoli and physically bigger chest cavities. One possible explanation for this, is the large TLC in Caucasians leads to an increased number of alveoli in the lung (7).

Donnelly et al.'s study has been frequently quoted, but has the limitation of a small sample size.

1.6.3 Maximal respiratory pressure

One important but little-studied factor that may explain the difference in lung function between different ethnic groups is Maximal Respiratory Pressure. This term includes Maximal Inspiratory Pressure (MIP), which is the biggest subatmospheric pressure that can be created through inspiration against an occluded airway, and Maximal Expiratory Pressure (MEP), which is the greatest pressure that can be generated during a forceful expiratory effort against an occluded airway (81).

MIP and MEP have been considered essential factors by which to measure the power of respiratory muscles. MIP has also been used to investigate ventilatory failure. It has been deemed an independent predictor of all causes of mortality (17).

To measure MIP and MEP a non-invasive test should be used, which is dependent on the forced expiratory manoeuvre of the subject, and which should be fast. The range of normal values is wide. The interpretation should be relative to the limit of normal values for age and gender of the subject (82).

A study of 112 healthy white adolescents and adults was conducted to measure the normal values for MIP and MEP. The study outcomes have found that MIP and MEP values in healthy males are significantly bigger than in healthy females (15).

A study of 370 normal white adults and children measured MIP and MEP (16). This study measured three variables: age, height, and weight. In men, MIP and MEP were found to be significantly correlated only with age, while in women MIP and MEP were correlated only with height. In boys and girls, MIP appeared only to be related only to weight, while MEP was related only to age (16).

An American study was conducted to examine MIP of 3849 adults aged 45-84 from large multi-ethnic groups: non-Hispanic white, African-American, Hispanic and Asian (of Chinese origin) (17). This work found that important correlates to higher MIP values observed across the multi-ethnic groups in this study were the male sex, a younger age, obesity, higher FVC and shorter height. However, the differences in MIP by ethnicity were small (17). Indeed, this study was limited in the sense that it addressed only one variable, MIP, across four ethnic groups. So, in the present project, I considered MIP and MEP across different ethnic groups, to investigate the relationship between MIP and MIP and lung function in different ethnic origins.

A study of 100 non-smoking Brazilian males and females aged 20-80 measured MIP and MEP (81). They observed that MIP and MEP values were larger in men than women after adjusting for age, and a significant negative impact of age was found ($P< 0.05$). However, height and weight showed a significant positive correlation with MIP and MEP (81).

One study of 392 volunteer children aged 8 to 17 years has been conducted to establish reference values of maximal static inspiratory pressure and maximal static expiratory pressure. This research measured three variables: age, height and weight. MIP and MEP values increase with age. In all age groups, MIP and MEP values were larger in boys than girls. Weight, height, and age were included in the predictive equations for MIP in boys and girls, and MEP in boys (83). Moreover, there are large individual differences in normal values of MEP and MIP (84). The important correlates to MIP and MEP were height and age (84).

A study has been conducted to establish normal MIP and MEP values for children by studying 334 healthy boys and girls aged 7 to 14 years, using a portable pressure meter (85). This work assessed various anthropometry variables: age, height (standing and sitting), and weight. For males, age was the only significant independent variable for all MIP and MEP measurements,

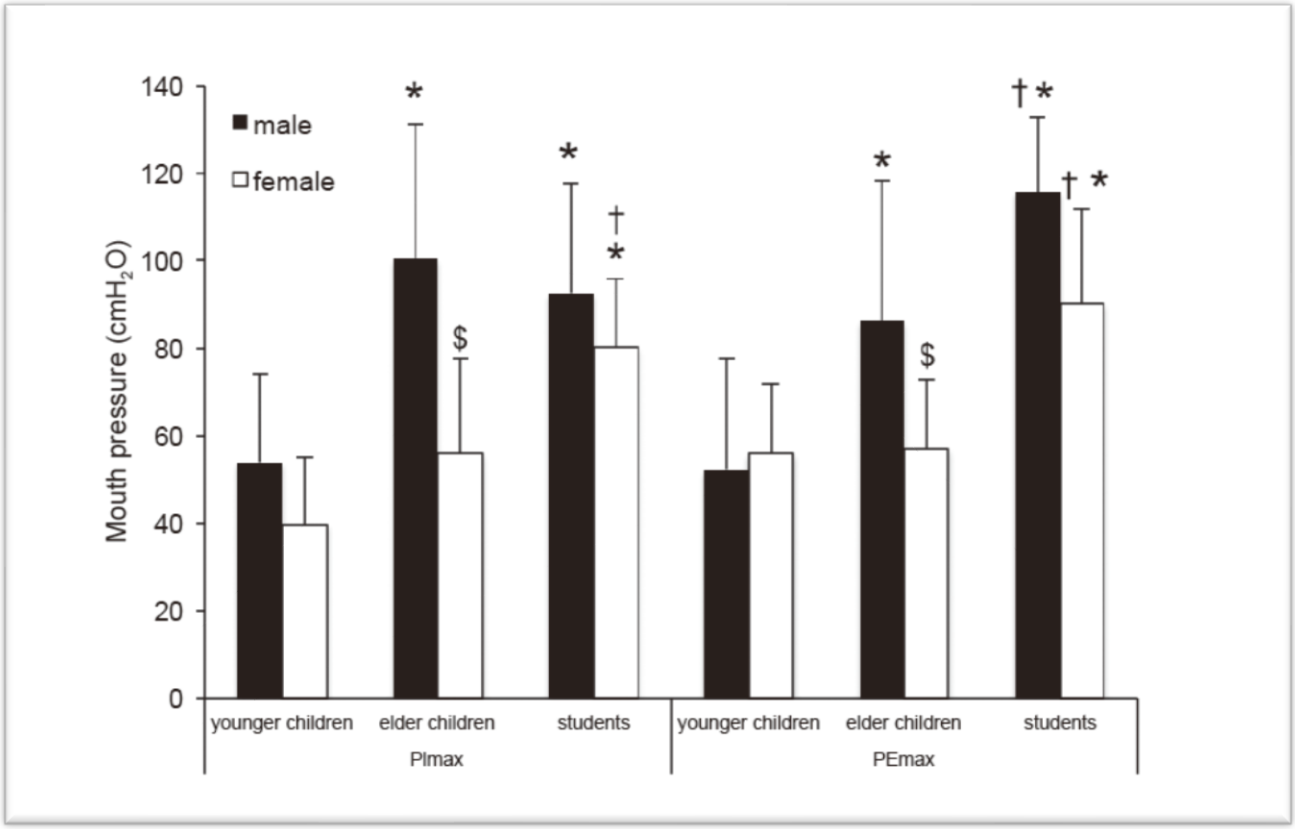
but in females, it was significant only for MIP in a standing position. Correlations between MIP and MEP with anthropometry were more significant in boys than girls ($P<0.001$)(85).

All researchers agree that the values of MIP and MEP depend on sex with biggest values found in males (85). However, when taking into account other anthropometric determinants considerable disagreements can be found between studies. For example, Karvonen et al., in an adult study, demonstrated that age had little impact on the maximal respiratory pressure in healthy males and females (86). Black and Hyatt found that MIP and MEP were correlated with age (87), while other work has reported a non-linear relation to age and body surface area by studying 625 healthy subjects aged 18 to 70 years (88). Smyth et al. did not find a significant association between maximal respiratory pressure and anthropometric data (15). In addition to this, Wilson et al. confirmed the relationship between MIP and weight and MEP to age, in both boys and girls in study of 137 boys and 98 girls (16). A study of 40 children found a significant correlation between pressures to height and age in boys, but not in girls (89).

Recently, work has been undertaken to establish the normal values for inspiratory muscle function in children by studying 301 children of school age, that is, 6 to 16 years (90). Maximal inspiratory pressure was measured after exhalation to residual volume (MIP). The gender-specific and age-dependent percentile curves for MIP were generated with 5%, 10%, 25%, 75% and 95% percentiles. The results showed that MIP values were significantly larger in boys than in girls (90).

A recent study was conducted to examine the respiratory muscle strength between healthy elementary school children and college students by studying a total of 56 males and females (91). The work samples were divided into three groups: 15 were younger children aged 6-9 years, 13 were older children aged 10-12 years, and 28 were college students. Fig 1.5 shows MIP and MEP were larger in the older children than in the younger children. MIP and MEP in both of the younger age groups and in the college students were larger in boys than in girls. MIP and MEP were found to have a significant association with age, height, and weight (91).

Figure 1-5 Respiratory muscles in children.



Legend: Respiratory muscle strength in younger children (6-9 years), older children (10-12 years), and college students. *p < 0.05 vs. younger children, †p < 0.05 vs. elder children, $p < 0.05 vs. males in the same age group. Adopted from (91).

Table 1.1 summarises the outcomes from different studies to explain the correlation between maximal respiratory pressure and different variables, namely age, height and weight.

Table 1-1 Some MIP and MEP study outcomes.

Studies	No. of subjects	Ethnicity	Age	Correlation MIP and MEP with Age	Correlation MIP and MEP with Height	Correlation MIP and MEP with Weight	Males MIP cmH_2O Mean and SD	Males MEP cmH_2O Mean and SD	Females MIP cmH_2O Mean and SD	Females MEP cmH_2O Mean and SD
Smyth, et al. 1984	112	Caucasian	13-18	No correlation	No correlation	No correlation	107±26	114±35	76±25	86±22
Wilson, et al. 1984	135	Caucasian	>18	MIP and MEP correlates with age in men but not women	MIP and MEP correlates to height in women but not men	No correlation	106±31	148±34	73±22	93±17
	235	Caucasian	6-18	MIP–no correlation MEP correlates in boys & girls	No correlation	MIP correlates with weight in boys & girls. MEP-no - correlation	5±23	96±23	63±21	80±21
Sachs, Enright et al.2009	3849	Four groups non-Hispanic white, African-American, Hispanic and Asian	45-84	Significant correlation	Significant negative correlation	Significant correlation with higher BMI only for women	97±29	---- MEP not measured	73±26	----
Neder, et al. 1999	100	Brazilian (heterogeneous)	20-80	Significant correlation in both sexes	No correlation	Weight correlates with MIP in males only	129.3±17.6	147.3±110	101.6±13.1	114.1±14.8
(Domènech-et al. 2003)	392	Ethnicity not stated, study was done in Valencia	8-17	Significant correlation with age in both sexes	MEP correlates with height for both sexes, and MIP in males	MEP correlates with weight for both sexes, and MIP in males	79± 31	95±34	68±24	82±29
Tomalak, et al. 2002	334	Ethnicity not stated, study was done in Poland	7-14	The significant correlation for MIP & MEP of boys.In girls, only MIP correlates with age in standing position	No correlation except for MEP in girls, in standing position	No correlation	Sitting position 84.53±27.43 Standing position 83.51±27.83	81.88±23.65 80.96±23.65	66.58±20.29 67.30±20.70	70.46±18.25 80.96±23.65
Mellies, et al. 2014	301	Ethnicity not stated, study was done in Germany	6-16	Significant in both sexes	No correlation	No correlation	69.34±22.43	---- MEP not measured	59.14±24.47	----
Ogawa, et al. 2014	56	Ethnicity not stated, study done in Japan	6-12	Significant correlation	Significant correlation	Significant correlation				

Legend: Summary of outcomes from different studies to explain the relationships between maximal respiratory pressure (MIP, MEP) and different variables: age, height and weight. Mean values of MIP and MEP are not strictly comparable because they are measured using different equipment and techniques and are taken from different age groups.

1.7 Inspiratory muscle strength and sniff nasal inspiratory pressure

Besides the MIP test, sniff nasal inspiratory pressure (SNIP) is considered another non-invasive method which has been used to assess the strength of inspiratory muscles in children and adults. SNIP can be measured by asking the subject to occlude one nostril before taking a maximal breath in through their nose (92).

SNIP has the advantage that it is a more natural action than MIP at the mouth and does not require a mouth seal around a mouthpiece to be effective (93). SNIP measurements also have reference data for children (94). However, it has been shown that SNIP manoeuvres require a long learning time and may take up to 20 attempts to obtain a maximal value, which makes them cumbersome when trying to assess respiratory muscle strength in practice. SNIP measurements also suffer from the same limitations as MIP and MEP in that they are volitional and are therefore effort-dependent (95).

The maximal sniff test has a wide range of applications, where it has been applied and validated as a repeatable and reliable test by which to assess inspiratory muscle function. Therefore sniff pressure has been deemed one of the more useful methods by which to detect mild to moderate muscle weakness in adults (94).

Furthermore, measurement of respiratory muscle strength is important in the assessment of respiratory and neuromuscular diseases. A few simple tests of respiratory muscle strength are applicable in children, where MIP has been deemed the most widely applied test to measure the strength of inspiratory muscles in children (96) and (16). MIP is not easy to perform, because it requires cooperation and motivation on the part of the subject leading to outcomes that might be submaximal and variable. A normal value of MIP excludes inspiratory muscle weakness; small values may be difficult to interpret, because they might equally reflect either inspiratory muscle weakness or the poor performance of the measurement. Besides, this test requires a mouthpiece, and therefore subjects with neuromuscular diseases might not find this easy to use (94).

Several researchers have attempted to find an additional test by which to assess the strength of inspiratory muscles in subjects with neuromuscular disorders by measuring the pressure which developed during a maximal sniff, namely natural effort which adult patients may find easy to perform (97).

Miller et al. reported that oesophageal pressure (Pes) was greater during a maximal sniff than during MIP and had a narrow range of normal values and was more repeatable (97). The

measurement of sniff Pes is invasive, and requires the positioning of an oesophageal balloon, and is thereby not ideal for use with children (98), (99) and (100).

A study of 116 normal children (boys and girls) aged 4 to 11 years from different ethnic groups (Caucasian, Afro-Caribbean, and Asian) was established to investigate the advantages of using the SNIP test in children (94). They made a comparison between the findings of the SNIP technique and those collected using MIP, and further obtained a range of normal values for SNIP. The investigators used a tube mouthpiece to measure the MIP, and a tightly fitting plug in one nostril for SNIP, while a sniff was performed through the other nostril. Both methods were performed from functional residual capacity; pressure was measured with a differential pressure transducer. Weight, standing height, sitting height, gender, and age were recorded (94).

The outcomes of the above study highlighted, the fact that SNIP was significantly higher than MIP ($P<0.01$) in both genders, and that regression analysis illustrated highly significant correlation ($P<0.01$) between SNIP and MIP, and between weight, standing height and age for MIP. In addition to this, SNIP and MIP were greater in boys than girls, but these differences were only significant for MIP ($P<0.05$), and that SNIP values were significantly larger than MIP ($P<0.01$) in both boys and girls. In terms of ethnic origin, SNIP values were greater than MIP in Afro-Caribbean boys and girls, where a similar correlation was noticed in Caucasian children. This observation was supported as SNIP exceeded MIP in 18 of the 24 males (75%) and 13 of the 15 females (86.6%). Additionally, there were no statistically significant variations in the age, height, weight, and inspiratory pressure among ethnic groups for males, while weight and height were significantly higher in Afro-Caribbean females than Caucasian females. On the other hand, there was no significant difference noticed in inspiratory pressure and growth parameters when groups matched for both height and weight were compared (94).

Rafferty et al. suggested that SNIP can be considered as an additional method by which to measure the strength of inspiratory muscles in children aged 5 years and above. The availability of the second method of measuring inspiratory muscles strength might well be considered useful, both when interpreting the outcomes collected from MIP effort, and when assessing subjects with neuromuscular diseases, predominantly those who do not find a mouthpiece easy to use (94).

Another study was conducted to establish the reference values in Caucasian children by studying 180 healthy children (males and females) aged 6 to 17 years (92). Caucasian children only were studied due to the potential ethnic variations in respiratory muscle strength and nasal

configuration. All efforts were performed in the sitting position; the SNIP was measured by using a catheter occluding one nostril during maximal SNIP effort through the contralateral nostril from FRC, while the MIP was measured from FRC and RV, and MEP from FRC and TLC. All respiratory pressures were related to age, height, and weight, except MEP, which was not associated with age or height (92). The results showed that the SNIP values were larger in boys than girls, and that SNIP had an association with age, weight, and height in boys, but not in girls. This observation could reflect the greater increase of muscle mass in males, mainly after puberty. Furthermore, in both boys and girls, SNIP was bigger than MIP as measured at the same pulmonary volume FRC ($P<0.0001$). SNIP values were equal to or greater than those of MIP in 73 of 93 males and 79 of 87 girls (92).

In this study, we did not include SNIP for a number of reasons: -

1- We were measuring expiratory as well as inspiratory pressures, and there is no SNIP equivalent for expiratory pressures.
2- SNIP is significantly correlated with MIP (94).
3- Our study focusses on ethnic differences in healthy children. We considered that the method by which pressures were measured was less important than consistency between measurements (of the children).
4- Time available for measurements in schools was always limited.

1.8 Lung function and physical activity

Several studies have found a positive correlation between lung function and physical activity. One previous study investigated the relationship between lung function and physical activity by studying 622 healthy boys and girls aged 5 to 18 years from different locations, both urban and rural, and different ethnic origins, namely European and African (28). An increased habitual activity and exercise performance led to increases in VC, TLC, and Transfer Factor (28).

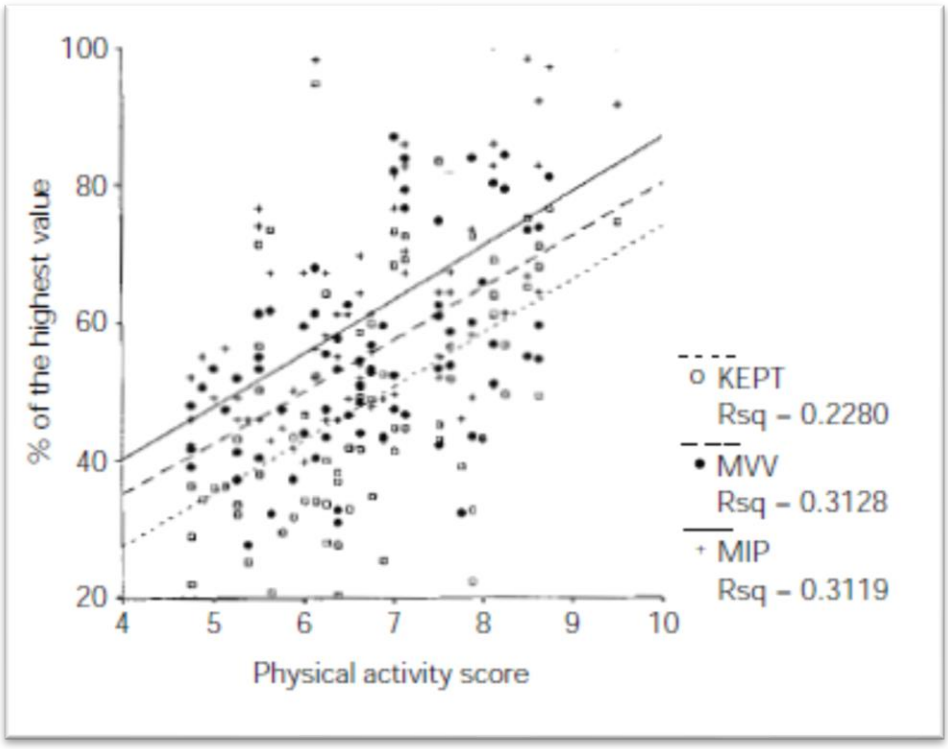
Another study was conducted to evaluate the association between increased exercise capacity, lung function improvement and physical activity in children with cystic fibrosis (101). They studied 78 boys and girls aged 6 to 16 years using the modified shuttle walk test (MSWT) to measure exercise capacity. Following a two month period of regular exercise, the patients that showed improved exercise capacity had a significant increase in median percent predicted FEV_1 (6%*vs.*-3%, p=0.03) compared to patients that did not show improved exercise capacity. Furthermore, no differences were recorded in change in Body Mass Index (BMI) percentile for

age. The outcomes of this study indicated that regular exercise over a two-month period leads to improved exercise capacity, and therefore improved lung function and physical activity in children with cystic fibrosis (101).

A study performed in Brazil to investigate the relationship between respiratory muscle strength, the regular level of physical activity and VO_2max, by evaluating 100 non-smoking males and females aged 20 to 80 (81). Physical activity was assessed in this study by using questionnaire, participants rated their habitual physical activity during the previous two weeks using a scale of one to five (five representing the most active) with eight questions about occupation, four about sport activities and four about habitual leisure habits. Results were reported as sum of scores. On the basis of the questionnaire, 88 subjects were considered to be sedentary with a total score below 8 (of these, 67 subjects had scores between 6 and 8, and 21 had scores below 6). The remaining 12 subjects had scores above 8, being considered physically more active but still nontrained subjects (102) and (81).

A significant linear correlation between respiratory muscle strength (MIP, MEP, and MVV), and the physical activity level, independent of gender and age, was noted (Fig 1.6) (81).

Figure 1-6 Physical activity.



Legend: Positive correlation between physical activity score (6) and various indexes of muscular strength such as peripheral (knee extensor peak torque, KEPT) and respiratory (maximal voluntary ventilation, MVV and maximal inspiratory pressure, MIP) strength. P < 0.001 for all correlations. Adopted from (81).

A significant positive correlation between height, weight, lean body mass and regular amounts of physical activity is shown (Table 1.2). Adopted from (81).

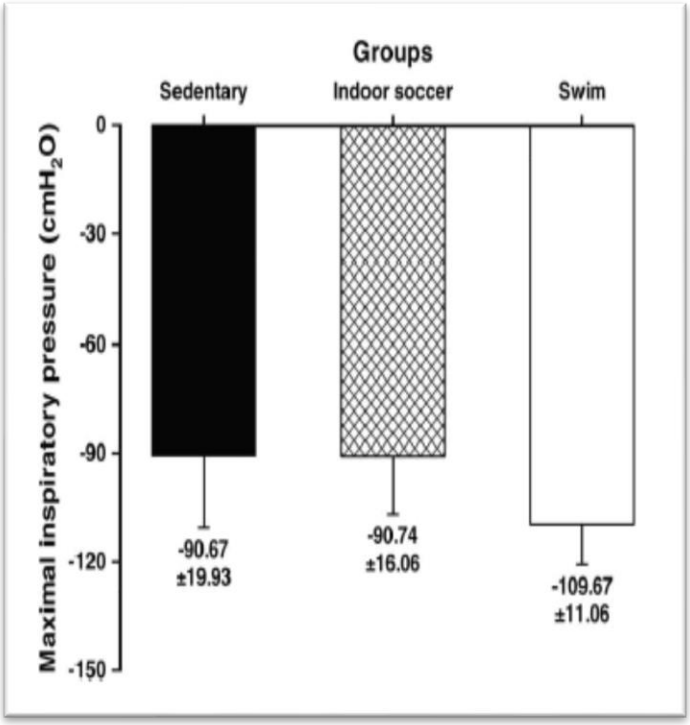
Table 1-2 The correlation between height, weight, lean body mass and level of physical activity.

	Age	Height	Weight	LBM	PAS	$\dot{V}O_2max$	Leg strength	MIP	MEP	MVV
Age	1.00									
Height	-0.22*	1.00								
Weight	-0.01	0.54**	1.00							
LBM	-0.24*	0.79**	0.84**	1.00						
PAS	-0.28**	0.38**	0.23*	0.42**	1.00					
$\dot{V}O_2max$	-0.61**	0.67**	0.50**	0.77**	0.58**	1.00				
Leg strength	-0.71**	0.71**	0.46**	0.79**	0.47**	0.86**	1.00			
MIP	-0.54**	0.49**	0.36**	0.66**	0.47**	0.81**	0.76**	1.00		
MEP	-0.51**	0.59**	0.49**	0.70**	0.46**	0.85**	0.79**	0.85**	1.00	
MVV	-0.56**	0.63**	0.38**	0.67**	0.48**	0.81**	0.81**	0.67**	0.72**	1.00

*Legend: A significant positive correlation between height, weight, lean body mass and regular amounts of physical activity is shown. LBM = Lean body mass; PAS = physical activity score; VO_2max = maximum oxygen uptake; MIP = maximal inspiratory pressure; MEP = maximal expiratory pressure; MVV= maximal voluntary ventilation. *P<0.05. **P<0.01. Adopted from (81).*

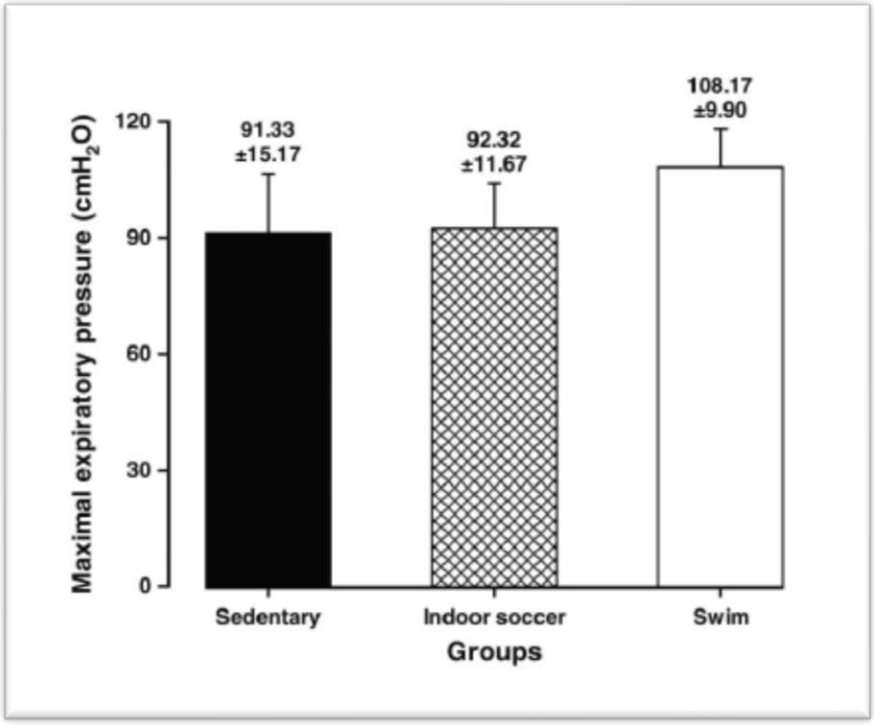
Another Brazilian study was conducted to measure respiratory muscle strength in children by recruiting 75 boys aged 7 to 8 years who practiced swimming or indoor football and their more sedentary counterparts (103). Study samples were divided into three groups: 25 boys were swimmers, 25 boys were played indoor football, and 25 boys were relatively sedentary. Fig 1.7 and Fig1.8 showed that the swimmers group had a bigger MIP and MEP than both indoor football players and sedentary subjects, and no significant difference was found among the outcomes for football players and the sedentary group (103).

Figure 1-7 Maximal inspiratory pressure.



Legend: Maximal inspiratory pressures in boys aged 7 and 8years who were sedentary, practised indoor football or practised swimming. ⊥Standard deviation; ⁎Highest significant difference. Adopted from (103).

Figure 1-8 Maximal expiratory pressure.



Legend: Maximal expiratory pressures in boys aged 7 and 8 years who were sedentary, practised indoor football or practised swimming. ⊥Standard deviation; ⁎Highest significant difference. Adopted from (103).

1.8.1 Exercise and lung function in adults

Several studies have shown that exercise has beneficial effects on the respiratory system in adults, leading to increased values for maximal aerobic capacity (VO2 max) (104), FVC and FEV_1 (105). Athletes who practise regular exercise for more than 15 hours per week have been shown to have significantly higher parameters for FVC and lung volumes than reference ranges (106), regardless of the sport they practice. However, the study showed that endurance athletes had the greatest lung volumes recorded. This finding has been supported by a separate study which showed that there are differences in the breathing mechanics of marathon runners when compared to a control group, with marathon runners breathing with a greater tidal volume and less frequency compared to the control group when undertaking strenuous exercise (107).

The same study was able to show that despite no differences in the Maximal Inspiratory Pressure (MIP) between the groups, the marathon runners were capable of generating greater threshold inspiratory pressures over a sustained period, indicating that they were less prone to respiratory muscle fatigue (107).

1.8.2 Exercise and lung function in children

Studies of the effects of exercise on respiratory function in children and adolescents also show changes in simple parameters of respiratory function. Overweight teenagers who undertook a 24 weeks treadmill-based training regime showed significant increases in FVC and FEV_1 at the end of the programme compared to the beginning (108).

Increases in lung function are also not just limited to children with initially below average parameters. In a group of elite male football players below the age of 15, regularly undertaking a speed dribbling test over an 8 weeks period led to an increased maximal oxygen uptake of 10% (109).

1.8.3 Exercise and respiratory muscle strength in children

With regards to the specific effect of exercise on the respiratory muscles in children, studies show that regular exercise can lead to increased performance values. A study of Brazilian boys aged 7-8 carrying out regular sporting activity found that while practising football had no impact on maximal respiratory pressures, undertaking regular swimming significantly increased both maximal inspiratory and expiratory pressures (103).

The effect of exercise upon respiratory muscle strength has also been shown in the work of Wells et al. in which a specific respiratory muscle strength training regime for nationally competitive adolescent swimmers saw a significant increase in the maximal inspiratory and expiratory pressures they were able to generate, alongside many other different parameters of lung function (110).

Dassios et al. found that in a sample of adolescent patients with cystic fibrosis, those who exercised regularly were capable of generating significantly greater maximal inspiratory and expiratory pressures than those who did not. This study had the benefit of assessing a group of subjects who traditionally have lower values for respiratory muscle strength and highlighted the potential impact exercise can have on increasing their muscle function (111).

However, the study acknowledged that these results may have been affected by the fact that those with greater respiratory muscle strength could have generally better lung function and hence may feel more able to undertake exercise, rather than exercise increasing their respiratory muscle strength.

In contrast to the previous studies, a longitudinal study assessing young female swimmers (112) found only significant increases in maximal expiratory pressures before the age of 10, with no differences in either inspiratory or expiratory pressures seen in the adolescent age groups when compared to age and height-matched controls.

The effect that exercise has on the respiratory system seems to generally be beneficial. Regular exercise in children shows improvements in parameters of lung function, while specific exercises regimes such as swimming have been shown to increase respiratory muscle strength. The effect of less intensive exercise on the strength of the respiratory muscles is more uncertain, although it has been shown to increase the maximal pressures of cystic fibrosis sufferers.

1.9 Lung function and diet

There is considerable body of evidence that demonstrates that nutrition has an effect on respiratory health (113), (114), (115) and (116). Nutrition scholars have investigated the relationship between lung function and intake of fruit, vegetables, and antioxidant micronutrients. They found that the intake of the above play an important role in protecting the lungs from damage (114), (115), (116) and (113).

A cross-sectional study investigated the correlation between lung function and antioxidant vitamins A, C, E, fruit, juice, and vegetable intake (115). They studied 2650 school age children with wheeze in England and Wales. The outcomes indicated that FEV_1 was positively correlated with the frequency of consumption of fresh fruit but less correlated with a green vegetable and salad consumption; however, FEV_1 was not correlated with serum levels of vitamin C, indicating that other micronutrients in fruit were important. Moreover, according to the findings of this work, low total vitamin C intake (≤ 10th percentile) was correlated with a reduction in FVC for both males and females and with greater reduction in flow found for females. Additionally, low dietary vitamin E intake was correlated with lower FEF25-75 in females and males. In girls, the reduction in FEF 25-75 was associated with low dietary vitamin A intake and with low total vitamin A intake in boys with asthma. Moreover, other results indicated that low intakes of orange and other fruit juices, which were the highest source of vitamin C, could be correlated with a reduction in FVC and FEV_1 in males, so pulmonary function values were lower in children with inappropriate dietary antioxidant vitamin intake (115).

A substantial body of evidence indicates that nutrition influences respiratory health (113), (114) and (115). Data was available for 2,566 subjects in Gilliland' study (113), 2650 subjects in Cook' study (115) and 2,633 subjects in Britton' study (114), the larger number of subjects participated in these studies give the power for the work to examine any interactions between lung function and healthy diet with great confidence, and to confirm that there was a significant correlation between lung function and health diet.

1.10 Alternative explanations for lung function differences between children of different ethnic origins

Several studies were conducted to assess factors which might be considered to have an effect on lung function, for example, cultural factors, socioeconomic status, birth weight, breastfeeding, environmental exposures, genetic factors and family histories of disease (117), (118), (119), (120) and (11).

A study was conducted to explain lung function differences between white and South Asian children (11). They studied 1088 white and 275 South Asian children born in the UK aged 9 to 14 years, where anthropometry variables were appropriately adjusted. Five different models were used and adjusted for cultural factors, socioeconomic factors, perinatal factors, environmental exposures, personal and family histories of wheeze. It was found that important differences in lung volume between South Asians and white children were evident. The causes for these variations are not clear; they could reflect either genetic differences affecting body habitus or respiratory muscles strength to various degrees, or reflect differences in the environment between ethnic groups. (11). This study did not explain why these differences occurred between ethnic groups.

The difference in socioeconomic factors between ethnic groups is considered key to an understanding of lung function variation. Parents of black and Hispanic children are more likely to be poor and with lees educational opportunities than their non-Hispanic white peers. Children living in poor conditions are more likely to report respiratory problems than those who living in good conditions (117) and (118).

However, studies conducted in a number of countries, England, China, and Malaysia, to investigate the relationship between lung function and socioeconomic status did not find any correlation between lung function and socioeconomic status (11), (121), (122) and (123).

Rates of breastfeeding and smoking have an effect on lung function among children; decreased rates of smoking among Hispanic parents may help to protect their children's respiratory health (117) and (120). Low levels of breastfeeding between black and Hispanic women could be related to increasing levels of respiratory problems among their children (119) and (118). It is clear that lower rates of breastfeeding and higher rates of smoking have a negative effect on children's health with regards to respiratory disorders.

1.11 Respiratory muscles

1.11.1 Respiratory muscles structure

Respiratory muscles are skeletal muscles; they are composed of different kinds of fibres. The fibres are characterised by different functional or molecular properties (Table 1.3). They have different speeds of contraction and resistance to fatigue. The name of each of these types of fibres depends on the genes expressed in each type, for example; the SERCA1 gene is responsible for the expression of fast skeletal muscle fibres, so the fibre is called fast 2A (124). These fibres help the respiratory muscles to adapt differently to recruitment for either short intense or prolonged activity with low or high force development. For example, slow fibres are resistant to fatigue because of their highly oxidative metabolic mechanism, whereas 2X and 2B fibres are easily fatigued, and fast 2A fibres exhibit an intermediate resistance to fatigue (125) and (126).

Slow and fast fibres are present in equal proportions in the adult human diaphragm, while intercostal muscles contain a higher proportion of fast fibres. The typical components of diaphragm fibres are small in fibre size with numerous capillaries and a high aerobic oxidative enzyme activity, providing the diaphragm with the resistance to fatigue that its continuous activity requires. Due to their fibre composition, intercostal muscles are less resistant to fatigue (125).

The structural and functional features of respiratory muscles fibres are not fixed, so they can be modified in response to different physiological and pathological conditions, for instance training (adaption to changes in respiratory load), adaptation to hypoxia, age-associated changes, and changes related to respiratory disorders. In addition, parts of respiratory muscle fibre can be modified by pharmacological agents, for example, ß$_2$ agonists and some types of corticosteroids can be used for the treatment of respiratory diseases (127), (126) and (125). The classification of human skeletal muscle fibres reported in (Table 1.3).

Table 1-3 Classification of human skeletal muscles fibres.

Table 1 Classification of human skeletal muscle fibres and distinctive functional or molecular properties of each fibre type

Classifications:			
Myosin based classification	Slow or type 1	Fast 2A	Fast 2X
Classification based on metabolism and time course	Slow oxidative (SO)	Fast oxidative (FOG)	Fast glycolytic (FG)
Classification based on fatigue resistance	Slow fatigue resistant (S)	Fast fatigue resistant (FFR)	Fast fatiguable (FF)
Properties:			
Myosin isoforms	1 or slow	Fast 2A	Fast 2X
Maximum shortening velocity	Slow	Fast	Very fast
Myofibrillar ATPase activity	Low	High	Very high
Calcium uptake in the SR	Slow	Fast	Fast
Time course of the twitch	Slow	Fast	Fast
Resistance to fatigue	High	Intermediate	Low
Metabolism	Oxidative	Oxidative glycolytic	Glycolytic

SR, sarcoplasmic reticulum.

Legend: Classification of human skeletal muscles fibres. Adopted from (125).

1.11.2 Respiratory muscles function

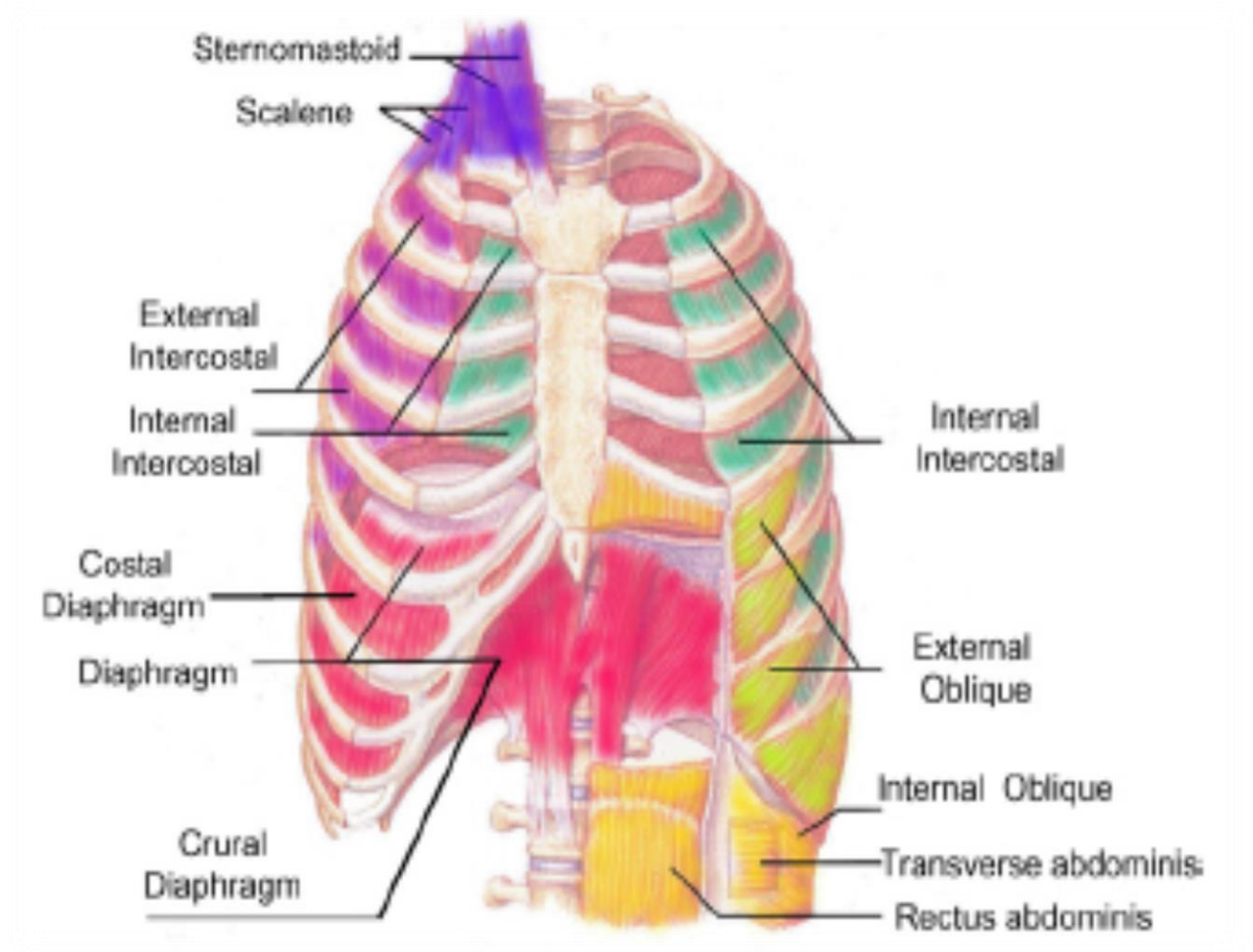
The respiratory muscles provide the motive power for the breathing. The alternating air flow to and from the alveolar surface is driven by pressure gradients generated by the respiratory muscles. The respiratory muscles have the same basic structure and function as all other limb and trunk muscles. The plasticity and specialisation of respiratory muscles are driven directly from the features of the fibres which they are composed (128), (127), (126) and (125).

Muscle fibres have the ability to generate force and mechanical power; the time of relaxation, contraction, and the resistance to fatigue differ from fibre to fibre. The myofibrillar protein composition and the myosin isoform composition play important role in helping a muscle fibre to generate tension, to shorten and to produce mechanical power. Myosin is the motor of the muscle contraction; it is able to convert the chemical energy of ATP into work energy. The myosin molecule is a hexameric protein, comprising of two heavy chains (MyHC) and four light chains (MyLC). Both these chains exist in several isoforms (125) and (126).

1.11.3 Classification of respiratory muscles

Respiratory muscles are classified into two groups: inspiratory and expiratory muscle groups. Inspiratory muscle groups comprise the diaphragm, external intercostals, parasternal, sternomastoid and scalene muscles. The expiratory muscle groups include the internal intercostal, rectus abdominis, external and internal oblique and transverse abdominis muscles (127) and (129). A schematic description of the anatomy of human respiratory muscles is given in (Fig 1.9) (129).

Figure 1-9 Human respiratory muscles.



Legend: Schematic description of the anatomy of human respiratory muscles. Adopted from (129).

1.11.3.1 Inspiratory muscles

The diaphragm is considered to be the main muscle of inspiration; it is a thin, flat musculotendinous structure separating the thoracic cavity from the abdominal wall. The muscle fibres of the diaphragm provide from the central tendon to either the three lumbar vertebral bodies, via the crural diaphragm, or to the inner surface of the lower six ribs, via the costal diaphragm (129). The costal fibres of the diaphragm include a two-sided muscle sheet. During contraction, the tension within the diaphragmatic muscle fibres generates a caudal force on the central tendon that descends in order to expand the thoracic cavity along the craniocaudal axis. At the same time, the costal diaphragm fibres apply a force to the lower six ribs which lifts and rotates them outward (127) and (129).

The external intercostal muscles are another type of inspiratory muscle. They are comprised of thin layers of muscle fibres that run obliquely downward and ventrally from each rib to the neighbouring rib below. Also, there is another type of inspiratory muscle collectively referred to as the accessory muscles that comprise such structure as the sternomastoid and the scalene muscles (126), (126) and (129). The sternomastoid muscles descend from the mastoid process to the ventral surface of the manubrium sterni and the medial third of the clavicle. The scalene muscles comprise three bundles that run from the transverse processes of the lower five cervical vertebrae to the upper surfaces of the first two ribs. Contraction of these muscles raises the sternum and the first two ribs and thus assists the expansion of the rib cage (130).

1.11.3.2Expiratory muscles

The internal intercostals muscles are thin muscle fibres that run obliquely downward and dorsally from each rib to the neighbouring rib below. During contraction, the lower insertion of these muscles is less distant from the rib axis rotation than the upper one, and therefore, they lower the ribs (129) and (130).

The abdominal muscles are composed of four abdominal muscle pairs forming the abdominal wall: rectus abdominis, external oblique, internal oblique and transverse abdominis. Contraction of the abdominal muscles pulls the abdominal wall inward, and therefore the diaphragm moves into the thoracic cavity and pulls the lower ribs to deflate the rib cage (130) and (129).

1.11.4 Respiratory muscle strength and puberty

Puberty has been shown to influence the respiratory system in a number of ways; chiefly in that it stimulates growth in mass and size of the respiratory muscle fibres (77). Pubertal development also causes changes in the chest wall dimensions of boys and girls and leads to central nervous system maturation, influencing the contractility of the respiratory muscle fibres (77).

Studies have shown that pre-pubertal children have a reduced respiratory muscle endurance compared to those of a similar age who have undergone puberty (78). A separate study has shown a sharp increase in values for FVC and FEV_1 for girls and boys at the average time of the onset of their pubertal growth spurt (10 and 12 years respectively) (62).

Whilst having an influence on the respiratory system and muscles, puberty itself has been shown to be affected by BMI and body weight. Studies have shown that girls who are classed as being overweight according to their BMI show signs of sexual maturation (Tanner staging) earlier than girls who are classed as underweight (131) and (132).

Work by Wang et al. also showed that girls with greater BMI were more likely to be in advanced stages of development, but in contrast found that the heaviest boys generally underwent development later compared to their peers (133). These findings were corroborated by another study which showed that boys with a BMI value classified as overweight were more likely to undergo puberty earlier than boys who were classified as having an ideal BMI value, but that those who were classified as obese underwent puberty later than both the boys in the ideal and overweight categories (134).

The proposed mechanism for this finding in boys is the activity of the aromatase enzyme, found in adipose tissue and therefore in greater quantities in obese boys (134). This enzyme produces oestrogen, which delays male pubertal development by counteracting the effect of testosterone.

1.12 Respiratory system elasticity

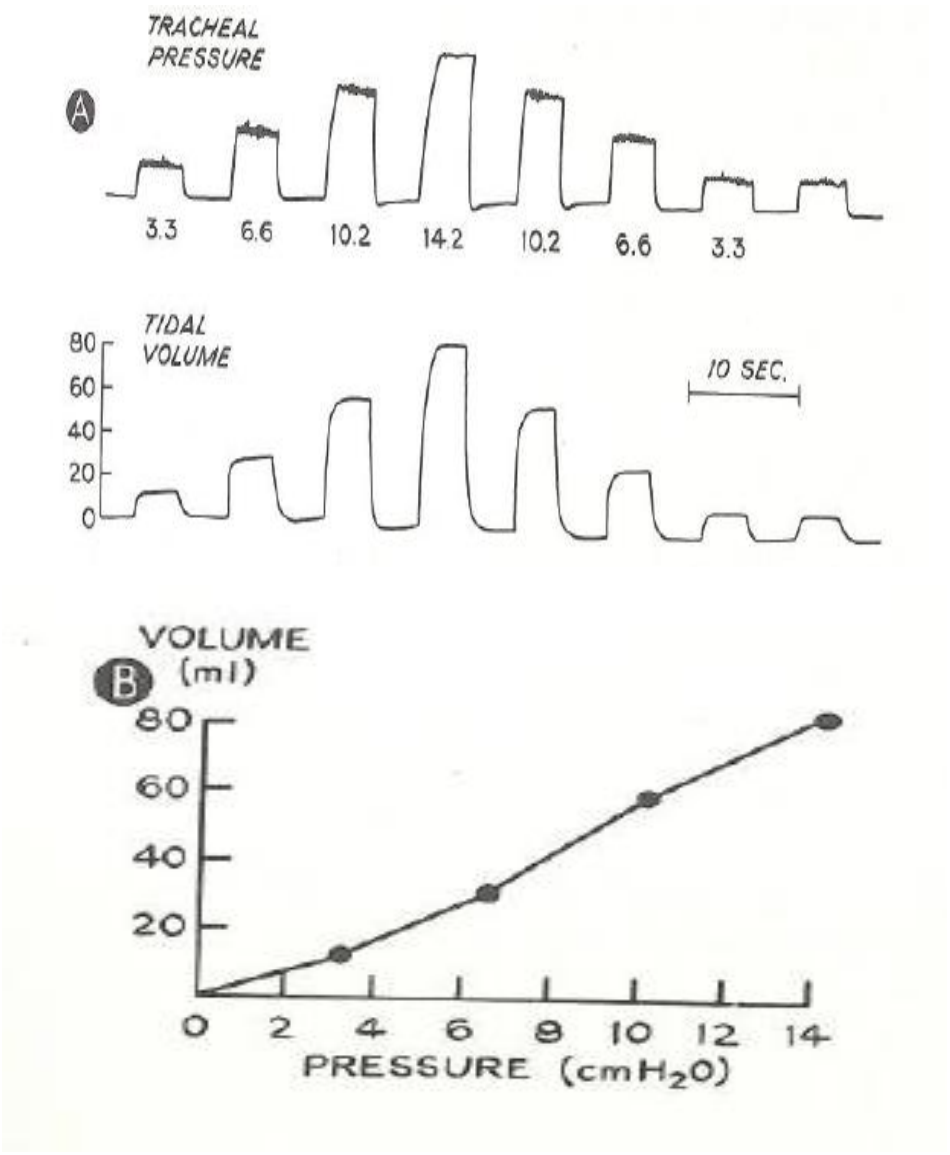
1.12.1 Elastic recoil of the lungs

The lungs are elastic structures which change in volume when appropriate pressures are produced through the inspiratory and expiratory muscles. When the respiratory muscles are relaxed the respiratory system returns to the resting volume. This is the end-expired volume or functional residual capacity (FRC) when alveolar pressure is equal to atmospheric pressure (82).

The tissues of the lungs and chest cage contain fibres, collagen, cartilage, epithelial and endothelial cells, smooth muscles, glands, nerves, blood and lymph vessels. Some of these components are elastic like springs. Therefore, when the lung is acted on by an external force these tissues are stretched during inhalation, and when this external force is removed, the tissues recoil to their resting position (135), (136) and (137).

Lung compliance can be measured easily in an anaesthetised animal. An animal model has been used to measure pulmonary elasticity with a tracheal cannula and an open chest cage. A known volume of gas was pushed into the trachea, then the trachea was closed and the static pressure of lung recoil was measured. The next step was to inject another volume of gas and to measure lung recoil pressure under static conditions. This procedure was repeated for several larger volumes. Another method that has been used to measure pulmonary compliance was to inflate the lungs using several known pressures and measuring the associated volume change. In both approaches, a graph relating pressure change to volume change was plotted. The gradient of plot is expressed as L/cm H_2O is compliance (Fig1.10) (135).

Figure 1-10 Pulmonary compliance.



Legend: (A) a pump inflates the lungs of an anaesthetized animal 6 times/minute with increasing and then decreasing pressure. However, for each inflation, the pressure becomes constant (at 3.3, 6.6, 10.2 or 14.2 cmH_2O via an overflow tube set at the desired pressure. Note the increase in tidal volume with increasing pressure. (B) a static pressure-volume curve has been constructed from the end –inflation values (when there is no air flow). Adopted from (135).

An unanaesthetised human model (man) was used to measure pulmonary compliance by measuring the pressure in a balloon in his intrathoracic oesophagus at the end of a normal exhalation, which was repeated after he exhaled a known volume of gas and held his breath. This gives a measure of static compliance. This was then repeated several times with larger inspired volumes. The changes in oesophageal pressure versus changes in pulmonary volume were plotted (135) and (136).

There is an important question to ask. Is it possible to measure or estimate the elastic recoil of the lungs purely by measuring or determining the intrapleural pressure (intra-oesophageal) at only one lung volume for example function residual capacity?

The answer will definitely be no because the oesophageal balloon technique is more ideally suited to measuring changes in the intrathoracic pressure than measuring absolute pressure. Therefore, another approach has been used to overcome this gap in this measurement, as based on measuring the elastic recoil of the lungs at two points of zero flow during each respiratory cycle, end-expiration and end- inspiration (Fig 1.11). Therefore, when there is zero flow, no pressure is required to overcome airway resistance, and the entirety of the transpulmonary pressure at these two points is required to overcome pulmonary compliance; this is dynamic compliance (135) and (137).

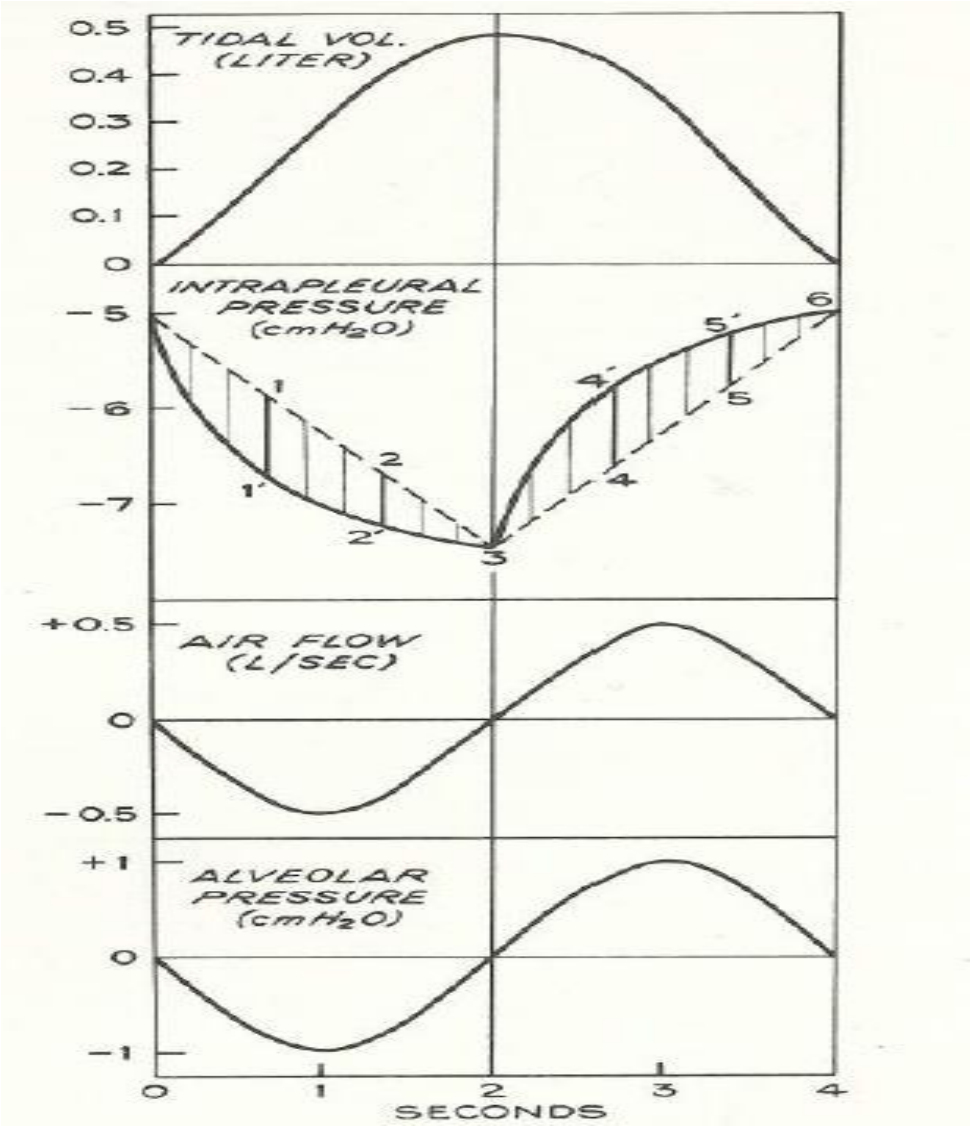
If pressures have been recorded at these two points, and the effort was performed at a series of tidal volumes of increasing depth, the line connecting between these two points can be plotted as change in volume versus change in oesophageal pressure or of compliance (135) and (136).

If the effort was achieved by breathing in and out very slowly, and intrapleural pressure and respired volume are recorded, flow is slow, therefore a very small pressure is needed to overcome airway resistance in relation to that required to overcome elastic recoil, and in this case one line without a loop explains the pressure-volume association during inhalation and exhalation (135) and (138).

When the manoeuvre is performed faster and faster, a greater pressure is needed for flow, and the pressure-volume curve, in this case, becomes a loop- narrow at lower flows and thicker and thicker as flow gets faster. The model was used to apply these approaches was the man who is healthy and the line for his measurements at the end -inhalation and end-exhalation remained the same up to rates of 60-90 breaths/ minute. In the same model, the compliance was measured at

different of breathing rates (fast, slow and under static conditions), where the lung compliance was equal at all rates (135) and (139).

Figure 1-11 Volume and pressure changes during a single inspiration-expiration cycle.



Legend: Volume and pressure changes during a single inspiration-expiration cycle. All measurements were made continuously and simultaneously during one cycle. If transpulmonary pressure was needed only to overcome elastic recoil, intrapleural pressure fluctuations during the respiratory cycle would follow the straight dashed lines. However, an additional pressure (that between 1 and 1', 2 and 2', etc., on the intrapleural pressure record) was recorded to overcome tissue and airway resistance during flow. At end-inspiration (point of no flow), lung volume had increased 0.48L and intrapleural pressure had decreased 2.4 cm H_2O; compliance =0.48/2.4=0.2L/cm. This figure is schematic; inspiration and expiration are not usually equal in time. Adopted from (135).

1.12.1.1Factors influencing elasticity of the lungs

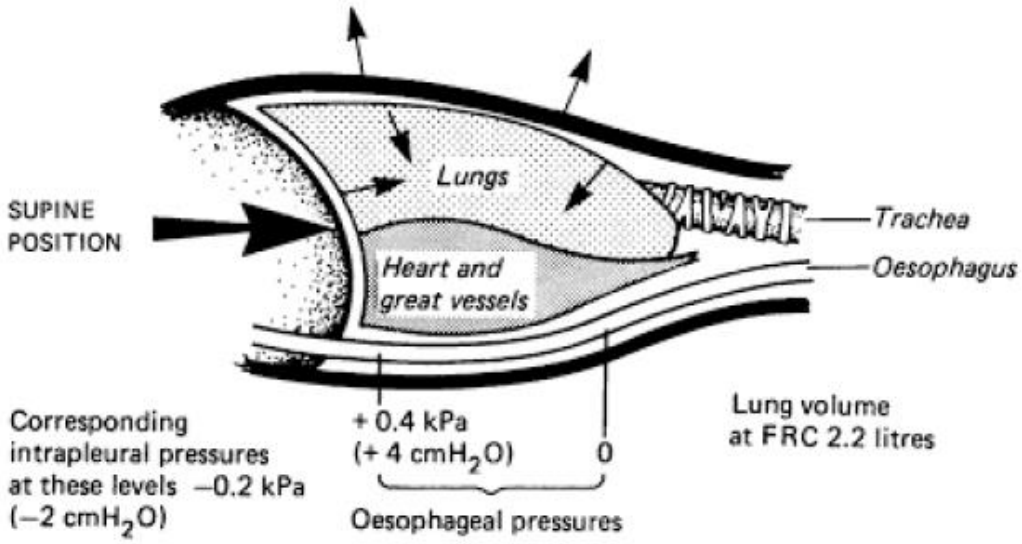
1.12.1.2 Lung volume

It has been known that elastic recoil of the lungs is related to the lung volume. Lung volume is entirely related to functional residual capacity (FRC) to yield the specific compliance, for example, compliance/FRC which is usually constant across both sex and age down to newborns (138) and (139).

1.12.1.3 Posture

Lung volume changes with posture. It has been noticed that in the supine posture the weight of the heart might cause an artefact in recorded volume (Fig1.12), but at the point when oesophageal pressure is equal to atmospheric pressure there is always a zone at some 32-40 cm beyond this point, and it might be only approximately 0.2 kPa (2 cm H_2O) above the nearest intrathoracic pressure. When alveolar pressure equals mouth pressure, no gas is flowing and lung compliance cannot be measured directly (138).

Figure 1-12Measuring lung compliance in the supine position.



Legend: Intrathoracic Pressure: Static relationship in the resting end-expiratory position. The lung volume corresponds to the functional capacity (FRC). The heavy arrow in indicates the displacement of the abdominal viscera. Adopted from (138).

1.12.1.4 Pulmonary blood volume

It has been detected that the pulmonary venous congestion leads to reduce lung elasticity (138).

1.12.1.5 Age

It is generally expected that age will have an influence on the elasticity of the lung as with any other organ in the body, but it has been found that pulmonary volume was increased and lung elasticity decreased in the young subjects compared with the more elderly (18). Butler et al showed that there was not relationship between age and lung compliance (140).

Total respiratory compliance was measured by studying 70 healthy males aged 4 to 70 years (132). Age influences total respiratory compliance and appears to increase through the first three decades and decrease in subsequent decades. Respiratory compliance was correlated to the height, body surface area, TLC, and VC. Furthermore, vital capacity appeared the best association with respiratory compliance. The difference in respiratory compliance with age did not appear to be due to differing body size. However, when considering the corrected TLC, there was a steady decline in total compliance with age which could possibly be attributed to an increase in resistance of the chest wall (132).

1.12.1.6 Restriction of chest expansion

Elastic strapping of the thorax decreases both lung volume and compliance. On the other hand, when the pulmonary volume is returned to normal either by removal of the restriction or by a more forceful inspiration, the lung elasticity remains reduced. However, normal compliance can be restored by taking a single deep breath (140) and (138).

1.12.1.7 Recent ventilatory history

It is known that lung compliance is controlled by rhythmic cycling with the effect being dependent on tidal volume (TV). Therefore, a period of hypoventilation without regular deep breaths might lead to decreased lung compliance (140).

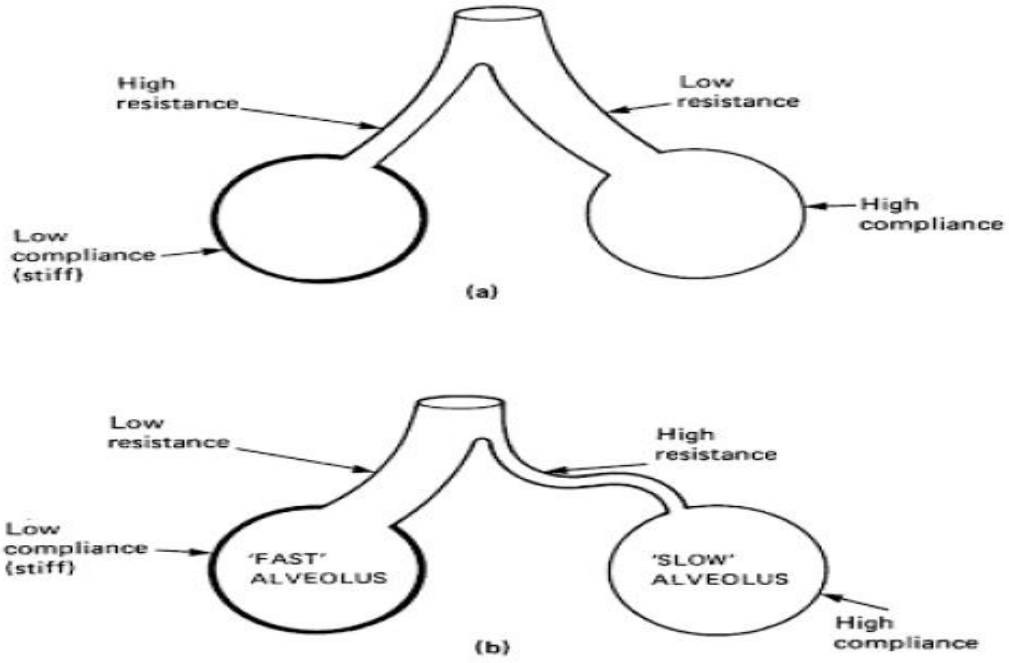
Butler et al. pointed out that lung compliance is decreased if the lung volume is restricted, and explained that compliance reduction following a period of breathing within the expiratory reserve is because of elastic strapping of the rib cage (141).

1.12.1.8 Disease

It has been found that most changes in lung pressure/volume associations are due to lung diseases; for instance, in emphysema, lung compliance is increased because of the destruction of lung tissue and loss of either elastin or surface retraction, such that FRC is consequently

increased. By contrast, inspired gas compliance is usually decreased (Fig1.13) and, accordingly dynamic compliance is usually decreased. In a patient with asthma, the pressure/volume curve is displaced upwards without a change in compliance, despite the fact that the lung elastic recoil is reduced at normal transmural pressure and therefore FRC is increased (142). It should be expected that most other types of lung disease will cause reduced lung compliance, either dynamic and/ or static (138).

Figure 1-13 Schematic diagrams of alveoli to illustrate conditions under which static and dynamic compliance may differ.



Legend: (a) represents an idealised state which is probably not realised even in a normal subject, where the reciprocal relationship between resistance and compliance results in gas flow being preferentially delivered to the most compliant regions, regardless of the rate of inflation. Static and dynamic compliance is equal. (b) illustrates a state which is typical of many patients with respiratory disease. The alveoli can conveniently be divided into fast and slow groups. The direct relationship between compliance and resistance results in inspired gas being preferentially delivered to the stiff alveoli if the rate of inflation is rapid. An end-inspiratory pause then permits redistribution from the fast alveoli to the slow alveoli. Adopted from (138).

1.12.2 Studies on lung elasticity

One previous study investigated the relationship between the chest wall, pulmonary distensibility and age by studying 42 healthy males aged 24-78 (18). It was found that pulmonary volume was increased, and lung elasticity decreased, in younger subjects compared with the more elderly. Chest wall compliance was decreased in older people. This may in part explain why Vital Capacity decreases but the Residual Volume increases in older people (18).

A study of 63 healthy children aged 2 to 7 years measured the total respiratory compliance and functional residual capacity (143). A positive association was found between respiratory system compliance (CRS) and height and age, and also between FRC and height. The outcomes of CRS and FRC showed that no differences were found between boys and girls. Besides, CRS- could be positively associated with FRC (143).

A study was conducted to measure respiratory system compliance (CRS) in 33 healthy black infants and 33 healthy white infants (144). The findings showed that CRS was greater in white infants than in black infants when adjusted for body weight. This might be related either to a lower lung compliance or probably attributed to a lower lung volume in black infants, or to a lower chest wall compliance (144).

Binder et al. attempted to explain the difference in lung function between black and white children by studying 393 children aged 9 to 17 years (14). They hypothesised that the pulmonary volume in black children may be decreased with increasing elastic recoil, but no evidence appeared to confirm this hypothesis (14).

A previous study measured lung compliance in 70 healthy young adults (145), the results of which showed that there was a positive relationship between lung compliance, height, body surface area, and vital capacity, but showed a negative association with age (range: 18-39 years) and sex (145).

1.12.3 Elastic recoil of the chest

The chest cage, as an organ in the body, also has tissues, which themselves have elastic properties. When the lungs are in a relaxed state, this means they are not acted on by external forces (such as the pull of the chest) that might collapse the lungs normally to an airless state beyond residual volume (RV), while if the chest cage is not acted on by any external forces (such as the pull of the lungs), this can expand the chest from their rest volume by approximately 600 ml (135).

Chest elastic recoil can be measured directly and/or calculated by subtracting lung compliance from combined lung-chest wall compliance. Rahn et al have attempted to measure chest compliance in a healthy man using two manometers, one connected to an oesophageal balloon to measure any change in intrapleural pressure, and the other connected either with the mouth or a nostril to measure alveolar pressure (Fig1.14) (146).

The volunteer was asked to inhale a known volume of gas and hold his breath with his glottis open, therefore any change that occurred in oesophageal pressure was equal to the pressure change in lung elastic recoil. He was then asked to close his nose and mouth and relax all his respiratory muscles. Thereby, the nose or mouth pressure was equal to the total lung and chest recoil pressures through active contraction of the inspiratory muscles. Similarly, oesophageal pressure was equal to the chest pressure due to the pressure of the water manometer connected to the nose or mouth, leading to a balance in the elastic force of the lung in this closed system (146).

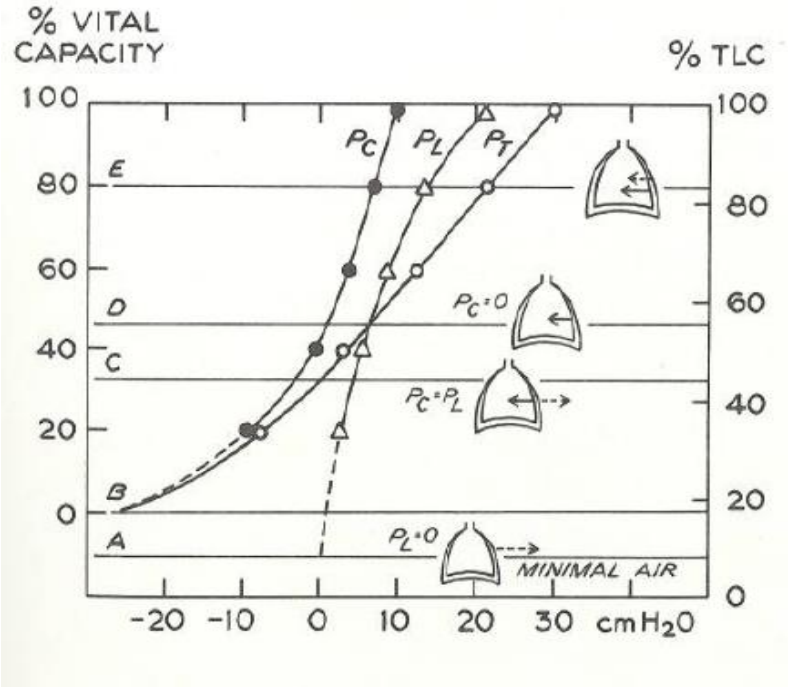
Rahn et al. gave a mathematical approach to calculating thorax compliance. They noted that when data were obtained concurrently for the lungs' elastic recoil alone and the pulmonary and chest cage together (total compliance), that chest compliance alone can be calculated using the equation 1 (146).

Equation 1 chest compliance.

$$\frac{1}{\text{Total compliance}} = \frac{1}{\text{Pulmonary compliance}} + \frac{1}{\text{thoracic cage compliance}}$$

Adopted from (135, 146) and (135).

Figure 1-14 Pressure-volume curves of lung and chest cage.



Legend: Pressure-volume curves. P_L =pressure exerted by lung at each volume (expressed as percentage of total lung capacity, TLC). P_C =pressure exerted by the chest cage. P_T =pressure exerted by the total system (lungs + chest cage). A= minimal air (volume of gas remaining in lungs when the thoracic cage is open to atmospheric pressure); line B=residual volume; line C=FRC; line D= inspiration; lineE= deep inspiration. The "lungs-thorax" sketches arrows=chest cage tension; solid arrows =lung tension. Adopted from (146) and (135).

1.13 Background on measuring the elasticity of the respiratory system

Here, I have attempted to briefly review the history of measuring the compliance of the respiratory system. The function of the respiratory system was not clearly understood, and this could be the reason why breathing mechanics were widely ignored, until the end of the 17th century. The mechanics of the lung and chest wall were not clearly considered until the 1660s, when the first observations of respiratory movement were made by Sylvius who described the lungs as moving passively, following the motions of the rib cage and diaphragm. Furthermore, Sylvius noted that the lungs filled with air because they were being expanded, instead of the expansion of the lungs being as a result of them filling with air (135), (136) and (139).

In 1668, John Mayow was able to explain the bellows-like action of the thorax. By the following century, a mechanical/mathematical analysis of the respiratory movement of the chest had been developed by Hambergerb (147) and (137).

In 1820, the first attempt to measure the elastic recoil of the lung in various animal cadavers was made by Carson, who explained that there was a balance of forces between the lungs and the diaphragm (138).

Many attempts have been made to measure the elastic recoil of the lungs in humans, which were first attempted by Hutchinson, whose work is considered to be the first to measure pressure-volume curves in the isolated lungs of two human cadavers (135). Donders worked to extend Carson's work with the attempt to measure the elastic recoil of the lungs (also in human cadavers). In 1847 Ludwig attempted the indirect measurement pleural pressure with an oesophageal catheter (147).

In 1927, von Neergaard and Wirz became the first to measure the static lung compliance in living adults by measuring pleural pressure directly within a pneumothorax. They summarised that the benefit of measurements static compliance over dynamic compliance, and considered the effect of surface tension (148).

For many decades, researchers believed that the recoil of the lungs was due to stretching of the yellow elastin fibres present in the lung parenchyma. However, in 1929, von Neergaard determined the relationship between the lungs and surface tension. He showed that when the lungs are filled and immersed in water, it had an elastane value which was smaller than the normal value collected when the lungs were filled with air. Therefore, he clearly showed that much of the elastic recoil effect was related to surface tension acting throughout the vast air/water interface lining the alveoli (127).

In the 1950s, measurement of the static recoil of the lungs became more widespread, and early studies showed the relationship between compliance, lung size, body size and age (149) and (150).

Buytendijk and Schilder et al. gave considerable attention to improving the oesophageal balloons, and presented strong evidence that the change in oesophageal pressure was equivalent to a change in pleural pressure (128) and (129).

Ethnic differences in lung function have been well documented and the importance of adjusting for ethnicity has been emphasised (19), (20), (1) and (2). However, the paucity of spirometry studies that have given appropriate consideration to ethnicity, especially in children, is currently impeding diagnosis and clinical management of lung disease, and complicates interpretation of clinical trials where lung function is a primary outcome (21). The recently published Global Lung Function Initiative (GLI)-2012 multi-ethnic spirometry equations (22) provide a good fit for contemporary individuals of black-African origin and white- London primary schoolchildren (23), and although the published equations did not cover all ethnic groups, a preliminary coefficient for South-Asian children based on GLI-2012 has also been developed (24) and (25). Nevertheless, ascribing ethnicity is a complicated but necessary area of study in an increasingly multi-ethnic society. Most lung function prediction equations are derived from studies of white-ethnicity, and, non- whites are thereby at risk of misclassification and potentially inappropriate therapy if they are assessed using ethnically-inappropriate prediction equations.

The rationale for the proposed study is based on the potential misclassification of children if assessed using ethnically-inappropriate prediction equations. Such ethnic differences have not apparently been lessened by generation since migration to the UK (26), and nor can they be explained on the basis of chest dimensions or differences in cormic index (1). In this study, we wanted to explore the physiological basis for ethnic differences.

We have found evidence for ethnic differences in lung function, but have no real explanation for them. One possibility, however, could be respiratory muscle strength and this is the main focus of this study. An alternative explanation could be differences in lung elasticity, and we therefore attempted to see if would be possible to measure this elasticity.

A limited number of studies have considered ethnic differences in respiratory muscle strength. An American study examined MIP in adults, but was limited because it addressed only one variable, MIP, choosing not to include measurements of MEP. In this study we attempted to address this particular gap in knowledge.

2 CHAPTER 2 AIMS AND HYPOTHESIS

2.1 Aims

This study aimed to compare lung function in white children with children whose ethnic origins lay in the Indian subcontinent (South Asian children) and who are aged between 5 and 11. We aimed to test the hypothesis that differences in lung function between white and South Asian children can be explained in part by differences in the relative strengths of their respiratory muscles. An alternative explanation for the ethnic-related differences in spirometry might be that the elasticity of the lung (or of the chest wall) varies with ethnic group. There is little data available in the literature on elasticity (or compliance) of the respiratory structures, possibly because it is not easy to measure in the relaxed, awake state, so accordingly we additionally attempted to measure static recoil pressures.

2.2 Where are the gaps in knowledge?

2.2.1 Spirometry

Ethnic differences in lung function are well documented and the importance of adjusting for ethnicity has been emphasised (19), (20), (1) and (2). However, the paucity of spirometry references that take ethnicity into account, especially in children, impedes diagnosis and clinical management of lung disease, and complicates the interpretation of clinical trials where lung function is a primary outcome (21).

There are abundant studies that have shown that divisions of lung volume measured by spirometry in the white population are greater than in other ethnic groups, after adjustment for age, height and gender (1) and (2). Previous studies have compared South Asian children (who have their origins in the Indian subcontinent) with their white counterparts and shown a relative reduction in lung function (FVC, forced vital capacity) of 13.4% (1), 9% (3) and 13% (4) and (FEV_1, forced expiratory volume in 1second) of 10.6% (1), 8% (3) and 13% (4).

The recently published Global Lung Function Initiative (GLI)-2012 multi-ethnic spirometry equations (22) provide a good fit for contemporary Black-African origin and white London primary schoolchildren (23) , and although the published equations did not cover all ethnic groups, a preliminary coefficient for South-Asian children based on GLI-2012 has been developed (24) and (25). Nevertheless, ascribing ethnicity is complicated in an increasingly multi-ethnic society. Most lung function prediction equations are derived from whites; thereby,

those of non-white are at risk of misclassification and potentially inappropriate therapy if they are assessed using ethnically-inappropriate prediction equations.

The rationale for the proposed study is based on potential misclassification of children if they are assessed using ethnically-inappropriate prediction equations. Ethnic differences are not lessened by generation since migration to the UK (26), nor can they be explained on the basis of chest dimensions or differences in cormic index (1). In this study, we wanted to explore the physiological basis for these ethnic differences. The population we studied is broadly similar to other studies. This is important because we found that there are differences in lung function between white and South Asian children which other studied have found.

2.2.2 Respiratory muscle strength

As spirometry is a measure of FVC (force vital capacity), expiratory muscle strength could feasibly influence the values seen for spirometry. Greater expiratory muscle strength would not influence total lung capacity, but as FVC and FEV_1 are both forced volumes rather than absolute volumes, greater expiratory muscle strength could feasibly increase the volume of air exhaled in these manoeuvres, thereby decreasing RV.

One important little-studied factor that may explain the difference in lung function between different ethnic groups is respiratory muscle strength. This is assessed using the measurements of Maximal Inspiratory Pressure (MIP) and Maximal Expiratory Pressure (MEP). Previous studies in adolescents and adults have shown that MIP and MEP values in healthy males are significantly larger than in healthy females (15).

A limited body of work has considered ethnic differences in respiratory muscle strength. An American study has examined the MIP of 3849 adults from four groups: non-Hispanic white, African-American, Hispanic and Asian (of Chinese origin) (17). It was found that important correlates of higher values of MIP observed through multi-ethnic groups in this study were males, those of younger age, obesity, higher FVC and those of shorter height. The differences in MIP by ethnicity, however, was small (17). This study was limited because it addressed only one variable (MIP) and did not include measurements of MEP. It also did not include subjects of South Asian origin, the main minority group forming the population of Leicester and Leicestershire. There is therefore a gap in knowledge relating to differences in respiratory muscle strength.

Our study seeks to address this knowledge gap. To the best of our knowledge, this is the first study conducted to investigate the ethnic differences in respiratory muscle strength between white and South Asian children.

2.2.3 Lung volume measured by plethysmography

Ethnic differences in lung function have in the past relied almost exclusively on spirometric indices of forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1). Much less data exists regarding measurements of absolute lung volume. By measuring total lung capacity (TLC) and residual volume (RV) where possible, we aimed to determine whether the reduced vital capacity in South Asians results from a lower TLC, a raised RV, or a combination of the two.

2.2.4 Distensibility of respiratory system

The lungs are elastic structures that change volume when the pressures are produced through the inspiratory and expiratory muscles. An alternative explanation to respiratory muscle strength for the ethnic differences in spirometry might be that the elasticity of the lung (or of the chest wall) varies with ethnic group.

There is little published data on elasticity (or compliance) of the respiratory structures, possibly because it is not easy to measure in the relaxed, awake state. One previous study investigated the relationship between the chest wall, pulmonary distensibility and age by studying 42 healthy males aged 24-78 (18), which found that pulmonary volume was increased and lung elasticity decreased in younger subjects compared with the more elderly, but no consideration was given to ethnicity (18).

Our proposed project aimed to measure a surrogate static recoil of the respiratory system in children of different ethnic groups. The measurement of the distensibility of the respiratory system in awake subjects is difficult because of the need for relaxation. We hypothesised that we could measure a surrogate for respiratory system distensibility in children while distracted. To the best of our knowledge, this is the first study that has been conducted to investigate the ethnic differences in distensibility between. The measurement of the distensibility of the respiratory system in awake subjects is difficult because of the need for relaxation. We hypothesised that we could measure a surrogate static recoil of the respiratory system in children while distracted.

2.3 Objectives

- To compare forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) measured by spirometry between white and South Asian children. Chapter 5.
- To compare maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP) in white and South Asian children. Chapter 6.
- We assessed whether the decrease in Vital Capacity (VC) observed in South Asians was predominantly due to a decrease in Total Lung Capacity (TLC) or an increase in Residual Volume (RV). Chapter 7.
- To measure a surrogate static recoil pressure of the respiratory system in both ethnic groups. Although this is a non-invasive measurement, there is a currently little existing data. We recognised that it might prove difficult to measure reliably. Chapter 8.

3 CHAPTER 3 METHODS

3.1 Study design

This was a cross-sectional observational study in children of primary school age. Different aspects of lung function were measured and compared in children of different ethnic origins. The study took place over a two-year period. This study aimed to compare lung function in white children and children whose ethnic origins lay in the Indian subcontinent (South Asian children), and who were aged between 5 and 11. Three hundred seven children have been included in this study. This project was conducted with children because they are less likely to have had occupational exposures or indulged in activities that might influence muscle strength such as body building or extensive sporting activities.

The effect of puberty on lung function and respiratory muscle strength is an interesting question, but beyond the realms of this project. The age group we recruited was specifically chosen to minimise the complications of the puberty. If the question of puberty were to be addressed then pubertal status would need to be determined, and this would be unjustifiable in the context of the present study. In this study we did not attempted to ask either the parents or their children a personal question about puberty status because this might have prevented families and schools taking part in our study.

3.1.1 Primary outcome measures

Primary outcome variables were MIP and MEP. The first objective was to support or refute the hypothesis that there are differences in MEP and MIP between children of different ethnic groups. In conjunction with these measurements we also measured spirometry (FEV_1 and FVC). It was important to confirm that there were no unexpected or freak findings in spirometry, and that the children in the study demonstrated the anticipated ethnic differences.

This study presented us with the opportunity to explore how the absolute lung volumes related to differences in spirometry. Our secondary outcomes therefore included Total Lung Capacity (TLC), Functional Residual Capacity (FRC) and Residual Volume (RV).

Finally, we intended to measure the distensibility of the respiratory system. There was very little data on this variable reported in human studies, with the exception of new-borns. This was an exploratory study with outcomes comprising overall success in making measurements and, potentially, pressure-volume relationships in children of different ethnicities.

3.2 Power calculation

The main outcome variable were MIP and MEP. Based on data from boys aged 10 years, in whom MEP measured at TLC had a mean (SD) value of 123(27) cmH_2O, we have calculated that 86 boys would be needed to detect a difference of 13.5 cmH_2O (equivalent to 0.5SD) between white and South Asian boys, should such a difference exist (96). This assumes the usual significant level of 0.05 and a power of 90%. We aimed to study 344 children (172 boys). Since we included children in the primary school age range, and another outcome variable (MIP) was also studied.

Our study was not aiming to identify differences in spirometry. Our focus was MIP and MEP, and it would not have been appropriate to attempt power calculations based on spirometry.

Within the published work on which we based the power calculation, the standard deviations for MIP and MEP were not the same. However, we based our power calculation on differences relating to changes in the number of standard deviations, considering that a change of 0.5 SD was meaningful. The number of children in the study would be the same had we used MIP for the basis of our calculations.

There are no preliminary data that might enable power calculations for studies of distensibility, which was mainly a novel attempt at assessing feasibility.

3.3 Recruitment procedures

3.3.1 Ethics Approval

Research Ethics Committee approval was obtained for this study and written informed consent was obtained for all children involved in this project.

3.3.2 Local Education Authority (LEA)

The LEA gave permission to carry out the study in Leicester Primary Schools and provided the contact details of nine schools in the designated area. It was requested that they chose a school where between 50 and 80% of the children were of Asian ethnic origin. In fact, the proportion of Asian children in the schools suggested by the LEA was significantly greater than this. Hence, it was necessary to recontact the LEA part way through the study and ask for the contact details of the schools where the children were predominantly white Caucasian. It was stressed that the children should be from a similar area and of similar socio-economic background. The proportion of children that received free school meals was used as a measure of socio-economic

status. Although, our study attempted to control for differences in socio-economic background, no detailed analysis of socio-economic status was performed.

3.3.3 Contacting the school

The first contact with schools was made via a telephone call to the head teacher. The aim of the project and what would be involved in the school if they agreed to take part was explained. The head teacher was informed that they would be receiving an information pack through the post containing a letter for the school, an example of an article they may wish to include in a school newsletter, and a copy of the information that would be sent out to parents. The head teacher was then re-contacted, having allowed them an appropriate amount of time to read the information, consider the value of the study and its implications for the school. The headteacher was given the opportunity to ask for more information or clarification on any aspects of the project. In some instances, the project needed to be approved by the appropriate board of governors.

3.3.4 Assemblies and talks to staff

When a school agreed to take part in the project, we offered to give a presentation to the children during a school assembly and/or talk to the staff to inform them about the study. Presentations in school assemblies were given to allow children the opportunity to make an informed decision regarding their participation in the study. It was explained to the children what would be required of them if they wanted to take part and demonstrations of how to perform spirometry manoeuvres, and respiratory muscle strength were given.

3.3.5 Informed consent

Parental consent

Parents/guardians were provided with an information sheet, in the form of a letter, which their child brought home from school. There was also an information sheet for the child. Enclosed within the information pack was a consent form for the parent to sign and return via the school. Written parental consent was therefore normally taken without face-to-face contact between the parents and the investigator. The information sheet contained contact details of the researchers for parents to contact us if they wish. One of the options on the form that parents were requested to return to the school was for a request for someone to contact them to discuss the study further. Parents were contacted by telephone if they had any questions or wanted to discuss any aspect of the study. It was made clear to the parents that they are welcome to meet us at the school, without any obligation on their part to consent to their child's participation. The named person responsible for collecting the consent forms and responding to any parents were Dr Caroline

Beardsmore and Miss Nidhal Gharbawi. They countersigned and dated the parental consent forms as they were received. The information sheet for parents contained full details of the study procedures and made it clear that consent could be withdrawn at any time without the need to give a reason. It was made clear that we would also gain consent from their child at the time of the study and would ensure that the child knew that they may stop at any time and would not be expected to do anything they were not willing to do. Parents were free to discuss their child's participation with anyone they chose and were given as much time as they needed or wanted before returning their forms to the school.

Consent from Children

Each child needed to give consent for their own participation (i.e., not just the parents or guardians). The information sheet for each child included a space for the child to write his/her name to signify that they were happy to participate. This could be returned along with parental consent or at the time when measurements were made. However, we always kept the children informed they did not have to do anything they were not happy to do, and could stop at any time if they wanted. This form of consent (or assent) was of the utmost importance for us to be sure that we did, indeed, have the full consent of each child.

3.3.6 Recruitment packs and collection

The recruitment pack contained a letter/consent form for the child, an information sheet for the parents/guardians, a consent form for the parents/guardians and a questionnaire. The information was available in English. In our study we did not have any non-English speaking parents. The recruitment packs were distributed by the school, completed by the parents/guardians, and then returned to the school. The letter to the children outlined the project in basic terms and asked them to sign their name in a box if they wanted to help, thus establishing paediatric consent. The questionnaire was designed to obtain contact details and to determine ethnicity and eligibility for the project.

Replies were collected three weeks after distribution of the recruitment packs. The subsequent collection was made as necessary. The replies were sorted according to the parents' responses. Incomplete replies were not followed up.

3.3.7 Health questionnaire

The health questionnaire was designed to determine the ethnicity and eligibility and to provide information on any respiratory disorders and tobacco smoke exposure. It contained questions about any past or current health problems, any use of medication specific to asthma and any symptoms of common inflammatory conditions such as asthma, hay fever and eczema. The questionnaire was designed to detail each child's level of health and basic levels of physical activity. The questionnaire also asked whether each child took part in regular vigorous physical activity, and if so, how regularly they did so. Sample questionnaires are included in the (Appendix 10.7) (151) and (152).

3.3.8 Preparation for the visit to the school to make measurments

Replies were sorted according to the name of class teacher and eligibility was verified using the questionnaire. If a child had asthma, a note was made on the front of the reply, and their medication was checked on the morning of the visit. Prior to the visit, a phone call was made to the school to confirm our requirements and a list of the children we wanted to see was faxed to the school.

3.4 Inclusion and exclusion criteria

Inclusion criteria

Children were eligible to take part if they were aged 5.0 to 11.99 years and parental and personal consent had been given. For inclusion, children had to have been born full-term (i.e., at least 37 completed weeks gestational age) and have no personal history of significant cardio-respiratory conditions. Children with mild asthma were eligible for inclusion unless they required daily medication. The health questionnaire was designed to determine the eligibility and provide information on respiratory disorders. It contained questions about any past or current health problems, any use of medications specific to asthma and any symptoms of common inflammatory conditions such as asthma. Sample questionnaires are included in the (Appendix 10.7). Children were only eligible if, in the opinion of the investigators, they understood what was involved and were clearly willing to participate. This was particularly important for the measurements made in schools because parents were not nominally expected to be present.

Exclusion criteria

Children of ethnic origins other than those being investigated or who were of mixed race would not be excluded from taking part, although their results were expected to be insufficient for statistical analysis and would be used for descriptive purposes only. Exclusion criteria included:

- Children born preterm (less than 37 completed weeks).
- Children with major cardiopulmonary conditions.
- Children with chest wall deformities.
- Asthmatic children who were taking daily medication.
- Children who had had a cough or cold within three weeks prior to testing.
- Any other factor which, in the opinion of the investigators, would render the child unsuitable for the study, e.g., severe growth deficiency.

3.5 School visits

A series of visits were arranged with the schools. On the day of the visit, the children whose parents had consented to their participation were seen in same-sex pairs in a private area. After introductions, the study was explained simply to the children. Before beginning the measurements, the child was asked about any recent illnesses, in particular coughs and colds. Confirmation of assent and signing of forms was taken from each child.

School visits included:

- Anthropometric measurements including height (standing and sitting) and weight.
- Lung function test using spirometric techniques.
- Respiratory muscle strength MIP and MEP.

3.6 Laboratory visits

The families who were willing for their children to do additional measurements were invited to the physiological laboratory based in the Leicester Royal Infirmary (LRI) Hospital. The parental reply sheet included a box for them to tick to indicate that they were willing to consider coming to the lab for additional tests. An information pack was sent to families including a letter of explanation, and a questionnaire to determine ethnicity, eligibility, and to provide information on respiratory disorders. An appointment was made on a date suitable for the families to attend the lung function lab in the LRI. Written informed consent was obtained from parents of all

children, and each child gave assent at the time when measurements were made in the laboratory.

Laboratory visits included:

- Anthropometric measurements including height and weight.
- Measurements of absolute lung volume (TLC, FRC and RV) which could not otherwise be measured using spirometric techniques.
- Spirometry and respiratory muscle strength measurements to confirm the repeatability of the measurements.
- Respiratory system elasticity measurements.

3.7 Measurements of anthropometry

3.7.1 Standing height

The subject was asked to take off their shoes before the starting the measurements. Standing height was measured using the Leicester Height Measure (Seca, Birmingham) according to the policy of national child measurement programme to an accuracy of 0.1 cm (153). Care was taken to:

- Ensure that 4 points of the child's body touched the scales - heel, buttock, shoulder, back of head.
- Ensure that head was positioned in the Frankfurt plane (i.e. external auditory meatus should be level with the base of the orbit).
- Legs were placed close together and flat on the measuring surface.

The height measure was mounted on a base and stood upright against the wall. Children were measured while standing erect with their backs against the vertical column of the height measure. The child’s head was positioned in the Frankfurt horizontal plane by placing a hand on either side of their the mandible. A plastic plate was brought down to rest on the top the head, with height measured at full inspiration to the nearest millimetre. We used the same Leicester Height Measure for all schools we visited, and we confirmed the accuracy of the measurements by measuring a flat wooden stool of known height (37.2cm) in the lab. We measured the same stool again in the school to confirm we got the same measurement.

3.7.2 Sitting height

Sitting height was measured asking the child to sit on a flat wooden stool that was placed on the base of the height measure. The subject was instructed to sit erect with their back in contact with the vertical column of the height measure. The child was observed to confirm that he/she was not falsely increasing his/her height by contracting their gluteal muscles. Moreover, the head was positioned in the Frankfurt plane and the plastic plate brought down to rest on the head. The measurement was made at full inspiration and to the nearest millimetre. The height of the stool was subtracted from the measured height to give the true sitting height. Sitting height data was not used for analysis within this project.

3.7.3 Weight

The child's weight was measured whilst wearing indoor clothing but without their shoes using electronic scales. The weight was measured once and recorded to the nearest 100g.

3.8 Measurements of lung functions

3.8.1 Spirometry

3.8.1.1 Equipment and calibration

Spirometry was performed using a portable spirometry equipped with a pneumotachograph and Sentry Suite software (CareFusion, Germany). The machine detects and displays ambient conditions, temperature, barometric pressure and humidity, and these were checked using a portable sensor. Equipment calibration was performed once daily on site (in the school) using a 3-litre syringe. Calibration was performed at medium, slow, and high flow rates to account for any non-linearity that might occur at extremes of flow.

3.8.1.2 Spirometry performing and measurements

The child was asked to sit and wear a nose clip (Fig 3.1). The subject was given a demonstration as to how to perform the effort through giving verbal instruction, a demonstration, and with encouragement given as necessary. The subject was given positive feedback after each manoeuvre and was encouraged to exceed the previous manoeuvre; incentive spirometry was also used if it was felt the subject would respond well to it (for younger children, prolonged expiration was encouraged using incentive spirometry). The child was observed to confirm that a good seal around the mouthpiece has been made and maximum inspiration reached, and thus they got off to a good start with continuous exhalation with the maximum manoeuvre. All measurements were made in accordance with American Thoracic Society guidelines (154) and (64), and a minimum of three and maximum of eight efforts were performed.

Subjects were studied seated and using a nose clip (Fig 3.1). They breathed quietly through the tube from the flow head of the spirometer. When breathing was regular, they were asked to take a deep breath in until full inspiration, and then asked to blow out as hard as possible until they could not blow out any further. This was repeated with short breaks until three reproducible measures had been recorded (FVC and FEV_1 within 10%) up to a maximum of eight attempts. At the end of the test sessions, flow-volume curves were visually inspected. Technically unsatisfactory manoeuvres were excluded. At the end of each FVC effort, acceptability and repeatability checks were applied, and the best three flow-volume curves from the test session were selected. The higher FEV_1 and FVC from the three best acceptable FVC efforts are reported herein. Standard spirometric measurements comprised forced vital capacity (FVC) and forced expired volumes in 1 second (FEV_1).

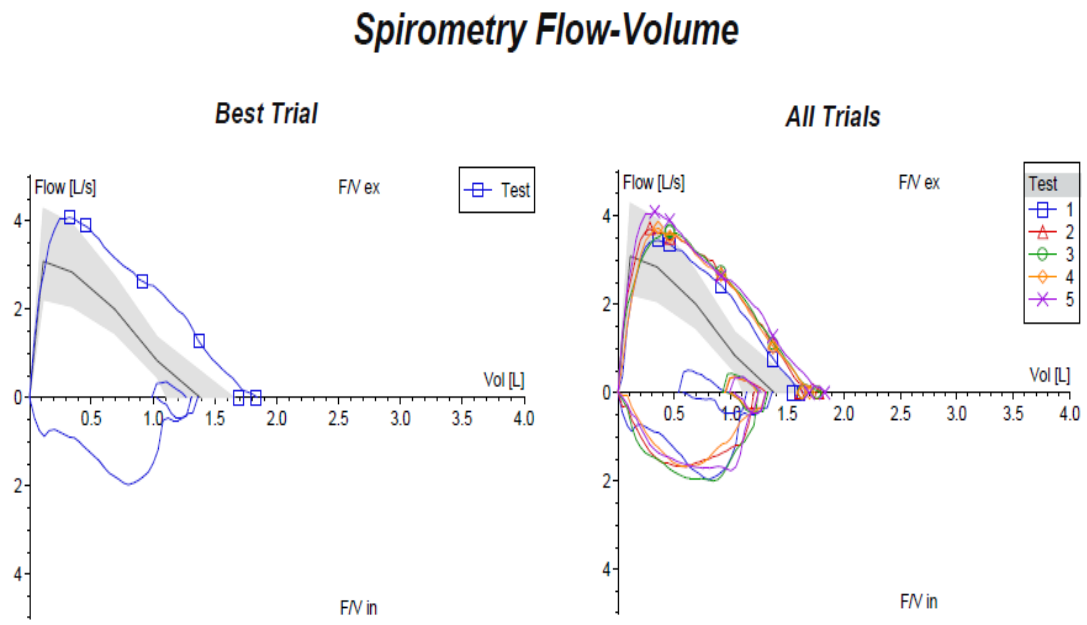
To allow standardisation of results, and adjust for age, height, sex and ethnicity FEV_1 and FVC were expressed as Z-scores, based on predicted values for white children. The predicted values were taken from the all-age spirometry reference values (155). The z-scores were considered normal if within the 95% confidence intervals, i.e. between -1.96 – 1.96. As in spirometry lower values are indicative of poorer lung function; values below -1.96 were considered to be abnormally low.

A Z-score is the deviation of an individual's value from the mean value of a reference population, divided by the standard deviation of the reference population (22), (156). FEV_1 in this study was expressed as a Z- score and not a predicted percent because the Z-score is independent of age, height, and sex, unlike the use of percent predicted, and is recommended by ATS/ERS (20) and (157). Acceptable and repeatable manoeuvres are shown in (Fig 3.2).

Figure 3-1Spirometry manoeuvre.

Legend: A subject performs a spirometry manoeuvre (photo with permission).

Figure 3-2 Spirometry Flow-Volume Curve.



Legend: Spirometry *manoeuvres obtained from a healthy boy aged 6 years. Efforts represent acceptable and repeatable manoeuvres. The flow/volume curve shows a rapid rise to peak flow without artefact and steady descent to zero flow at the end of the manoeuvre. All measurements were made accordance with the American Thoracic Society guidelines (154), with a minimum of three and maximum of eight efforts.*

3.8.1.3 Reporting of outcomes

The manoeuvres were examined to investigate repeatability and acceptability; manoeuvres were excluded if they did not meet the criteria for repeatability and acceptability. The highest or best values for FEV_1, and FVC were recorded.

3.8.1.4 Acceptability criteria (64)

The spirometry manoeuvre was considered acceptable if it met the following criteria.

- The spirogram was free from artefacts including: a cough during the first second of expiration, glottis closure that impacted the measurement, early termination, a manoeuvre that was not maximal throughout, leak, and obstructed mouthpiece.
- It had a good start: extrapolated volumes <5% of FVC or 0.15L, whichever was greater.
- It showed complete exhalation: duration of ≥ 6 seconds (3 seconds for children).

3.8.1.5 Selection of values

Technically unsatisfactory manoeuvres were excluded. At the end of each FVC effort, acceptability and repeatability checks were applied, and the best three flow-volume curves from the test session were selected. The higher FEV_1 and FVC from the three best acceptable FVC efforts are reported herein.

3.9 Measurements of lung volume

3.9.1 Whole-body plethysmography

3.9.1.1 Equipment and calibration

Plethysmography was performed with a Jaeger MasterScreen Body Plethysmography (Care Fusion GmbH, Leibnizstrasse, Germany). The equipment detects and displays ambient conditions, temperature, barometric pressure and humidity. The calibration of the machine was performed once daily in two steps, in accordance with the manufacturer's instructions. The first step was the pneumotachograph calibration, which was performed using a 3L calibration syringe that was attached to the mouthpiece and pumped at a high, medium and low flow rate to assess changes in flow and volume through the pneumotachograph. The second step was the box pressure calibration, which was performed automatically to assess the background leak and calibration factor with the door closed and cabin empty. Ideally, the background leak should have a half-life of 4 to 7 seconds to avoid any source of error in measurements.

3.9.1.2 Lung volumes performance and measurements

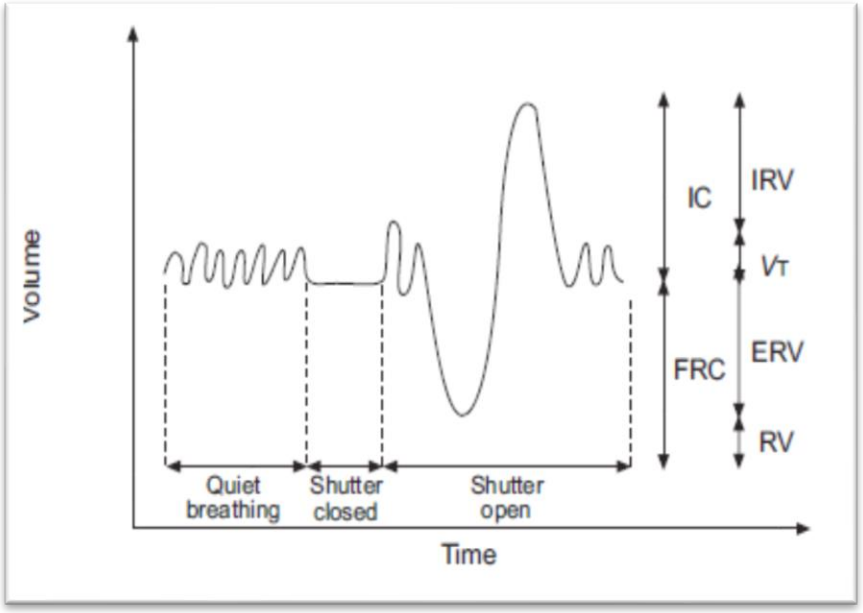
Lung volumes were measured by plethysmography. The child was asked to sit comfortably in the body box while the door was closed and the subject wearing nose clips (Fig 3.3), and was able to reach the mouthpieces without having to flex or extend the neck. The child was asked to put their hands-on their cheeks. Then, the child breathed through a mouthpiece connected to a pneumotachograph to measure the volume of air breathed in and out. After several steady breaths, the operator activated a shutter that briefly closed the tube through which the child was breathing. This transient period of shutter closure was very brief and the sensation was that, for a split second, it became hard to breathe. The short period when the shutter was closed is shown in (Fig 3.4). During the manoeuvre, the changes in pressure at the mouthpiece and within the cabin were used to calculate the volume of air in the lungs Functional Residual Capacity (FRC). After each measurement, the child was asked to inspire and exhale maximally, so we could measure Total Lung Capacity (TLC) and what volume remained when the child had breathed out as far as they could, giving the Residual Volume (RV). The test was repeated until we obtained at least

three technically acceptable FRCpleth measurements. The measurements were accepted if loops were closed, the zero-pressure line had been crossed without thermal drift or excessive efforts and three FRCpleth values, repeatable within 5%, had been obtained according to the ATS/ERS recommendations (65). The mean value for FRCpleth was reported and used with the mean inspiratory capacity (IC) to determine total lung capacity (TLC). The highest vital capacity (VC) was then subtracted from the TLC to obtain the residual volume (RV). Z-scores for plethysmography (for both ethnic groups) were based on reference values derived from white children (63). At the end of the test sessions, FRCpleth traces were visually inspected. Some acceptable and repeatable plethysmography manoeuvres are shown in (Fig 3.5). Measurements were made according to criteria set by American Thoracic Society (154).

Figure 3-3 Plethysmography manoeuvre.

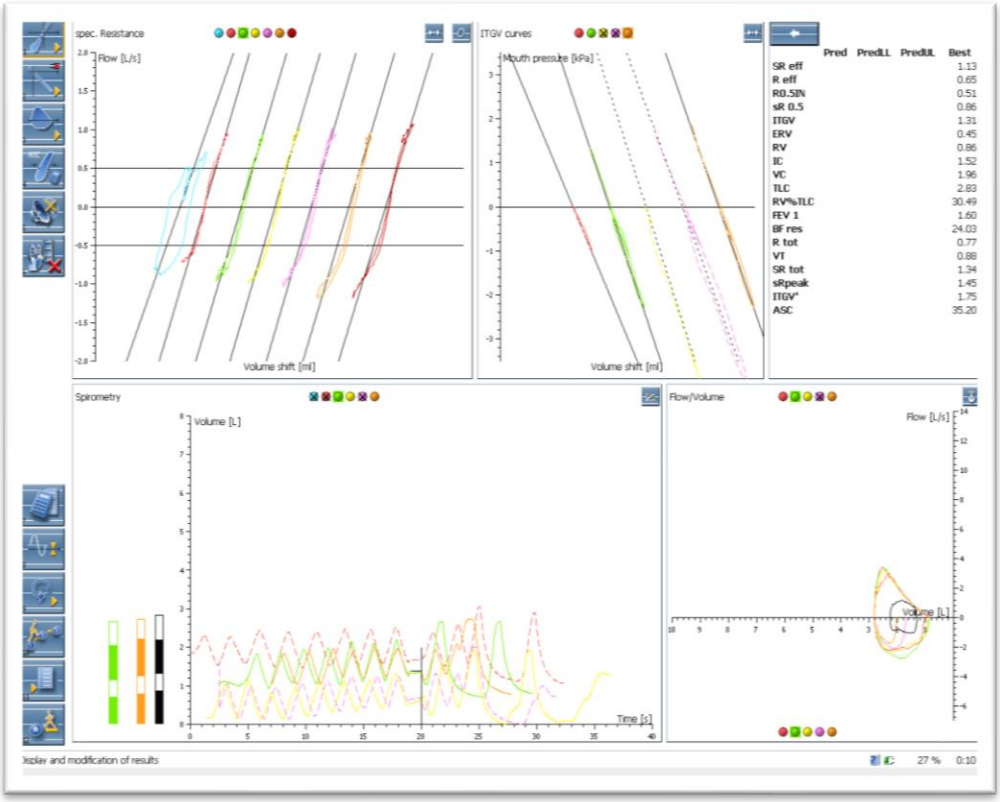
Legend: A subject sits comfortably in the body box to perform the plethysmograph manoeuvre (photo with permission).

Figure 3-4 Volume-time.



Legend: Volume–time display showing the sequence of quiet breathing and, after a stable end-expiratory level was achieved, a short period when the shutter was closed to determine the thoracic gas volume, followed by an open-shutter period during which the subject stayed on the mouthpiece and performed an expiratory reserve volume (ERV) manoeuvre followed by a slow inspiratory vital capacity manoeuvre. All volumes were determined without the subject removing off the mouthpiece in a ''linked'' manoeuvre. IC: inspiratory capacity; FRC: functional residual capacity; IRV: inspiratory reserve volume; VT: tidal volume (TV); RV: residual volume. Adopted from (65).

Figure 3-5 The plethysmography manoeuvres.



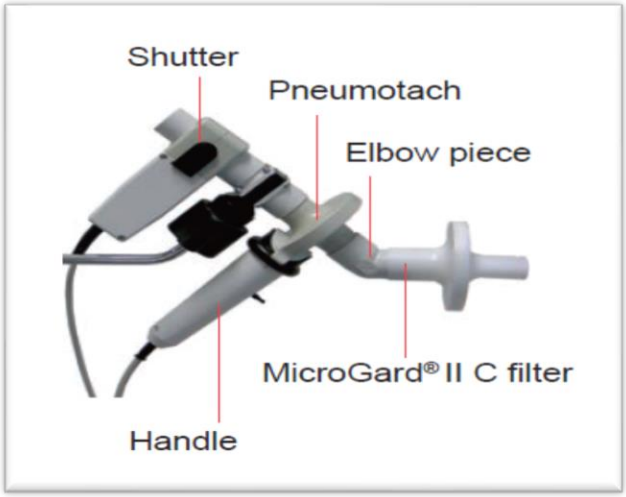
Legend: Some acceptable and repeatable plethysmography manoeuvres. The top first window on the left illustrates a specific resistance; it measures the pressure in the cabin against the flow. The second window on the right illustrates the measurement of mouth pressure plotted against cabin pressure. The bottom third window illustrates volume–time display showing the sequence of quiet breathing and after stable end-expiratory level was achieved, a short period when the shutter was closed to determine the thoracic gas volume, followed by an open-shutter period during which the subject stayed on the mouthpiece and took a breath into TLC and breathed out to RV, followed by a return back to normal breathing.

3.10 Measurements of respiratory muscle strength

Respiratory muscle strength was assessed by measurement of maximum expiratory and inspiratory pressures (MEP and MIP, respectively). Hand-held portable devices (Vyntus) equipped with a pneumotachograph and the Sentry Suite software (CareFusion, Germany) were used. For both measurements, the child breathed through a flow meter attached to a shutter. To measure MEP, after several quiet breaths, the child was asked to breathe in until their lungs were full, and the shutter was activated during this large breath. S/he was then encouraged to try and breathe out hard against the obstruction. The peak pressure was recorded, and the manoeuvre was repeated several times. Measurement of MIP was similar, except that the child breathed out as far as possible and then made a forceful inspiratory effort. The subject performed inspiratory manoeuvres from residual volume (RV) and expiratory manoeuvres from total lung capacity (TLC).

The system was supplied with a small leak (approximately 2-mm internal diameter and 20-30 mm in length) to prevent glottic closure during the MIP attempts and to decrease the use of buccal muscles during MEP attempts. The inspiratory and expiratory pressure must be sustained for ideally, at least 1.5 seconds in order to record the maximum pressure sustained for 1 second. The values of MIP and MEP were calculated by the software and displayed. The maximum value of three attempts that differed by less than 20% was recorded. Measurements were made according to the American Thoracic Society and European Respiratory Society criteria (ATS/ERS) (158). The equipment used to measure maximal respiratory pressures is shown in (Fig 3.6). Performing the maximal respiratory pressure manoeuvre is shown in (Fig 3.7). Some acceptable and repeatable manoeuvres for MIP and MEP are shown in (Fig 3.8).

Figure 3-6 Equipment.

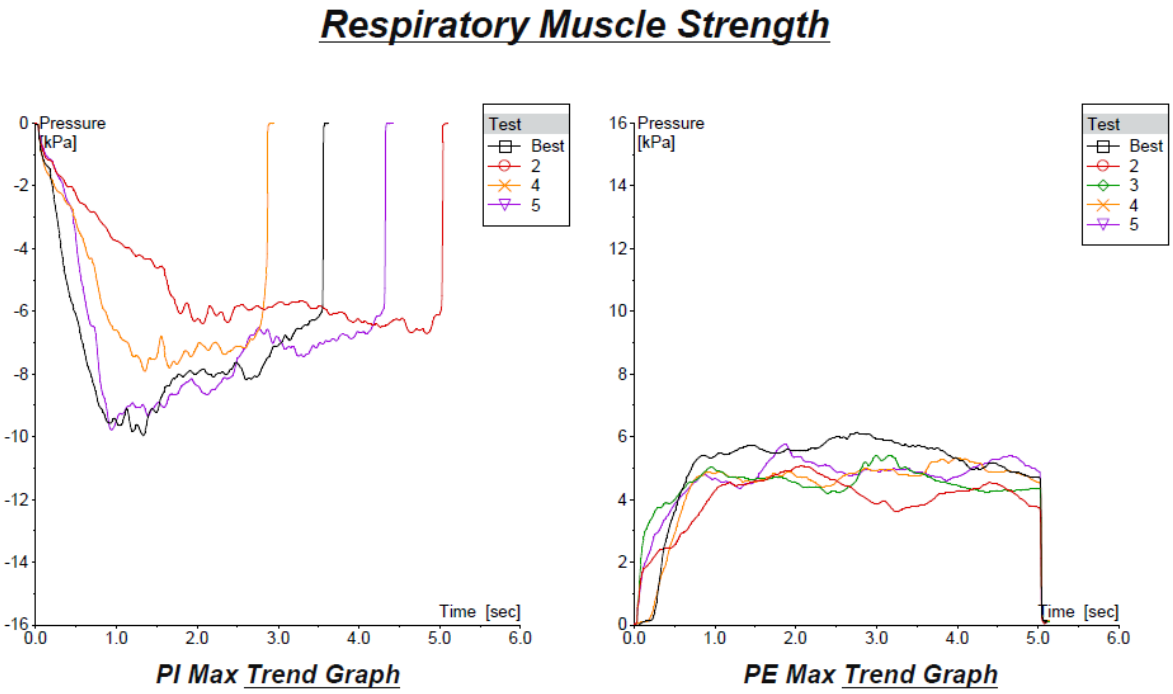


Legend: Equipment used to measure maximal respiratory pressures. Adopted from Sentry Suite online manual.

Figure 3-7 Maximal respiratory pressure manoeuvre.

Legend: A subject performs a maximal respiratory pressure manoeuvre (photo with permission).

Figure 3-8 MIP and MEP manoeuvres.



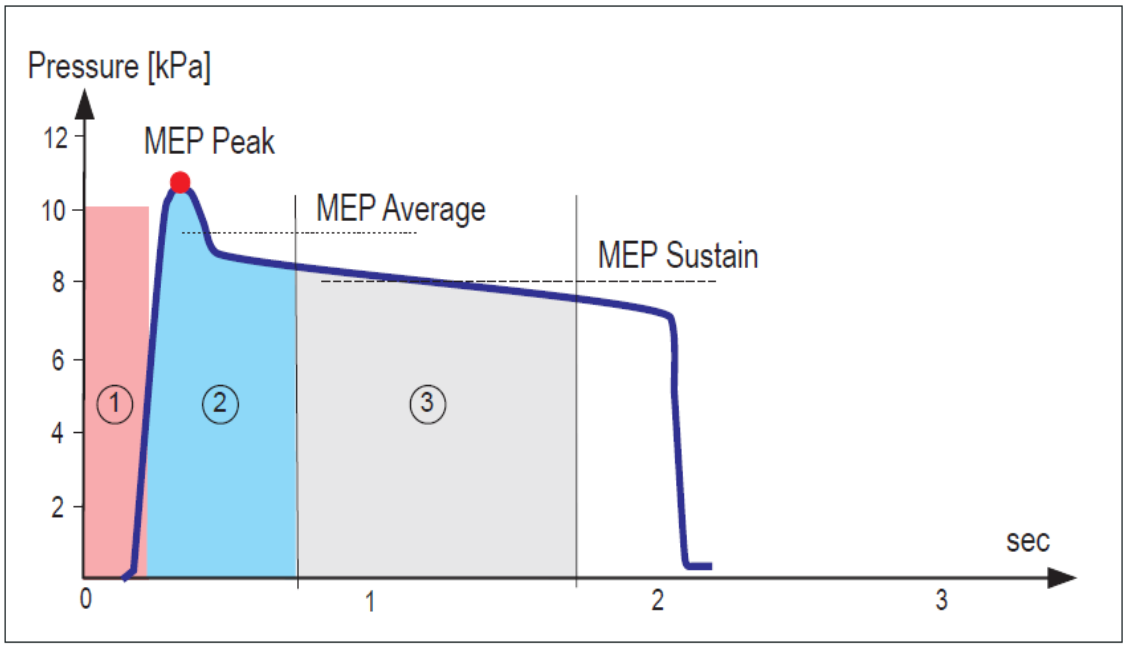
Legend: MIP (left panel) and MEP (right panel) manoeuvres obtained from a healthy boy aged 10 years. Respiratory efforts were maintained for over 2 seconds in each case. Repeatability (highest two peak MIP or MEP values) was 1% or less, thereby easily meeting the criteria for acceptability. Adopted from (158).

The definitions and (Fig 3.9) below explain the parameters used for measuring MIP and MEP: -

- MIP =Maximum inspiratory pressure.
- MIP Peak = Maximum MIP value reached.
- MIP Average = Average MIP value reached over a period of x seconds.
- MIP Sustain = Maximum MIP value sustained over a period of x seconds.
- TTOT MIP = Total MIP time in seconds.
- MEP = Maximum expiratory pressure.
- MEP Peak = Maximum MEP value reached.
- MEP Average = Average MEP value reached over a period of x seconds.
- MEP Sustain = Maximum MEP value sustained over a period of x seconds
- ERV MIP = Expiratory reserve volume.
- IC MEP = Inspiration capacity.

In each case the value of x seconds could be configured by the user. For the current study a value of one second was taken.

Figure 3-9 Maximal respiratory pressure parameters.



Legend: Maximal respiratory pressure parameters: MEP peak, MEP Average and MEP Sustain. 1= ignore time, 2= time for the calculation of the average pressure, 3= time for the calculation of the sustained pressure. Adopted from (Sentry Suite online manual).

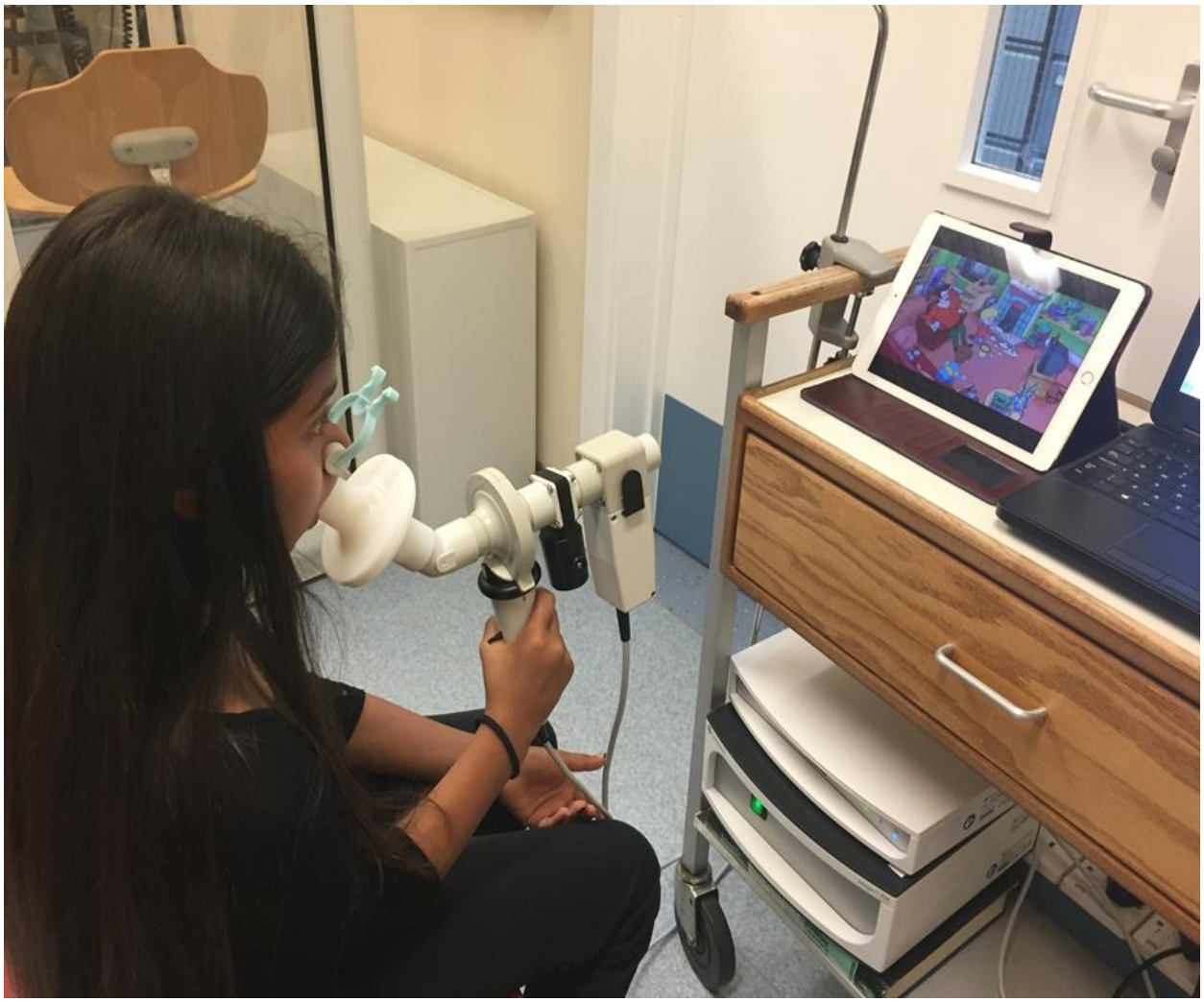
3.11 Measurement of distensibility of the respiratory system

The distensibility of the respiratory system was measured. This involved the child breathing through the mouthpiece and tube, which was then transiently occluded, and the child encouraged to relax against the obstruction. An iPad was used to help children to feel more relaxed, with, cartoon film or games displayed if they wanted (Fig 3.10). The relaxed pressure was measured and related to the volume inspired above the end-expiratory (resting) lung volume. Then, the manoeuvres were repeated until ten acceptable manoeuvres were obtained (the maximum allowed per test by the equipment), after which the test was repeated to obtain twenty or more additional manoeuvres. Children showing any reluctance to participate or contribute were not pressured to do. After we saw the first few children in the lab, we performed the distensibility measurements before MIP and MEP, so that the children did not think that they had to make particular efforts and were more likely to remain relaxed.

The child was asked to sit on a chair and wear a nose clip. The subject was asked to take slow breaths in then relax when breathing out. After five or more breaths the shutter was closed at the onset of expiration, and the subject relaxed against the shutter, without initially making any further effort to breathe. The shutter opened after 1 second. The inspiratory volume before the shutter was closed was measured. To obtain different volumes at the end of tidal breathing before the shutter closed, the subject was sometimes asked to breathe more deeply. Then the manoeuvres were repeated until ten acceptable manoeuvres were obtained (the maximum allowed per test by the equipment). Tests could be repeated many times. For most recordings, the subject was asked to breathe in a slow and relaxed manner, and breathing frequency (BF) was recorded.

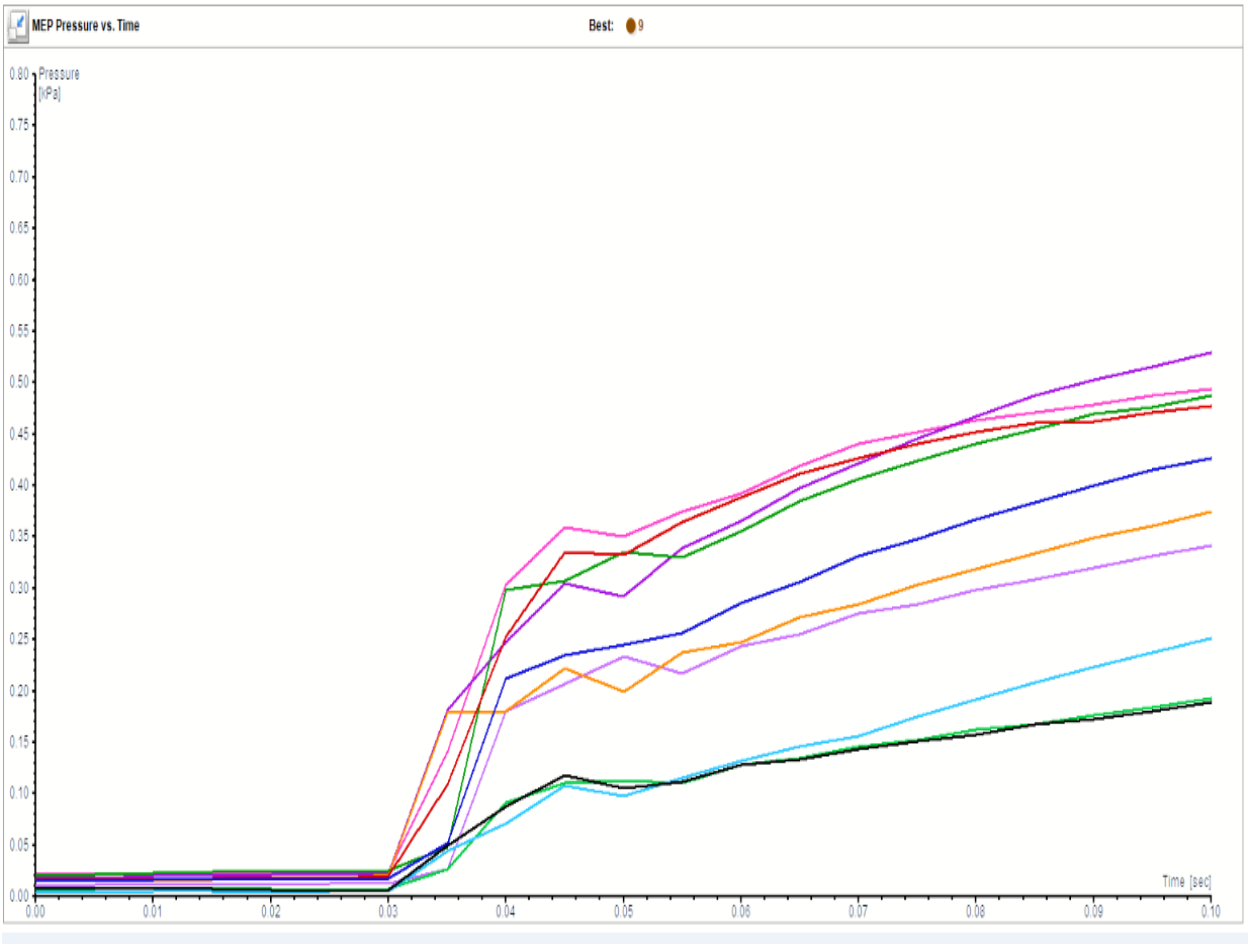
The recordings of pressure against time were displayed on the computer screen. The initial rise in pressure corresponds to shutter closure; the continuing gradual increase in pressure is assumed to relate to decay of inspiratory muscle activity, which is known to regulate tidal expiration. The pressure was measured off the screen at different time points, 0.1 seconds, 0.08 seconds and 0.06 seconds using a ruler. The axes of pressure and time were changed depending on which data time point was being measured, as shown in (Fig 3.11). The pairs of measurements (pressure and volume) were plotted against each other, and a regression line drawn through the data points; we took the gradient of this line as the measure of distensibility. The graphs were inspected independently by two observers who could exclude up to four outlying points, and they had to agree whether the data were acceptable or otherwise.

Figure 3-10 Measurement of the distensibility of the respiratory system.



Legend: Child breathing through flow meter and shutter (photo with permission).

Figure 3-11 Screenshot.



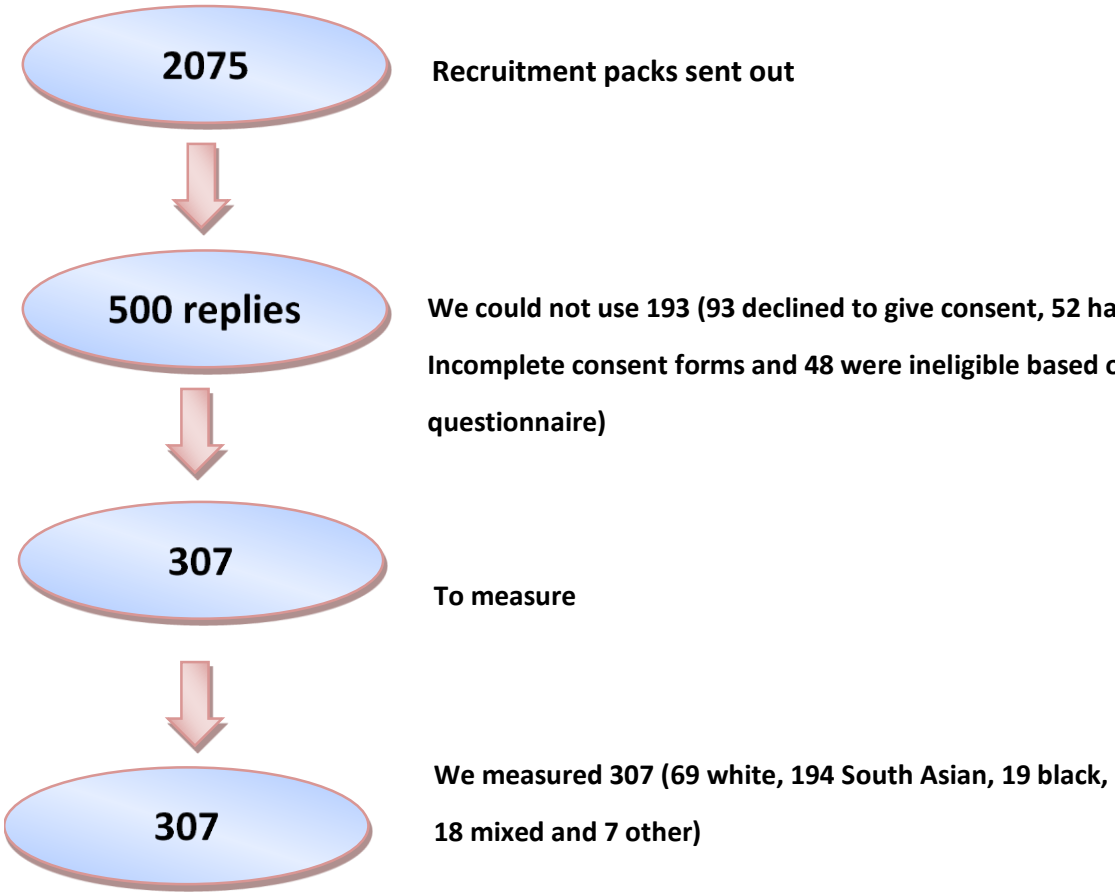
Legend: Screenshot showing pressure data point measurements at 0.1 sec. Pressure is on the Y axis and Time on the X axis. The recordings of pressure against time were displayed on the computer screen. The pressure was measured off the screen at time points 0.1 seconds using a ruler.

4 CHAPTER 4 RESULTS OF STUDIES IN SCHOOLS: SUBJECT RECRUITMENT AND TEST SUCCESS

4.1 Subjects and recruitment

We recruited children from five primary schools. Presentations were given in school assemblies in these five schools to explain our study. The recruitment process is shown in (Fig 4.1).

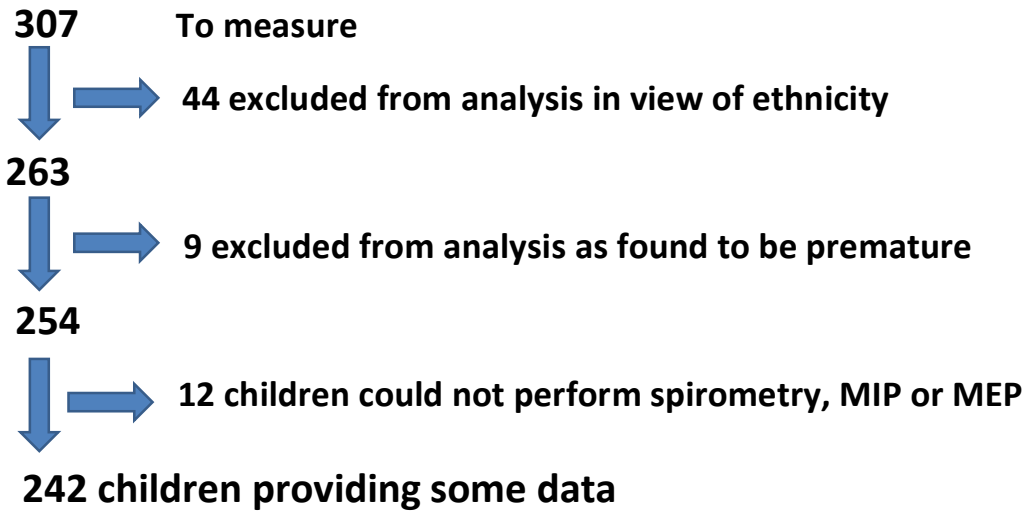
Figure 4-1 Recruitment process.



Legend: Recruitment process; 2075 recruitment packs were sent out, and a total of 307 children were recruited and measured.

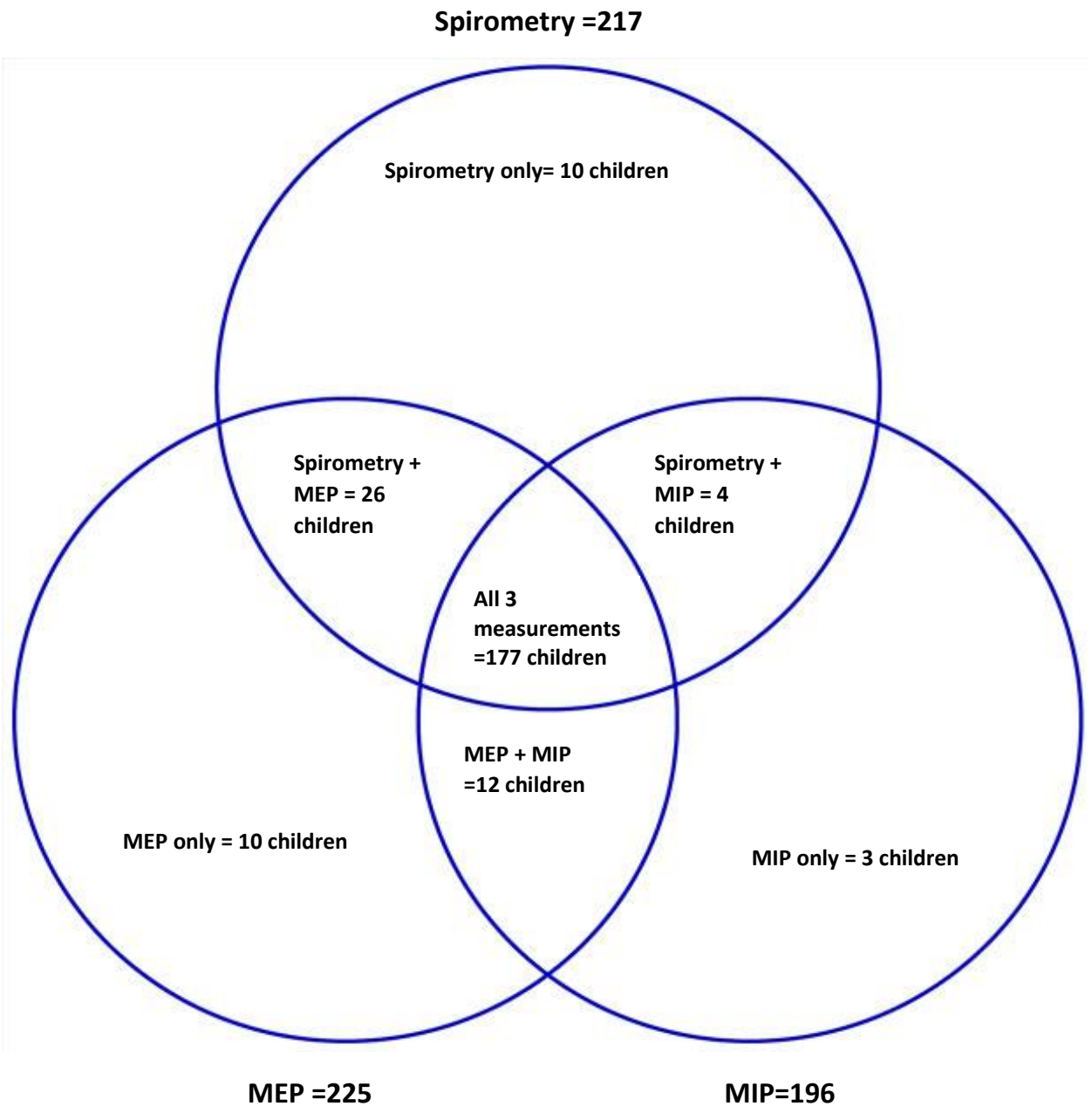
A summary of the number of children omitted from the study from the time of initial recruitment to measuring and analysing is shown (Fig 4.2).

Figure 4-2 Summary of the children included in our study.



The usable data for spirometry, MIP and MEP is shown (Fig 4.3).

Figure 4-3 The usable data for spirometry,MIP and MEP.



Based on the acceptable data, we were able to analyse:

- Spirometry on 217 children (62 white and 155 South Asian) (chapter 5)
- MIP on 196 children (53white and 143 South Asian) (chapter 6)
- MEP on 225 children (62 white and 163 South Asian) (chapter 6)

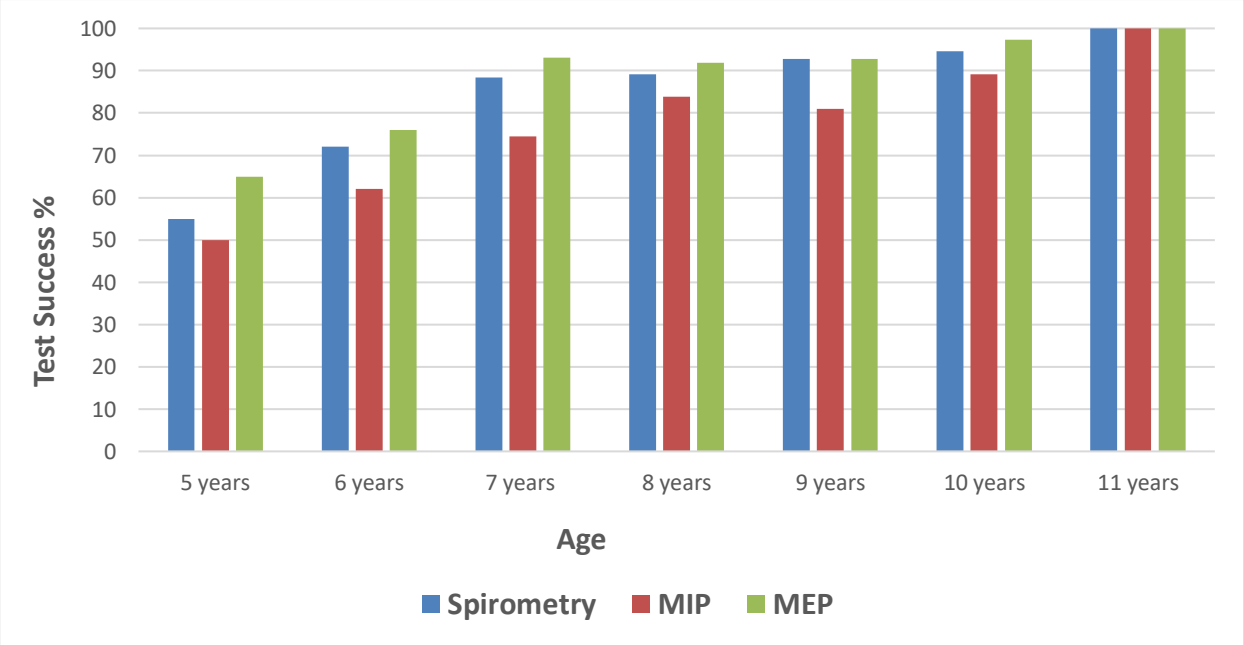
The number of children with complete data on spirometry, MIP, and MEP was 177.

4.2 Number of attempts and test success

Although each child was required to perform a minimum of three attempts for spirometry, MIP and MEP, in reality the average number of attempts was higher for each measure. Of the acceptable manoeuvres, the mean (SD) number of attempts was 6.2 (1.89) for spirometry, 7.0 (2.15) for MIP and 6.8 (2.15) for MEP.

The success rate for all of the tests performed was: 85.4% for spirometry, 88.6% for MEP and 77.2% for MIP. However, the test success rate varied between each age group, with the younger children demonstrating a lower success rate than the older children. MIP was the test with the lowest success rate across all age groups (Fig 4.4).

Figure 4-4 Test success rate ages of subjects studied.



Legend: Test success rate for different ages of subjects studied, 20 children aged 5 years, 50 children aged 6 years, 43 children aged 7 years, 37 children aged 8 years, 42 children aged 9 years, 37 children aged 10 years and 25 children aged 11 years.

4.3 Subjects recruited for laboratory studies

As presented in chapter 3 (section 3.6) 37 families came to the laboratory for studies of lung volumes and distensibility. Details of these studies and results are presented in chapters 7 and 8.

5 CHAPTER 5 ETHNIC DIFFERENCES IN SPIROMETRY

5.1 Background

Ethnic variations in lung function have been well documented in children and adults. Several studies have shown that divisions of lung volume measured by spirometry in the white population are larger than in other groups (1) and (2). It is not clear why lung function differs between ethnic groups, and many studies have attempted to describe the factors that might explain this (1), (2), (8), (7), (9), (10), (11), and (12). White children have an FVC that was 13.4% was larger than South Asian children (who have their origins in the Indian subcontinent) of the same height, whilst white children's FEV_1 was 10.6% greater than for the Asian group (3), (4) and (1).

5.2 Aims

- To compare forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV_1) measured by spirometry between white and South Asian children.
- To determine the effect of smoke exposure and wheezing in last 12 months on lung function.

5.3 Methods

5.3.1 Recruitment

Details about recruitment of the subjects for this study are given in chapter 3 (section 3.3). In brief, this study was conducted at Leicester, as the largest ethnic minority groups having their origins in the Indian subcontinent live within this city. The children included in this study were recruited from five primary schools and were aged 5-11years. Research Ethics Committee approval was obtained for this study (ref ULH 11456) see (Appendix 10.1). Presentations were given in school assemblies in these five schools to explain our study. The children's families were contacted through their schools. Written informed consent was obtained for all children involved in this work. An information pack was sent to families including a letter of explanation, consent form and questionnaire to determine the ethnicity and eligibility and provide information on respiratory disorders and smoke exposure. See (Appendix 10.7).

If forms were returned incomplete, they would be returned to the child's parent or guardian for completion. If the consent form and questionnaire were returned completed, the child's eligibility for the study would be assessed by their responses to the health questionnaire. Children aged 5-11 were eligible if they were healthy and if parental consent was given. Each child gave assent at the time when measurements were made in the school. In order to avoid

making these children feel excluded, ineligible children were allowed to attempt the manoeuvres if they so wished, although their data was not included in the analysis. The protocol for the study made allowance for providing the opportunity for such children to enjoy the experience of 'blowing tests' rather than returning them to the classroom without having the chance to take part alongside their peers.

5.3.2 Anthropometry measurements

Measurements of height (standing and sitting) and weight are given in detail in chapter 3 (section 3.7).

5.3.3 Spirometry

Details of lung function test are given in chapter 3 (section 3.8). Briefly, spirometry was performed using a portable spirometer equipped with a pneumotachograph and using the Sentry Suite software (CareFusion, Germany). The machine detected and displayed ambient conditions, temperature, barometric pressure and humidity, and these were verified using a portable sensor. To take spirometry measurements, the child was seated and breathed quietly through the flow head of the spirometer. When the breathing was regular the child was asked to take a big breath in until full inspiration, and then asked to blow out as hard as possible until s/he could not blow out any further. This was repeated with short breaks until three reproducible measurements had been recorded (FVC within 10%) up to a maximum of eight attempts. All measurements were made in accordance with American Thoracic Society guidelines (154) and (64). At the end of the test sessions, flow-volume curves were visually inspected.

FEV_1 and FVC were expressed as predicted Z-scores, as based on predicted values for white children. Regardless of the ethnicity of the child, we used the Z-score based on white children. Predicted values and Z-scores for spirometry parameters were based on all-age spirometry reference values (155). A Z-score is the deviation of an individual's value from the mean value of a reference population, divided by the standard deviation of the reference population (22) and (156). FEV_1 in this study was expressed as a Z-score and not percentage predicted because Z-score is independent of age, height, sex, and ethnic group, unlike the use of percentage predicted and is recommended by ATS/ERS (20) and (157).

5.4 Analysis and results

5.4.1 Subjects and Recruitment

We achieved reportable spirometry data in 217 children (62 white and 155 South Asian).

5.4.2 Data entry and Statistical Analysis

The questionnaire data, results from anthropometry measurements and lung function tests were entered into a spreadsheet (Microsoft Excel) and analysed using the Statistical Package for the Social Sciences version 24(SPSS). The tests applied included ANCOVA and t-tests.

The fidelity of the data was assured via the following steps:

1- We tried to avoid errors at the data collection stage by going through the paper forms after each visit to a school.
2- Questionnaire data was coded (for example, yes /no questions were coded as 0- no, 1- yes, 99 no answer given). The replies were reviewed by two of the study team.

5.4.3 Descriptive Statistics

5.4.3.1 Spirometry data

A total of 307 children were studied from different ethnic groups. Only children whose families' ethnicity was white or South Asian were included in the analysis. Children belonging to any other ethnicity (for example: black, mixed and other) were excluded from the analysis, leaving 254 children, of whom 37 were excluded from the analysis due to their responses to health questionnaire or use of asthma medication on the day of testing. This left us with 217children included in the analysis.

5.4.4 Subjects demographics

The analysis was controlled for age, gender, height, weight and ethnicity. The main two ethnic groups in our study were white and South Asian (Table 5.1). Z scores for height, weight, and BMI were calculated from international references (159) and (160).

Table 5-1 Descriptive statistic for children split by gender and ethnic origin.

Variables	**White boys n=30**	**South Asian boys n=86**	**White girls n=32**	**South Asian girls n=69**
Age (years)	8.73(1.65)	8.85(1.72)	7.78(1.52)	8.75(1.80)
Standing height (cm)	134.44(10.29)	134.14(12.09)	127.90(10.68)	132.01(13.03)
Standing height Z-score	0.17(0.95)	0.10 (1.21)	0.07(1.09)	0.19(0.88)
Sitting height (cm)	71.80(4.98)	70.34(5.53)	68.90(4.84)	69.31(5.77)
Weight (kg)	32.14(10.32)	31.51(10.28)	28.76(7.86)	31.36(11.34)
Weight Z-score	0.64(1.03)	0.24(1.47)	0.43(0.92)	0.49(0.98)
BMI (kg/m^2)	17.39(3.42)	17.15(3.42)	17.32(2.76)	17.50(3.36)
BMI Z-score	0.78(1.16)	0.31(1.45)	0.49(1.2)	0.52(1.16)

Numbers represent means with standard deviation in brackets.

All children studied have a normal distribution for age, height (standing and sitting height), weight and BMI. However, South Asian girls were significantly older, taller and heavier than their white peers.

5.4.5 Spirometry

FEV_1 and FVC were expressed as Z-scores, based on predicted values for white children. Predicted values and z-scores for spirometry parameters were based on all-age spirometry reference values (155). FEV_1 and FVC were expressed as Z- score and not percentage predicted because Z-score is independent of age, height, and sex, unlike the use of percentage predicted and is recommended by ATS/ERS (20) and (157).

There were significant differences in mean FEV_1 and FVC Z-scores between white and South Asian children; South Asian children had lower FEV_1 and FVC Z-scores than white children (Table 5.2).

Table 5-2 Mean FEV_1 and FVC Z-scores for South Asian and white children.

Variables	**White n= 62**	**South Asian n= 155**	**P**	**Mean differences**	**95% confidence interval**
Mean (SD)FEV_1Z-score	0.17(1.01)	-0.55(0.97)	<0.001	0.72065	(0.4224,1.0189)
Mean (SD)FVC Z-score	0.36(1.02)	-0.67(0.94)	<0.001	1.02350	(0.7261,1.3208)

Numbers represent means with standard deviation in brackets.

We adjusted for sex, age and height to account for the impact of anthropometry on the spirometry values recorded for each group, and Univariate Analysis of Variance was applied. The results showed that the white children demonstrated greater values of FEV_1 and FVC than South Asian children. (Table 5.3).

Table 5-3 Mean values for lung function parameters-adjusted for sex, age, height and weight.

Variables	**White n=62**	**South Asian n=155**	**P**
FEV_1 (L)	1.71(0.37)	1.66(0.45)	0.03
FVC (L)	2.00 (0.47)	1.87(0.53)	0.000

Numbers represent means with standard deviation in brackets.

5.4.6 Effect of risk factors on lung functions

Our study was not designed to assess the impact of exposure to smoking on lung function, and the low rates of smoking amongst South Asian mothers would in any case limit our power to examine any interactions between ethnicity and smoke exposure. Descriptive data on exposure to environmental tobacco smoke and wheezing for all children were studied, as shown in (Table 5.4). None of the risk factors analysed had any effect on FEV_1 or FVC in this study.

Table 5-4 Descriptive data on exposure to environmental tobacco smoke and wheezing for children as split by sex and ethnic group.

	Mother is a smoker		Maternal smoking during pregnancy		Household smokers		Wheezing past 12 months	
	Yes	No	Yes	No	Yes	No	Yes	No
white boys n =30	11	19	10	20	14	16	0	30
white girls n = 32*	11	21	9	23	11	20	4	27
South Asian boys n=86	3	83	1	85	11	75	13	73
South Asian girls n=69	2	67	0	69	4	65	6	63

**Questions relating to household smoking and wheezing past 12 months were unanswered by parents of one white girl.*

Multivariate analysis was completed via separate regression of various risk factors on the outcomes. The analysis was controlled for age, sex, height and ethnicity (Table 5.5). None of the risk factors analysed had any effect on lung function values in this study.

Table 5-5 Effect of risk factors on lung function-multivariate linear regression (controlled for age, sex, height and ethnicity).

Multivariate linear regression

Explanatory variable	Coefficient	P value	95% Confidence interval
Outcome variable: FEV_1			
Wheeze past in 12 months	0.052	0.447	(-0.005,0.012)
Mother is a smoker	0.038	0.673	(-0.181,0.279)
Maternal smoking during pregnancy	-0.057	0.533	(-0.347,0.180)
Household smokers	0.027	0.699	(-0.007,0.011)
Outcome variable: FVC			
Wheeze past in 12month	0.043	0.530	(-0.007, 0.014)
Mother is a smoker	0.006	0.950	(-0.268,0.285)
Maternal smoking during pregnancy	-0.006	0.946	(-0.328,0.306)
Household smokers	0.063	0.899	(-0.006,0.015)

5.5 Discussion

5.5.1 Key Findings

1- There were significant differences in mean FEV_1 and FVC Z-score between white and South Asian children. South Asian children had a lower FEV_1 and FVC compared with their white counterparts.

2- There were significant differences in mean absolute value FEV_1 and FVC between white and South Asian children. South Asian children had a lower FEV_1 and FVC compared with their white counterparts. This result was unchanged after adjustment for age, height, weight and sex.

3- None of the risk factors studied had any effect on lung function in this study.

5.5.2 Lung function and demographics

All the children studied had normal distributions for age, height (standing and sitting), weight and BMI. The normality of the data was tested using histograms and normality tests (Shapiro-wilk). There were significant differences in mean FEV_1 and FVC between white and South Asian children. South Asian children had a lower FEV_1 and FVC compared with their white counterparts. This result was unchanged after adjustment for age, height, weight and sex.

Our result is consistent with other studies which have shown that South Asians and black Caribbean children have smaller FEV_1 and FVC than white children after adjustment for standing height (3), (4) and (1).

The present results are in agreement with those of Whitrow et al., who observed that FEV_1 and FVC were lower in black Caribbean, black African and South Asian children than white children after adjusting for standing height (2).

5.5.3 Spirometry

There were significant differences in mean FEV_1 and FVC Z-score between white and South Asian children. South Asian children had a lower FEV_1 and FVC compared with their white counterparts, in agreement with previous studies that have shown a reduction in FVC and FEV_1 between white European and Indian children amounting to 13% for both indices at a given stature (4). Our data showed smaller percentage differences in FEV_1 and FVC (Table 5.3), but overall our findings are consistent in direction with those of Johnston et al., Whitrow et al. and Whittaker et al. They reported that white children have an FVC that was 13.4% greater than that

of South Asian children (who have their origins in the Indian subcontinent) of the same height, whilst FEV_1 was 10.6% greater in white children than the Asian group (3), (4) and (1).

Comparing our findings to studies conducted in India, Asian children residing in the Indian subcontinent showed a reduction in the lung function of 6 to 13% compared to white populations (53) and (55). Our results corroborate the Kuehni et al. study, who reported that FVC and FEV_1 in Asian children born in the UK were 11% and 9% smaller than their white peers (26).

No difference was observed in absolute value FEV_1/FVC between white and South Asian children. These findings are in agreement with other studies which have shown that no difference was found in FEV_1/FVC in white and South Asian children (1) and (11).

5.5.4 Effect of a risk factor on lung function

The effect of smoking on lung function is well known, and smoking is considered as a causative factor of chronic obstructive pulmonary disease (COPD), which is characterised by a decrease in spirometric indices and damage to the peripheral architecture of the lung (emphysema) (161). Upton et al. reported that exposure to environmental tobacco smoke (ETS) during childhood and young adulthood can be correlated to declining lung function in adulthood (162).

It has been reported that exposure to ETS during the antenatal period can also be linked to decreased lung function in childhood (163) and (164). The impact of environmental tobacco smoke on lung function has been considered to be one of the childhood risk factors correlated with the development of COPD in later life (165).

In the present study, however, we did not find a detrimental association between ETS exposure and lung function. It should be noted, however, that the studies that linked ETS exposure with decreased lung function had far more subjects than our study. For example, in Moshammer's study, 626 children had complete lung function and questionnaire data while Gilliland had 3357 subjects with complete data (163) and (164).

Similarly, data was available for 15901 subjects in Svanes' study (165) and 2195 subjects in Upton's study (162). Our study was not designed to assess the impact of exposure to smoking on lung function, and the low rates of smoking in South Asian mothers limit the power of the current work to examine any interactions between ethnicity and smoke exposure with any great confidence.

6 CHAPTER 6 RESPIRATORY MUSCLE STRENGTH

6.1 Background

Respiratory muscle strength can be assessed by measuring Maximal Inspiratory Pressure (MIP), which is the biggest sub-atmospheric pressure that can be created through inspiration against an occluded airway, and Maximal Expiratory Pressure (MEP), the greatest pressure that can be generated during a forceful expiratory effort against an occluded airway (73).

There has been little research that has considered ethnic differences in respiratory muscle strength. One study in adults measured MIP in four ethnic groups (not including South Asians) (17). It has been found that important correlates of higher values of MIP observed in multi-ethnic groups were male sex, younger age, obesity, higher FVC and shorter height. The differences in MIP with ethnicity were small (17). This study is limited because it has addressed only one variable (MIP) and not included measurements of MEP, and has not included South Asians, who represent the main minority group in the population of Leicester and Leicestershire; we have attempted to address this particular gap in knowledge.

In this project, we considered MIP and MEP across different ethnic groups, to test the hypothesis that differences in lung function between white and South Asian children can be explained in part by differences in the strength of respiratory muscles.

6.2 Aims

- To test the hypothesis that differences in lung function between white and South Asian children can be explained in part by differences in the strength of respiratory muscles.

6.3 Methods

6.3.1 Recruitment

Details about subject recruitment for this study are given in chapter 3 (section 3.3). In brief, this study was conducted in Leicester, as the largest ethnic minority groups who have their origins in the Indian subcontinent live in this area. The children included in this study were recruited from five primary schools aged 5-11years. Research Ethics Committee approval was obtained for this study (ref UHL 11456). The children's families were contacted through school. Written informed consent was obtained for all children involved in this work. An information pack was sent to families including a letter of explanation, consent form and questionnaire to determine ethnicity and eligibility, and to provide information on respiratory disorders and smoke

exposure. The questionnaire also asked whether each child took part in regular vigorous physical activity, and if so, how regularly they did so.

If forms were returned incomplete, they would be returned to the child's parents or guardians for completion. If the consent form and questionnaire were returned completed, the child's eligibility for the study would be assessed by their responses to the health questionnaire. Children aged 5-11 were eligible if they were healthy and if parental consent was given. Each child gave assent at the time when measurements were made in the school.

6.3.2 Anthropometry measurements

Measurements of height (standing and sitting height) and weight are given in detail in chapter 3 (section 3.7). In brief, each child gave assent at the time when measurements were taken in the schools, where we measured height and weight.

6.3.3 Respiratory muscle strength test

Details of respiratory muscle strength measurements are given in chapter 3 (section 3.10). Briefly, respiratory muscle strength was assessed by measurement of maximum expiratory and inspiratory pressures (MEP and MIP, respectively). Hand-held portable devices equipped with a pneumotachograph and the Sentry Suite software (CareFusion, Germany) were used.

For both measurements, the child breathed through a pneumotachograph attached to a shutter. To measure MIP, after several quiet breaths, the child exhaled maximally and the shutter was activated. The child made an inspiratory effort against the shutter and peak pressure was recorded. The test was repeated several times. Measurements of MEP were similar, except that the child inhaled maximally and then made a forceful expiratory effort. The inspiratory and expiratory pressure must be ideally maintained for at least 1.5 seconds in order for the maximum pressure sustained for 1 second can be recorded. The maximum value of three attempts that differed by less than 20% was recorded. Measurements were made according to the American Thoracic Society and European Respiratory Society criteria ATS/ERS (158).

6.4 Analysis and results

6.4.1 Descriptive Statistics

We studied 307 children from different ethnic groups, selecting only children whose families' ethnicity was white or South Asian for inclusion in the analysis. Children who belonged to any other ethnicity were excluded from the analysis, leaving 254 children. We obtained usable data for MIP in 196 children (53 white and 143 South Asian) and MEP in 225 children (62 white and 163 South Asian).

6.4.2 Univariate analysis

Univariate analysis was completed by regression to account for the effects of age, sex, height, weight and ethnicity upon the values recorded for each group, whilst a one-way ANCOVA was conducted to calculate mean values for the MIP and MEP for all children included in the analysis.

6.4.3 Analysis of maximal respiratory pressure data

There were no significant differences between unadjusted MIP and MEP in white and South Asian children. This finding was unchanged after adjustment for sex, age, height and weight (Table 6.1) and (Table 6.2).

Table 6-1Mean MIP for white and South Asian children.

Variables	**White n=53**	**South Asian n=143**	**P**
Mean (SD) MIP unadjusted (kPa)	7.36(2.14)	7.10(2.02)	0.40
Mean (SD)MIP adjusted (kPa)	7.51(1.99)	7.02(1.91)	0.14

Numbers represent means with standard deviation in brackets.

Table 6-2 Mean MEP for white and South Asian children.

Variables	**White n=62**	**South Asian n=163**	**P**
Mean (SD) MEP unadjusted (kPa)	6.23(1.52)	6.50(1.74)	0.29
Mean (SD)MEP adjusted (kPa)	6.29(1.58)	6.46(1.53)	0.48

Numbers represent means with standard deviation in brackets.

6.4.4 Respiratory muscle strength and demographics

Multivariate regression analysis was used to explore the association between MIP, MEP and demographics. MIP was significantly associated with sex (p=0.001), while MEP was significantly correlated with sex and weight (p= 0.000, and p= 0.001 respectively) (Table 6.3). Boys have larger MIP and MEP values than girls (p=0.000, and p=0.000 respectively) (Table 6.4). Heavier children have larger values for MEP.

Table 6-3 Multivariate regression analysis for MIP and MEP and demographics.

Multivariate linear regression

Explanatory variable	Coefficient	P value	95% Confidence interval
Outcome variable: MIP			
Sex	-0.225	0.001	(-1.467, -0.382)
Age	0.37	0.776	(-0.257,0.344)
Height	0.193	0.278	(-0.027,0.092)
weight	0.146	0.213	(-0.016, 0.073)
Ethnicity	-0.109	0.100	(-1.106,0.097)
Outcome variable: MEP			
Sex	-0.275	0.000	(-1.326, -0.523)
Age	0.147	0.219	(-0.085,0.368)
Height	-0.096	0.557	(-0.58,0.031)
Weight	0.345	0.001	(0.022,0.091)
Ethnicity	0.039	0.521	(-0.299,0.588)

Table 6-4 Mean MIP and MEP adjusted values for boys and girls.

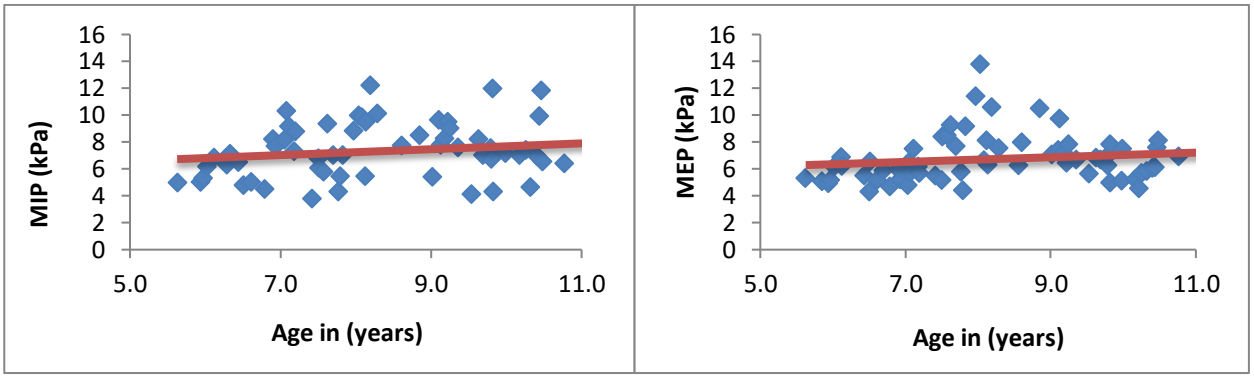
Variables	**Sex**	**Number**		**P**
Mean (SD)MIP (kPa)	Boys	102	7.69(2.07)	0.00
	Girls	94	6.60(1.89)	
Mean (SD)MEP (kPa)	Boys	116	6.92(1.83)	0.00
	Girls	109	5.87(1.32)	

Numbers represent means with standard deviation in brackets.

6.4.4.1 Age

No significant association was found between MIP, MEP and age in boys (regression analyses p=0.17, and p=0.20 respectively) (Fig 6.1).

Figure 6-1 Left panel MIP and Right panel MEP vs. age in boys.

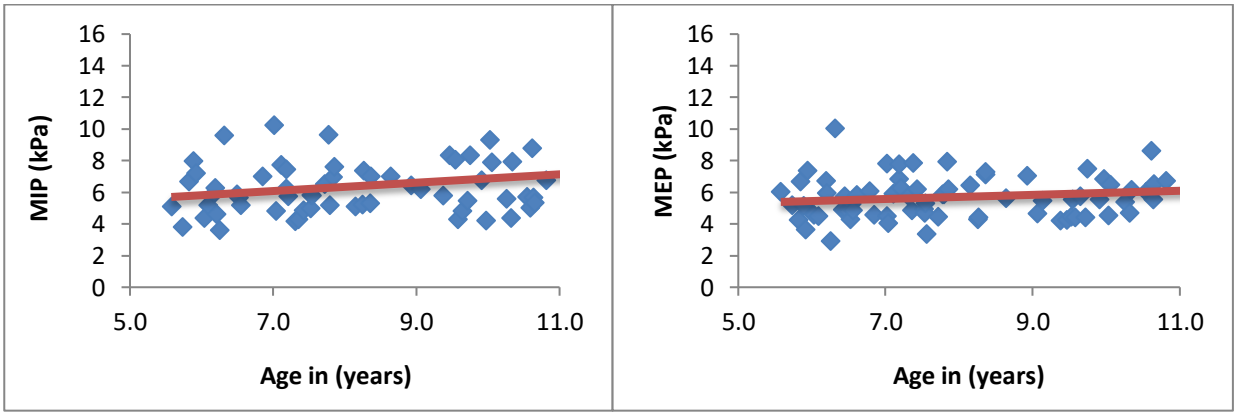


Legend: MIP vs. age in boys (regression analysis p=0.17).

Legend: MEP vs. age in boys (regression analysis p=0.20).

A significant correlation was detected between MIP and age in girls (regression analysis p=0.04) (Fig 6.2), but not with MEP (regression analysis p=0.16).

Figure 6-2 Left panel MIP and Right panel MEP vs. age in girls.



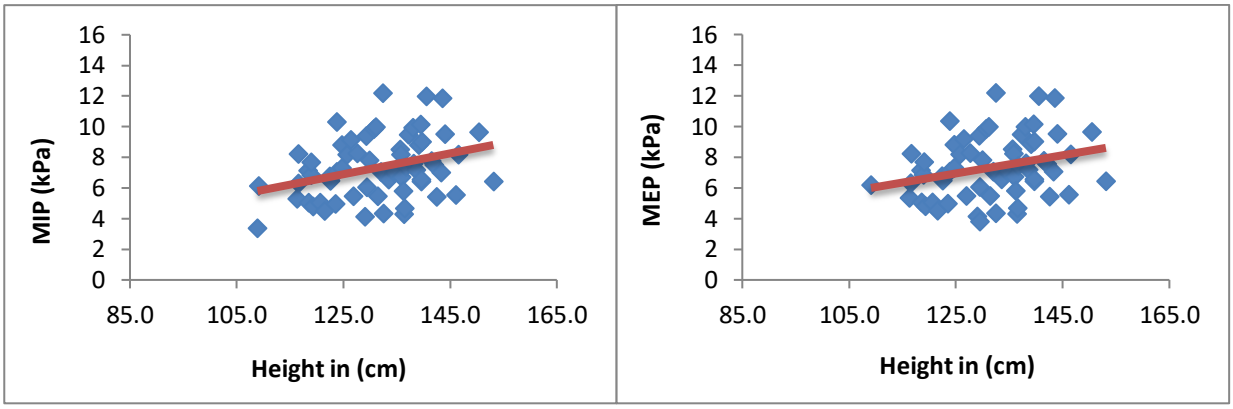
Legend: MIP vs. age in girls (regression analysis p=0.04).

Legend: MEP vs. age in girls (regression analysis p= 0.16).

6.4.4.2 Height

A significant relationship was found between MIP, MEP and height in boys (regression analyses p=0.007, and p=0.02 respectively) (Fig 6.3).

Figure 6-3 Left panel MIP and Right panel MEP vs. height in boys.

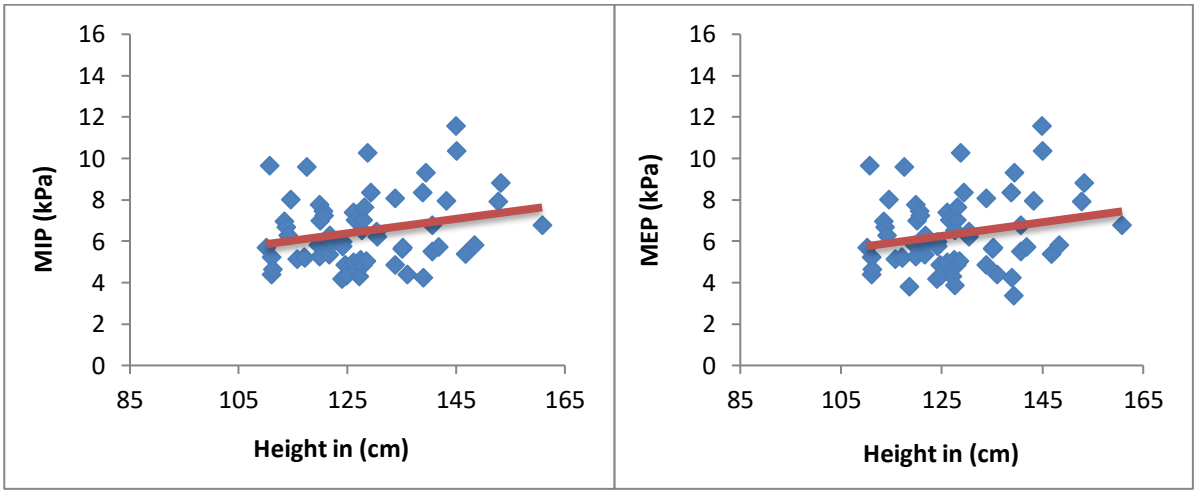


Legend: MIP vs. height in boys (regression analysis p=0.007).

Legend: MEP vs. height in boys (regression analysis p=0.02).

There was no significant association detected between MIP, MEP and height in girls (regression analyses p=0.05, and p=0.08 respectively) (Fig 6.4).

Figure 6-4 Left panel MIP and Right panel MEP vs. height in girls.



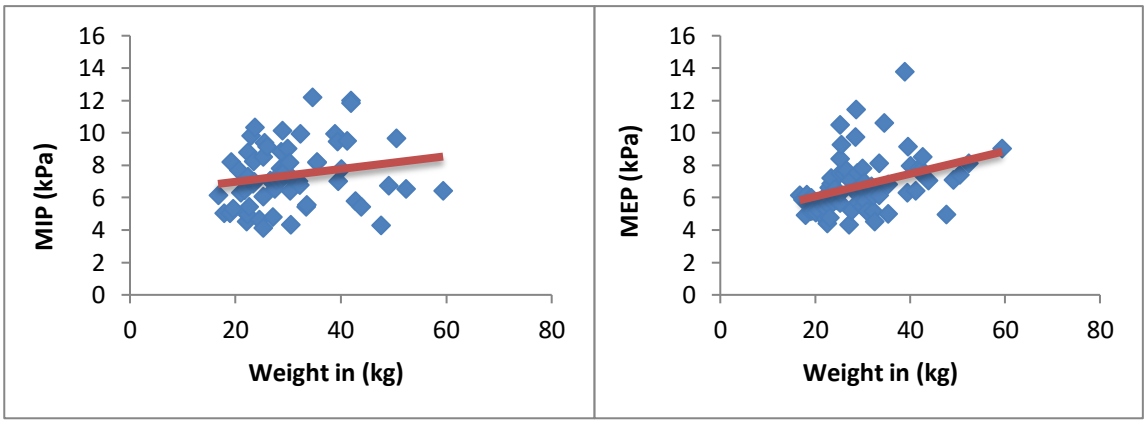
Legend: MIP vs. height in girls (regression analysis p=0.05).

Legend: MEP vs. height in girls (regression analysis p=0.08).

6.4.4.3 Weight

No significant correlation was detected between MIP and weight in boys (regression analysis p=0.14). However, a significant relationship was found between MEP and weight in boys (regression analysis p=0.002) (Fig 6.5).

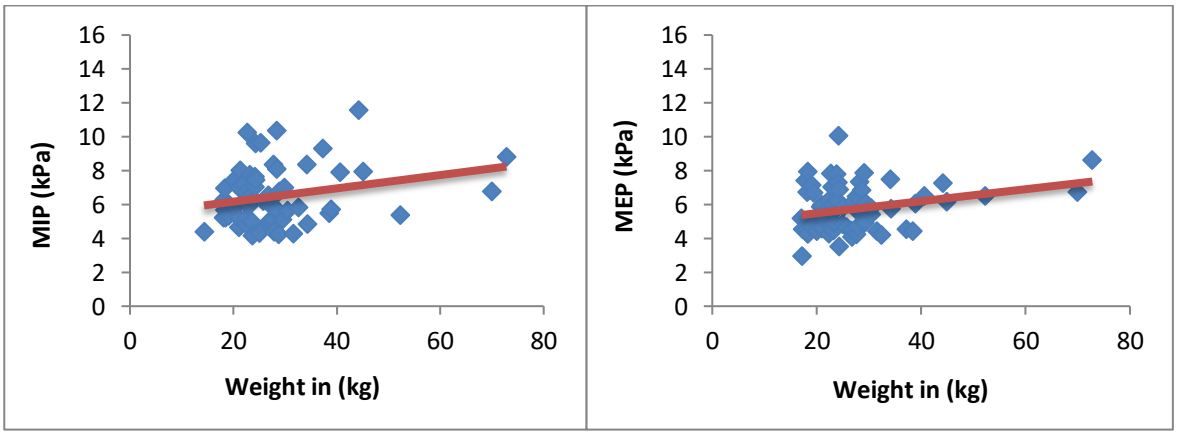
Figure 6-5 Left panel MIP and Right panel MEP vs. weight in boys.



Legend: MIP vs. weight in boys (regression analysis p=0.14). *Legend: MEP vs. weight in boys (regression analysis p=0.002).*

Similarly, in girls, no-significant association was found between MIP and weight (regression analysis p=0.05). However, a significant association has been detected between MEP and weight (regression analysis p=0.01) (Fig 6.6).

Figure 6-6 Left panel MIP and Right panel MEP vs. weight in girls.

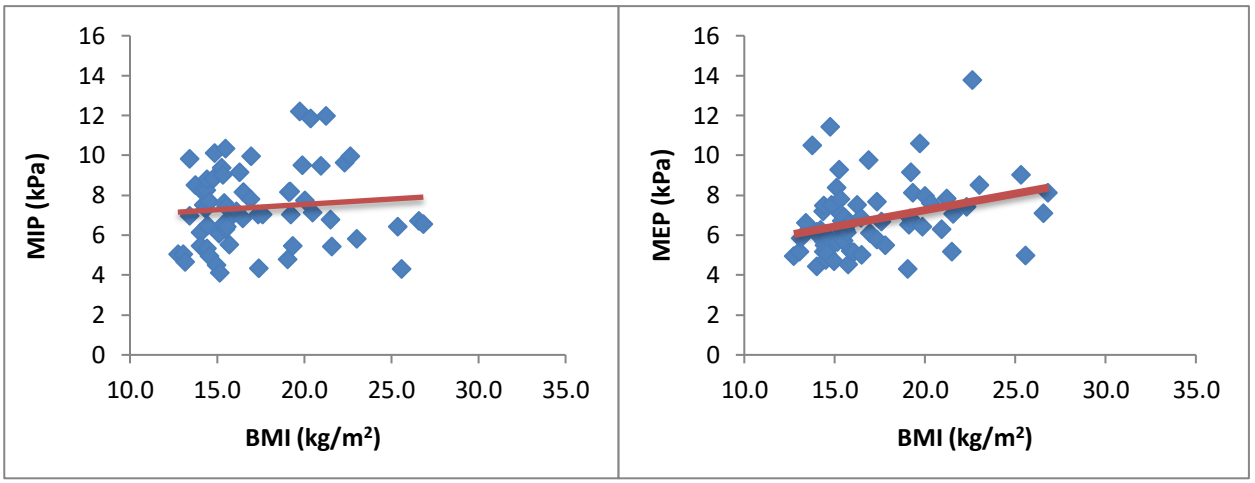


Legend: MIP vs. weight in girls (regression analysis p=0.05). *Legend: MEP vs. weight in girls (regression analysis p=0.01).*

6.4.4.4 Body mass index (BMI)

No significant association was detected between MIP and BMI in boys (regression analysis p=0.44), while a significant relationship was found between MEP and BMI in boys (regression analysis p=0.007) (Fig 6.7).

Figure 6-7 Left panel MIP and Right panel MEP vs. BMI in boys.

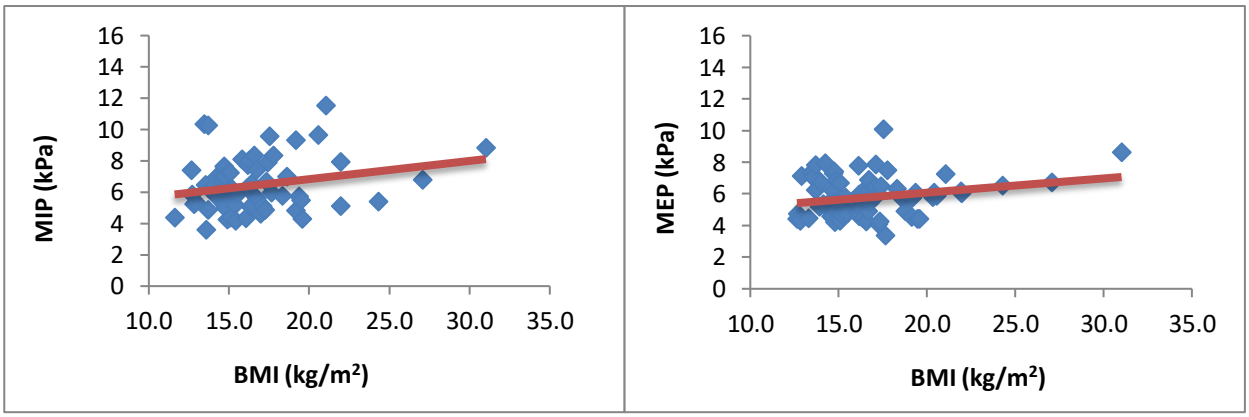


Legend: MIP vs. BMI in boys (regression analysis p=0.44).

Legend: MEP vs. BMI in boys (regression analysis p=0.007).

Similarly, in girls, no significant association was found between MIP and BMI (regression analysis p=0.07). However, a significant association was detected between MEP and BMI (regression analysis p=0.04) (Fig 6.8).

Figure 6-8 Left panel MIP and Right panel MEP vs. BMI in girls.



Legend: MIP vs. BMI in girls (regression analysis p=0.07).

Legend: MEP vs. BMI in girls (regression analysis p=0.04).

6.4.5 Effect of risk factors on respiratory muscle strength

Multivariate analysis was done by regression of various risk factors separately on the outcomes. The analysis was controlled for age, sex, height and ethnicity (Table 6.5). None of the risk factors analysed had any effect on MIP or MEP in this study.

Table 6-5 Effect of risk factors on MIP and MEP- multivariate linear regression (controlled for age, sex, height and ethnicity).

Multivariate linear regression

Explanatory variable	Coefficient	P value	95% Confidence interval
Outcome variable: MIP			
Wheeze in past 12 months	-0.058	0.424	(-0.058,0.24)
Mother was a smoker	-0.073	0.491	(-1.837,0.884)
Maternal smoking during pregnancy	0.121	0.255	(-0.598,2.244)
Household smokers	0.057	0.438	(-0.026,0.059)
Outcome variable: MEP			
Wheeze in past 12 months	-0.062	0.356	(-0.049,0.018)
Mother was a smoker	-0.137	0.128	(-1.594,0.202)
Maternal smoking during pregnancy	0.086	0.339	(-0.526,1.522)
Household smokers	0.091	0.187	(-0.011,0.058)

6.5 Discussion

6.5.1 Key Findings

1- There was no significant difference between unadjusted MIP and MEP in white and South Asian children. This result was unchanged after adjustment for age, height, weight and sex.

2- Boys have larger values of MIP and MEP than girls. MEP shows a significant correlation with weight.

3- None of the risk factors studied had any effect on MIP or MEP in this study.

6.5.2 Respiratory muscle strength

To the best of our knowledge, this is the first study conducted to investigate the ethnic differences in respiratory muscle strength between white and South Asian children. Only one other study has studied four groups: non-Hispanic white, African-American, Hispanic and Asian (of Chinese origin) (17). This study is limited because it addressed only one variable (MIP) and not included measurements of MEP, and did not include South Asians.

In our study, there were no significant differences between unadjusted MIP and MEP in white and South Asian children. This finding was unchanged after adjustment for sex, age, height and weight. MIP was significantly associated with gender, while MEP was significantly correlated with sex and weight. Boys have bigger MIP and MEP values than girls.

We did not find any significant differences in respiratory muscle strength between the two ethnic groups. The greater FVC in white children might have been attributable to increased inspiratory muscle strength, leading to a greater volume at the start of the manoeuvre, but this was not the case. An increase in expiratory muscle strength would be less likely to increase FVC since the end of expiration occurs when there is airway closure. whereas FVC measures the total volume of air in a forced expiration. This suggests that increased expiratory muscle strength may not necessarily lead to increases in indices measured in early expiration, but may have a measurable impact upon the end stages of the expiratory manoeuvre. It may be that increased expiratory muscle strength allows for a greater reduction of the volume of the thoracic cavity, thus causing a greater compression of the lungs and forcing more air out at the end of when FVC is measured.

It was found that important correlates of higher values of MIP observed through multi-ethnic groups were the male sex, younger age, obesity, higher FVC and shorter height. The differences

in MIP by ethnicity were small (17). Santos et al. reported that MIP and MEP were larger in boys than in girls (103).

We found no significant relationship between MIP and age in boys, while in girls a significant relationship was found MIP in this regard. These results agree with other study which have shown that MIP was correlated with age in girls but not in boys (16). In contrast to Tomalak et al., who showed that MIP was significantly correlated with age in boys (85).

However, in the present study, no significant association was found between MEP and age in either sex. In contrast to Wilson et al., Domènech et al. and Tomalak et al. reported that MEP was correlated with age in both sexes (16), (83) and (85). The most likely explanation for the contradictory result is their use of a wider age range than we used in our study; for example, Domènech et al. studied children aged 8 to 17 years old, and Tomalak et al. studied children aged 7 to 14 years old.

We found that MIP and MEP were significantly correlated with height in boys but not in girls. This result is consistent with Ogawa et al., who studied children of a similar age to ours, and showed that MIP and MEP were significantly associated with height in boys (91).

In our population, weight was not correlated with MIP in either sex. This result is in good agreement with that of Mellies et al., who reported that MIP was not correlated with weight in either sex (90). However, the current findings showed that MEP was significantly associated with weight in either sex. This finding is in accordance with that of Ogawa et al., who pointed out that MEP was significantly correlated with weight in both sexes (91).

Our findings show that BMI was not significantly associated with MIP in either sex, though, there was significant relationship detected between BMI and MEP in both sexes. This result corroborates that of Sachs et al., who found that BMI was not correlated with MIP in either sex, but correlated with MEP in both sexes (17).

6.5.3 Effect of a risk factor on respiratory muscle strength

None of the risk factors analysed had any effect on MIP or MEP in this study. However, we did not find any detrimental association between ETS exposure and respiratory muscle strength. Studies on the effect of environmental tobacco smoke exposure (ETS) on respiratory muscle strength in childhood and young adulthood are still lacking.

7 CHAPTER 7 HOW DO DIFFERENCES IN ABSOLUTE LUNG VOLUMES CONTRIBUTE TO ETHNIC DIFFERENCES IN SPIROMETRY?

7.1 Background

Divisions of lung volume measured by spirometry of white people are larger than in other ethnic groups after adjustment for age, height and sex (1), (2) and (13). The development of multi-ethnic reference values for spirometry represented a significant advance in the assessment of lung function in several ethnic groups (156), but data relating to peoples from the Indian subcontinent could not be incorporated within the reference values. This was because the populations within this subcontinent are ethnically heterogeneous, and the datasets available for potential inclusion showed considerable variation. Previous studies comparing South Asian children (who have their origins in the Indian subcontinent) with their white counterparts have shown a reduction in forced vital capacity (FVC) of 13.4% (1), 9% (3) and 13% (4) and forced expiratory volume in 1 second (FEV_1) of 10.6% (1), 8% (3) and 13% (4). If South Asian children are assessed using ethnically inappropriate prediction equations, they are left at risk of misclassification and potentially inappropriate therapy.

It is not clear why lung function differs between ethnic groups, and attempts have been made to define what factors might explain this observation such as chest dimensions (1) and (7), socioeconomic status (2),respiratory disorder (2),ethnic origin (8),birth weight, breastfeeding, environmental exposures, genetic factor and family histories of disease (7), (24), (10), (11), and (12).

Factors known to affect measurements of lung function include sex, height, and age. When white people are compared with Afro-Caribbeans, differences are less (but not negligible) when lung function is related to sitting height because Afro-Caribbean people have longer legs than their white counterparts (13). When South Asian children were compared with their white counterparts, we showed that differences in the proportions of leg length to standing height were trivial and did not explain the ethnic differences observed in spirometry (1). Measurements of chest dimensions also failed to account for spirometric differences (2). In contrast, in a comparison of children aged 11-13, it was reported that ethnic differences in FVC between white and Indian children were reduced by 29% (boys) and 25% (girls) if the adjustment was made on

the basis of the upper body segment rather than standing height (2). Differences in the age of the children studied may contribute to the small discrepancies between the two reports.

Ethnic differences in lung function have, in the past, relied almost exclusively on the spirometric indices FVC and FEV_1. Much less data exists on measurements of absolute lung volume in children, few studies have reported plethysmographically-determined lung volumes in children of different ethnicities, but TLC has been shown to be smaller in black children (primarily of African or Caribbean descent) when compared to whites (24), In this study (where children of both ethnicities were studied) results showed significant differences between observed and percentage predicted based on published equations derived from white children. FRC and TLC in black subjects were on average 14 and 6% lower than predicted. RV was slightly higher in black children, but the difference was not statistically significant (24).

In contrast, a study of 551 Chinese children and adolescents compared measured values of TLC, FRC and RV with prediction equations derived from white children (50). The values of FRC and TLC from Chinese children were broadly comparable with predicted value in white subjects. The RV was lower in the Chinese children, more markedly so in the girls. The authors attributed this to the rigorous screening procedures and adherence to stringent standards of lung volume measurements rather than a physiological difference in airway function. The drawback of this comparison is that the two ethic groups were not studied as part of the same set of investigations, so conclusions should be interpreted with caution.

In adult studies, TLC, FRC and RV have been shown to be reduced in Indians, when expressed as percent predicted for a white population, compared to their white or Chinese counterparts (7), the numbers of subjects in each group was small (11-14 individuals from each ethnicity), and it is not clear whether the differences in vital capacity (VC) are predominantly associated with changes in Total Lung Capacity (TLC) or Residual Volume (RV). To the best of our knowledge there are no studies comparing plethysmographic measurements of absolute lung volumes in white and South Asian children.

The aim of this study was to determine which of these alternatives predominated, or if both contributed to the reduced VC in South Asians. This will aid in the interpretation of other measurements of lung function, and inform our understanding of ethnic variation that has important implications for health care.

7.2 Aims

- To determine the ethnic differences in divisions of lung volume, specifically whether the reduced VC in South Asians is associated with a relatively increased Residual Volume (RV) or a reduced Total Lung Capacity (TLC).

7.3 Methods

7.3.1 Recruitment

The children included were recruited from two studies, the first was a study of respiratory muscle strength and ethnicity described in preceding chapters of this thesis. Research Ethics Committee approval was obtained from the University of Leicester Ethics Committee (ref UHL 11456) (Appendix 10.1).

The second study formed the focus of earlier work from our laboratory looking at lung development (151, 166). This was the basis of the PhD of Dr Manjith Narayanan (166), and he has provided me with data of measurements of lung volume that he obtained. For his study, subjects were recruited from Leicestershire Respiratory Cohorts (LRC) (152). Ethics approval was obtained from Leicestershire Local Research Ethics Committee One (ref 04/Q2501/114, Sponsorship numbers UHL 09580).

7.3.1.1 The first study recruitment and data collection

The children included in this study were recruited from five primary schools and were aged 5-11years. All the children who participated in studies of lung volume had been seen in the schools and had provided data on spirometry, MIP and MEP. At the time of the school-based study, parents had the opportunity to indicate on the questionnaire whether they may be prepared to consider bringing the child for additional measurements in the laboratory. One hundred and twenty-nine families were prepared to consider attending the laboratory and they were all sent letters of explanation. The families were then contacted by telephone, and 37 of them agreed to attend. An appointment was made on a date suitable for each family to attend the lung function lab in the Leicester Royal Infirmary (LRI), and a texted message reminder was sent one day before the day of the test. Children who attended the laboratory were included in plethysmographic studies of lung volume and studies of distensibility (reported in chapter 8). Children aged 5-11 were eligible if they were healthy and if parental consent was given. Written consent was taken from parents and children in the laboratory at the time of their visit. We sent out thank you letters to all families who attended our laboratory after the visit.

7.3.1.2 The second recruitment and data collection

The subjects included were recruited from Leicestershire Respiratory Cohorts (LRC). This study focussed on lung development. Children aged 7-16 were eligible if they were healthy and if parental consent was given. This study recruited some children who had been born pre-term, but only data from term-born children (at least 37 weeks completed gestation) were included in the analysis presented below. We got permission from Dr Narayanan to use lung volume raw data of white and South Asian children aged 7-16 years to include in this part of our study.

7.3.2 Inclusion and exclusion criteria

Inclusion and Exclusion criteria were the same for both studies (the first and second study) apart from where indicated below.

Inclusion criteria

Children were eligible to take part if they were aged 5 to 11 years (7 to 16 years for study 2) and where parental and personal consent had been given. For inclusion, children had to have been born full-term (i.e., at least 37 completed weeks gestational age) and have no personal history of significant cardio-respiratory conditions. (Study 2 recruited some children who had been born pre-term, but only data from term-born children were included in the analysis presented below). Children with mild asthma were eligible for inclusion unless they required daily medication. Children were only eligible if, in the opinion of the investigators, they understood what was involved and were clearly willing to participate.

Exclusion criteria

Children of ethnic origins other than those being investigated or who were of mixed race would not be excluded from taking part, although their results were expected to be insufficient for statistical analysis. Exclusion criteria included:

- Children born preterm (less than 37 completed weeks).
- Children with major cardiopulmonary conditions.
- Children with chest wall deformities.
- Asthmatic children who were taking daily medication.
- Children who had had a cough or cold within three weeks prior to testing.
- Any other factor which, in the opinion of the investigators, would render the child unsuitable for the study, e.g., severe growth deficiency.

7.3.3 Laboratory visit

Laboratory visits for children from both studies took the same format. Written consent was taken from parents and children prior to anthropometric measurements, followed by spirometry and plethysmography. The same equipment was used for all children.

7.3.4 Anthropometry Measurements

7.3.4.1 Standing height

The subject was asked to remove their shoes before starting the measurements. Standing height was measured using the Leicester Height Measure. The height measure was mounted on a base and stood upright against the wall. Children were measured while standing erect with their backs against the vertical column of the height measure. The child's head was positioned in the Frankfurt horizontal plane. A plastic plate was brought down to rest on the top their head, and height was measured at full inspiration to the nearest millimetre.

7.3.4.2 Sitting height

Sitting height was not measured in the study focussing on lung development (i.e. data provided by Dr Narayanan) and will not be considered further in this chapter.

7.3.4.3 Weight

The child's weight was measured whilst wearing indoor clothing but without their shoes using electronic scales. The weight was measured once and recorded to the nearest 100g.

7.3.5 Lung function measurements

7.3.5.1 Spirometry

Spirometry was performed with a Jaeger MasterScreen Body Plethysmograph (Care Fusion GmbH, Leibnizstrasse, Germany). The machine detects and displays ambient conditions, temperature, barometric pressure and humidity, and these were verified using a portable sensor. Equipment calibration was performed once daily using a 3-litre syringe. Calibration was performed at medium, slow, and high flow rates to account for any non-linearity that may occur at extremes of flow.

The child was seated and breathed quietly through the flow head of the spirometer. When the breathing was regular, the child was asked to take a deep breath in until completely full, and then asked to blow out as hard as possible until s/he could not blow out anymore. This was repeated with short breaks until at least three reproducible measurements had been recorded (variability of FVC within 10%) up to a maximum of eight attempts. Flow-volume curves were visually inspected to confirm the repeatability and acceptability of the measurements, and technically unsatisfactory manoeuvres were excluded. The largest FEV_1 and FVC from the acceptable FVC manoeuvres were reported. All measurements were made and reported in accordance with American Thoracic Society guidelines (64).

FEV_1 and FVC were expressed as Z-scores based on predicted values for white children from the all-age spirometry reference values (155) of the Global Lung Function Initiative. Lung Function in Growth and Aging (www.lungfunction.org).

7.3.6 Lung volume measurements

7.3.6.1 Plethysmography

Plethysmography was performed with a Jaeger MasterScreen Body Plethysmograph (Care Fusion GmbH, Leibnizstrasse, Germany). The equipment detects and displays ambient conditions, temperature, barometric pressure and humidity. The calibration of the machine was performed once daily in two steps, in accordance with the manufacturer's instructions. The first step was the calibration of the pneumotachograph, which was performed using a 2-litre calibration syringe attached to the mouthpiece and pumped at a high, medium and low flow rates to assess changes in flow and volume through the pneumotachograph. The second step was the

box pressure calibration, which was performed automatically to assess the background leak and calibration factor with the door closed and cabin empty. Ideally, the background leak should have a half-life of 4 to 7 seconds to avoid any source of error in subsequent measurements.

The child sat comfortably in the closed plethysmograph and breathed through a mouthpiece connected to a pneumotachograph and shutter. After several steady breaths, the operator activated the shutter while the child continued to make respiratory efforts. The resultant changes in pressure inside the plethysmograph and within the mouthpiece were used to calculate Functional Residual Capacity (FRCpleth). After each measurement, the child was asked to inspire and exhale maximally, so that VC, TLC and RV could measure. The test was repeated until we obtained at least three technically acceptable measurements, that were in accordance with ATS/ERS recommendations (65). The mean value for FRCpleth was reported and used with the mean inspiratory capacity (IC) to calculate the TLC. The largest VC was then subtracted from the TLC to obtain the RV. Z-scores for plethysmography (for both ethnic groups) were based on reference values derived from white children (63). At the end of the test sessions, FRCpleth traces were visually inspected.

7.3.7 Statistical methods

We only analysed data from children where we have complete spirometry and lung volume measurements. The statistical analyses were performed using the Statistical Package for the Social Sciences version 24 (SPSS). Summary statistics for the continuous variables are presented in tables. Z -scores for FEV_1, FVC, TLC, FRC, and RV were calculated and then compared between white and South Asian children using the two-independent-samples t-test. Using adjusted mean values, the percentage differences between TLC, FRC and RV in the two ethnic groups were calculated to determine whether any differences were proportional. Linear regression was performed to explore the association between subject characteristics such as sex, age, height and weight and ethnic group and FEV_1 or FVC. The normality of the data was tested using histograms and normality tests (Shapiro-wilk).

7.4 Results

7.4.1 Subjects and demographics

From the first study, 37 children attended the laboratory. Spirometry and plethysmography were attempted in all children. We obtained technically satisfactory complete spirometry and plethysmography data from 25 children (9 white, 16 South Asian). From the second study, data were potentially available from 139 healthy children (103 white and 36 South Asian). Technically satisfactory complete spirometry and plethysmography data were available from 122 of these children (92 white and 30 South Asian). A summary of the number of children included from the first and second studies is shown (Fig 7.1 and Fig 7.2).

Figure 7-1 Summary of the children included from first study.

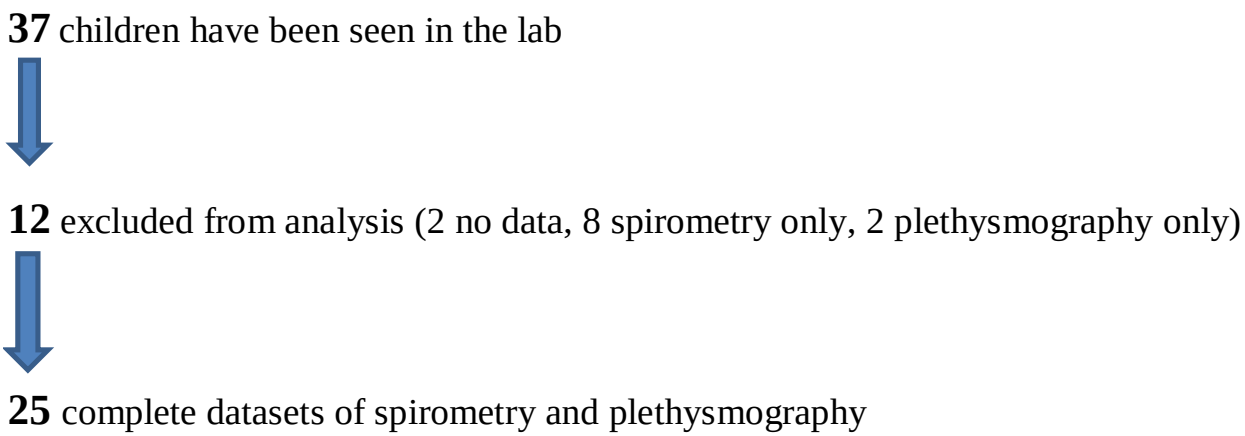
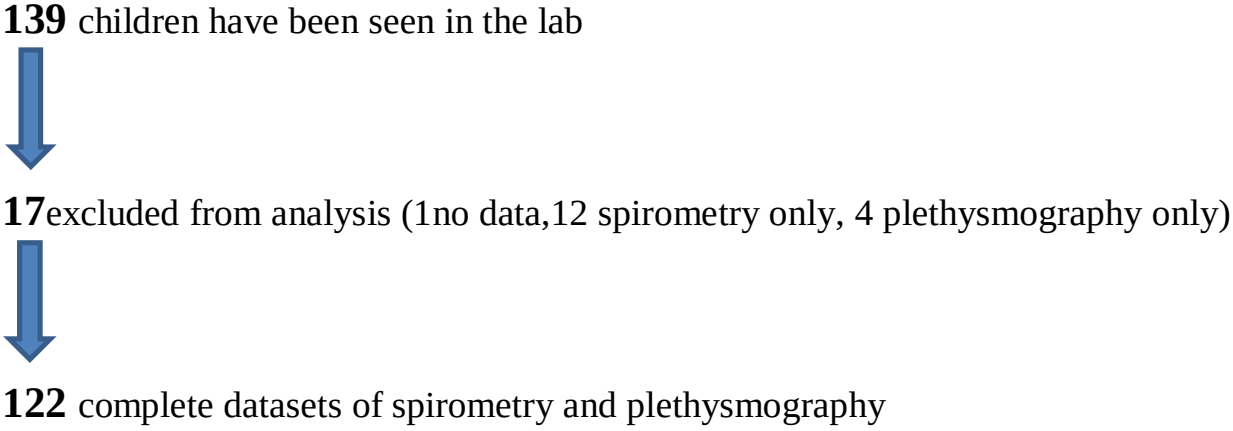


Figure 7-2 summary of the children included from second study.



Mean age, height, and weight for children from the two studies is shown (Table 7.1).

Table 7-1 Descriptive statistics for mean age, height and weight for subject with data used in analysis.

	First study subjects *25 (9 white, 16 South Asian)*	*Second study subjects ** *122 (92 white, 30 South Asian)*
Mean (SD) Age (years)	*8.86(1.66)*	*12.43(2.53)*
Mean (SD) Height (cm)	*134.47(9.07)*	*153.12(14.65)*
Mean (SD) Weight (kg)	*32.45(6.97)*	*47.61(14.92)*

**Second study -data provided by Dr* Manjith Narayanan (166). NB Eligibility criteria for first study had an age range 5-11 years and for the second study it was7-16 years.

Combining both datasets, complete data were obtained on 147 subjects (101 white and 46 South Asian). The mean (SD) age for white and South Asian children was 12.08(2.75) and 11.18(2.74) years, respectively, mean (SD) height was 151.06(15.40) and 145.10(14.54) cm, respectively, and the mean (SD) weight was 45.67(13.85) and 43.75(17.53) kg, respectively (Table 7.2). Z scores for height ,weight and BMI were calculated from international references (159) and (160).

Table 7-2 Mean age, height and weight for complete datasets white and South Asian children.

	White ***n=-101***	***South Asian*** ***n=46***
Age (years)	*12.08(2.75)*	*11.18(2.74)*
Standing height (cm)	*151.06(15.40)*	*145.10(14.54)*
Standing height Z-score	*0.07(1.09)*	*0.06(1.08)*
Weight (kg)	*45.67(13.85)*	*43.75(17.53)*
Weight Z-score	*0.06(1.10)*	*0.04(1.12)*
BMI (kg/m^2)	*18.4(3.1)*	*18.3(3.3)*
BMI Z-score	*0.51(3.1)*	*0.79(1.17)*

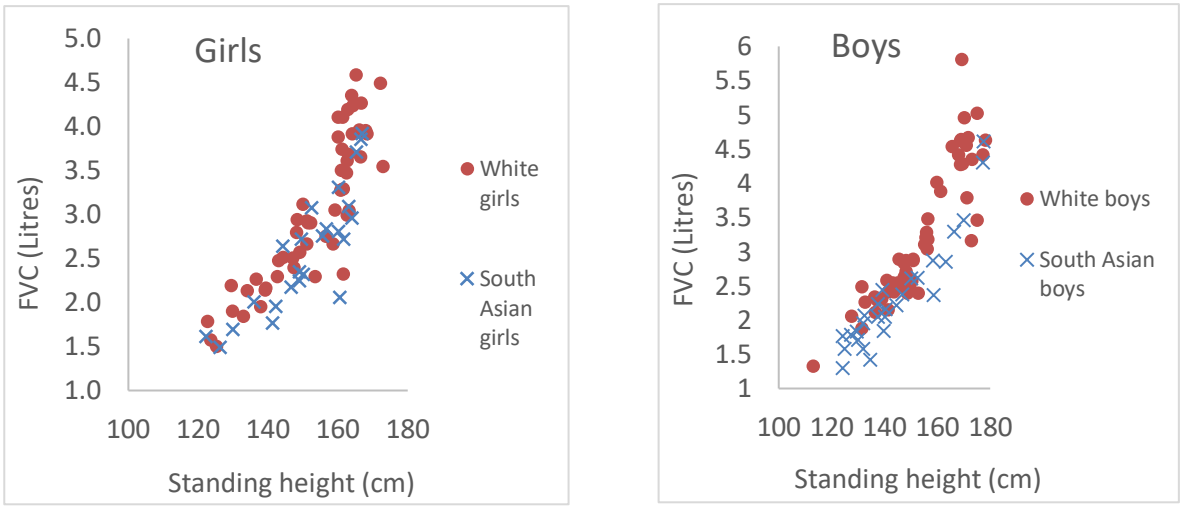
Numbers represent means with standard deviation in brackets.

7.4.2 Lung function tests

7.4.2.1 Spirometry

We had useable spirometry data on 147 children (101 white and 46 South Asian). Fig 7.2 shows scatter plots of FVC versus standing height for white and South Asian girls and boys.

Figure 7-3 Scatter plots of FVC vs. standing height for white and South Asian girls and boys.



When FEV_1 and FVC were expressed as Z-scores based on predictions for white children in both groups, there were significant differences between South Asian and white children. Mean (SD) FEV_1 Z-scores in South Asian and white children were -0.77(1.04) and 0.001(0.95) respectively ($p < 0.000$) while mean (SD) FVC Z-scores in South Asian and white groups were -0.84(0.90) and 0.16(0.97), respectively ($p < 0.000$) (Table 7.3). FEV_1 was significantly associated with age and height in all children. FVC was significantly associated with sex, age, height and weight in all subjects (Table 7.4).

Table 7-3 Mean FEV_1, FVC and Lung volume Z-scores For South Asian and white children, with z-scores being based on predicted values for white children (24) and (70).

	South Asian	**White**	**P**	**Mean differences (white-SA)**	**95% confidence interval**
Mean (SD)FEV_1 Z-score	-0.77(1.04)	0.001(0.95)	0.000	0.769	(0.408,1.131)
Mean (SD)FVC Z-score	-0.84(0.90)	0.16(0.97)	0.000	0.998	(0.670,1.326)
Mean (SD) TLC Z-score	-0.59(0.82)	0.29(0.90)	<0.001	0.872	(0.573,1.171)
Mean (SD) FRC Z-score	-0.82(0.91)	-0.49(0.94)	0.045	0.340	(0.008,0.656)
Mean (SD) RV Z-score	-0.28(0.89)	0.04(0.76)	0.039	0.317	(0.016,0.618)

Numbers represent means with standard deviation in brackets

Table 7-4 Multivariate linear regression for lung function parameters and demographics.

Multivariate linear regression

Explanatory variable	Coefficient	P-value	95% confidence interval
Outcome variable: FEV_1			
Sex	-0.055	0.137	(-0.212,0.029)
Age	0.168	0.040	(0.002,0.099)
Height	0.602	<0.001	(0.022,0.043)
Weight	0.132	0.080	(-0.001,0.015)
Outcome variable: FVC			
Sex	-0.102	0.005	(-0.337, -0.062)
Age	0.175	0.026	(0.008,0.117)
Height	0.495	<0.001	(0.020,0.044)
Weight	0.238	0.001	(0.006,0.025)

7.4.2.2 Plethysmography

Plethysmographic lung volumes were bigger in relation to height in white children than their South Asian counterparts. Plots of TLC and RV against standing height for boys and girls are shown Fig 7.4 and Fig 7.5.

Figure 7-4 Scatter plots of TLC vs.standing height for white and South Asian girls and boys.

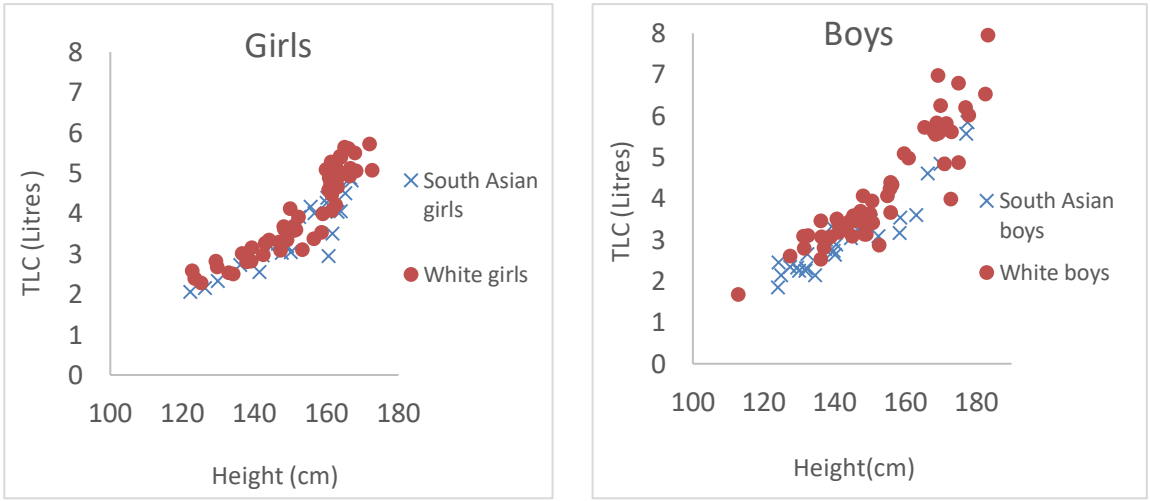
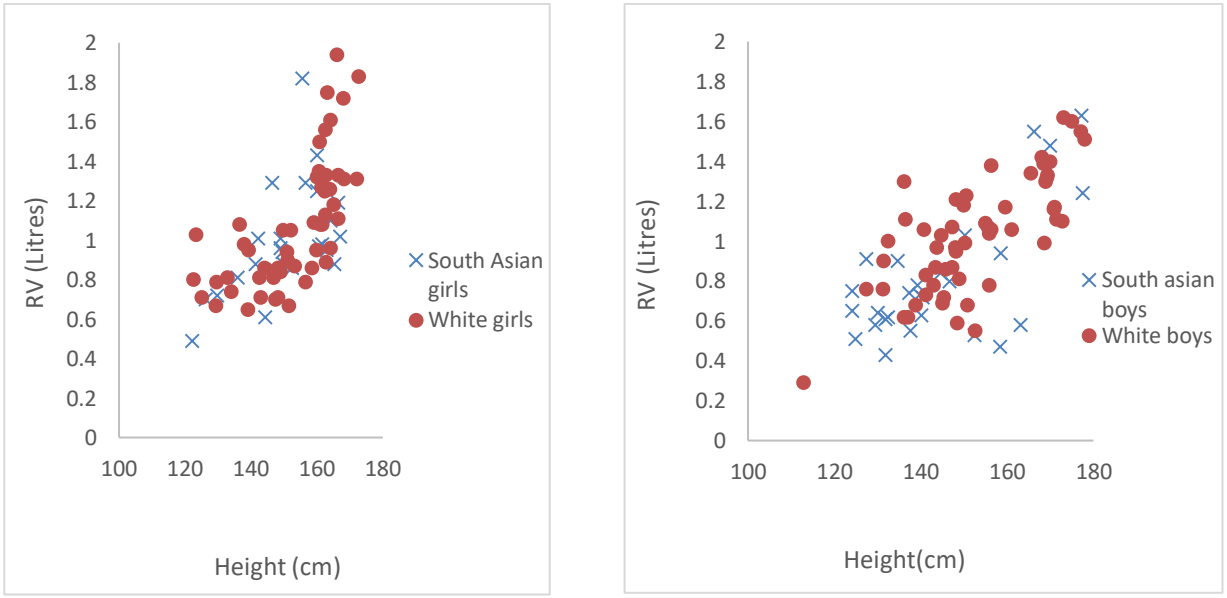


Figure 7-5 scatter plots of RV vs. standing height for white and South asian girls and boys.



The plethysmographic lung volumes of FRC, TLC and RV, expressed as Z-scores based on predictions for white children, were all significantly larger in white children than South Asians (Table 7.3). The mean (SD) TLC Z-score was -0.59(0.82) in South Asian children and 0.29(0.90) in white children, whilst the mean RV was -0.28(0.89) in South Asian children and 0.04(0.76) in white children. All mean Z-scores in South Asians fell below reference values for white children (Table 7.3). The major difference was in TLC, which differed by almost 1 Z-score. FRC and RV in white children were only marginally higher than South Asian children.

The percentage differences in TLC, FRC and RV between white and South Asian children were 10.03%, 6.91% and 8.57% respectively. These percentage differences were not statistically significantly different from each other. Thus, although the biggest difference in absolute lung volumes between the two ethnicities was TLC, the reductions in plethysmographic lung volumes seen in South Asian children were proportional.

The strongest relationships for all absolute volumes (TLC, FRC and RV) were with height. Relationships with age and weight were less clear-cut (Table 7.5).

Table 7-5 Multivariate linear regression for lung volume parameters and demographics.

Multivariate linear regression

Explanatory variable	Coefficient	P value	95% confidence interval
Outcome variable: TLC			
Sex	-0.057	0.110	(-7.367,4.570)
Age	0.148	0.057	(-0.002,0.134)
Height	0.754	<0.001	(0.045, 0.074)
Weight	0.031	0.659	(-0.009,0.014)
Outcome variable: FRC			
Sex	-0.054	0.241	(-4.347, -2.433)
Age	0.223	0.028	(0.006,0.099)
Height	0.796	<0.001	(0.023, 0.043)
Weight	-0.181	0.048	(-0.015,0.000)
Outcome variable: RV			
Sex	0.072	0.210	(-0.029,0.130)
Age	0.181	0.147	(-0.008,0.054)
Height	0.874	<0.001	(0.013,0.026)
Weight	-0.369	0.001	(-0.014, -0.003)

7.5 Discussion

There were significant differences in mean FEV_1 and FVC Z-score between white and South Asian children. South Asian children had a lower FEV_1 and FVC compared with their white counterparts, in agreement with previous studies (1), (3), (4), (2), (152) and (167).

Within this thesis there are measurements of FEV_1 and FVC from 217 healthy children studied in primary schools (Table 5.2), and 147 seen in the laboratory (Table 7.3). Twenty-five children were common to both studies. There are modest differences in the Z-scores for FEV1 and FVC between school and laboratory measurements. However, these are considerably smaller than the differences between children of different ethnicities. They might have arisen because of the different populations seen in the two locations, one group having a wider age range, or because of differences in the equipment used for the measurement. While the spirometry was always performed using equipment from a single manufacturer, it was not identical between school and laboratory.

The magnitude of the differences also varies between different publications, with direct comparisons made more difficult by some studies reporting an increased FEV_1 and FVC in white children and others reporting a decrease in South Asians. The most modest reported differences are a reduction in South Asian of below 10% for both FEV_1 and FVC (3) and (2). Differences approximating 13% have been reported elsewhere (4). When measurements have been made on the Indian subcontinent, Asian children residing in the Indian subcontinent shown a reduction in the lung function of 6 to 13% compared to white populations (53) and (55), and it has been previously shown that spirometry in South Asians is not affected by generation since migration (152).

In the present study, we have chosen to report differences in Z-scores, in part because of small differences in heights of the ethnic groups. In all cases the white children have z-scores marginally above what is expected. All the South Asian children have values below those predicted for whites, ranging from -0.55 to -0.84.

All absolute lung volumes were significantly smaller in South Asians than in white children. Few studies have reported plethysmographically-determined lung volumes in children of different ethnicities, but TLC has been shown to be smaller in black children (primarily of African or Caribbean descent) when compared to whites (24). In this study (where children of both ethnicities were studied) results showed significant differences between observed and

percentage predicted based on published equations derived from white children. FRC and TLC in black subjects were on average 14 and 6% lower than predicted. RV was slightly higher in black children, but the difference was not statistically significant.

In contrast, a study of 551 Chinese children and adolescents compared measured values of TLC, FRC and RV with prediction equations derived from white children (50). The values of FRC and TLC from Chinese children were broadly comparable with predicted value in white subjects. The RV was lower in the Chinese children, more markedly so in the girls. The authors attributed this to the rigorous screening procedures and adherence to stringent standards of lung volume measurements rather than a physiological difference in airway function. The drawback of this comparison is that the two ethic groups were not studied as part of the same set of investigations, so conclusions should be interpreted with caution.

In adult studies, TLC, FRC and RV have been shown to be reduced in Indians, when expressed as percent predicted for a white population, compared to their white or Chinese counterparts (7). While the numbers of subjects in each group was small (11-14 individuals from each ethnicity), this pattern of differences parallels our findings when comparing South Asian and white children. The differences between TLC, FRC and RV between Caucasians and Indians in the adult study were 17%, 11% and 6%, in contrast to our finding of 10.03%, 6.91% and 8.57% respectively. Whereas the decrements in all three lung volumes in the South Asian children are proportional, we cannot be sure that this is the case in the adult study.

There is one plausible explanation for these results, namely that a greater alveolar number in the lung lead to a larger TLC in white population (7). The reduction in VC in South Asian children could be associated with a reduction in TLC and not with an increased RV. Comparing our finding to studies that were conducted in India, white children had lung volumes 17% greater than Indian children (55) and (53).

In summary, our study characterised the differences in lung volumes between white and South Asian children. After adjustment for height and sex, we found that South Asian children had lower values of FEV_1 and FVC than their white peers, in line with previous reports. When measuring absolute lung volume by plethysmography, we showed that the major difference between the two groups was in TLC but, surprisingly, RV in South Asian was also somewhat reduced in comparison to white children.

8 CHAPTER 8 DISTENSIBILITY OF RESPIRATORY SYSTEM

8.1 Background

The lungs are elastic structures that change volume when the pressures are produced through the inspiratory and expiratory muscles. An alternative explanation to respiratory muscle strength for the ethnic differences in spirometry might be that the elasticity of the lung (or of the chest wall) varies with ethnic group. There is little published data on elasticity (or compliance) of the respiratory structures, possibly because it is not easy to measure in the relaxed, awake state.

One previous study investigated the relationship between the chest wall, pulmonary distensibility and age by studying 42 healthy males aged 24-78 (18), which found that pulmonary volume was increased and lung elasticity decreased in younger subjects compared with the more elderly, but no consideration was given to ethnicity (18). Our proposed project aimed to measure static recoil of the respiratory system in children of different ethnic groups.

Moreover, Binder et al. investigated lung function between black and white children by studying 393 children (14). They suggested that lung volume in black children might be decreased by increased elastic recoil, though, no other studies have appeared to confirm this hypothesis (14). We wanted to address the elastic recoil between different ethnic groups to investigate the correlation between elastic recoil and pulmonary function in different ethnic origin.

A study of 63 healthy children aged 2 to 7 years measured the total respiratory compliance and functional residual capacity (143). A positive association was found between respiratory system compliance (CRS) and height and age, and also between FRC and height. The outcomes of CRS and FRC showed that no differences were found between boys and girls. Besides, CRS- could be positively associated with FRC (143).

A previous study measured lung compliance in 70 healthy young adults (145), the results of which showed that there was a positive relationship between lung compliance, height, body surface area, and vital capacity, but showed a negative association with age (range: 18-39 years) (145).

The measurement of the distensibility of the respiratory system in awake subjects is difficult because of the need for relaxation. We hypothesised that we could measure a surrogate for lung distensibility in children while they were distracted.

8.2 Aims

To measure a surrogate for static recoil pressure of the respiratory system in both ethnic groups. Although this is a non-invasive measurement, there is a currently little existent data and it may prove difficult to measure reliably.

8.3 Methods

8.3.1 Recruitment

The children included in this study were recruited from five primary schools and were aged 5-11years. Research Ethics Committee approval was obtained for this study (ref ULH 11456) (Appendix 10.1). All the children who participated in studies of distensibility had been seen in the schools and had provided data on spirometry, MIP and MEP. At the time of the school-based study, parents had the opportunity to indicate on the questionnaire whether they may be prepared to consider bringing the child for additional measurements in the laboratory. One hundred and twenty-nine families were prepared to consider attending the laboratory and they were all sent letters of explanation. The families were then contacted by telephone, and 37 of them agreed to attend. An appointment was made on a date suitable for each family to attend the lung function lab in the Leicester Royal Infirmary (LRI), and a texted message reminder was sent one day before the day of the test. Children who attended the laboratory were included in plethysmographic studies of lung volume (reported in chapter 7) and studies of distensibility. Children aged 5-11 were eligible if they were healthy and if parental consent was given. Written consent was taken from parents and children in the laboratory at the time of their visit. We sent out thank you letters to all families who attended our laboratory after the visit.

8.3.2 Measurements of anthropometry

Measurements of height (standing and sitting) and weight are given in detail in chapter 3 (section 3.7).

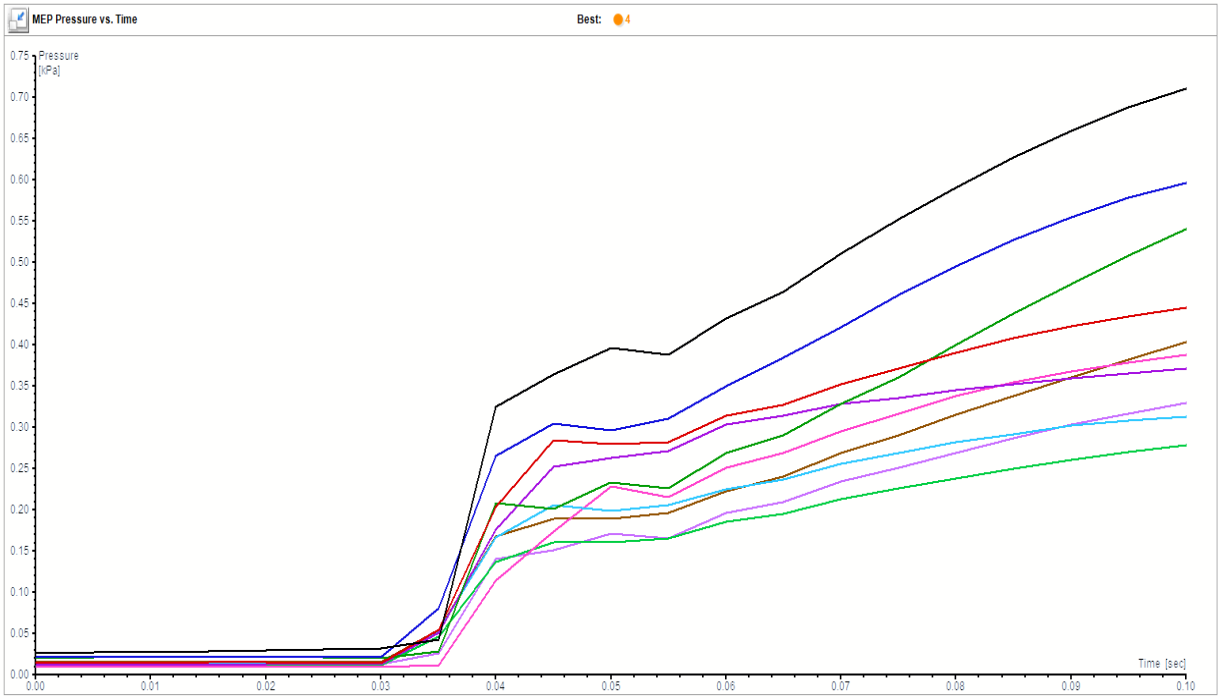
8.3.3 Lung distensibility measurements

8.3.3.1 Measurements of Pressure and Volume

The child was asked to sit on a chair and wear a nose clip. Each child breathed through the equipment. An iPad was used to help children to feel more relaxed, with a cartoon film or video games displayed if they wanted. The tidal volume was observed on the laboratory computer so we could judge when the child was breathing regularly. During regular breathing, the shutter was transiently closed at end-inspiration (by the operator keying on the computer) and this was done out of the sight of the child. Interruptions were repeated at intervals of about 15seconds so that the child returned to tidal breathing between interruptions. The equipment allowed up to 10 measurements at a time before it was necessary to pause and save the data. If the child was engrossed in the cartoon, we could recommence data collection for another 10 measurements without disturbing the child. In most cases, we performed 30 interruptions. The respiratory rate immediately before each interruption was recorded automatically.

The recordings of pressure against time were displayed on the computer screen. (Fig 8.1). We measured mouth pressure at pre-determined times after occlusion, relating pressure to the volume inspired above resting end-expiratory level. The volume above the end-expiratory level was available from the computer display. The pressure at the chosen time point was taken directly off the computer screen. A ruler was held up to the screen to assist the accuracy of the pressure measurement. The scaling of both axes (time and pressure) was adjusted to facilitate the measurements. The pressure was measured off the screen at specific time points, e.g. 0.06, 0.08, and 0.1 seconds. We tabulated the measurements of pressure and volume (Table 8.1). The respiratory frequency immediately prior to the interruption was available directly from the computer display and was also recorded.

Figure 8-1 Screenshot of changes in pressure plotted against time for ten consecutive interruptions in one child.



Legend: Pressure is on the Y axis and time on the X axis. The time axis has been truncated at 0.1 s to aid measurement of pressure at this specific time point. The pressure for each individual interruption is shown (Table 8.1), along with pressures from the same recordings, made at 0.06 and 0.08 sec.

Table 8-1 Pressure measured at different time points (0.1sec,0.08sec,and 0.06sec) immediately after interruptions,and volume above end expiration at the time of interruption. Data are from recordings showen above (Fig8.1).

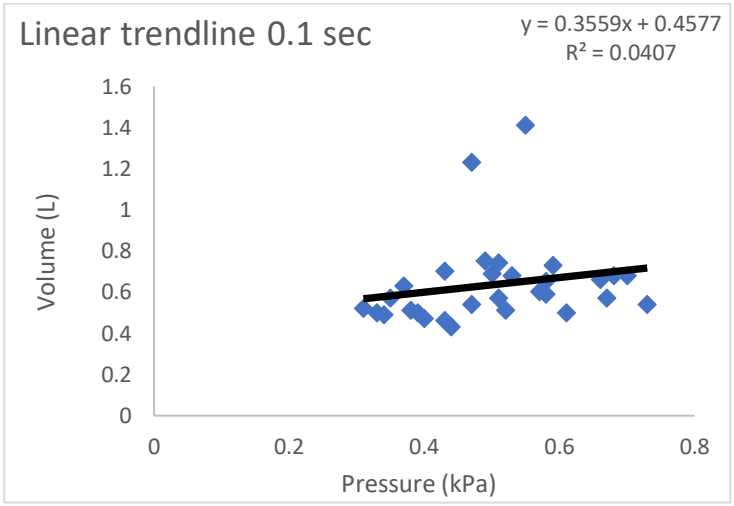
Colours of traces as shown in Fig 8.1	***Pressure measured at different time points (kPa)***			***Volume above end expiration at time of interruption (L)***	***Breathing frequency (BF) Breaths/ min***
	0.1 sec	0.08 sec	0.06 sec		
Black	0.71	0.60	0.42	1.25	22.17
Dark blue	0.59	0.49	0.35	1.17	23.29
Dark green	0.54	0.41	0.28	1.92	20.24
Red	0.44	0.40	0.31	1.51	21.76
Brown	0.41	0.32	0.22	1.28	23.37
Pink	0.39	0.34	0.25	0.52	22.74
Dark purple	0.36	0.31	0.30	0.42	21.42
Light purple	0.32	0.26	0.20	0.70	23.66
Light blue	0.31	0.26	0.23	1.43	17.49
Light green	0.28	0.25	0.19	0.48	26.09

Legend: Table shows data collected from 10 consecutive interruptions to breathing in one child (ID RM04). At this point the equipment requires that the data are saved. In most cases we recorded 30 interruptions from each child.

8.3.3.2 Generation of pressure volume plots and regression equations, and choice of standard analysis technique

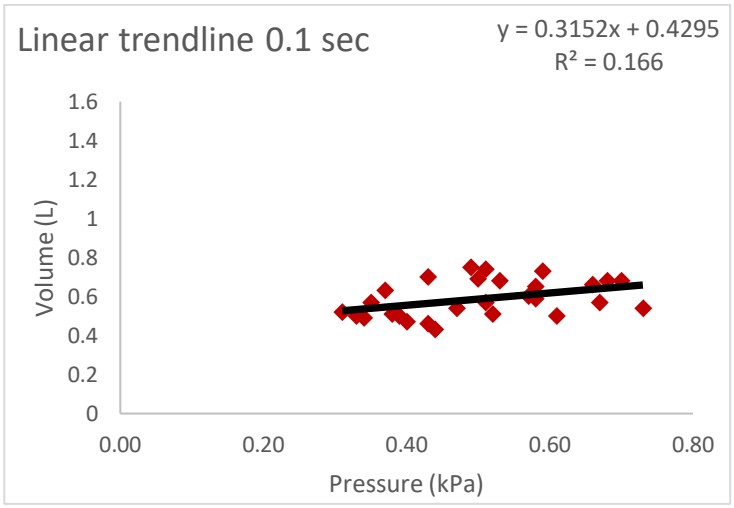
Pressure-volume plots were created from the datasets of pressure and volume, and inspected. The graphs were inspected independently by two observers, to see whether there appeared to be any outlying data points. After exclusion of up to four outlying points, linear and exponential regression equations were generated and the plots and regression equations were examined. An example of data before and after exclusion of outlying data points is shown (Fig 8.2 A and B). The data were inspected in an attempt to judge whether data plots generated at one time point appeared to have less scatter than the others, and whether exponential regression equations appeared superior to linear regression equations.

Figure 8-2 A. Data before exclusion of outlying data points. Subject RM0247.



Legend: Pressure vs volume before excluding 2 outlying data points. Pressure was measured at 0.1 sec after interruption.

Figure 8.2 B. Data after exclusion of outlying data points. Subject RM0247.



Legend: Pressure vs volume after excluding 2 outlying data points (Volume 1.41 and 1.23).

8.3.3.3 Viability of measurements in children

Following review of data collected on the first seven children, I analysed data where pressure was recorded at 0.1 sec following interruption. Data from these and all other children tested were visually inspected by two researchers working independently, each of whom could exclude up to four outlying data points. The data were subjected to linear and exponential regression and the regression lines were shown (Appendices 10.18,10.19 and 10.20). Each independent researcher divided the data into that which was considered worth further exploration, that which was uninterpretable, and others that were uncertain. The two researchers then compared their categorisation, and discussed the cases where there was uncertainty over the category.

Initially, data from each child were considered acceptable if the slope of volume against pressure was positive, and exceeded 0.1 $L.kPa^{-1}$, based on the linear regression analysis. This was a pragmatic decision. The rationale for this was to avoid inclusion of data where there was a level of uncertainty about whether or not it represented distensibility of the respiratory system. We plotted the slopes against height and I divided the slopes (of the acceptable data) by FRC to standardise for lung size.

8.4 Results

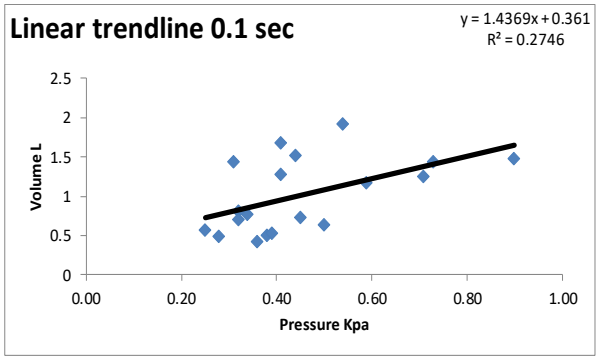
8.4.1 Preliminary studies to determine the time points after interruption to measure pressure

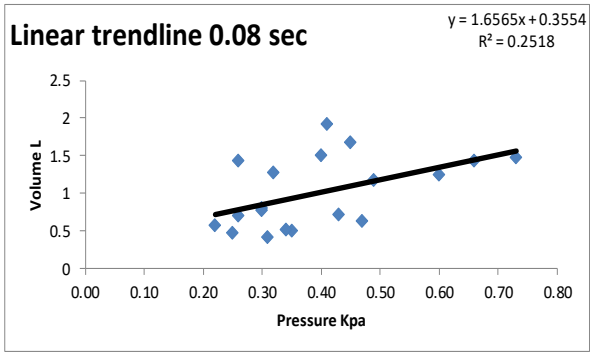
In order to measure distensibility we needed to measure volume and pressure following interruption to tidal breathing. We measured the pressure at different time points after interruption (0.1sec, 0.08sec, 0.06 sec) in seven children. The plots of volume against pressure for one child (RM04) are shown (Fig 8.3), including trend lines for linear and exponential regressions. There is a pair of plots relating to each time point at which pressure was measured.

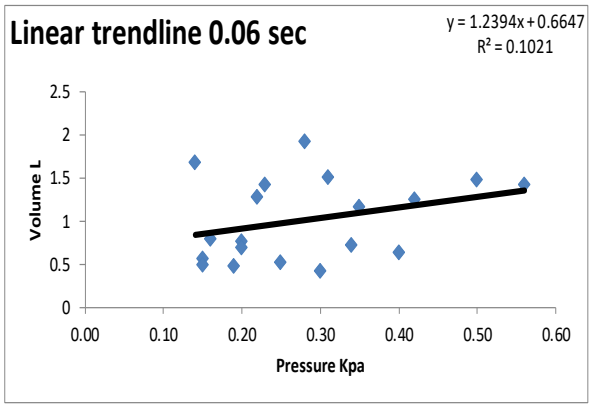
Data from all seven children where analysis was performed at these three time points are in Appendix 10.18. Inspection of the data showed that there was no consistent advantage to selecting one time point over the others. Therefore, further analysis was based on the data where pressure was measured at 0.1 sec after interruption. (Fig 8.3).

Figure 8-3 Pressure vs volume. (A) Linear trendline and (B) Exponential trendline in data points 0.1sec,0.08sec and 0.06sec. Child(RM04).

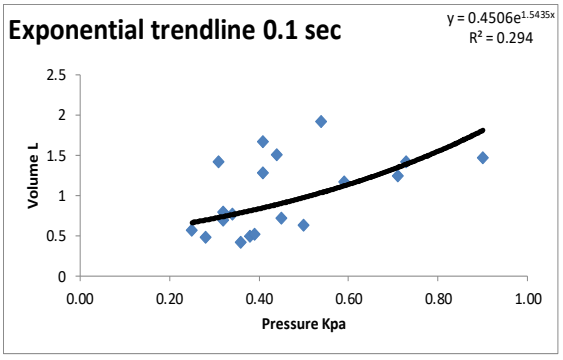
(A) Linear trendline

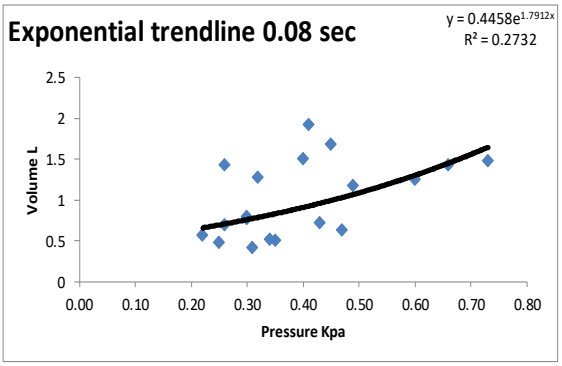


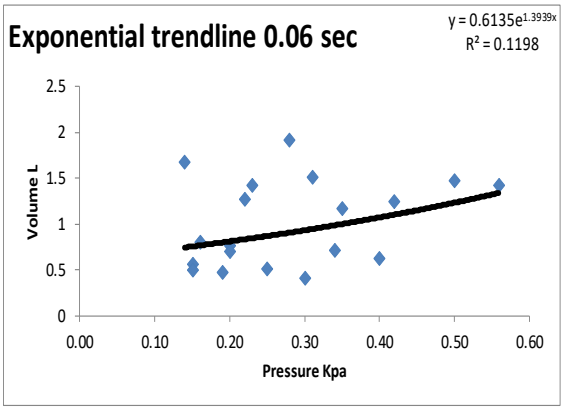




(B) Exponential trendline







8.4.2 Preliminary studies to decide whether to use linear or exponential regression

Pressure and volume data for each child were plotted and both linear and exponential regression were done. The trendlines were compared to see whether an exponential fit was substantially better than a linear fit (see Fig 8.3 for example. All data are in Appendices 10.19 and 10.20). Inspection of the data showed that there was no substantial advantage to an exponential regression. Furthermore, more in-depth analysis comparing different groups of children (e.g. those of different heights, genders or ethnic origins) is more straightforward with a linear regression, when it is possible, for example, to compare mean slopes. Therefore, remaining results are based on linear regression to determine the slopes of volume against pressure.

8.4.3 Proportion of data deemed to be acceptable

Thirty-seven children were studied. Based on the criteria stated in (section 8.3.3.3), we found acceptable data in 16 children (43%). Their pressure-volume plots and regression equations are shown in (Appendix 10.19). The plots and regression equations for the remaining 21 children are shown in (Appendix 10.20).

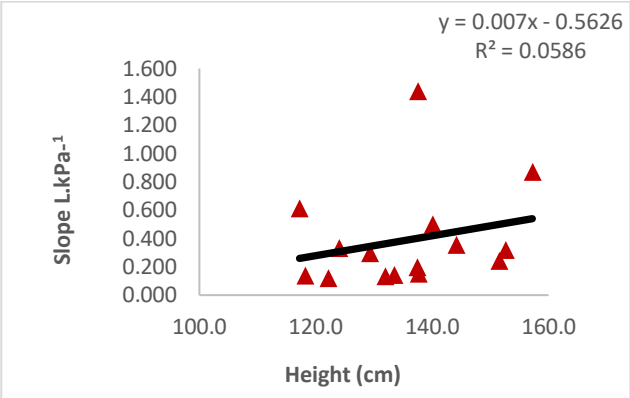
One of the children whose data met the criteria for acceptability (RM0131) had an obstructive pattern on spirometry on the day of the test. Therefore, his data have been included in the assessing the feasibility of the technique but not in looking at more detailed analyses. We compared the breathing frequency for acceptable and non-acceptable data to see whether breathing frequency was different between two groups of data. There were no significant differences in breathing frequency between acceptable and non-acceptable. The breathing frequency means (SD) for acceptable and non-acceptable data were 27.70 (6.05) and 30.97 (7.95) respectively, P-value was p=0.17.

8.4.4 Slopes and Slopes /FRC comparisons

We had sixteen sets of data where the pressure-volume relationships appeared to be a realistic approximation of distensibility. One of these was not considered further, as the child had evidence of obstruction on spirometry. Of the remaining 15 children, nine were south Asian and 6 were white. Eight were boys and seven were girls.

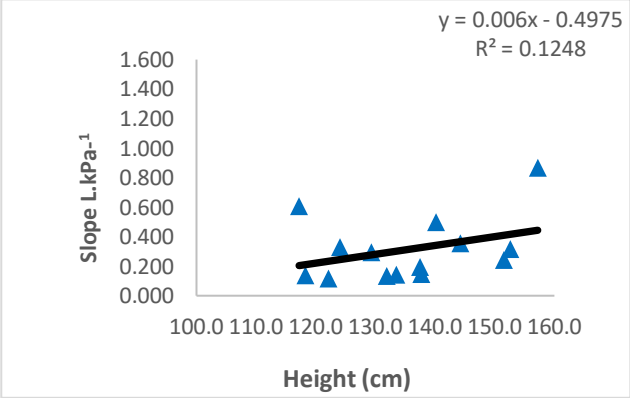
We have taken the pressure-volume slopes obtained for children as a surrogate for distensibility of the respiratory system. The slopes were plotted against height (Fig 8.4), which showed that distensibility increased with height. The data point with the greatest slope seemed to be an outlier compared to the remainder of the data. The relationship with height has been recalculated without the outlying point and displayed (Fig. 8.5) for comparison.

Figure 8-4 Slope vs. height,15 data points.



Legend: Plot showing the distensibility of the respiratory system increased with height (y=0.007x - 0.5626, R_2 =0.0586).

Figure 8-5 Slope vs. height,14 data points.



Legend: Plot showing the pattern of increase in distensibility of the respiratory system with height, after outlying point was removed (y=0.006x - 0.4975, R_2 =0.1248).

We compared slopes for white and South Asian children, there were no significant differences between two groups Table 8.2. Also, we compared slope/FRC between white and South Asian groups (the slope/FRC is a correction for lung size); there were no siginificant differences between white and South Asian children (Table 8.2).

Table 8-2 The slope and Slope/FRC means (SD) for white and South Asian children.

	White children	South Asian Children	P-value
Mean (SD) Slope $L.kPa^{-1}$	0.41(0.25) n=6	0.37(0.43) n=9 0.24 (0.17) n=8*	0.84 0.19*
Mean (SD) Slope/FRC kPa^{-1}	0.27(0.15) n=6	0.28(0.36) n=8 0.15 (0.05) n=7§	0.92 0.12*

Legend*: *These data have been calculated after omitting the outlying data point from the child (a South Asian boy) with the greatest value of slope/height. One South Asian girl did not have FRC available, so pressure slope/FRC for South Asian children is based on 8 children when using all available data, and §7 children when the outlying data point is excluded.*

We compared slopes and slopes/FRC between boys and girls to see if there were any gender differences. There were no significant differences between boys and girls (Table 8.3).

Table 8-3 The slope and slope/FRC means (SD) for boys and girls.

	Boys	Girls	P- Value
Mean (SD) Slope $L.kPa^{-1}$	0.48(0.46) n=8 0.34(0.26) n=7*	0.28(0.174) n=7	0.28 0.63*
Mean (SD) Slope/FRC kPa^{-1}	0.34(0.36) n=8 0.22(0.15) n=7*	0.19(0.07) n=6§	0.27 0.58*

Legend: **These data have been calculated after omitting the outlying data point from the child (a South Asian boy) with the greatest value of slope/height, so pressure slope and pressure slope /FRC for boys based on 8 boys when using all available data, and *7 boys when the outlying data point is excluded. §One South Asian girl did not have FRC available, so pressure slope/FRC for South Asian girls based on §6 girls.*

There were no significant differences between children of different ethnicities or genders (Table 8.4).

Table 8-4 The slope and slope/FRC means (SD) for white and South Asian boys and girls.

	White boys	*South Asian boys*	*White girls*	*South Asian girls*
Mean (SD) Slope L.kPa-1	*0.45(0.31) n=4*	*0.50(0.63) n=4* *0.19(0.05) n=3**	*0.31(0.03) n=2*	*0.27(0.21) n=5*
Mean (SD) Slope/FRC kPa-1	*0.26(0.19) n=4*	*0.40(0.51) n=4* *0.14(0.01) n=3**	*0.23(0.03) n=2*	*0.16(0.07) n=4§*

Legend: The South Asian boys' data have been calculated after omitting the outlying data point from one boy with the greatest value of slope/height, *so pressure slope and pressure slope/FRC for South Asian boys based on 4 boys when using all available data, and *3 boys when the outlying data point is excluded. One South Asian girl did not have FRC available, so pressure slope/FRC for South Asian girls based on §4 girls.*

8.5 Discussion

To the best of our knowledge, this is the first study that has been conducted to investigate the ethnic differences in distensibility between white and South Asian children. Measurement of distensibility of the respiratory system in awake, conscious subjects is difficult because of the requirement for relaxation.

8.5.1 Key Findings

1- The data point 0.1 sec appeared to be a suitable data time point to explore the relationship between pressure and volume.

2- The linear regression appeared to be a suitable format to illustrate the association between pressure and volume.

3- We have got acceptable data in almost half subjects.

4- There was no significant differences in breathing frequency rate between acceptable and non-acceptable data.

5- Based on the small number of subjects, we did not detect major differences between children of different ethnicities or genders.

8.5.2 Preliminary study of feasibilty

The distensibility of the respiratory system was not easy to measure because of the requirement for relaxation. The measurement was challenging, but it seemed possible in approximately half the children while they were distracted by an iPad. This should therefore be considered a preliminary study of feasibility, whose validity is as yet unproven and for which a proper interpretation of the data remains to be determined.

There is a lack of studies that have attempted to measure lung distensibility in awake subject because of the requirement for relaxation.

Studies have used the weighted spirometer technique to measure total respiratory compliance in adults and infants and found it to be reproducible (168) and (169).

Greenough et al. have measured total respiratory compliance in 63 healthy children using a water-sealed spirometer and face mask (143).

The studies that measured total lung compliance had far more subjects than our study. For example, in Cherniack's study, 70 children had complete total respiratory compliance while Naimark had 24 subjects with complete data (168) and (169).

In our study we do not have enough complete data of lung distensibility to confirm the reproducibility of the measurements. However, we got a good data in 16 children (43%). More data would help us to see children more than once to examine test reproducibility. It is a limitation that the acceptability criteria were not validated by anyone else. No other group has attempted to measure distensibility along the same lines or define criteria for acceptability.

8.5.3 Acceptable criteria

To the best of our knowledge, this is the first study that has been conducted to investigate the ethnic differences in distensibility between white and South Asian children, so there is a lack of studies that attempted to measure lung distensibility in the awake subject. Also, there are no external guidelines and this was a first attempt to review the data. Our challenge was to find acceptable criteria that suited our measurements.

This was a pragmatic approach. Should we have lots more data, we might modify the acceptability criteria. More data would enable us to: -

- Better define which data points should be considered as outliers.
- Judge what was most likely to represent data from a ‘relaxed’ subject.
- Look in detail at test repeatability.
- Use of Electromyograph (EMG) might help to determine whether the subject was relaxed or not.

8.5.4 Breathing frequncy

We noticed that during the time of measurement some children appeared to find it difficult to stay relaxed, particularly when the shutter was activated, even though they were watching the iPad. We thought that data obtained when the children had a high respiratory rate might prove to generate pressure-volume slopes that were unacceptable. This did not turn out to be that case.

8.5.5 Slopes and Slopes/FRC

We have taken the pressure-volume slopes obtained for children as a surrogate for distensibility of the respiratory system. The slopes were plotted against height showed that distensibility increased with height.

A study of 63 healthy children aged 2 to 7 years measured the total respiratory compliance and functional residual capacity found that total respiratory compliance increased with height (143).

A previous study measured lung compliance in 70 healthy young adults (145), the results of which showed that there was a positive relationship between lung compliance and height.

We have compared our slope against height equation with Greenough et al. equation using height range 110 cm to 140 cm and we confirm that lung distensibility increased with height. Athought, Greenough’s study measured total respiratory compliance, we measured distensibility of respiratory system.

We have the data for children of different heights, based on our data and Greenough’s data. Our values are all smaller, but our regression was based on fewer children, different technique, different height range. In our data if child with height 120cm his or her lung compliance will be 21.82 ml. cmH_2O^{-1}, while in Greenough’s data if child with height 120cm his or her lung compliance will be 62.8 ml. cmH_2O^{-1}.

8.5.6 Strengths and Limitations of the study

The strengths of the study include the fact that this was the first study has been conducted to investigate the ethnic differences in distensibility between white and South Asian children. The measurements were made in awake children, using a non- invasive method.

However, the limitations of the study can be summarised: -

- Ideally, more children of both ethnicities would have been included.
- Parents often find it difficult to bring children to the lab for testing, when this involves driving, parking (even if expenses paid) and taking time away from work or home
- It was a challenge to determine when the child was truly relaxed.
- There are no gold standard guidelines and it was a first attempt to review the data.

8.5.7 Conclusions

Lung distensibility was not easy to measure but was possible in some children while they were distracted. Ethnic differences in lung distensibility was an alternative explanation for ethnic difference in lung function, but our study cannot support or reject this hypothesis because of the relatively small numbers of participants and the limited time available for the study. Future work could increase the number of children as this would allow for further comparison between two groups of children to test this hypothesis.

9 CHAPTER 9 OVERALL DISCUSSION

9.1 Summary of results

In this chapter, I have opted to discuss material that has not been previously discussed in detail in chapters 5-8, which provided a detailed discussion of the results pertinent to each chapter.

The key findings of this work can be summarised as below:

1-There were significant differences in mean FEV_1 and FVC Z-score between white and South Asian children. South Asian children had a lower FEV_1 and FVC compared with their white counterparts.

2-There was no significant difference between unadjusted MIP and MEP in white and South Asian children. This result was unchanged after adjusted for age, height, weight and sex.

3-All absolute lung volumes were significantly smaller in South Asians than white children. The major difference was in TLC, which differed by almost 1 Z-score. All mean Z-scores in South Asians fell below the reference values for white children.

4- The reduction in VC in South Asian subjects can be associated with a reduction in TLC and not with increased RV.

5- Distensibility of the respiratory system was not easy to measure because of the requirement for relaxation. The measurement was challenging but it seemed ultimately possible for approximately half the children while they were distracted by an iPad. This is a preliminary study of feasibility and the validity is as yet unproven, and interpretation of the data remains to be determined.

9.2 Test Success and repeatability

The overall rates of test success for the three tests (spirometry, MIP and MEP) were high, particularly for spirometry and MEP. However, the fact that there was a difference in the success rate in all three tests between the age ranges reflects the fact that the younger children found the tests more difficult to execute than the older children. While none of the tests were strenuous in nature, they did require a certain level of coordination to be executed properly, with some of the younger children having difficulty in maintaining a tight seal with their lips around the mouthpiece while performing the manoeuvre. Most of these issues could be rectified with practice, although some younger children were continuously unable to grasp the concept, leading to the assessor to deem their efforts as unacceptable. As shown in (Fig 4.4), the MIP test had the lowest success rate across all ages. Subjects, particularly those who were younger, commonly had initial difficulties maintaining a maximal inspiratory effort after the activation of the shutter. This difficulty is shown by the low success rate for MIP of the age 5 and 6-year-old (50%) and (62%) respectively.

While the success rate for spirometry was above 88% for all children above the age of 6, it was lower in children aged 5 and 6 (54%) and (72%) respectively. As spirometry is such a commonly used tool for the assessment of lung function, several studies have attempted to assess its feasibility in young children.

Pesant et al. reported a success rate of 78% for the performance of two acceptable spirometric manoeuvres for children aged 3-5 (170), while Nystad et al. found a success rate of 92% for the performance of two acceptable manoeuvres in children aged 3-6. It may be that the environments of these two laboratory-based studies were more conducive to producing greater levels of success in the youngest children than that of our school-based study, which was limited by not being able to spend an extended period demonstrating and repeating spirometry (171).

The feasibility of assessing respiratory muscle strength in younger children has also previously been studied. Heinzmann-Filho et al. studied the reproducibility of measuring respiratory muscle strength in children aged 4-12, using similar methods to the ones used in this study (172). The study reported an overall test success rate of 92.3% for both MIP and MEP, greater than that reported in our study. However, Heinzmann-Filho et al. reported a significant difference in the success rate of young children (aged 4-5) compared to older children (aged 6-12), thus also indicating that the coordination required to adequately perform the test may develop with age (172).

The greater success rate reported by Heinzmann-Filho et al. may have also been influenced by the acknowledgement in that study that the "experienced study assessor" was "interested in achieving as much success as possible" in the tests. This may have produced greater levels of success than in our work, which, as a school-based study, may have been limited by not being able to keep children out of class for an extended period to repeat measurements.

9.3 Relationship between spirometry and muscle strength

As spirometry is a measure of expiration, expiratory muscle strength could feasibly influence the values seen for spirometry. Greater expiratory muscle strength would not influence total lung capacity, but as FVC and FEV_1 are both forced volumes rather than absolute volumes, greater expiratory muscle strength could feasibly increase the volume of air exhaled in these manoeuvres. The PEFR could also conceivably be increased by a greater expiratory muscle strength, as a measure of the initial forceful exhalation of air.

From our analysis, the heavier children demonstrated the greatest values for expiratory muscle strength. However, this finding was not repeated for FEV_1, but only for FVC. While these findings may be influenced by the distribution of body fat in the obese children, it was surprising that there was not a higher correlation between MEP and FEV_1.

This suggests that increased expiratory muscle strength may not necessarily lead to increases in indices measured in early expiration, but may have a measurable impact upon the end stages of the expiratory manoeuvre. It may be that increased expiratory muscle strength allows for a greater reduction of the volume of the thoracic cavity, thus causing a greater compression of the lungs and forcing more air out at the end of the manoeuvre, when FVC is measured.

9.4 Conclusion

Our study characterised the differences in lung volumes between white and South Asian children. After adjustment for height and sex, we found that South Asian children have lower values of FEV_1 and FVC than their white peers, in line with previous reports. When measuring absolute lung volumes by plethysmography, we showed that the major difference between the two ethnic groups was in TLC but, surprisingly, RV in South Asians was also somewhat reduced in comparison to white children.

We did not find significant differences in respiratory muscle strength between the two ethnic groups, so our hypothesis was not supported by the data. The differences in FVC remain unexplained. Ethnic differences in lung distensibility might be an alternative explanation for ethnic differences in lung function.

Lung distensibility was not easy to measure but was possible in some children while they were distracted. Ethnic differences in lung distensibility was an alternative explanation for ethnic difference in lung function, but our study cannot support or reject this hypothesis because of the relatively small numbers of participants and the limited time available for the study. Future work could increase the number of children as this would allow for further comparison between two groups of children to test this hypothesis.

9.5 Strength of the study

The strengths of the study include the fact that the sample included a large number of children from a wide age range. The presence of two different ethnic groups from the same region, with fewer environmental factors at play was also highly significant.

9.6 Limitation of the study

9.6.1 Power calculation and sample size

For MIP and MEP study, a sample size of 344 subjects was predicted to be sufficient to detect significant correlations with a power of 90% at a two-sided 5% significance level. Based on data from boys aged 10 years, in whom MEP measured at TLC had a mean (SD) value of 123 (27) cm H_20, we have calculated that 86 boys would be needed to detect a difference of 13.5 cmH_20 (equivalent to 0.5 SD) between white and South Asian boys, should such a difference exist (96).

Within the published work on which we based the power calculation, the standard deviations for MIP and MEP were not the same. However, we based our power calculation on differences relating to changes in the number of standard deviations, considering that a change of 0.5 SD

was meaningful. The number of children in the study would be the same had we used for MIP for the basis of our calculations.

Our study was not primarily aiming to identify differences in spirometry, since these are already documented. Our focus was MIP and MEP. We stopped the recruitment after we analysed the existing data, and showed that we were not finding significant differences in MIP and MEP between two ethnic groups. The differences we were finding were so small that, for them to turn out to be statistically significant, would have required a much bigger study.

Because of the exploratory nature of this study, we could not do a precise power calculation, and were dependent on published data from other centres using different equipment. Retrospectively, our results regarding MIP and MEP may have been underpowered, and it would have been valuable to include a larger number of children, particularly of white ethnicity.

Our original intention was to complete MIP and MEP measurements in schools' children who were willing to participate in our study. Ultimately, we were able to measure MIP and MEP in 307 children from different ethnicities. The reasons for the inability to increase the number of children, particularly white subjects, was because most of the schools we visited had a large majority of South Asian children, and the time frame available for the study, which prevented us from recruiting more children.

All of the above factors may have an effect upon the robustness of our findings although, they were consistent with results from previous cross-sectional studies. However, it should be noted that our study is considered to be the first study that measured MIP and MEP in two different ethnic groups, namely white and South Asian children.

To sum up, previous studies looking at the MIP and MEP in different ethnic groups have had their limitations, including small sample sizes, differences in measurement procedures, equipment and analysis software. These, together with the different populations studied, have made it difficult to find such a difference exits in lung function between different ethnicities. The reference values appear to be equipment and/or software-specific and based mainly cross-sectional samples. The contribution of our work is that we attempted to explain the differences in lung function in white and South Asian children by measuring MIP and MEP, lung distensibility and absolute lung volume using plethysmography.

9.7 Future work

Lung distensibility was not easy to measure but was possible in some children while they were distracted. Ethnic differences in lung distensibility was an alternative explanation for ethnic difference in lung function, but our study cannot support or reject this hypothesis because of the relatively small numbers of participants and the limited time available for the study. Future work could increase the number of children as this would allow for further comparison between two groups of children to test this hypothesis.

It would be of interest to explore whether ethnic differences in lung distensibility could explain ethnic differences in lung function between South Asian and white children.

To develop lung distensibility measurements, future work could use objective way to improve the test repeatability, more data would help to see children more than once to examine test reproducibility and see if there is difference between the tests, also collecting more data would enable future study to:

- Better define which data points should be considered as outliers.
- Judge what was most likely to represent data from a ‘relaxed’ subject.
- Use of Electromyograph (EMG) might help to determine whether the subject was relaxed or not.

10 APPENDICES

10.1 Ethics Approval form

RESEARCH & INNOVATION

University Hospitals of Leicester NHS
NHS Trust

DIRECTORATE OF RESEARCH & INNOVATION

Director: **Professor Nigel Brunskill**
Assistant Director: **Dr David Hetmanski**
Head of Research Operations: **Carolyn Maloney**

Direct Dial: (0116) 258 4199
Fax No: (0116) 258 4226

Research & Innovation Office
Leicester General Hospital
Gwendolen Road
Leicester
LE5 4PW

24/09/2015

Miss Nidhal Gharbawi
University of Leicester
PhD Student
Dept of 3 I's
LRI

Dear Miss Nidhal Gharbawi

Ref: UHL 11456
Title: Lung function in children of different origins Version 1

Thank you for sending documents for your research study to the University Hospitals of Leicester Research & Innovation Office.

Yours study has been entered onto the UHL Research Database, and for administrative purposes has been allocated the reference number **UHL 11456**. Please use this number when enquiring about the status of your study, the approval process or in any correspondence specific to this study.

Your study has been forwarded to a Research Support Officer who will commence a review, and will progress your study through to full approval. Zaynab Khan will be in touch with you in due course.

Please be aware that any research activity that has not been formally approved by the University Hospitals of Leicester NHS Trust R&I Office does not have Trust R&I Approval to commence and would constitute Research Misconduct.

Yours sincerely

Sharon Turner

Sharon Turner

Carbon Copy: Dr Caroline S Beardsmore

10.2 Head Teacher Information Letter

University of Leicester

Department of Infection, Immunity and Inflammation

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Tel: +44(0)116 252 2941 (Direct Line)
Fax: +44 (0)116 252 5030
E-mail: sam20@le.ac.uk *(Secretary)*
E-mail: pwa@le.ac.uk

Head of Department and Professor of Microbial Pathogenesis
Professor Peter W Andrew

Draft letter to head teachers

Dear (name of head teacher)

Several years ago I headed a study of lung function in children in which pupils from nine primary schools were involved. <name of school> was one of the schools that helped us in this piece of work, which was subsequently published (Whittaker, Sutton et al. 2005). We are now planning to extend this work and I am writing to you to ask for the help of <name of school> once more.

Study of lung function in children of different origins

I am seeking your help with a study that we are conducting on children of primary school age in Leicester. With your permission we would like to come to your school and make some simple measurements on lung function and respiratory muscle strength. This study has the approval of the University of Leicester Ethics Committee.

British studies comparing Asian children with their White counterparts have shown a reduction in lung function in Asian children between 9% and 13%. This is important because when measurements on Asian children are related to predicted values derived from the white population, there may be errors in interpretation and hence treatment. It is not known why such differences exist and we now want to see if they are explained by differences in strength of respiratory muscles. The project will show whether ethnicity-specific equations for predicting lung function should be developed, so that in the future lung function measurements for Asian children can be related to appropriate expected values.

Although we are particularly interested in White and Asian children, we would like to include children of all races and of mixed race in the study, to prevent anybody feeling picked on or left out. Results from these children may be written up in an anecdotal format.

What do the tests involve?

The parents/guardian of each child would receive an envelope prepared by us and sent out through the school containing:

- A letter explaining the reasons for the request and an outline of what the tests involve.
- A consent form.
- A simple questionnaire, asking about past medical history.
- An envelope for returning the consent form and questionnaire to the school, where we would collect it.

Parents would be invited to be present on the day of the testing if they so wished.

We would arrange to visit the school on mutually convenient occasions to see the children whose parents had consented to the study. The tests would be described to the children and their written assent sought. Children would be measured in same sex pairs; this would hopefully avoid any nervousness and put the children at ease. The measurements would include standing height, sitting height, and weight. We would then ask the children to do the breathing tests, which involve breathing in fully and blowing out with maximum effort into a machine which records how much and how fast air can be blown out. This gives important information about the capacity of the lungs and the state of the airways. When we measure the strength of the respiratory muscles, we ask the child to try to breathe in or out from a sealed tube, and measure the maximum pressure they can achieve. Breathing tests are repeated 3 or 4 times (maximum 8 times) to obtain the best values possible. The tests are not unpleasant in any way and many children enjoy them. If any child indicated that they did not want to take part or wished to stop, this would be respected.

Arrangements for the tests

As you are not at liberty to provide us with the names and addresses of the children in your school, we would ask you to distribute the (plain unmarked) envelopes containing the letters etc for all of the children in each class. This way the parents can divulge such information to us if they so wish. We would ask the children to return the consent form and questionnaire to the class teacher in the envelope provided, and then we would collect these from the school. We would leave 2-3 weeks for the children to return the information, after which time we would arrange dates, convenient to the school, to come and make the measurements.

What would be asked from the school?

Provided that the school is happy to help with the study, we will need a small room in which to work on the day of the visit. In the past we have usually used the medical room, with the proviso that the needs of a sick child or one involved in an accident take priority. We have also used the school library in the past.

We would also ask the class teacher to distribute the information packs. The testing period for each pair of children would take approximately 30 minutes. From previous experience, some schools are prepared for the children to miss part of a class, whereas in others the measurements are restricted to break times and lunchtime. We are happy to work with the requirements of each individual school.

We recognise the part that we have to play in safeguarding children, and we need to be alert to signs of possible abuse or neglect. We are aware that there is a possibility that a child may disclose that s/he is a victim of abuse to one of the study team. We are familiar with current government guidance ('What to do if you're worried a child is being abused' DFE-00124-2015).In the event of any concerns on our part, we would report these to the designated safeguarding lead for your school, in line with government advice, unless the concerns warranted immediate reporting to Children's Social Care Services or the police. As you would expect, all members of the study team who come into contact with children have an enhanced DBS check.

I appreciate that this letter contains a lot of information. I would welcome the opportunity to meet you and any other members of the school staff to discuss the study, if you think it would be helpful. Naturally we would not be able to proceed without your full approval and written consent.

I should be most grateful if you would let us know whether you would agree in principle for us to carry out this work at your school. I enclose a draft of an item suitable for inclusion in a school newsletter, which you would be welcome to use if you so wished. We would also be happy to talk about the study in a school assembly if you deemed this appropriate.

If you would like to discuss this matter further please do not hesitate to contact me by telephone on 0116 2525811 or by e-mail at the following address csb@le.ac.uk. I will telephone you a few days after posting this letter to answer any questions you may have.

Yours sincerely,

Dr Caroline Beardsmore
Senior Lecturer and Postgraduate Tutor

10.3 Head Teacher Consent Form

University of Leicester

Department of Infection, Immunity and Inflammation

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E-mail: sam20@le.ac.uk *(Secretary)*
E-mail: pwa@le.ac.uk

Head of Department and Professor of Microbial Pathogenesis
Professor Peter W Andrew

Lung Function in Children of Different Origins

Principal Investigator: Dr Caroline Beardsmore

This form should be read in conjunction with the Letter to Head Teachers Version 1 dated 23 April 2015

I have read the letter sent to me and had the opportunity to ask questions relating to all aspects of the study. I understand that I am under no obligation to allow <name of school> or its pupils to be involved in the study. I understand that if I agree to grant permission for <name of school> to be involved I may withdraw my permission at any time without justifying my decision.

Please initial as appropriate:

☐ I grant permission for <name of school> to take part in the study

☐ I do not grant permission for <name of school> to take part in the study

Signed…… Date……

Name……

10.4 Information Leaflet for Parents

UNIVERSITY OF LEICESTER

Department of Infection, Immunity and Inflammation
Maurice Shock Building
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Head of Department and Professor of Respiratory Medicine
Professor Andrew Wardlaw

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E ajb64@le.ac.uk *(Secretary)*
E aw24@le.ac.uk

Information Leaflet for Parents

Dear Parent/Guardian

RE: Lung function in children of different origins

Principal investigator: Dr Caroline Beardsmore
You may contact Dr Caroline Beardsmore on 0116 252 5811or by e-mail csb@le.ac.uk

I am writing to tell you about a study that we are conducting with children at primary schools in Leicester, and to ask if you would consider allowing your child to take part.

What is the purpose of the study?
British studies comparing children of different ethnic backgrounds have shown differences in lung function of between 9% and 13%. This means that when some children have breathing tests the results may be wrongly interpreted. We do not know why the differences exist, but we think it might be related to strength of respiratory muscles, or the elasticity of the lungs.

We will be visiting your child's school in a few weeks time to measure the children's lung function and strength of respiratory muscles, and we would like to ask you to consider giving your consent for your child to participate. For families who are able to come to the laboratory at Leicester Royal Infirmary, there is also an opportunity to be involved with more detailed tests later on.

The information from the study should help us to understand more about why children from different backgrounds have different lung function and, ultimately, improve our interpretation of tests carried out with patients.

Who is organising and funding this study?
The study is funded in part by the Ministry of Higher Education and Research, Iraq, and the University of Leicester. The study sponsor is the University of Leicester. The study has the approval of the University of Leicester Ethics Committee.

What will be involved if I allow my child to take part in the study?
This is a study that will continue for up to 3 years, but we only need to see your child on one occasion for approximately 30 minutes. We will come to your child's school to make the measurements.

On the day of the visit to the school, the tests will be described and demonstrated to the children. Children will be asked if they agree to take part and, if they do, they will be asked to sign an assent form. We will explain that they are free to stop at any time and will not have to do anything they do not want to do. No measurements will be made unless the child has given their assent.

Children would be measured in pairs to put them at ease. The measurements would include height and weight, and we would ask a small number of questions about diet and activity. We would ask the child to do the breathing tests, which involve breathing in fully and blowing out with maximum effort into a machine which records how much and how fast air can be blown out. When we measure the strength of the respiratory muscles, we ask the child to try to breathe in or out from a sealed tube, and measure the maximum pressure they can achieve. During the tests the children need to wear a nose clip rather like those used by some people for swimming. These breathing tests give important information about the capacity of the lungs and the state of the airways (breathing tubes). Breathing tests are repeated 3 or 4 times to obtain the best values possible.

If you agree to let your child participate in the study then we would also need you to complete a questionnaire about your child's health. If you would like to accompany your child during the tests, then this can be arranged. For parents/guardians who might consider additional simple measurements in our laboratory, further information will be provided after the school visit and you will have the chance to consider this and decide separately whether or not to take part.

What are the possible benefits or risks of taking part?
There is no direct benefit to any of the children taking part in this project. We cannot identify any risks to the children who do take part. The tests are not unpleasant in any way and many children enjoy them. No child would be expected to do anything they, or their parents did not want. No child would be expected to do more than she/he felt able to do, and would be free to stop at any time.

These types of tests are performed frequently on a routine basis, and should any problems arise, medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

Will information obtained in the study be confidential?
All the information gathered during this study will be kept entirely confidential. The identifiable research data may be examined by the study sponsor (University of Leicester) or UHL-NHS Trust for the purposes of monitoring or audit. The results of the study may be presented or published for scientific purposes. In all cases, neither your child's name nor identity will be disclosed and confidentiality will be maintained at all times.

We recognise the part that we all have to play in safeguarding children. In the event that we had any concerns about a child, we would report these to the designated safeguarding lead for your child's school, in line with government advice.

How will I find out about the results of the study?
Because this is a study of healthy children, we must assume that all the measurements we collect represent normal values and we will not be providing results from individual children to their parents. We will be providing an overview of our findings to each school taking part, soon after the completion of measurements in that school and again at the end of the whole study, in a format suitable for publication in a school newsletter. In the unlikely event that we were concerned about your child's breathing, we would contact you and ask for your permission to write to your GP explaining what we had found.

What happens if I do not wish for my child to participate in the study or wish to withdraw my child from the study?
If you do not wish for your child to participate in this study or if you wish to withdraw your child from the study you may do so without justifying your decision and your future treatment will not be affected. If you decide to withdraw your child from the study please contact Dr Caroline Beardsmore by telephoning 0116 252 5811. Your child may withdraw from the study at any time by telling any member of the research team that they do not want to take part or continue. If a child is withdrawn part-way through the study then we would intend to use any data collected up to the point of withdrawal.

If you agree to your child taking part, could you please complete the enclosed questionnaire and return it, with the consent form, in the envelope provided to your child's class teacher.

If you would like to speak to somebody about the project please telephone
0116 252 5811, leaving a message on the answer phone if there is no reply.

Yours sincerely,

Caroline Beardsmore Nidhal Talib

Dr Caroline Beardsmore, Dr Erol Gaillard, and Miss Nidhal Gharbawi

Athena SWAN Silver Award

10.5 Parental Consent Form

UNIVERSITY OF LEICESTER

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Head of Department and Professor of Respiratory Medicine
Professor Andrew Wardlaw

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T +44 (0)116 2522951 *(Secretary)*
F +44 (0)116 2525035

E ajb64@le.ac.uk *(Secretary)*
E aw24@le.ac.uk

Consent Form

Title of Project: Lung Function in Children of Different Origins
Study Number:
Name of Researcher: Dr Caroline Beardsmore

This form should be read in conjunction with the Information Leaflet for Parents

Please *initial* as appropriate:

- ☐ I confirm that I have read the information sheet dated 7 September 2015 version 2 for the above study. I have had the opportunity to consider the information and to ask questions by telephone.
- ☐ I understand that I am under no obligation to allow my child to take part, and that I may withdraw my child from the study at any time without justifying my decision, without his/her medical care or legal rights being affected.
- ☐ I understand that all data relating to the study will be confidential, but that it may be examined by the study sponsor (University of Leicester) or UHL-NHS Trust for the purposes of monitoring or audit.
- ☐ I understand that if there are any concerns about my child's breathing that I will be contacted by a member of the research team who will ask permission to contact my child's GP
- ☐ I am happy for my child to take part in the study
- ☐ Please contact me after the school visit to discuss what is required if we volunteer for the additional laboratory measurements

Consent Form Version 1 30 April 2015

☐ I would like to speak to somebody before deciding. Please telephone me.
The best time to ring is……..

☐ I do not wish my child to take part in the study

Signed……. Date…….

Name…….

Relationship to Child……..

Name of Child……. Date of birth……
Telephone number (should we need to contact you)…….

Please return this form to your child's class teacher in the envelope provided. Thank you!

10.6 Child Information and Assent Form

Children's Assent Form

Would you like to help?

Would you like to help us learn more about breathing?

We breathe air in through our mouths and noses and it goes into our lungs. Some people have bigger lungs than other people, which means they have more puff. This might be because the muscles used for breathing are stronger. We would like to ask you to help us with some special breathing tests to see how big your lungs are and how strong your breathing muscles are. We would also measure how tall you are, and how much you weigh. Lots of children have helped us with breathing tests in the past in the past and they usually enjoy them.

What we would ask you to do is breathe into a special tube, and then take your biggest breath ever and blow it all out as hard as you can. We would do this 3 or 4 times to see how much puff you have. The special tube is connected to a machine which can draw a picture of what your puff looks like. As well as this we would like to measure how strong your breathing muscles are, by asking you to try and breathe through a *very* tiny hole and seeing how hard you can try!

These tests will take about 30 minutes, with short breaks. These tests do not hurt at all, and if there is anything you do not want to do you can stop straight away.

We do not mind if you do not want to get involved, but if you would like to join in, please write your name below.

Children's Assent Form Version 1 30 April 2015

10.7 Health Questionnaire

Lung Function in Children of Different Origins

Questionnaire

Name of person completing the questionnaire:
Relationship to the child:
Date of completing of questionnaire:

Details of your child	
Name of child:	
Name of your child's class teacher:	
Date of Birth:	**Sex: male ☐ female ☐**
Address:	
What ethnic group do your family belong?	
A) White ☐	
B) Asian Originally from the Indian Subcontinent ☐	
C) Black ☐	
D) Mixed Please specify_____	
E) Other Please specify_____	

Questions on wheezing

1. Has your child had wheezing or whistling in the chest at any time in the past?
By wheezing we mean a high pitched whistling noise, coming from the chest, not the throat.

Yes ☐ **No** ☐

2. Has your child had wheezing or whistling in the chest in the last 12 months?

Yes ☐ **No** ☐

3. Has your doctor ever said your child has asthma?

Yes ☐ **No** ☐

4. In the last 12 months, has your child had wheezing or whistling in the chest even when she/he did not have a cold or flu?

Yes ☐ **No** ☐

Questions on Coughing

5. Does your child usually have a cough with colds?

Yes ☐ **No** ☐

6. Does your child usually have a cough apart from colds?

Yes ☐ **No** ☐

7. In the last 12 months, has your child had a dry cough at night, apart from a cough associated with a cold or chest infection?

Yes ☐ **No** ☐

8. Has you child ever had eczema?

Yes ☐ **No** ☐

9. Has your child ever had hay fever?

Yes ☐ **No** ☐

10. Is your child allergic to anything?

Yes ☐ **No** ☐

If yes, what is s/he allergic to?

Treatment

11. Does your child attend a clinic or see a doctor for wheezing?(Asthma or bronchitis)

Yes ☐ **No** ☐

12. Has your child ever taken any medication for wheezing? (asthma or bronchitis)

Yes ☐ **No** ☐

13. Has your child taken any of the following drugs in the past 12 months?

Salbutamol, Ventolin, Bricanyl or any other **blue** inhaler

Yes☐ **No** ☐ **Don't know** ☐

Clenil, Flixotide, Becotide, Pulmicort, or other Purple inhaler - Seretide inhaler

Yes ☐ **No** ☐ **don't know** ☐

Steroid tablets (prednisolone) for attacks

Yes ☐ **No** ☐ **Don't know** ☐

14. Does your child currently take any other regular medication?

Yes ☐ **No** ☐

If YES, what medication, and for what reason? _____

_____

Smoking

15. Does your child's mother smoke cigarettes?

Yes ☐ **No** ☐

16. Did your child's mother smoke during pregnancy?

Yes ☐ **No** ☐

17. Do any other household members smoke cigarettes?

Yes ☐ **No** ☐

18. Was your child born more than 3 weeks early?

Yes ☐ **No** ☐

19. Does your child have any other medical problems?

Physical activity

20. In a typical week, does your child do vigorous physical activities for at least 10 minutes at a time? (Vigorous activities cause a large increase in breathing and heart rate; they may include football, aerobics, fast cycling, or running).

Yes☐ No ☐

If Yes :

20a. On how many days does your child do vigorous physical activities in a typical week? ---------- days per week.

20b. How much time in total does your child usually spend on one of those days doing vigorous physical activities? ---------- hours ----------minutes.

21. How many hours per day does your child spend, on average, doing following activities, outside school time?

-watching TV , computer games, video games

none ☐ 0-1 hrs ☐ 1-2 hrs ☐ 2-4 hrs ☐more than 4 hrs

-quiet activities: reading, studying, listening to music

none ☐ 0-1 hrs ☐ 1-2 hrs ☐ 2-4 hrs ☐more than 4 hrs

THANK YOU FOR COMPLETING THIS QUESTIONNAIRE

Please return the questionnaire to your child's school

If you have any queries please contact Dr CS Beardsmore on 0116 2525811

10.8 Data Collection Form

Anthropometry and Lung Function

Name of Child | Study Number

Date of Birth | Date of Test

Name of School

Standing Height (cm) | Sitting height (cm) | Weight (Kg)

Child signed consent? | Current URTI? | Recent URTI?

Additional comments:

FEV_1 (L)	
FVC (L)	
FEV_1/FVC	
PEF ($L.s^{-1}$)	
Number of attempts	
Comment on spirometry	
MIP (peak) (kPa)	
MIP (average) (kPa)	
MIP (sustain) (kPa)	
Number of attempts	
MEP (peak) (kPa)	
MEP (average) (kPa)	
MEP (sustain) (kPa)	
Number of attempts	

10.9 Lab visit Information Leaflet for Parents

University of Leicester

Department of Infection, Immunity and Inflammation

Maurice Shock Building
University Road
Leicester LE1 9HN · UK
Tel: +44 (0)116 252 2951 *(Secretary)*
Tel: +44(0)116 252 2941 (Direct Line)
Fax: +44 (0)116 252 5030
E-mail: sam20@le.ac.uk *(Secretary)*
E-mail: pwa@le.ac.uk

Head of Department and Professor of Microbial Pathogenesis
Professor Peter W Andrew

Information Leaflet for Parents

Dear Parent/Guardian

RE: Lung function in children of different origins (additional measurements within the Paediatric Lung Function Laboratory at Leicester Royal Infirmary)

Principal investigator: Dr Caroline Beardsmore
You may contact Dr Caroline Beardsmore on 0116 252 5811or by e-mail csb@le.ac.uk

This information sheet relates to the study we are conducting with children of primary school age in Leicester, so you may consider whether you would allow your child to take part in additional tests in our Child Health Lung Function Laboratory.

What is the purpose of the study?
British studies comparing children of different ethnic backgrounds have shown differences in lung function of between 9% and 13%. This means that when some children have breathing tests the results may be wrongly interpreted. We do not know why the differences exist, but we think it might be related to strength of respiratory muscles, or the elasticity of the lungs.

We are visiting primary schools in Leicester to measure the children's lung function and strength of respiratory muscles, and we are grateful to you and your child for your participation in this to date. We would now like to ask you to consider giving your consent for your child to participate in more detailed tests to measure lung volume.

The information from the study should help us to understand more about why children from different backgrounds have different lung function and, ultimately, improve our interpretation of tests carried out with patients.

Who is organising and funding this study?
The study is funded in part by the Ministry of Higher Education and Research, Iraq, and the University of Leicester. The study sponsor is the University of Leicester.

What will be involved if I allow my child to take part in the study?
This study would involve a single visit to our laboratory, which is based at Leicester Royal Infirmary. This would be arranged at your convenience and would take 30 to 40 minutes. We would ask you whether there had been any changes to your child's health since completing the questionnaire. We would ensure that you and your child fully understood what you are being asked to do, and then ask you to sign a consent form. Your child will be asked if they agree to take part and, if they do, they will be asked to sign an assent form. We will explain that they are free to stop at any time and will not have to do anything they do not want to do.

We would measure your child's height and weight and ask him/her to do the breathing tests, which involve breathing in fully and blowing out with maximum effort into a machine which records how much and how fast air can be blown out. When we measure the strength of the respiratory muscles, we ask the child to try to breathe in or out from a sealed tube, and measure the maximum pressure they can achieve. During the tests the children need to wear a nose clip rather like those used by some people for swimming. These breathing tests give important information about the capacity of the lungs and the state of the airways (breathing tubes). Breathing tests are repeated 3 or 4 times to obtain the best values possible. These tests would be the same as those done at the school visit, but they would provide us with valuable information about how repeatable these tests can be. After that we would measure the volume of air within the lungs. This involves the child sitting inside a Perspex cabin, rather like a Wendy House or an old-fashioned telephone box, and breathing through a mouthpiece into a tube. From time to time we activate a shutter that briefly interrupts the breathing and enables us to measure how much air is in the lungs. The test is not difficult or unpleasant for the children. This is repeated 5 or 6 times, with a short rest in between. This particular test is not one that we can carry out in the schools because the cabin is not portable.

What are the possible benefits or risks of taking part?
There is no direct benefit to any of the children taking part in this project. We cannot identify any risks to the children who do take part. The tests are not unpleasant in any way and many children enjoy them. No child would be expected to do anything they, or their parents did not want. No child would be expected to do more than she/he felt able to do, and would be free to stop at any time.

These types of tests are performed frequently on a routine basis, and should any problems arise, medical research is covered for mishaps in the same way as for patients undergoing treatment in the NHS i.e. compensation is only available if negligence occurs.

Will we be paid for taking part?
There is no payment for taking part in the study. We will pay all reasonable expenses, including travel and parking costs and drinks for children and parents.

Will information obtained in the study be confidential?
All the information gathered during this study will be kept entirely confidential. The identifiable research data may be examined by the study sponsor (University of Leicester) or UHL-NHS Trust for the purposes of monitoring or audit. The results of the study may be presented or published for scientific purposes. In all cases, neither your child's name nor identity will be disclosed and confidentiality will be maintained at all times.

How will I find out about the results of the study?
Because this is a study of healthy children, we must assume that all the measurements we collect represent normal values and we will not be providing results from individual children to their parents. We will be providing an overview of our findings to each school taking part, soon after the completion of measurements in that school and again at the end of the whole study, in a format suitable for publication in a school newsletter. In the unlikely event that we were concerned about your child's breathing, we would contact you and ask for your permission to write to your GP explaining what we had found.

What happens if I do not wish for my child to participate in the study or wish to withdraw my child from the study?
If you do not wish for your child to participate in this study or if you wish to withdraw your child from the study you may do so without justifying your decision and your future treatment will not be affected. Your child may withdraw from the study at any time by telling any member of the research team that they do not want to take part or continue. If a child is withdrawn part-way through the study then we would intend to use any data collected up to the point of withdrawal.

Thank you for reading this information sheet. I will contact you again by telephone within two weeks to see if you would be happy for your child to participate and, if so, to make an appointment. If you would like to speak to me in the meantime please telephone 0116 252 5811, leaving a message on my voicemail if there is no reply.

Yours sincerely,

Dr Caroline Beardsmore
On behalf of the study team: Dr Caroline Beardsmore, Dr Erol Gaillard, and Miss Nidhal Gharbawi

10.10 Parental Consent Form Lab visit

University of Leicester

Department of Infection, Immunity and Inflammation

Maurice Shock Building
University Road
Leicester LE1 9HN · UK
Tel: +44 (0)116 252 2951 *(Secretary)*
Tel: +44(0)116 252 2941 (Direct Line)
Fax: +44 (0)116 252 5030
E-mail: sam20@le.ac.uk *(Secretary)*
E-mail: pwa@le.ac.uk

Head of Department and Professor of Microbial Pathogenesis
Professor Peter W Andrew

Consent Form

Title of Project: Lung Function in Children of Different Origins (Additional Measurements within the Paediatric Lung Function Laboratory at Leicester Royal Infirmary)
Study Number:
Name of Researcher: Dr Caroline Beardsmore

This form should be read in conjunction with the Information Leaflet for Parents

Please ***initial*** as appropriate:

☐ I confirm that I have read the information sheet dated..... version.....) for the above study. I have had the opportunity to consider the information and to ask questions by telephone.

☐ I understand that I am under no obligation to allow my child to take part, and that I may withdraw my child from the study at any time without justifying my decision, without his/her medical care or legal rights being affected.

☐ I understand that all data relating to the study will be confidential, but that it may be examined by the study sponsor (University of Leicester) or UHL-NHS Trust for the purposes of monitoring or audit.

☐ I understand that if there are any concerns about my child's breathing that I will be contacted by a member of the research team who will ask permission to contact my child's GP

☐ I am happy for my child to take part in the study

Consent Form Version 2 7 September 2015

Signed…… Date……

Name……

Relationship to Child……..

Name of Child…… Date of birth……

10.11 Appointment Letter for Lab visit

UNIVERSITY OF LEICESTER

Department of Infection, Immunity and Inflammation
Maurice Shock Building
University Road
Leicester LE1 7RH, UK

Head of Department and Professor of Respiratory Medicine
Professor Andrew Wardlaw

T +44 (0)116 2521555
T +44 (0)116 2522951 *(Secretary)*
F +44 (0)116 2525035

E ajb64@le.ac.uk *(Secretary)*
E aw24@le.ac.uk

Parents of (Child name)
Address

Dear Parents of (Child name)

Thank you for being willing to bring () for the breathing tests at Leicester Royal Infirmary. Please would you bring him/her to the Clinical Investigation Centre on:

Date and time ()

The Children's Respiratory Investigation Centre is on the ground floor of the Windsor Building, within the Child Development Centre at the Leicester Royal Infirmary. A map is enclosed for your reference.

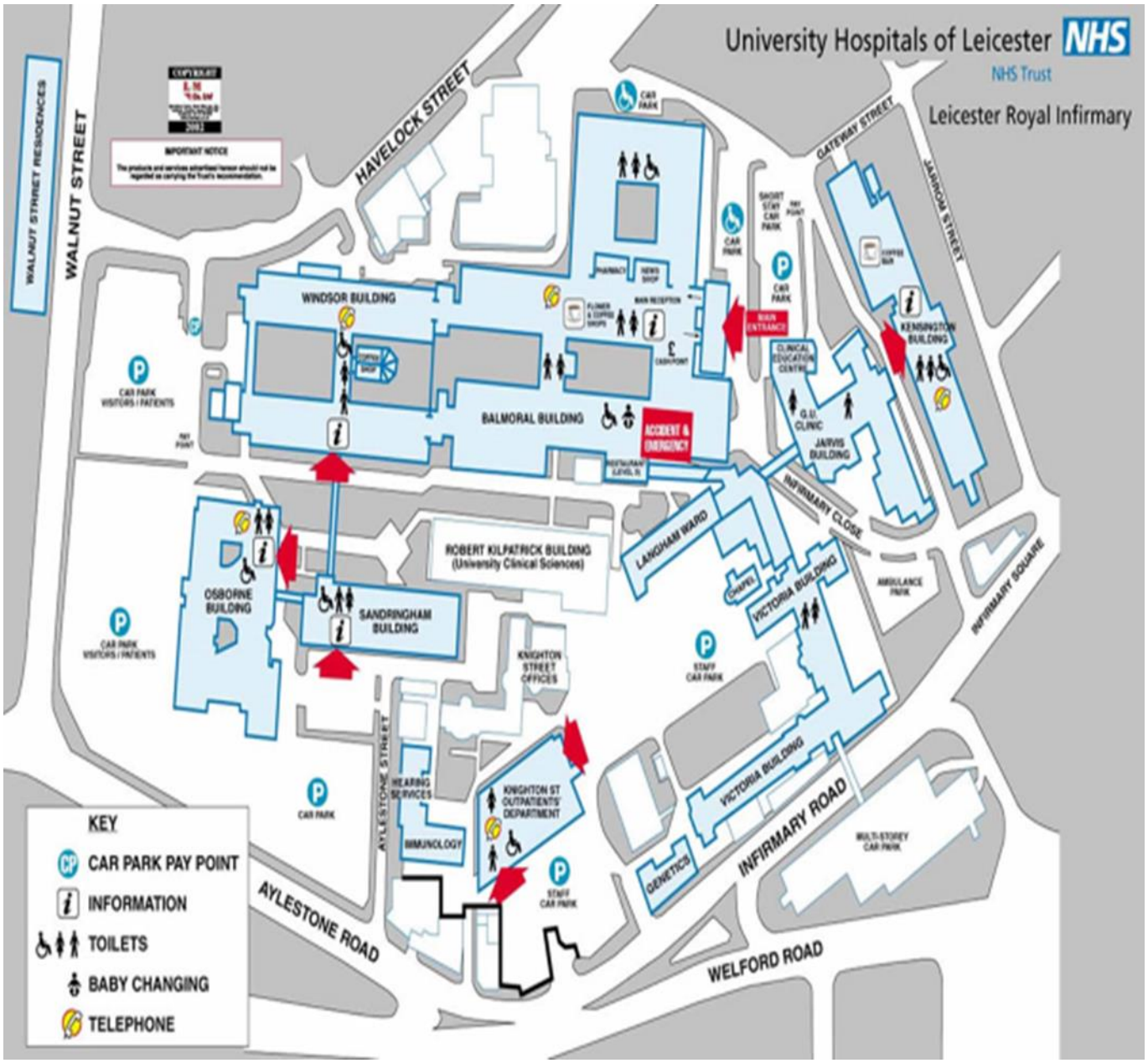
The tests are not painful or unpleasant and will take approximately 1 ½ hours. If you have any questions before coming, please telephone either Nidhal (07459 051507), or my office (0116 252 5811). We look forward to seeing you on (day of test). We will pay your travelling and parking expenses that afternoon.

Yours sincerely

Dr Caroline Beardsmore
Senior Lecturer
Department of Infection, Inflammation and Immunity (Child Health)

Telephone: 0116 252 5811 **E-mail:** csb@le.ac.uk

10.12 Leicester Royla Infirmary Site map



10.13 Children's Assent Form

Children's Assent Form

Would you like to help?

Would you like to help us learn more about breathing?

We breathe air in through our mouths and noses and it goes into our lungs. Some people have bigger lungs than other people, which means they have more puff. This might be because the muscles used for breathing are stronger. We would like to thank you for helping us with the special breathing tests at your school, and to ask you if you would be willing to do some extra tests to see how big your lungs are.

What we would ask you to do is repeat some of the tests you performed at your school, so we can see whether we get the same results when we repeat the measurements. Then we would ask you to do a different test that involves sitting inside a see-through cabin, like a special Wendy House. We would ask you to breathe in and out through a tube, and from time to time we close a little flap inside the tube so it feels a bit hard to breathe, just for a split second. The flap opens almost immediately and you continue breathing just as before. Altogether these tests will take about 30-40 minutes, with short breaks. These tests do not hurt at all, and if there is anything you do not want to do you can stop straight away.

We do not mind if you do not want to get involved, but if you would like to join in, please write your name below.

Additional tests_Children's Assent Form Version 1 30 April 2015

10.14 Lab visit additional measurment Anthropometry and Lung Function

Lab visit additional measurements Anthropometry and Lung Function

Name of Child Study Number

Date of Birth Date of Test

Name of School

Standing Height (cm) Sitting height (cm) Weight (Kg)

Child signed consent? Current URTI? Recent URTI?

Additional comments:

FEV_1 (L)	
FVC (L)	
FEV_1/FVC	
PEF ($L.s^{-1}$)	
Number of attempts	
Comment on spirometry	
ITGV	
ERV	
RV	
IC	
VC	
TLC	
Number of attempts	
Comment on body plethysmography	

10.15 Lab visit additional measurements MIP&MEP

Lab visit additional measurements MIP&MEP

Name of Child Study Number

Date of Birth Date of Test

MIP (peak) (kPa)	
MIP (average) (kPa)	
MIP (sustain) (kPa)	
Number of attempts	
MEP (peak) (kPa)	
MEP (average) (kPa)	
MEP (sustain) (kPa)	
Number of attempts	

Elastic Recoil measurements attempted?	
Do the recordings look reasonable?	
Any additional comments?	

10.16 Lab visit Elastic recoil Measurments

Lab visit Elastic recoil measurements

Study number **Date of test**

Color	Volume L	Pressure Kpa 0.1 sec	0.08 sec	0.06sec	BF MEP 1/min
Dark blue					
Red					
Dark green					
Orange					
Dark purple					
Light blue					
Pink					
Light green					
Brown					
Light Purple					

10.17 Thank you letter for children and family

UNIVERSITY OF LEICESTER

Department of Infection, Immunity and Inflammation
Maurice Shock Building
University Road
Leicester LE1 9HN UK

Head of Department and Professor of Microbial Pathogenesis
Professor Peter W Andrew

T +44 (0)116 252 2951 *(Secretary)*
T +44 (0)116 252 2941 *(Direct Line)*
F +44 (0)116 252 5030
E ajb64@le.ac.uk *(Secretary)*
E pwa@le.ac.uk

Mr and Mrs (surname)
Address

Date

Dear (Name of child) and Parents

This is to say 'Thank you' for coming to our laboratory at Leicester Royal Infirmary to help with breathing tests and measurements of respiratory muscle strength. We really appreciated the fact that you gave up your time to come and help us. We hope that (name of child) enjoyed himself/herself/ themselves, and that you found it interesting.

With best wishes,
Yours sincerely

Dr Caroline Beardsmore and Nidhal Gharbawi

10.18 Lung Distensibility Data

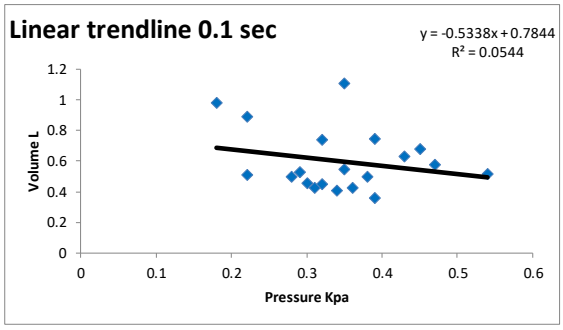
Data looking at lung distensibility data to choose the best data time point and trendline

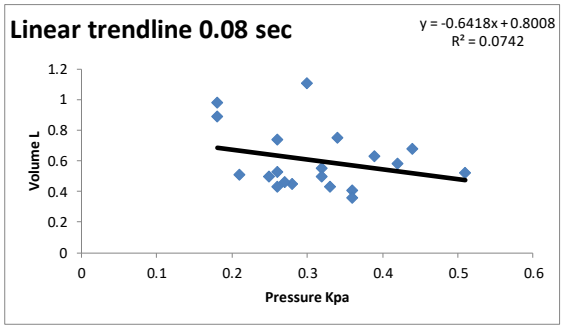
Data looking at distensibility data from individual children. In each separate graphical component, the volume above the end-expiratory level is plotted against the relaxation pressure at particular time points. In the left-hand columns, the linear regression line is shown, whereas in the right-hand column the exponential regression line is displayed. Figures 1 to 7 show data from children where I measured pressure at 0.06, 0.08 and 0.1 sec, in order to determine which time point (if any) provided clearer results than the others.

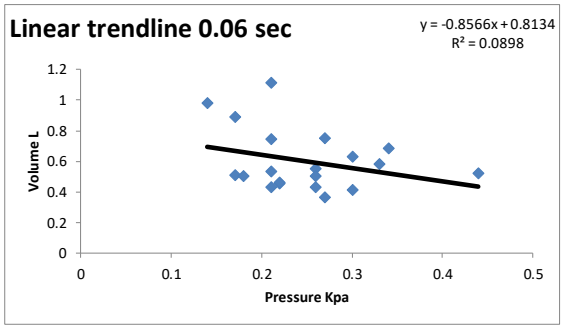
In all figures, a visual comparison of the goodness of the fit, combined with the R^2 value, was used to select the best regression to use for all further consideration.

Figure 1 Subject RM011

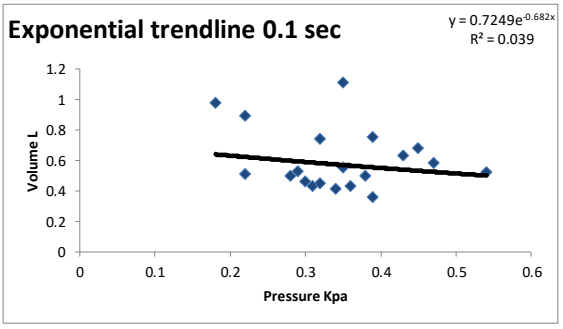
(A) Linear trendline

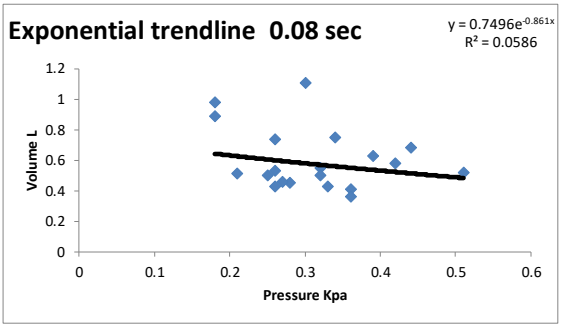






(B) Exponential trendline





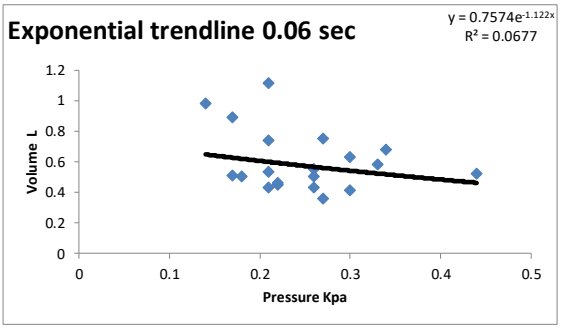
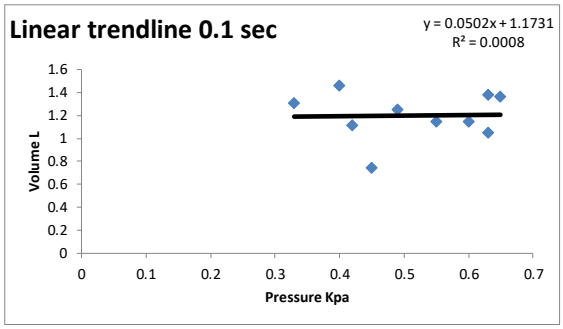
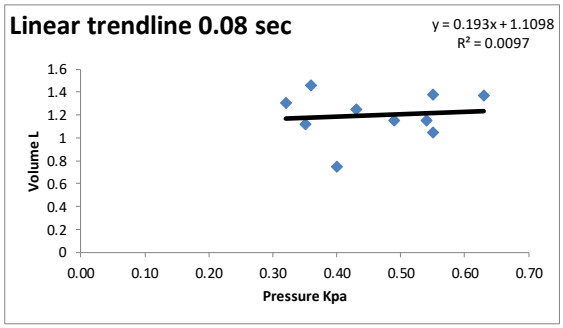
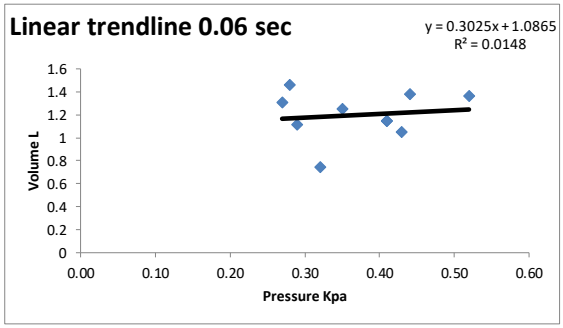


Figure 2 Subject RM012

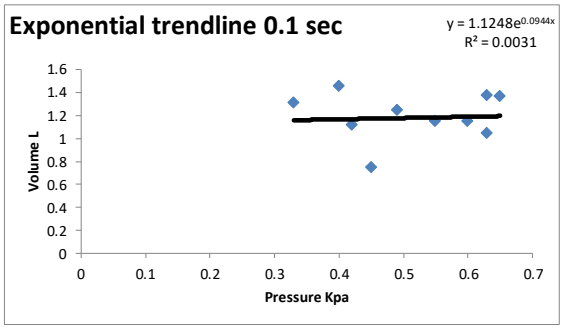
(A) Linear trendline

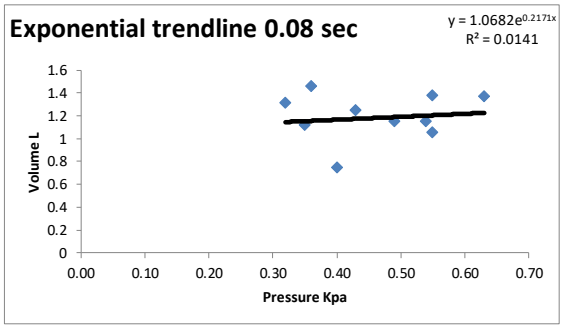






(B) Exponential trendline





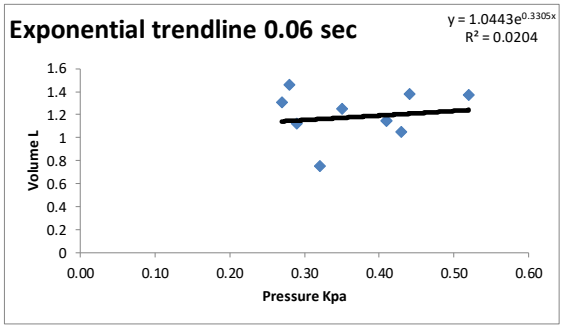
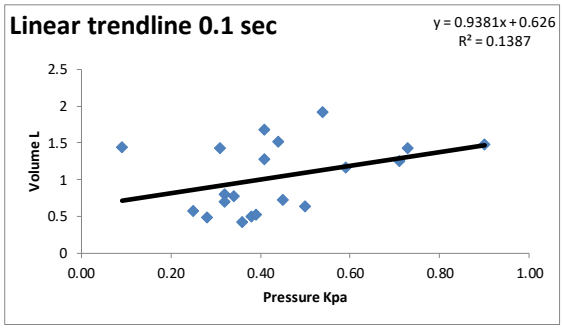
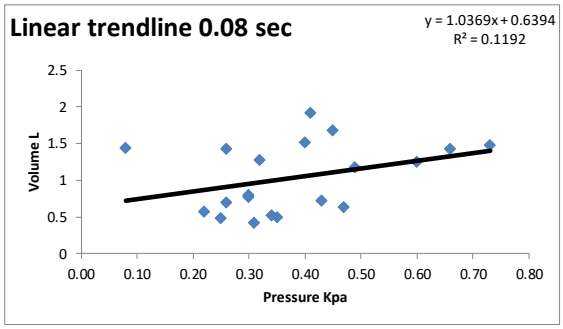
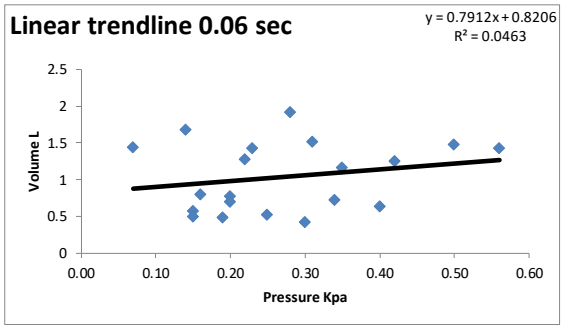


Figure 3 Subject RM04

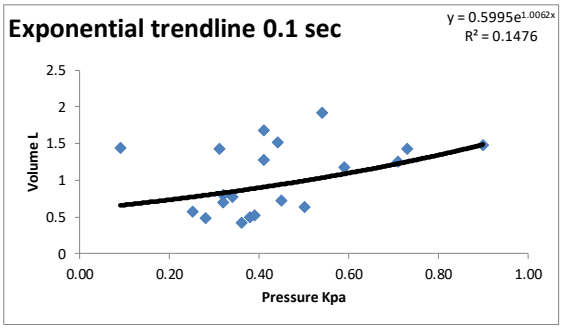
(A) Linear trendline

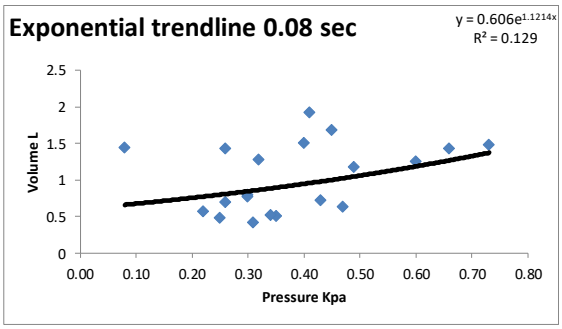






(B) Exponential trendline





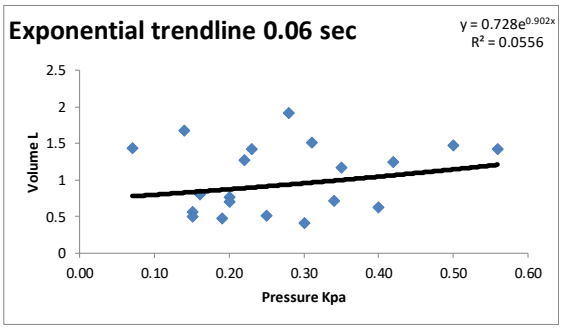
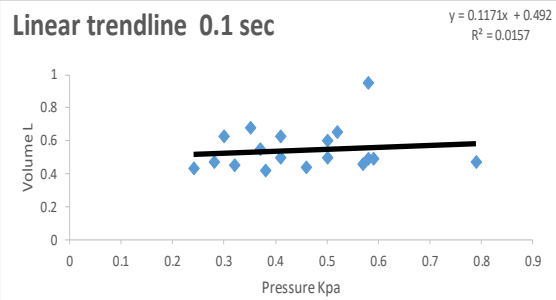
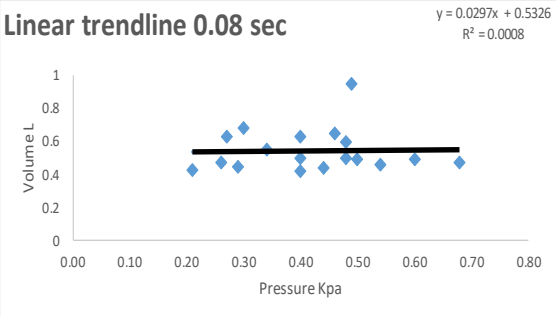
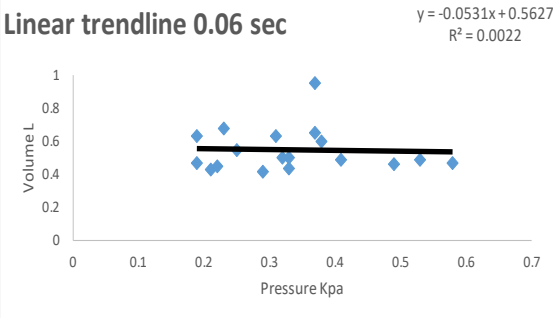


Figure 4 Subject RM019

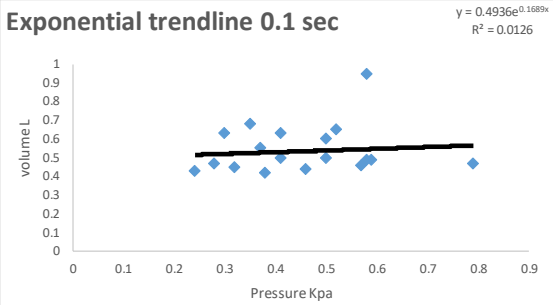
(A) Linear trendline

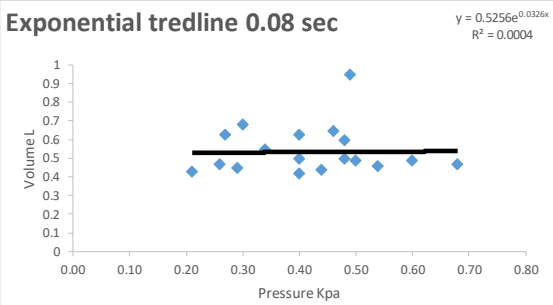






(B) Exponential trendline





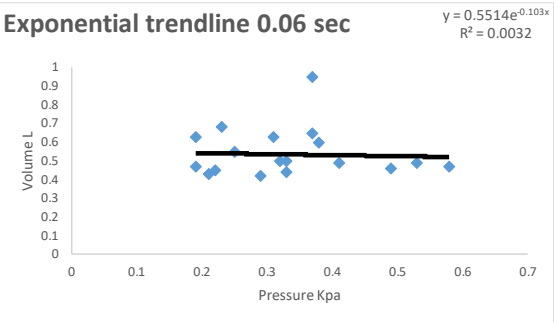
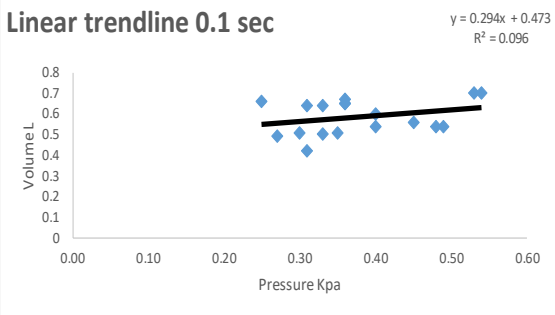
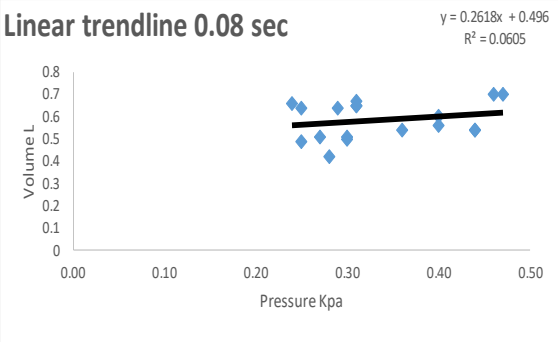
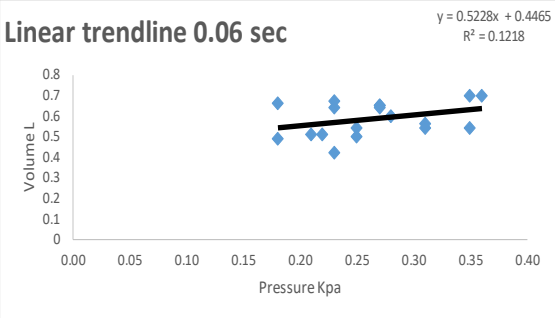


Figure 5 Subject RM030

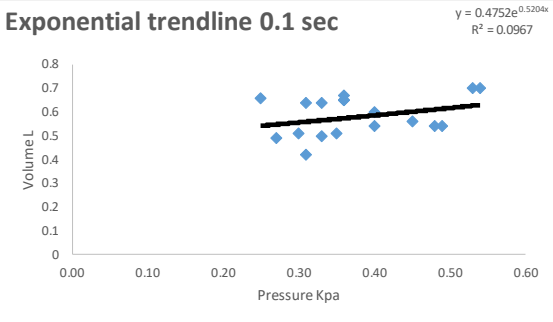
(A) Linear trendline

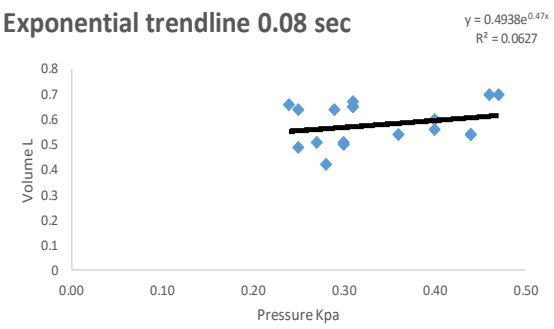






(B) Exponential trendline





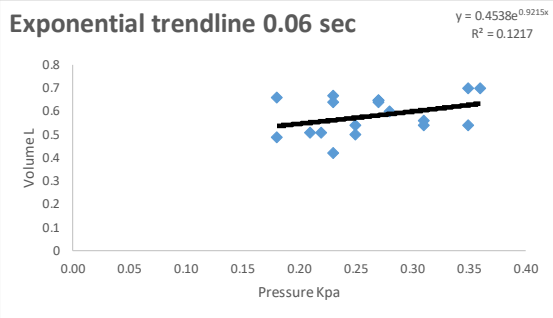
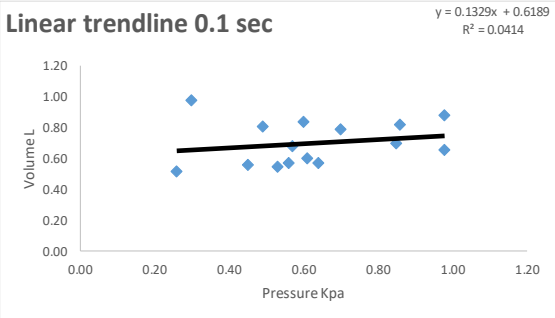
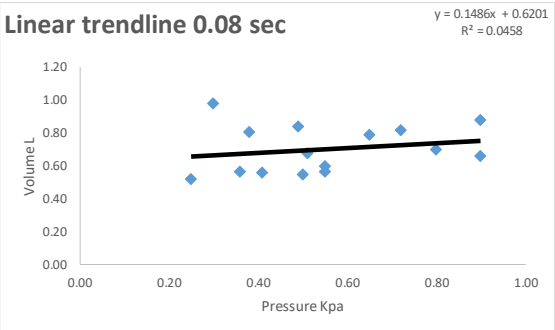
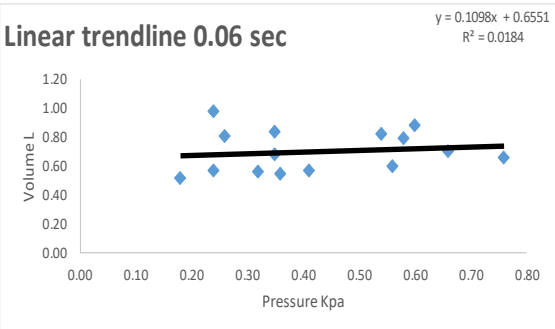


Figure 6 Subject RM068

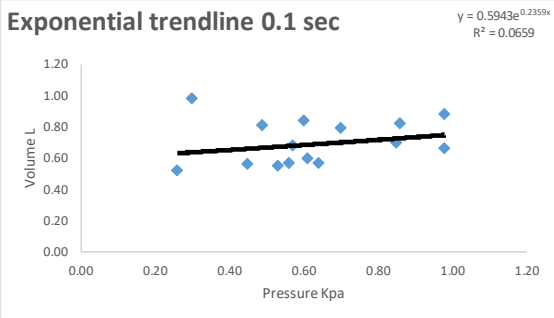
(A) Linear trendline

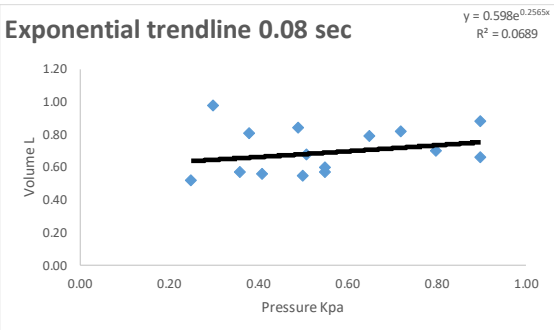






(B) Exponential trendline





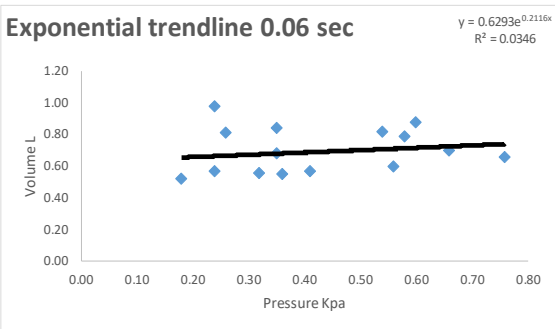
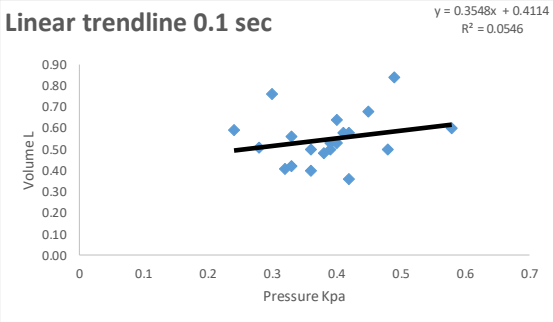
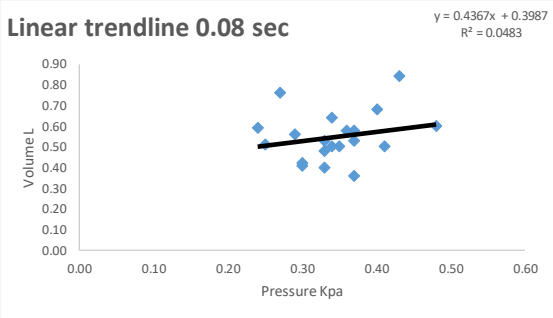
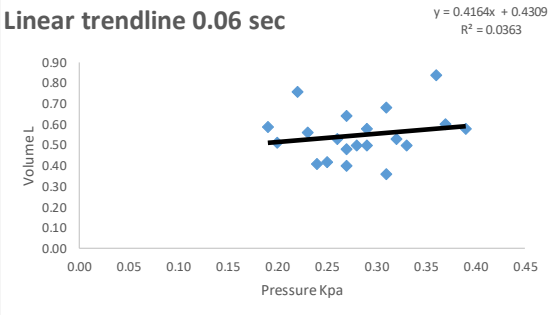


Figure 7 Subject RM073

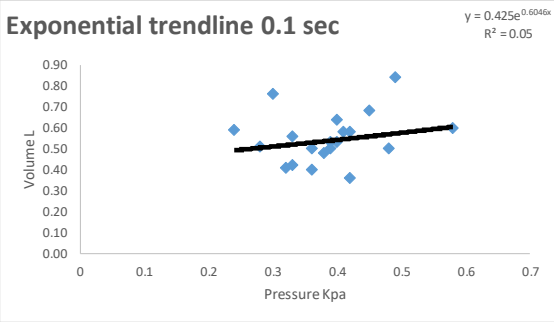
(A) Linear trendline

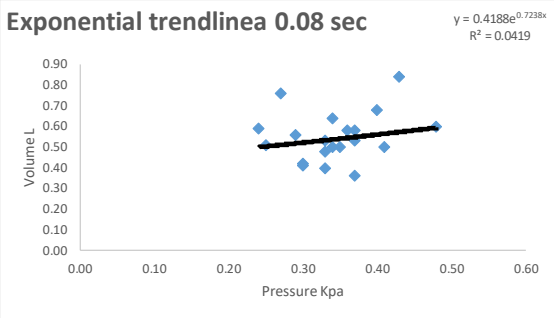


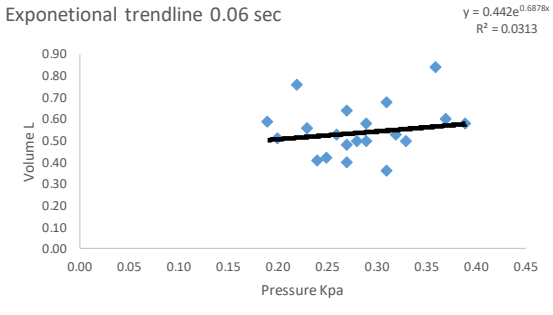




(B) Exponential trendline



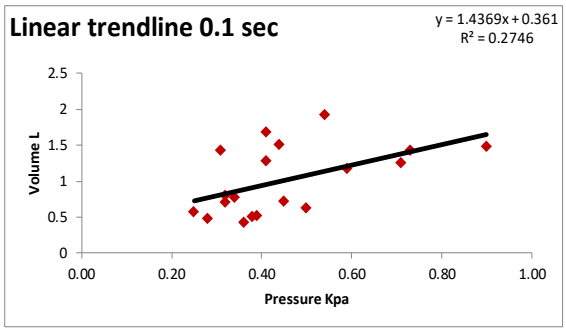




10.19 Lung distensibility data were deemed acceptable

Figure 1 Subject RM 04

(A) Linear trendline



(B) Exponential trendline

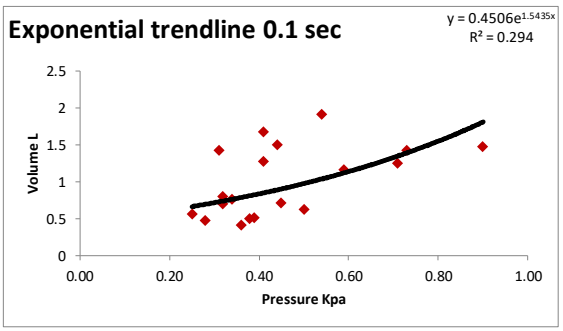
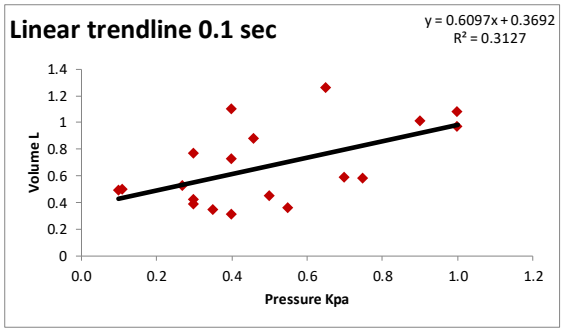


Figure 2 Subject RM 016

(A) Linear trendline



(B) Exponential trendline

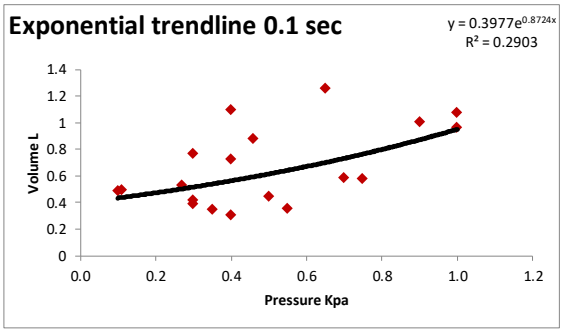
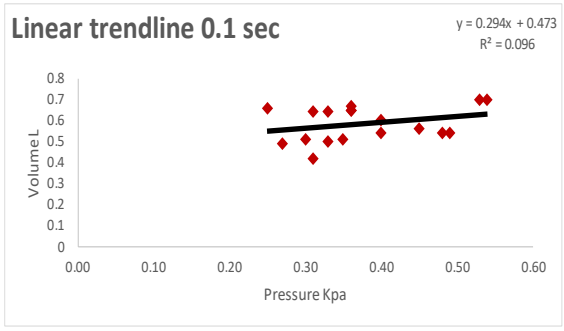


Figure 3 Subject RM 030

(A) Linear trendline



(B) Exponential trendline

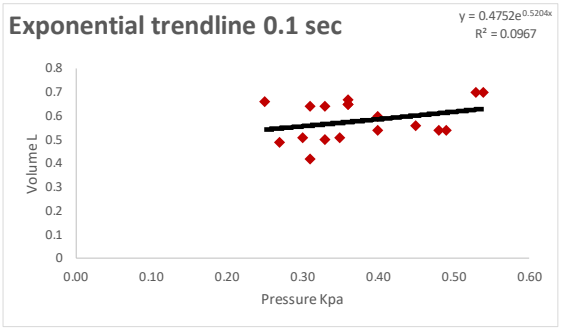
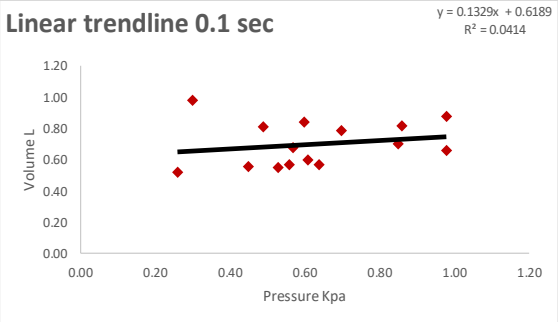


Figure 4 Subject RM 068

(A) Linear trendline



(B) Exponential trendline

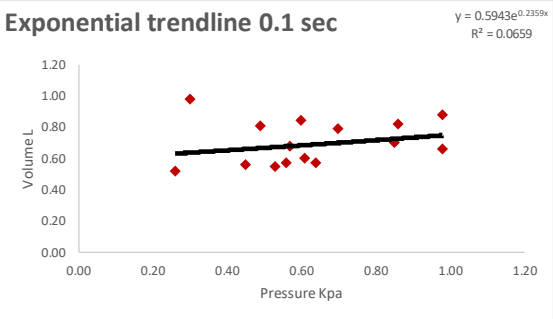
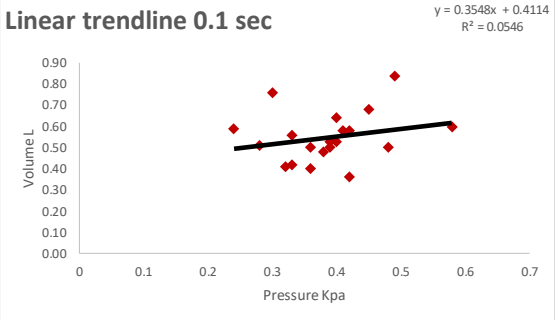


Figure 5 Subject RM 073

(A) Linear trendline



(B) Exponential trendline

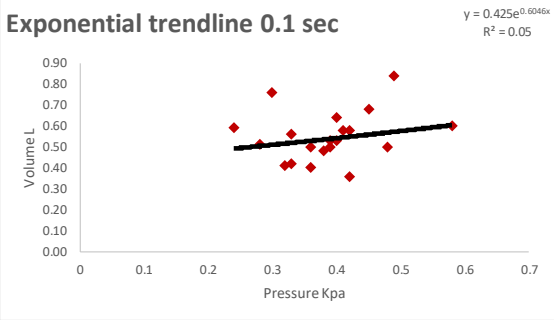
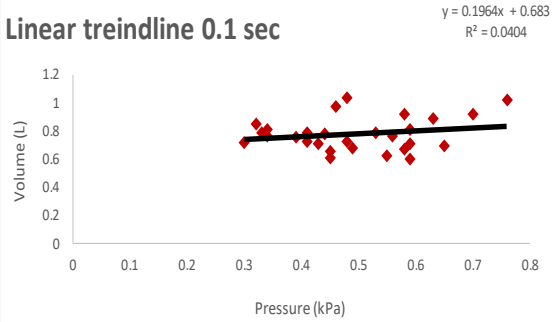


Figure 6 Subject RM 0231

(A) Linear trendline



(B) Exponential trendline

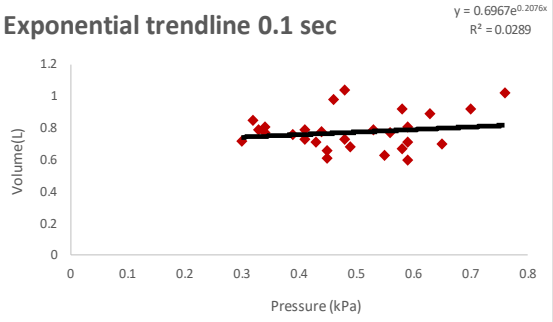
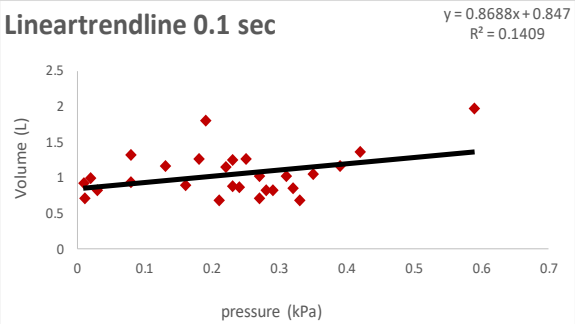


Figure 7 Subject RM 0303

(A) Linear trendline



(B) Exponential trendline

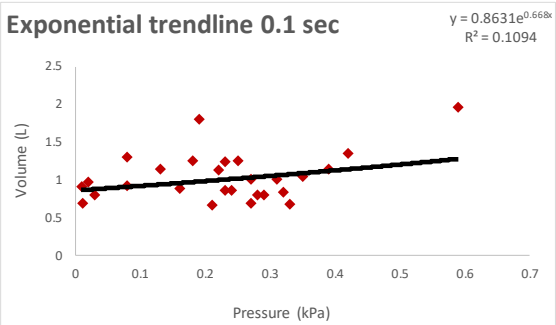
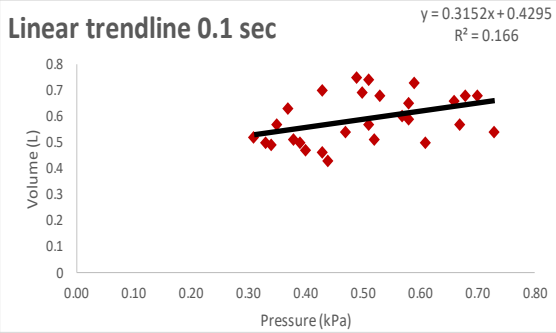


Figure 8 Subject RM 0247

(A) Linear trendline



(B) Exponential trendline

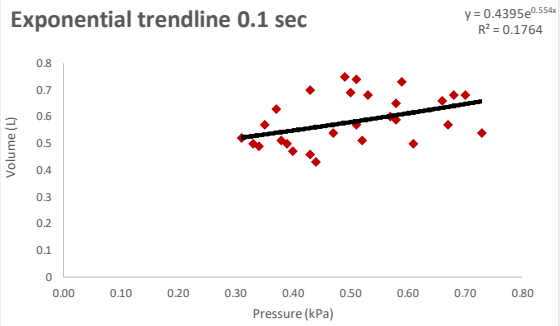
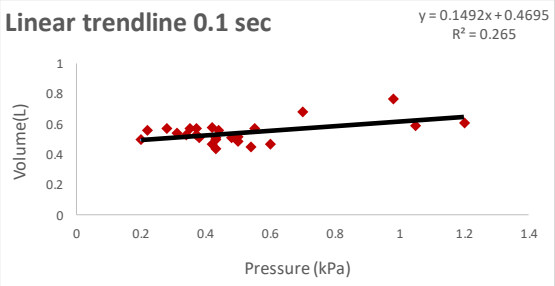


Figure 9 Subject RM 0289

(A) Linear trendline



(B) Exponential trendline

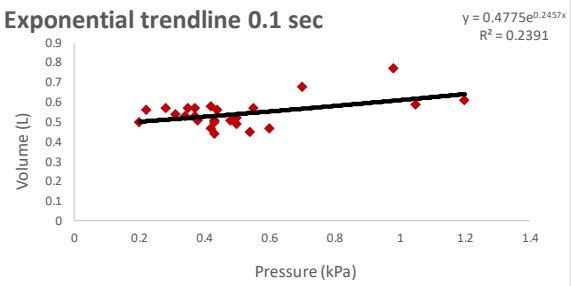
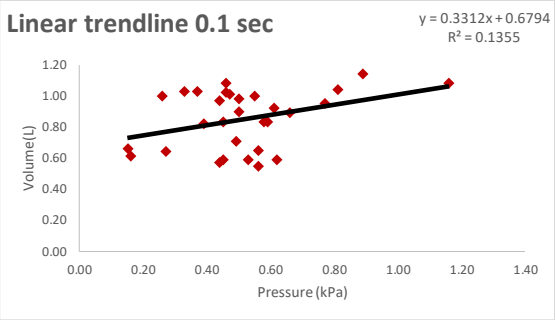


Figure 10 Subject RM 0313

(A) Linear trendline



(B) Exponential trendline

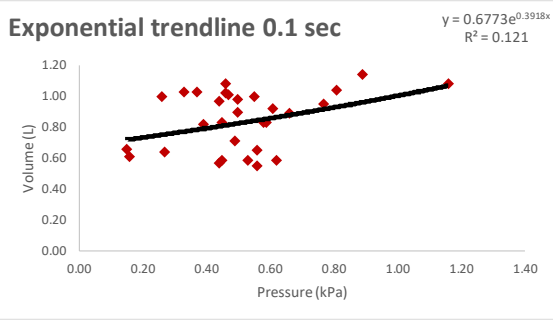
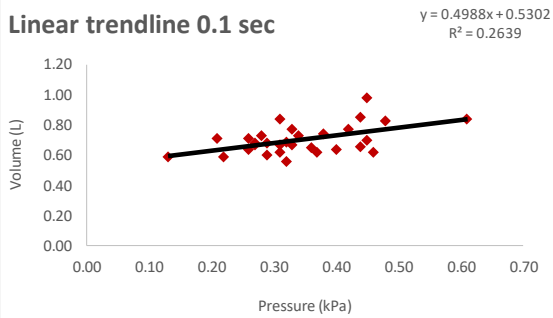


Figure 11 Subject RM 0284

(A) Linear trendline



(B) Exponential trendline

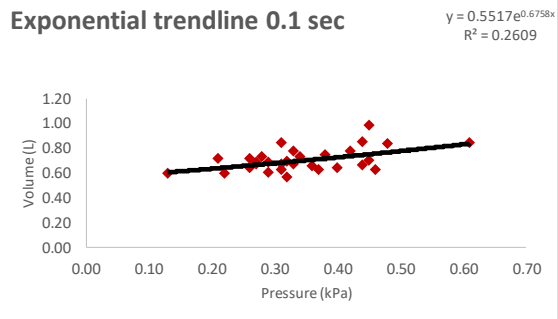
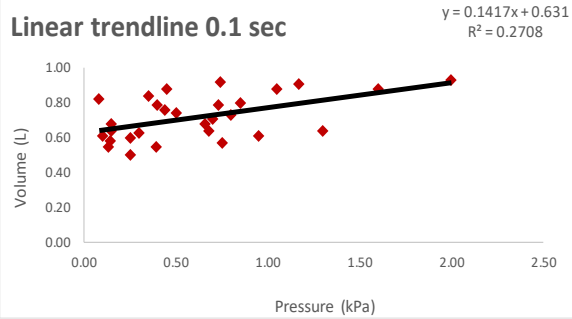


Figure 12 Subject RM 062

(A) Linear trendline



(B) Exponential trendline

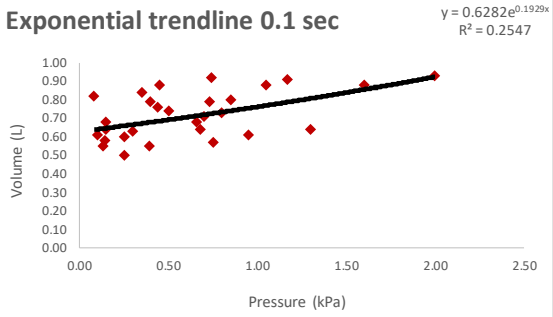
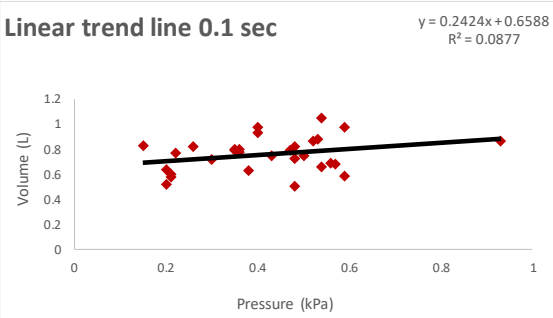


Figure 13 Subject RM 0190

(A) Linear trendline



(B) Exponential trendline

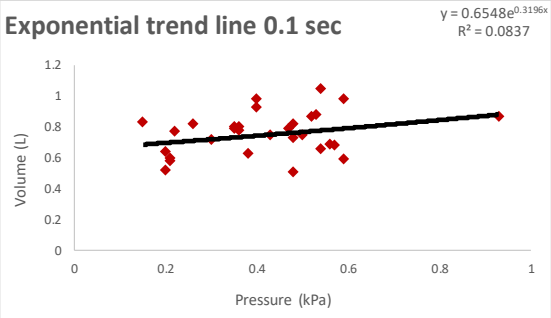
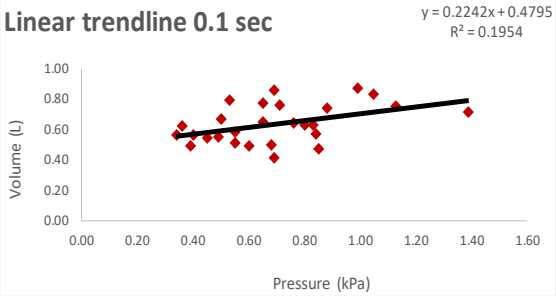


Figure 14 Subject RM 058

(A) Linear trendline



(B) Exponential trendline

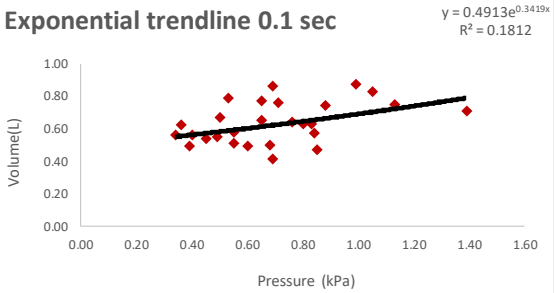
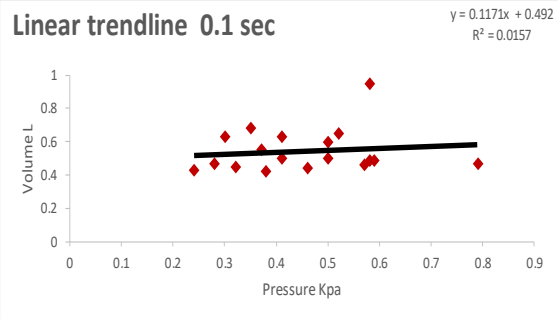


Figure 15 Subject RM 019

(A) Linear trendline



(B) Exponential trendline

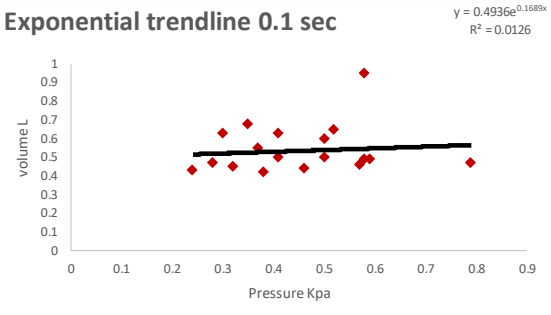
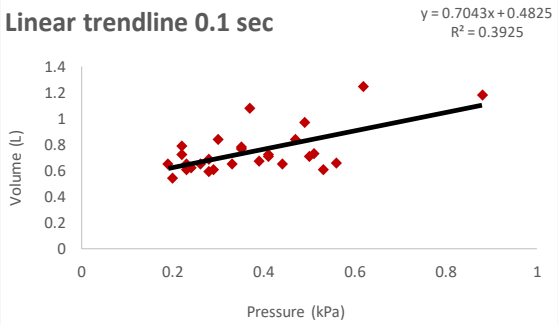
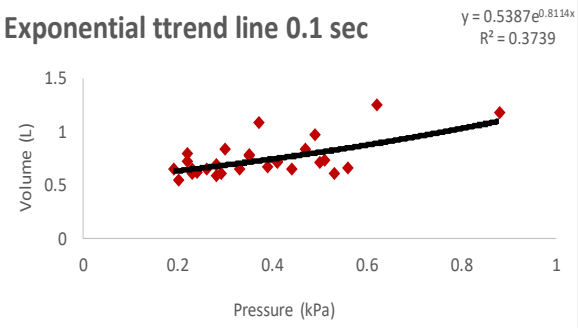


Figure 16 Subject RM 0131

(A) Linear trendline



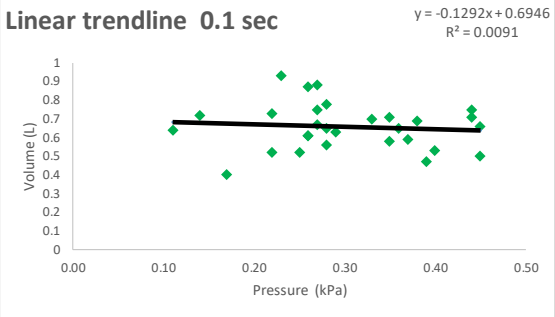
(A) Linear trendline



10.20 Lung distensibility data were deemed unacceptable

Figure 1 Subject RM 081

(A) Linear trendline



(B) Exponential trendline

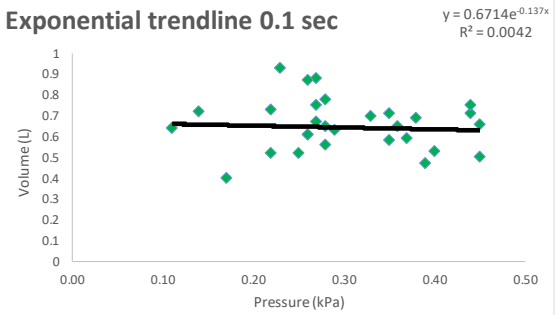
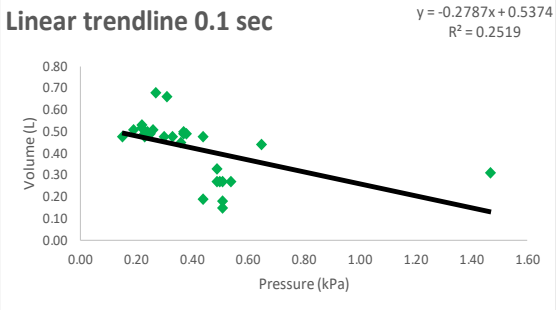


Figure 2 Subject RM 084

(A) Linear trendline



(B) Exponential trendline

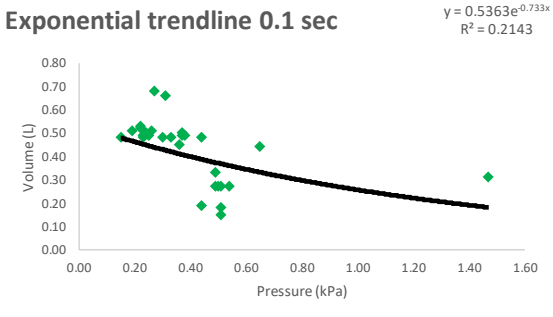


Figure 3 Subject RM 0161

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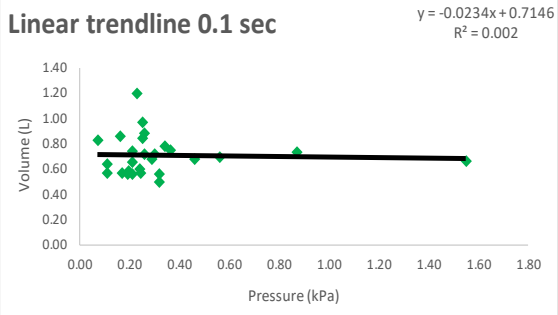


(B) Exponential trendline

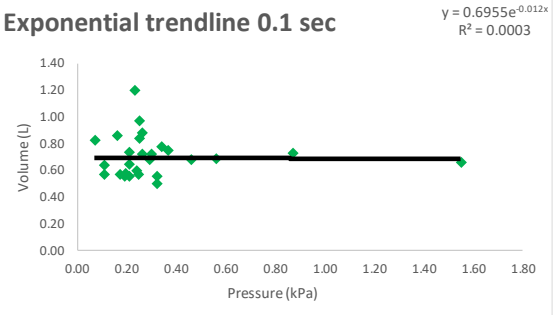
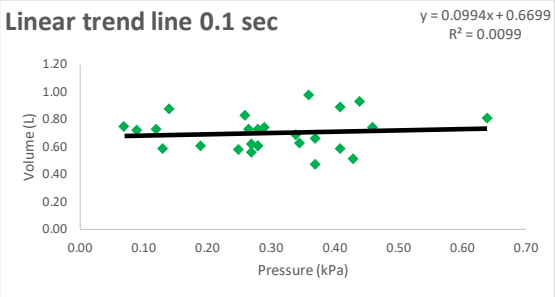


Figure 4 Subject RM 0187

(A) Linear trendline



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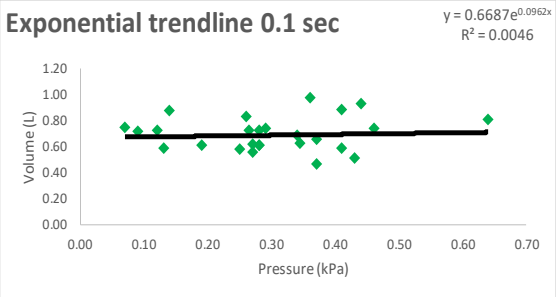
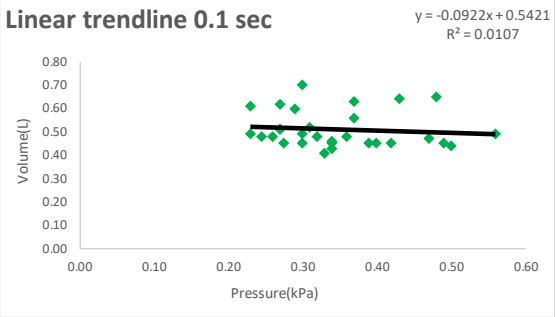


Figure 5 Subject RM 0196

(A) Linear trendline



(B) Exponential trendline

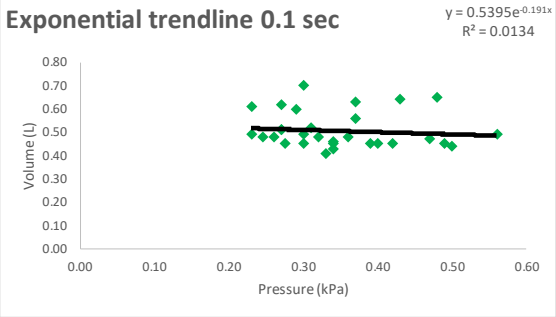
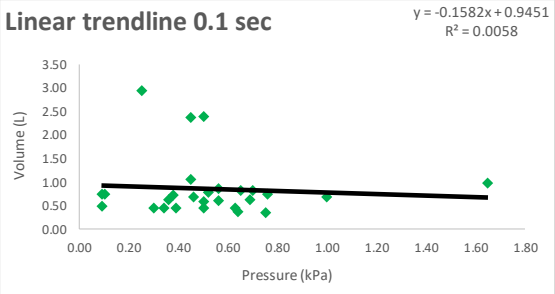


Figure 6 Subject RM 0174

(A) Linear trendline



(B) Exponential trendline

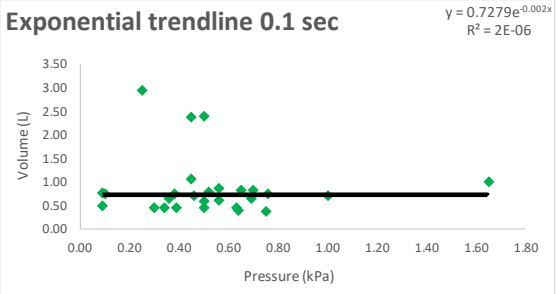
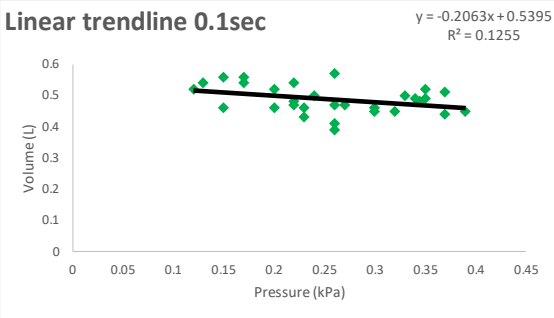


Figure 7 Subject RM 0220

(A) Linear trendline



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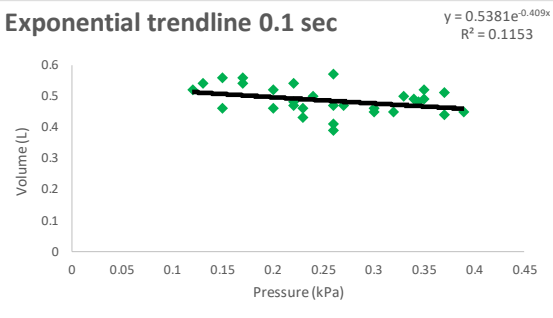
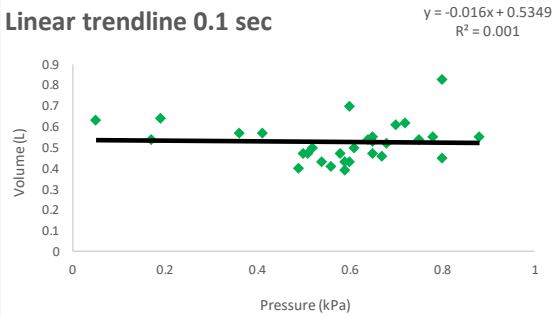


Figure 8 Subject RM 0214

(A) Linear trendline



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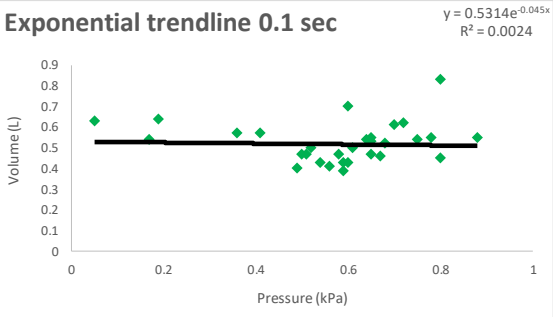
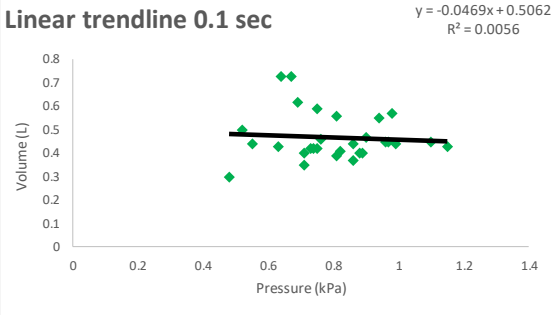


Figure 9 Subject RM 0236

(A) Linear trendline



(B) Exponential trendline

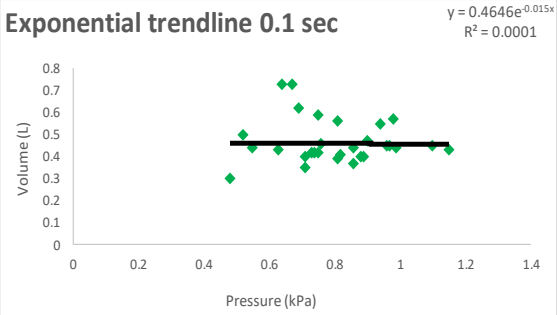
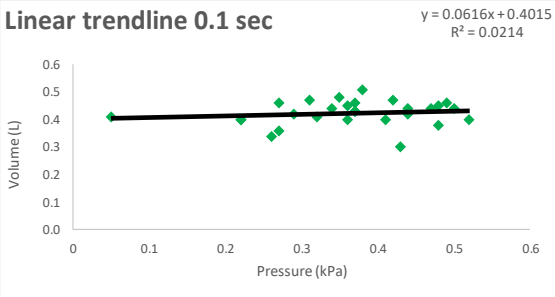


Figure 10 Subject RM 0243

(A) Linear trendline



(B) Exponential trendline

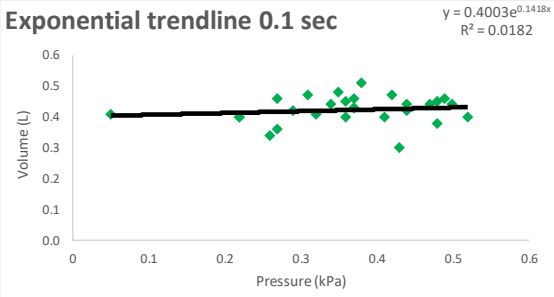
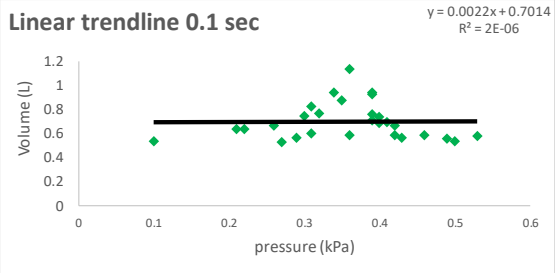


Figure 11 Subject RM 0286

(A) Linear trendline



(B) Exponential trendline

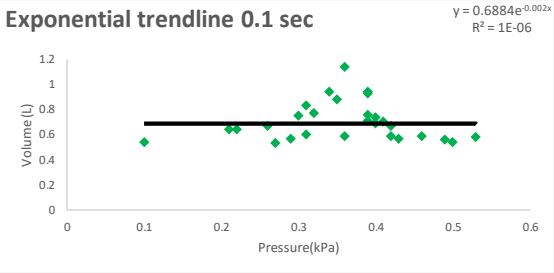
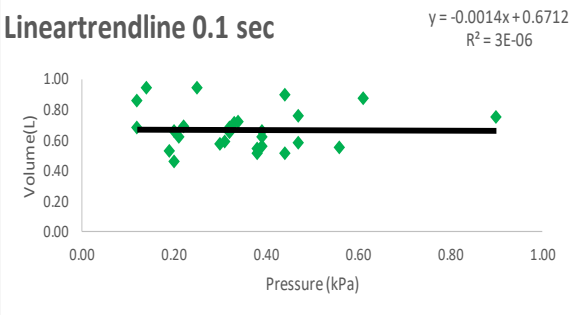


Figure 12 Subject RM 0310

(A) Linear trendline



(B) Exponential trendline

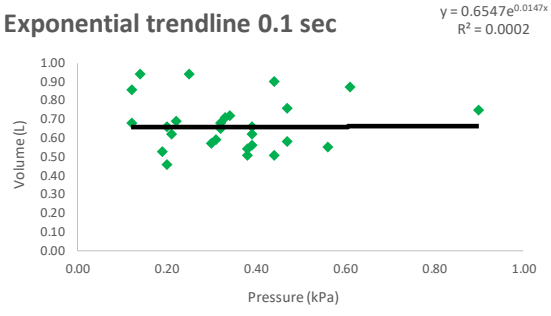
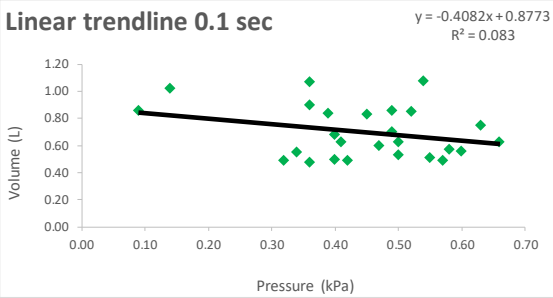


Figure 13 Subject RM 069

(A) Linear trendline



(B) Exponential trendline

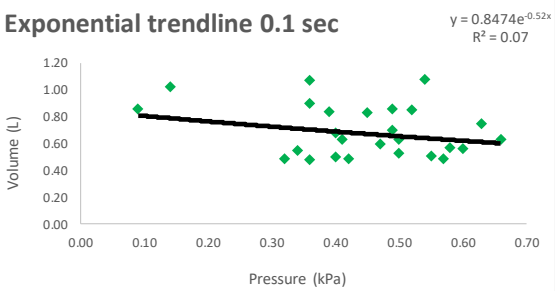
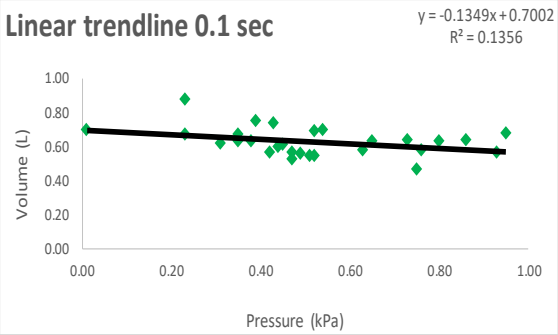


Figure 14 Subject RM 0113

(A) Linear trendline



(B) Exponential trendline

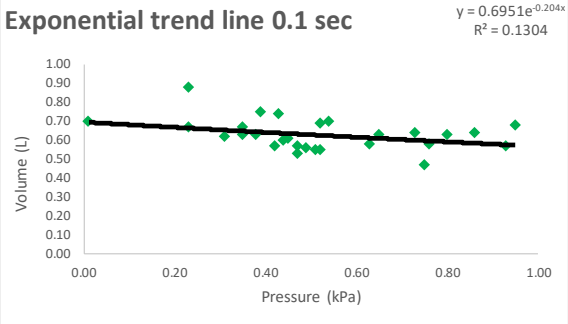
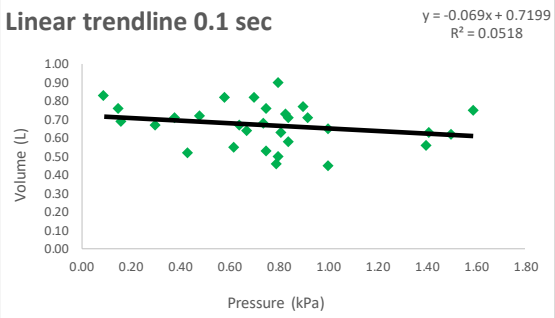


Figure 15 Subject RM 0116

(A) Linear trendline



(B) Exponential trendline

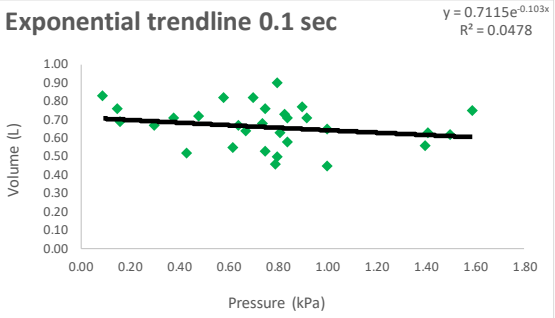
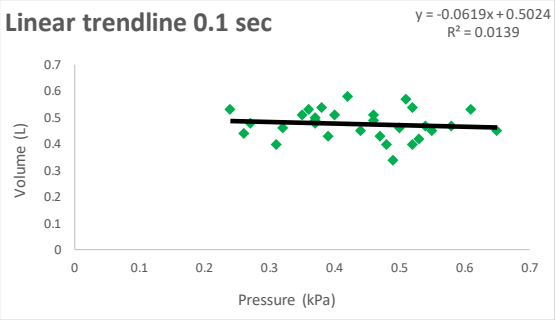


Figure 16 Subject RM 0138

(A) Linear trendline



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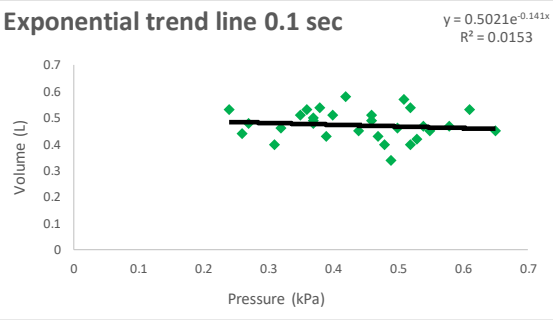
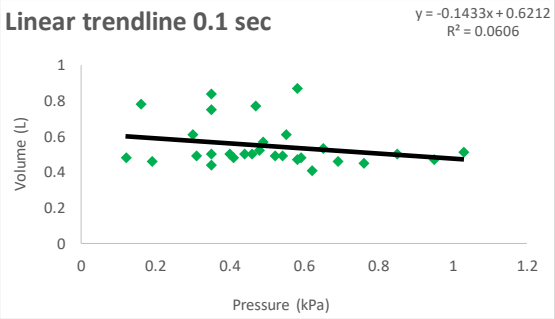


Figure 17 Subject RM 0157

(A) Linear trendline



(B) Exponential trendline

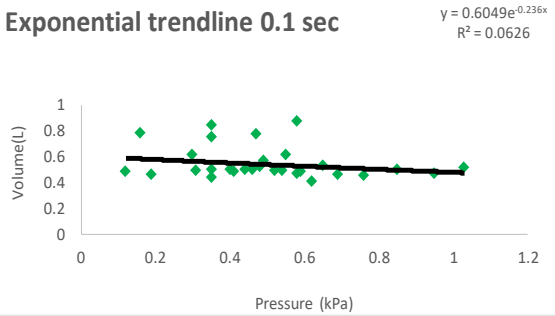
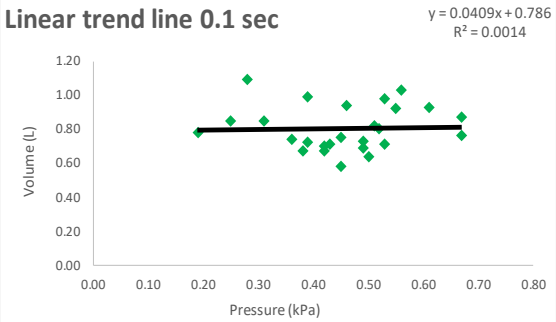


Figure 18 Subject RM 0198

(A) Linear trendline



(B) Exponential trendline

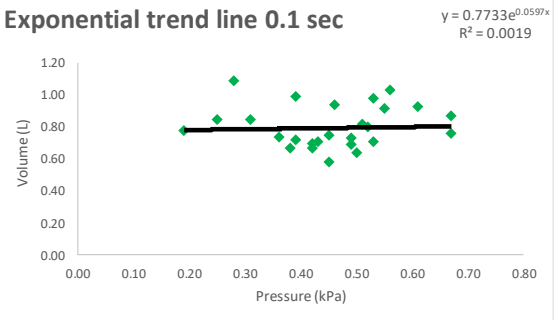
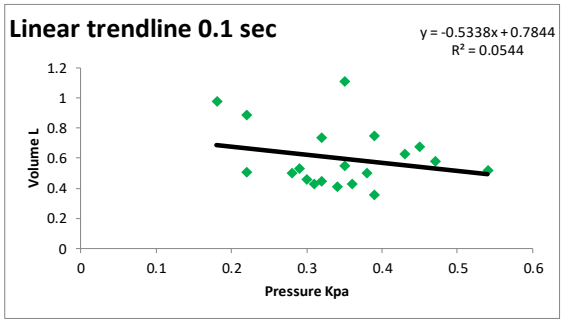


Figure 19 Subject RM 011

(A) Linear trendline



(B) Exponential trendline

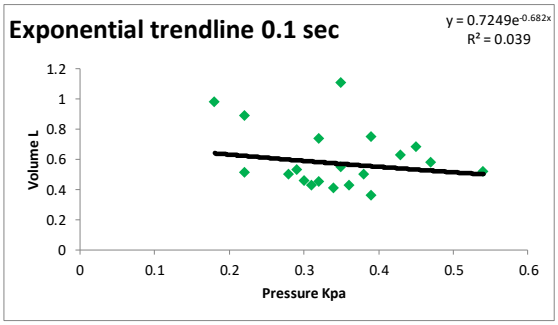
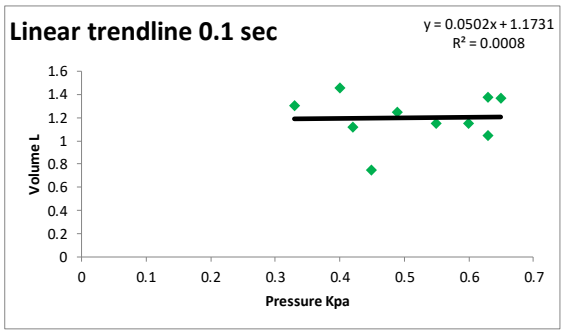


Figure 20 Subject RM 012

(A) Linear trendline



(B) Exponential trendline

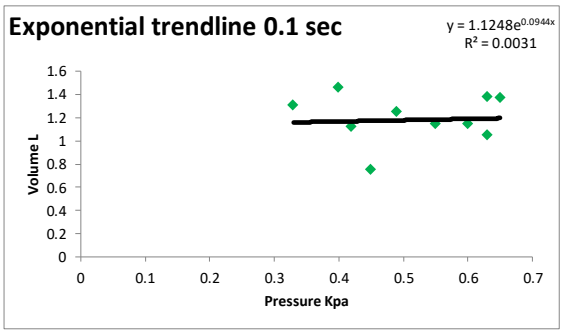
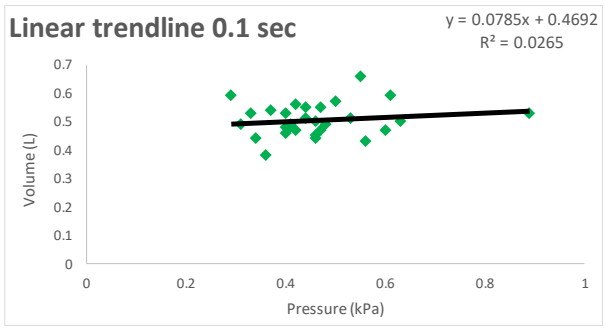
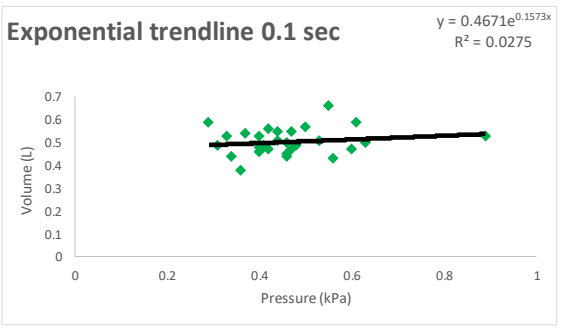


Figure 21 Subject RM 0239

(A) Linear trendline



(B) Exponential trendline



10.21 List of Abstract and Presentation

1-The relationship between respiratory muscle strength and exercise in primary school children in Leicestershire. Nidhal Gharbawi, Dr Erol Gaillard, Dr Maria Viskaduraki, Dr Caroline Beardsmore. Poster presented at the Postgraduate Research Festival P34 in Leicester July 2016.

2- The relationship between body mass index (BMI) and respiratory muscle strength in healthy children of primary school age. Nidhal Gharbawi, Dr Erol Gaillard, Dr Maria Viskaduraki, Dr Caroline Beardsmore. Poster presented at the Respiratory research day in Leicester May 2016. Respiratory research day booklet 4th May 2016 p27.

3- Does physical activity affect respiratory muscle strength? Nidhal Gharbawi, Dr Erol Gaillard, Dr Maria Viskaduraki, Dr Caroline Beardsmore. Poster presented at the European Respiratory Society (ERS) annual congress (London) in September 2016 PA 1219. European Respiratory Journal/Volume 48/Supplement 60.

4- Respiratory muscle strength measurement in primary school children. Nidhal Gharbawi, Dr Erol Gaillard, Dr Maria Viskaduraki, Dr Caroline Beardsmore. Spoken presentation and poster presented at the British Thoracic Society Winter meeting in (London) December 2016 P 256. Thorax Journal /Volume 71/ Supplement (3) A1-A288. A 226.

5- Are ethnic differences in lung function explained by differences in respiratory muscle strength? Nidhal Gharbawi, Dr Maria Viskaduraki, Dr Erol Gaillard, Gregory Duncan, Dr Caroline Beardsmore. Poster presented at the Midlands Academy of Medical Sciences research festival2017 P30. Midlands Academy of Medical Sciences research festival booklet 31 March 2017 P30 pp 55.

6- Are ethnic variations in FVC explained by differences in respiratory muscle strength in children? Nidhal Gharbawi, Gregory Duncan, Dr Erol Gaillard, Dr Maria Viskaduraki, Dr Caroline Beardsmore. Poster presented at the Respiratory research day in Nottingham May 2017 P14. Respiratory research day booklet 3rd May 2017 p35.

7- Does BMI influence spirometry and respiratory muscle strength in children? Gregory Duncan, Nidhal Gharbawi, Dr Erol Gaillard, Dr Maria Viskaduraki, Dr Caroline Beardsmore. Spoken presentation at the Respiratory research day in Nottingham May 2017. Respiratory research day booklet 3rd May 2017 p11.

8-How do differences in absolute lung volumes contribute to ethnic differences in spirometry? Nidhal Gharbawi, Dr Manjth Narayanan, Dr Maria Viskaduraki, Dr Erol Gaillard, Dr Caroline Beardsmore. Poster discussion presented at the European Respiratory Society (ERS) annual congress (Milan) in September 2017 PA 1682. European Respiratory Journal 2017/Volume 50/Supplement 61.

9- Measurement of lung distensibility in healthy children. NidhalGharbawi, Dr Maria Viskaduraki, Dr Erol Gaillard, Gregory Duncan, Dr Caroline Beardsmore. Poster presented at the European Respiratory Society (ERS) annual congress (Milan) in September 2017 PA 1403. European Respiratory Journal 2017/Volume 50/Supplement 61.

10- Are ethnic differences in lung function explained by differences in respiratory muscle strength in children? Spoken presentation presented at the British Thoracic Society Winter meeting in (London) December 2017. Nidhal Gharbawi, Dr Maria Viskaduraki, Dr Erol Gaillard, Gregory Duncan, Dr Caroline Beardsmore. Thorax Journal 2017/Volume 72/ Supplement 3 A1-278. A45.

11- How does BMI status influence spirometry and respiratory muscle strength in children? Poster presented at the British Thoracic Society Winter meeting in (London) December 2017. Gregory Duncan, Nidhal Gharbawi, Maria Viskaduraki, Erol Gaillard, Caroline Beardsmore. Thorax Journal 2017/Volume 72/ Supplement (3) A1-278. A 132.

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