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What is This?
Life-course of cardio-respiratory associations

Jacobien B Eising1, Cornelis K van der Ent1, Anne C van der Gugten1, Diederick E Grobbee2, Annemieke MV Evelein2, Mattijs E Numans2 and Cuno SPM Uiterwaal2

Abstract
Background: Several studies have shown that raised cardiovascular risk factors are associated with an impaired lung function in adulthood. Whether this association also exists in the young is unknown. Our aim was to study the relation between blood pressure and lung function from neonatal to elderly age.

Study design: This was a cross-sectional study in a general population cohort.

Methods: Within the Utrecht Health Project (UHP) 6673 adults (aged 18–91 years) had spirometry and blood pressure measurements taken. In the WHHeezing Illnesses STudy LEidsche Rijn (WHISTLER) study, a satellite birth cohort of the UHP, blood pressure and respiratory mechanics were measured using the single occlusion technique in 755 newborns and spirometry in 382 5-year-old participants. Linear regression analyses were performed with lung function as an independent variable and blood pressure as a dependent variable in different age groups. The analyses were adjusted for age, sex, weight and height.

Results: In infancy a more favorable lung function (higher compliance and lower resistance) was associated with higher blood pressure. In 5-year-old children and young adults higher forced expiratory volume in 1 second (FEV1) was associated with higher systolic blood pressure (p-values < 0.05). At the age of 5 the adjusted regression coefficient for systolic blood pressure was 4.8 mmHg/L (95% confidence interval (95% CI) 0.3–9.98). The association decreased with increasing age and reversed in the age groups above 40 years to 7.3 mmHg/L (95% CI 15.5–0.9) in those aged over 70 years of age. The association with pulse pressure showed a similar pattern.

Conclusions: A positive association between the mechanical properties of the respiratory system and blood pressure in childhood and young adulthood reverses in later adulthood.

Keywords
lung function tests, spirometry, blood pressure, child, adult, infant

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Introduction

Interactions between the pulmonary and cardiovascular systems are increasingly becoming a research focus.1,2 In adults, diseases of both systems often co-exist, which might suggest shared origins. In patients with mild to moderate chronic obstructive pulmonary disease (COPD), cardiovascular disease is the most common comorbidity and leading cause of hospitalization.3,4 A recent study showed that individuals with COPD had a twofold higher risk of carotid artery wall thickening on ultrasonography than control subjects with normal lung function. This risk was significantly higher with more severe airflow limitation.5 There are also other observations in adults showing that impaired lung function is related to cardiovascular disease.

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notably stiffer and thicker arteries and higher blood pressure. Major risk factors for both cardiovascular and respiratory disease, like age, cigarette smoking and chronic inflammation, only partially explain the associations.

Over recent decades, there has been growing interest in the early life origins of later life chronic disease. The Developmental Origins of Health And Disease (DOHAD) hypothesis proposes that early life adverse exposures lead to permanent metabolic or structural changes, that in later life result in cardiovascular or respiratory disease. Many studies have shown early life origins of cardiovascular disease and respiratory disease separately. However, while these diseases are clearly related in later adulthood, there is only scarce information about whether they might share early life origins. Such knowledge is important, because prevention of major later life chronic diseases needs to begin in childhood. Currently, prevention often focuses on single risk factors for separate diseases, while even within diseases a more integrated approach is probably required. If respiratory and vascular disease do share early life origins, it is very likely that prevention in early life will require an even wider scope.

To our knowledge, the only current available evidence for shared origins in healthy children is that lower forced expiratory volume in 1 second (FEV1) was found to be related to increased vascular stiffness measured by carotid augmentation index in 8-year-old children.

Further evidence comes mainly from paediatric patients. For instance, in obese children with obstructive sleep apnoea there are already arterial alterations and in children with diabetes mellitus type 1, higher recurrence of infection is related to pre-atherosclerotic change. Existence of such natural relations can best be investigated in healthy young individuals.

Blood pressure is a well-known cardiovascular risk factor of which the life-long natural history has been described. It is a clear indicator for arterial development from early age onwards. Likewise, lung function measurements are indicators of respiratory diseases at all ages. Both measurements can be performed relatively easily in large-scale population studies and nowadays even in neonates. Our aim was to study the relation between blood pressure and lung function from neonatal to elderly age.

**Methods**

**Setting and participants**

The adults were participants of the Utrecht Health Project (UHP), a large health monitoring study of residents of Leidsche Rijn, a newly built residential area near the city of Utrecht. The aim of this study was to create a solid and continuous research infrastructure to generate general medical and health care insights as a basis for evidence-based medicine and health policy. The UHP started to recruit participants in 2001 and invited each new inhabitant, irrespective of age, who registered with a general practitioner by mail to participate. An individual health profile is made for every participant that includes an interview-assisted questionnaire and physical examination. The children in our study were participants of the WHeezing Illnesses Study LEidsche Rijn (WHISTLER), a satellite cohort of UHP. WHISTLER is a prospective birth cohort study that was initiated in December 2001. Its focus is on early life determinants of respiratory and cardiovascular disease. Lung function, length and weight were measured between 3 and 8 weeks of age, before any respiratory infection occurred. Participants of this study were all born after January 2003, since blood pressure measurements at this visit were started in 2003. At the age of 5 years, the children who participated in infancy were invited for a second visit. The UHP and WHISTLER studies have been approved by the Medical Ethics Committee of the University Medical Centre Utrecht and conformed to the standards set by the declaration of Helsinki. Written informed consent was obtained from all (or of the parents of) participants.

**Measurements**

With a self-report questionnaire for adults, smoking status (never, former or current smokers) and a physician’s diagnosis of asthma or cardiovascular disease in the past year was assessed. Cardiovascular disease was defined as hypertension, myocardial infarction or stroke in the past year. For children health information was gathered by parental questionnaire. Questions for newborns included information about the smoking habits of the parents and feeding of the child. Questions for the 5-year-old participants included information about a physician’s diagnosis of asthma.

Height and weight were measured using a standard electronic scale and body length using an (infant) stadiometer.

**Lung function measurements**

In infancy, respiratory mechanics were measured using the single occlusion technique during natural sleep according to the guidelines of the European Respiratory Society. At least three technically acceptable flow-volume curves were used to calculate mean resistance and compliance. Lung function measurements were performed by WHISTLER staff.
Table 1. Characteristics per age group (in years)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>n</th>
<th>Male (%)</th>
<th>Smoking (%)</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>Lung function</th>
<th>Blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5</td>
<td>755</td>
<td>44.9</td>
<td>Yes: 17.6</td>
<td>0.9 (0.2)</td>
<td>4.5 (0.6)</td>
<td>45.2 (10.8)</td>
<td>Compliance (ml/kPa)</td>
<td>85.6 (10.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>46.6</td>
<td>No: 57.9</td>
<td>5 (0.3)</td>
<td>20.1 (2.8)</td>
<td>6.8 (2.1)</td>
<td>Resistance (kPa/L/s)</td>
<td>105.3 (7.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>34.2</td>
<td>Ever: 20.9</td>
<td>27 (3)</td>
<td>73.3 (14.4)</td>
<td>1.3 (0.2)</td>
<td>FEV1 (L)</td>
<td>3.6 (0.9)</td>
</tr>
<tr>
<td></td>
<td>382</td>
<td>47.7</td>
<td></td>
<td>35 (3)</td>
<td>77.8 (15.3)</td>
<td>3.6 (0.8)</td>
<td>PEF (L·s⁻¹)</td>
<td>7.6 (3.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49.6</td>
<td></td>
<td>45 (3)</td>
<td>78.5 (15.8)</td>
<td>3.3 (0.8)</td>
<td>FVC (L)</td>
<td>7.1 (2.3)</td>
</tr>
<tr>
<td></td>
<td>1662</td>
<td>44.3</td>
<td></td>
<td>55 (3)</td>
<td>78.7 (14.3)</td>
<td>2.9 (0.8)</td>
<td>MAP (mm Hg)</td>
<td>6.4 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>52.5</td>
<td></td>
<td>65 (3)</td>
<td>78.1 (13.9)</td>
<td>2.5 (0.7)</td>
<td>Systolic (mm Hg)</td>
<td>5.7 (2.2)</td>
</tr>
<tr>
<td></td>
<td>2817</td>
<td>55.7</td>
<td></td>
<td>76 (4)</td>
<td>73.7 (11.5)</td>
<td>2.1 (0.7)</td>
<td>Diastolic (mm Hg)</td>
<td>5.0 (2.1)</td>
</tr>
<tr>
<td></td>
<td>997</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>Pulse pressure (mm Hg)</td>
<td>2.8 (1.2)</td>
</tr>
<tr>
<td></td>
<td>663</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>MAP (mm Hg)</td>
<td>1.4 (0.2)</td>
</tr>
<tr>
<td></td>
<td>394</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>MAP (mm Hg)</td>
<td>1.4 (0.2)</td>
</tr>
<tr>
<td></td>
<td>140</td>
<td>&lt;0.01</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.01</td>
<td>MAP (mm Hg)</td>
<td>1.4 (0.2)</td>
</tr>
</tbody>
</table>

FEV1: forced expiratory volume in 1 second; PEF: peak expiratory flow; FVC: forced expiratory volume; MAP: mean arterial pressure.; Values are means and standard deviations, unless otherwise indicated.
Elaborate interrater reliability studies were performed as part of WHISTLER and showed satisfactory quality of lung function measurements. At the age of 5 years, lung function was evaluated using a heated Lilly head pneumotachometer system (Viasys Healthcare, Hochberg, Germany) and conform to the latest American Thoracic Society (ATS)/European Respiratory Society (ERS) statement for lung function measurements in preschoolers. At least two reproducible flow-volume curves were obtained. The largest FEV1 was selected from the curve with highest sum of FEV1 and Forced Vital Capacity (FVC). In adulthood lung function was evaluated with a Vitalograph 2120 (Vitalograph Ltd, Buckingham, UK). At least three forced expirations were performed in accordance with the guidelines of the ATS. The maximum of the three measurements was used for analyses.

**Blood pressure measurements**

Blood pressure measurements in infancy were started in January 2003 in neonates in whom lung function could be successfully measured. Blood pressure measurements were performed during natural sleep three times at the lower leg using an electronic device (DINAMAP; Criticon, model 1846SX). In children at the age of 5 years and in the adults blood pressure was recorded twice in sitting position at the brachial artery using a semiautomatic oscillometric device (DINAMAP; Criticon, Tampa, FL, USA) in children and an Omron M4 device (Medizintechnik Handelsgesellschaft mbH, Mannheim, Germany) in adults. In all individuals the average of blood pressure measurements was used for analyses.

**Statistical analysis**

Central estimators and variance measures to describe general characteristics of the participants were calculated. All variables were checked for normality of distribution and, if necessary, transformations were applied. Adults of UHP were divided into age groups. Differences between age groups were tested using analysis of variance or Chi-square tests whenever
appropriate. Linear regression analysis was performed for all associations between lung function and blood pressure. All analyses were adjusted for age, sex, weight and height. In WHISTLER infants compliance and resistance of the respiratory system were independent variables and blood pressure was a dependent variable, with additional adjustments made for smoke exposure of the mother during pregnancy and the nutrition of the child (breastfeeding, bottle feeding or a combination). In WHISTLER 5-year olds and adults of UHP, FEV1 was used as independent variable and blood pressure as a dependent variable. Multivariable models with the product of age and lung function as interaction term were applied to study the trend of the linear regression coefficients. In these models we also adjusted for smoking, asthma and cardiovascular disease.

The results are expressed as linear regression coefficients, p-values and 95% confidence intervals (CI). CI not including 0 and p-values < 0.05 were considered statistically significant. All analyses were performed using SPSS for windows (version 17.0).

Results
The baseline characteristics of the 7428 individuals are shown per age group in Table 1.

Figures 1 and 2 show the mean systolic and diastolic blood pressure and the mean FEV1 per age group, respectively. Systolic blood pressure increased at young age, stabilized around middle age and further increased in the elderly. Diastolic blood pressure increased at young age, stabilized around middle age and tended to decrease in the elderly. FEV1 increased in the very young, peaked in young adulthood and then gradually decreased with age.

In 755 newborns we analyzed the associations between lung function as measured by the single occlusion technique and blood pressure. Lung compliance was positively associated with systolic blood pressure (0.18 mm Hg/ml/kPa, 95% CI 0.11–0.26, after adjustment for age, sex, length and weight 0.08 mmHg/ml/kPa, 95% CI 0.00–0.15) and diastolic blood pressure (0.13 mmHg, 95% CI 0.07–0.19, after adjustment 0.09 mmHg/ml/kPa, 95% CI 0.03–0.16).

Figure 2. Mean (standard deviation) FEV1 per age group.
Lung resistance was negatively associated with systolic blood pressure (−0.72 mmHg/kPa/L/s, 95% CI −1.08–0.35, after adjustment −0.42 mmHg/kPa/L/s, 95% CI −0.80–0.05) and with diastolic blood pressure (−0.44 mmHg/kPa/L/s, 95% CI −0.75–0.13, after adjustment −0.27 mmHg/kPa/L/s, 95% CI −0.60–0.06). Adjustment for smoke exposure or nutrition of the child did not influence the associations.

Figure 3 shows associations between lung function measured by spirometry (FEV1) and systolic blood pressure from age 5 years onwards. The association was strongest in 5 year olds (4.8 mmHg/L, 95% CI −0.3–10.0, adjusted for age, sex, length and weight) and gradually decreased to the weakest in >70 year olds (−7.3 mmHg/L, 95% CI −15.5–0.9, adjusted for age, sex, weight and height), while apparently reversing direction between age 50 and 70 years. This decreasing trend of the linear regression coefficients across increasing age was statistically significant (linear regression coefficient of the interaction term: −0.191, p < 0.001). Adjustment for smoking, asthma or cardiovascular disease had no influence on the associations (linear regression coefficients age-interaction term: −0.189, −0.187 and −0.173 respectively, all with a p < 0.001).

Figure 4 shows similar results for associations between FEV1 and pulse pressure. Figure 5 shows associations between FEV1 and diastolic blood pressure. At the age of 5 years a higher FEV1 was associated with a higher diastolic blood pressure (4.6 mmHg/L, 95% CI −0.2–9.4, adjusted for age, sex, weight and height). In the older age groups the association
remained positive, but not statistically significant after adjustment for age, sex, weight and height.

**Discussion**

Our study shows that in contrast to findings in the elderly, in young individuals lung function and systolic blood pressure show a direct association. This association between mechanical properties of the respiratory system and blood pressure seems to reverse with aging.

To our knowledge, this is the first study investigating the association between blood pressure and lung function in a large unselected population across different ages, including the neonatal period, childhood and early adulthood. It is remarkable that a significant positive association in childhood and early adulthood was observed. Results are consistent in the early age groups and adjustments for the associations in infancy for smoking of parents, nutrition (breast or bottle feeding) and heart rate did not influence the results. This finding suggests that a relation between mechanical properties of the respiratory system and systemic blood pressure is part of normal physiology in early life.

Some characteristics of our research need to be considered. To be able to study lung function in early infancy we used the single occlusion technique, while we used spirometry in children and adults. Although we analyzed lung function as assessed by two different lung function techniques, it seems reasonable to assume that properties of lung function, including the size of the airways and lungs and the elastic recoil and resistance properties are adequately estimated by both techniques.

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**Figure 4.** Associations between pulse pressure and FEV1 at different ages.
The direction of the findings in infancy is similar to the findings at the age of 5 years (a lower lung function is associated with higher systolic blood pressure). A further limitation may be that we used cross-sectional analyses. Although we do consider our analyses valid and statistically robust, longitudinal analysis of change of the association within persons over time could possibly give further insight.

The association between blood pressure and lung function has not been studied before in healthy children. A relationship between lung function and arterial stiffness was found in 8-year-old children, with carotid augmentation index being inversely associated with FEV1. As an approximation of arterial stiffness we calculated pulse pressure and found an association in the opposite direction for pulse pressure and FEV1 in childhood and young adulthood. Our findings are more in agreement with cross-sectional findings in adults. In adults higher FEV1 is associated with lower pulse pressure among those aged 40 years and over, but below 40 years the opposite was found; however, this was not significant after adjustment for confounders.

Our findings in the elderly are also consistent with previous studies. The reversal of the association after the age of 40 might reflect several mechanisms. Firstly, it can be speculated that this change is associated with prolonged exposure to pulmonary and cardiovascular disease risk factors, like cigarette smoking and chronic inflammation. Long term exposure to these factors could...
lead to an increase in blood pressure and a decline in lung function. In a similar study in adulthood it was demonstrated that the interrelationship between FEV1 and pulse pressure in adults was not fully explained by factors such as smoking, systemic inflammation and other cardiovascular risk factors. In our study, we performed an analysis with adjustment for smoking, which had no effect on the association. In infancy and early childhood these factors are of minor importance. However, the effect of unknown unmeasured factors cannot be entirely ruled out.

A second explanation for the reversal of the cardio respiratory association might be tissue stiffening (aging) of the pulmonary and vascular system over time. Stiffening of respiratory tissue might simultaneously lead to an increase of airway resistance and fall in FEV1, as well as to an increase of resistance in vascular walls leading to rising blood pressures.

Third, it can be hypothesized that growth plays a role in the decrease of the direct association in childhood and early adulthood. In childhood accelerated weight gain is associated with higher blood pressure and lower lung function. In addition, the natural course of FEV1 and blood pressure, as shown in Figures 1 and 2, shows that in childhood and early adulthood the rise in FEV1 is steeper than the rise in blood pressure. After the age of 40 systolic blood pressure still increases, while FEV1 decreases. However, due to the cross-sectional design it is difficult to draw definite conclusions.

Finally, changes in the pulmonary and vascular system over time might be directly causally related. Recently, it was shown in a large longitudinal study that a decline in FVC from average age at peak (29.4 years) to 35 years significantly predicted incidence of arterial hypertension during the 10-year-follow-up. The direction of this association was specific for lung function change predicting hypertension. Changes in blood pressure did not predict loss of lung function. Although our observational findings preclude any conclusions about causal relationships, they do justify studies into the effects of respiratory interventions on the cardiovascular system.

The process of atherosclerosis starts in the young and risk factors for cardiovascular disease in childhood track into adulthood. Lung function is, together with smoking, one of the strongest predictors of COPD. Since the association of lung function and blood pressure is already present in childhood, future research to explore the association should not only focus on adults. It is important to consider prevention and early detection of chronic disease from a broader perspective.

This study provides the first evidence for a positive association of the mechanical properties of the respiratory system and blood pressure in childhood and young adulthood. As cardiovascular and respiratory diseases are a major health-economic burden, improved understanding of the association between these two diseases is needed.

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Conflict of interest

None declared.

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