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# Cardio-metabolic risk factors during childhood in relation to lung function and asthma

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## Abstract

**Background:** Cardio-metabolic risk factors might have an adverse effect on respiratory outcomes, but associations in children are unknown. We aimed to study the longitudinal associations of cardio-metabolic risk factors with lung function and asthma at school age. We also examined whether any association was explained by child's body mass index (BMI).

**Methods:** In a population-based cohort study among 4988 children, cardio-metabolic risk factors were measured at 6 and 10 years and included blood pressure, cholesterol, triglycerides, insulin, and C-reactive protein (CRP) concentrations. At age 10 years, lung function was measured by spirometry and current physician-diagnosed asthma was assessed by questionnaire.

**Results:** After adjustment for confounders, child's BMI, and multiple testing, we observed that a higher diastolic blood pressure at the age of 6 years was associated with a higher forced vital capacity (FVC) at the age of 10 years (Z-score difference (95% CI): 0.05 (0.01, 0.08), per SDS increase in diastolic blood pressure). Also, child's CRP concentrations above the 75th percentile at both ages 6 and 10 years were related to a lower FVC as compared to CRP concentrations below the 75th percentile at both ages (Z-score difference (95% CI) −0.21 (−0.36, −0.06)). No consistent associations of other cardio-metabolic risk factors with respiratory outcomes were observed.

**Conclusion:** Blood pressure and CRP, but not lipids and insulin, were associated with lower lung function but not with asthma. The underlying mechanisms and long-term effects of these associations require further investigation.

KEYWORDS

asthma, cardio-metabolic health, child, epidemiology, respiratory function test

## Key messages

Cardio-metabolic risk factors have been implicated as a pathogenic factor in the development of an adverse respiratory health, but associations in children are unknown. In this large population-based prospective cohort study, we showed that blood pressure and C-reactive protein, but not lipids and insulin, are associated with lower lung function but not with asthma at school age. These associations were independent of child's body mass index. Our findings suggest that cardio-metabolic risk factors are marginally related to respiratory outcomes in childhood.

## 1 | INTRODUCTION

Obesity and asthma in childhood are predictors of cardiovascular and chronic obstructive pulmonary diseases later in life.[1,2] Obesity is highly prevalent in children and has been associated with a higher risk of asthma.[3] It has been suggested that the obesity-asthma link is driven by an adverse cardio-metabolic profile, which comprises visceral adiposity, a high blood pressure, dyslipidemia, and insulin resistance.[4] These cardio-metabolic risk factors could influence respiratory health through multiple mechanisms, including immune system activation and airway smooth muscle proliferation, leading to airway inflammation and obstruction.[5] Previous studies in adolescents and adults showed that an adverse cardio-metabolic profile related to a lower lung function or higher risk of asthma symptoms.[6-8] However, studies on the associations of cardio-metabolic risk factors with respiratory outcomes in children are scarce and used a cross-sectional design.[9,10] We previously observed that higher visceral fat was associated with a lower forced expiratory volume in 1 second/ forced vital capacity ($FEV_1$/FVC) ratio and a 20% higher risk of asthma at school age.[9] A large population-based study showed that school-aged children with asthma had higher triglycerides and were more likely to have acanthosis nigricans, which is a marker of insulin resistance, compared with those without asthma.[10] These associations were regardless of the general fat mass, as defined by body mass index (BMI) or fat mass index, suggesting that cardio-metabolic risk factors are independent predictors of an adverse respiratory health. However, the longitudinal associations of cardio-metabolic risk factors throughout childhood with lung function and asthma are unknown.

Therefore, we examined in 4988 children, participating in a population-based cohort study, the associations of blood pressure, lipids, insulin, and C-reactive protein (CRP) concentrations at the ages of 6 and 10 years with lung function and asthma at the age of 10 years. We then examined whether the associations were independent of child's BMI.

## 2 | METHODS

### 2.1 | Design

This study was embedded in the Generation R Study, an ongoing population-based prospective cohort study from early fetal life onwards, as described previously.[11] A total of 4988 singleton children were included for the current analyses (Figure S1).

### 2.2 | Cardio-metabolic risk factors

At a median age of 6.0 years (95% range 5.6-7.6) and 9.8 years (95% range 9.3-10.4), cardio-metabolic risk factors including blood pressure, lipids, insulin, and CRP concentrations were measured. Blood pressure was measured at the position of the right brachial artery for four times with 1-minute intervals, using the validated automatic sphygmomanometer Datascope Accutorr PlusTM (Paramus, NJ, USA). The last three measurements were used to calculate the mean systolic and diastolic blood pressure. Thirty-minute fasting blood samples were collected to measure total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, insulin, and CRP concentrations on the Cobas 8000 analyzer (Roche, Almere, The Netherlands). We constructed sex-specific standard deviation scores (SDS) for all cardio-metabolic risk factors (observed value-mean/SD) to enable comparison of the effect estimates.

### 2.3 | School age lung function and asthma

At the age of 10 years, lung function was measured by spirometry (MS-Pneumo, Vyaire, Würzburg, Germany) according to the ATS/ERS recommendations. Lung function measures included $FEV_1$, FVC, $FEV_1$/FVC, and forced expiratory flow after exhaling 75% of FVC ($FEF_{75}$), which were converted into sex-, height-, age-, and ethnicity-adjusted z-scores according to the Global Lung Initiative reference values, which are recommended by the ATS/ERS.[12] Information on asthma was obtained using questions adapted from the ISAAC core questionnaires.[13] Current asthma was defined as ever physician-diagnosed asthma with wheezing and/or any asthma medication use in the past 12 months.

### 2.4 | Covariates

Information on potential covariates including sociodemographic, lifestyle and growth factors was collected as described in the supplemental methods.

### 2.5 | Statistical analyses

For non-response analyses, we assessed characteristics of children included and not included in the study using ANOVA, Mann-Whitney *U* tests, and chi-square tests. Linear and logistic regression models were used to examine the associations of cardio-metabolic risk factors with respiratory outcomes. We first studied the associations of cardio-metabolic risk factors at age 6 years with respiratory outcomes at age 10 years. Then, to obtain more insight into the associations of cardio-metabolic risk factors throughout childhood with respiratory outcomes, we created four groups per cardio-metabolic risk factor, including "normal-normal" (both at age 6 and 10 years <75th percentile), "normal-high" (at age 6 years <75th percentile, and at age 10 years ≥75th percentile), "high-normal" (at age 6 years ≥75th percentile, and at age 10 years <75th percentile) and "high-high" (both at age 6 and 10 years ≥75th percentile).[14] Higher HDL concentrations reflect a lower cardio-metabolic risk; therefore, we defined for HDL "normal" as an HDL >25th percentile and "low" as an HDL ≤25th percentile. More information on the models, confounders, additional analyses, multiple imputations, and adjustment for multiple hypothesis testing can be found in the supplemental methods.

Statistical analyses were performed using SPSS version 25.0 for Windows (IBM Corp., Armonk, NY, USA) and R version 3.6.1 (R Foundation, Vienna, Austria).

## 3 | RESULTS

### 3.1 | Subject characteristics

Table 1 shows the baseline characteristics of the participants. The prevalence of current asthma at age 10 years was 5.7%. Non-response analyses showed that children who were not included in our study mainly had mothers who were lower educated and less often had a European ethnic background, compared with children who were included in our study (Table S1).

### 3.2 | Cardio-metabolic risk factors and respiratory outcomes

We studied the associations of cardio-metabolic risk factors at the age of 6 years with respiratory outcomes at the age of 10 years and observed that after adjustment for confounders, a higher systolic and diastolic blood pressures were associated with a higher $FEV_1$ and FVC (Table 2). After further adjustment for child's BMI and correction for multiple testing, only the association of diastolic blood pressure with FVC remained statistically significant (Z-score difference (95% CI): 0.05 (0.01, 0.08), per SDS increase in diastolic blood pressure). We observed no consistent associations of blood pressure with other lung function measures or current asthma. Total cholesterol, HDL cholesterol, and triglycerides, as well as insulin and CRP at the age of 6 years, were not associated with respiratory outcomes at the age of 10 years. After combining cardio-metabolic risk factors measured at the age of 6 and at the age of 10 years in groups, we observed that, in the BMI model, those who had a "high-high" insulin level had a lower FVC as compared to those who had a "low-low" insulin level (Z-score difference (95% CI): −0.16 (−0.32, −0.00)) (Table 3). Children with a "high-high" CRP had a lower $FEV_1$ and FVC, as compared to those with a "low-low" CRP (Z-score difference (95% CI): −0.19 (−0.35, −0.03), −0.21 (−0.36, −0.06), respectively). However, after correction for multiple testing, only the association of CRP with FVC remained statistically significant. Other longitudinal groups of cardio-metabolic risk factors were not associated with respiratory outcomes.

We performed several additional analyses and did not find consistent associations with respiratory outcomes when we combined the cardio-metabolic risk factors in a cardio-metabolic risk cluster (Table S2). We observed effect modification by child's ethnic background with p-values for interaction ranging from 0.007 to 0.942. We subsequently repeated our BMI model restricted to children with a Dutch ethnic background, which is the largest ethnic group in our cohort, and mainly observed similar directions of the effect estimates as in the whole

**TABLE 1** Characteristics of children and their mothers

| | N = 4988 |
|---|---|
| Maternal characteristics | |
| Pre-pregnancy BMI ($kg/m^2$)[a] | 22.7 (17.9-34.4) |
| Educational level, higher (%) | 49.5 (2469) |
| Smoking during pregnancy, yes (%) | 24.2 (1207) |
| History of asthma or atopy, yes (%) | 36.9 (1840) |
| Parity, nullipara (%) | 56.3 (2807) |
| Birth and infant characteristics | |
| Sex, female (%) | 50.1 (2498) |
| Gestational age at birth (wk)[a] | 40.1 (35.7-42.3) |
| Birth weight (g) | 3433 (552) |
| Ethnic background, European (%) | 67.7 (3379) |
| Ever breastfeeding, yes (%) | 91.7 (4575) |
| Childhood characteristics, age 6 y | |
| Age (y) | 6.1 (0.5) |
| Physical activity (hours/day)[a] | 1.8 (0.5-5.1) |
| Body mass index ($kg/m^2$) | 16.1 (1.8) |
| Systolic blood pressure (mm Hg) | 102.4 (8.1) |
| Diastolic blood pressure (mm Hg) | 60.5 (6.8) |
| Total cholesterol (mmol/L) | 4.2 (0.6) |
| HDL cholesterol (mmol/L) | 1.3 (0.3) |
| Triglycerides (mmol/L)[a] | 0.95 (0.40-2.37) |
| Insulin (pmol/L)[a] | 114.6 (16.9-393.0) |
| CRP (mg/L)[a] | 0.3 (0.1-10.4) |
| Childhood characteristics, age 10 y | |
| Inhalant allergic sensitization | 32.4 (1617) |
| Systolic blood pressure (mm Hg) | 103.0 (7.9) |
| Diastolic blood pressure (mm Hg) | 58.3 (6.4) |
| Total cholesterol (mmol/L) | 4.3 (0.7) |
| HDL cholesterol (mmol/L) | 1.5 (0.3) |
| Triglycerides (mmol/L)[a] | 0.97 (0.41-2.65) |
| Insulin (pmol/L)[a] | 173.8 (34.5-637.5) |
| CRP (mg/L)[a] | 0.3 (0.3-5.5) |
| $FEV_1$ (z-score) | 0.17 (0.97) |
| FVC (z-score) | 0.21 (0.93) |
| $FEV_1$/FVC (z-score) | −0.10 (0.95) |
| $FEF_{75}$ (z-score) | 0.04 (0.92) |
| Current asthma, yes (%) | 5.7 (240) |

*Note:* Values are means (SD), [a]medians (2.5-97.5th percentile) or valid percentages (absolute numbers), based on imputed data. At the age of 6 years, data on systolic and diastolic blood pressure (n = 218), total cholesterol (n = 1495), high-density lipoprotein (HDL) cholesterol (n = 1491), triglycerides (n = 1502), insulin (n = 1524), and C-reactive protein (CRP) (n = 1487), and at the age of 10 years, data on systolic and diastolic blood pressure (n = 298), total cholesterol (n = 1576), HDL cholesterol (n = 1576), triglycerides (n = 1586), insulin (n = 1580), CRP (n = 1573), and forced expiratory volume in 1 second ($FEV_1$) (n = 500), forced vital capacity (FVC) (n = 500), $FEV_1$/FVC ratio (n = 500), forced expiratory flow after exhaling 75% of FVC ($FEF_{75}$) (n = 500) and current asthma (n = 240) were missing and not imputed.

**TABLE 2** Associations of cardio-metabolic risk factors at age 6 years with lung function and asthma at age 10 years

| Cardio-metabolic risk factor (Z-score) | $FEV_1$ Z-score change (95% CI) n = 4488 | FVC Z-score change (95% CI) n = 4488 | $FEV_1$/FVC Z-score change (95% CI) n = 4488 | $FEF_{75}$ Z-score change (95% CI) n = 4488 | Current asthma OR (95% CI) n = 4224 |
|---|---|---|---|---|---|
| Systolic blood pressure | | | | | |
| N | 4283 | 4283 | 4283 | 4283 | 4037 |
| Basic model | 0.05 (0.02, 0.08)** | 0.06 (0.04, 0.09)** | −0.03 (−0.06, −0.00)* | 0.00 (−0.03, 0.03) | 1.08 (0.94, 1.25) |
| Confounder model | 0.04 (0.01, 0.08)* | 0.06 (0.03, 0.10)** | −0.03 (−0.07, 0.00) | −0.00 (−0.04, 0.03) | 0.94 (0.80, 1.12) |
| BMI model | 0.02 (−0.02, 0.06) | 0.04 (0.00, 0.07)* | −0.03 (−0.06, 0.01) | −0.00 (−0.04, 0.03) | 0.93 (0.78, 1.10) |
| Diastolic blood pressure | | | | | |
| N | 4283 | 4283 | 4283 | 4283 | 4037 |
| Basic model | 0.03 (0.00, 0.06)* | 0.04 (0.02, 0.07)** | −0.02 (−0.05, 0.01) | 0.00 (−0.02, 0.03) | 1.10 (0.96, 1.27) |
| Confounder model | 0.04 (0.00, 0.07)* | 0.05 (0.02, 0.09)** | −0.02 (−0.06, 0.01) | −0.00 (−0.03, 0.03) | 1.00 (0.84, 1.18) |
| BMI model | 0.03 (−0.00, 0.07) | 0.05 (0.01, 0.08)** | −0.02 (−0.06, 0.01) | −0.00 (−0.04, 0.03) | 0.99 (0.84, 1.17) |
| Total cholesterol | | | | | |
| N | 3158 | 3158 | 3158 | 3158 | 2981 |
| Basic model | 0.03 (0.00, 0.07) | 0.03 (−0.01, 0.06) | 0.02 (−0.02, 0.05) | 0.03 (0.00, 0.07)* | 1.02 (0.87, 1.20) |
| Confounder model | 0.02 (−0.02, 0.05) | 0.01 (−0.03, 0.04) | 0.02 (−0.02, 0.06) | 0.02 (−0.02, 0.06) | 1.00 (0.82, 1.20) |
| BMI model | 0.01 (−0.03, 0.05) | −0.01 (−0.04, 0.03) | 0.02 (−0.02, 0.06) | 0.02 (−0.02, 0.06) | 0.99 (0.82, 1.20) |
| HDL cholesterol | | | | | |
| N | 3160 | 3160 | 3160 | 3160 | 2983 |
| Basic model | −0.01 (−0.04, 0.03) | −0.01 (−0.04, 0.02) | 0.02 (−0.01, 0.05) | 0.03 (−0.01, 0.06) | 0.96 (0.81, 1.13) |
| Confounder model | −0.01 (−0.05, 0.03) | 0.00 (−0.04, 0.04) | 0.00 (−0.04, 0.04) | 0.00 (−0.04, 0.04) | 0.89 (0.73, 1.08) |
| BMI model | −0.00 (−0.04, 0.04) | 0.01 (−0.03, 0.04) | 0.00 (−0.04, 0.04) | 0.00 (−0.04, 0.04) | 0.89 (0.73, 1.08) |
| Triglycerides | | | | | |
| N | 3149 | 3149 | 3149 | 3149 | 2977 |
| Basic model | −0.01 (−0.04, 0.03) | 0.01 (−0.02, 0.04) | −0.04 (−0.07, −0.01)* | −0.04 (−0.07, −0.01)* | 0.99 (0.84, 1.16) |
| Confounder model | −0.02 (−0.06, 0.02) | −0.02 (−0.06, 0.03) | −0.01 (−0.05, 0.03) | −0.03 (−0.07, 0.01) | 0.98 (0.80, 1.19) |
| BMI model | −0.02 (−0.06, 0.02) | −0.02 (−0.06, 0.02) | −0.02 (−0.06, 0.02) | −0.03 (−0.07, 0.01) | 0.97 (0.80, 1.18) |
| Insulin | | | | | |
| N | 3129 | 3129 | 3129 | 3129 | 2959 |
| Basic model | −0.02 (−0.05, 0.02) | −0.02 (−0.05, 0.02) | −0.00 (−0.04, 0.03) | −0.02 (−0.05, 0.02) | 0.98 (0.83, 1.16) |
| Confounder model | 0.01 (−0.05, 0.03) | −0.03 (−0.06, 0.01) | 0.02 (−0.02, 0.06) | 0.00 (−0.04, 0.04) | 0.90 (0.74, 1.10) |
| BMI model | −0.03 (−0.07, 0.01) | −0.05 (−0.09, −0.01)* | 0.02 (−0.02, 0.06) | −0.00 (−0.04, 0.04) | 0.89 (0.73, 1.09) |
| CRP | | | | | |
| N | 3164 | 3164 | 3164 | 3164 | 2988 |
| Basic model | 0.01 (−0.02, 0.05) | 0.01 (−0.02, 0.04) | 0.00 (−0.03, 0.04) | 0.02 (−0.01, 0.05) | 1.08 (0.92, 1.26) |
| Confounder model | −0.02 (−0.07, 0.02) | −0.01 (−0.05, 0.03) | −0.01 (−0.06, 0.03) | −0.01 (−0.05, 0.03) | 1.12 (0.94, 1.34) |
| BMI model | −0.03 (−0.07, 0.02) | −0.02 (−0.06, 0.03) | −0.01 (−0.05, 0.03) | −0.01 (−0.05, 0.03) | 1.12 (0.94, 1.33) |

*Note:* Values are derived from linear or logistic regression models and reflect changes in Z-scores or odds ratios (OR) (respectively) with 95% confidence interval (95% CI) per SD increase in cardio-metabolic risk factor. High-density lipoprotein (HDL) cholesterol, C-reactive protein (CRP), forced expiratory flow in 1 second ($FEV_1$), forced vital capacity (FVC), forced expiratory flow after exhaling 75% of FVC ($FEF_{75}$), body mass index (BMI). "N" represents the number of the total group. Basic models include child's sex and age. The confounder models are additionally adjusted for maternal pre-pregnancy BMI, educational level, smoking during pregnancy, history of asthma or atopy and parity and child's gestational age at birth, birthweight, ethnic background, ever breastfeeding, and physical activity. BMI models include the confounder models and are additionally adjusted for child's BMI at the age of 6 years.

*$P$ <.05 and; **$P$ <.009 (after multiple testing correction).

population (Table S3). There was no indication of non-linearity for the associations of cardio-metabolic risk factors with respiratory outcomes. When we performed sensitivity analyses and adjusted our models for the android fat percentage instead of BMI, or when we excluded children with extreme CRP values (>95th percentile), we observed similar directions and magnitudes of the effect estimates (Tables S4 and S5).

**TABLE 3** Associations of cardio-metabolic risk factors in longitudinal groups with lung function and asthma at age 10 years

| Cardio-metabolic risk factor | $FEV_1$ Z-score change (95% CI) n = 4488 | FVC Z-score change (95% CI) n = 4488 | $FEV_1$/FVC Z-score change (95% CI) n = 4488 | $FEF_{75}$ Z-score change (95% CI) n = 4488 | Current asthma OR (95% CI) n = 4224 |
|---|---|---|---|---|---|
| Systolic blood pressure | | | | | |
| Normal-normal (n = 2848) | Reference | Reference | Reference | Reference | Reference |
| Normal-high (n = 513) | 0.02 (−0.09, 0.13) | 0.05 (−0.05, 0.16) | −0.07 (−0.18, 0.04) | −0.01 (−0.11, 0.10) | 1.20 (0.72, 2.00) |
| High-normal (n = 566) | 0.07 (−0.04, 0.18) | 0.09 (−0.01, 0.20) | −0.03 (−0.14, 0.08) | 0.00 (−0.10, 0.11) | 0.84 (0.48, 1.48) |
| High-high (n = 556) | 0.07 (−0.04, 0.19) | 0.10 (−0.01, 0.20) | −0.03 (−0.15, 0.08) | 0.04 (−0.07, 0.15) | 1.19 (0.71, 1.99) |
| Diastolic blood pressure | | | | | |
| Normal-normal (n = 2688) | Reference | Reference | Reference | Reference | Reference |
| Normal-high (n = 708) | 0.06 (−0.04, 0.16) | 0.06 (−0.03, 0.16) | −0.04 (−0.14, 0.06) | 0.00 (−0.09, 0.10) | 1.20 (0.75, 1.92) |
| High-normal (n = 619) | 0.09 (−0.01, 0.20) | 0.13 (0.03, 0.23)* | −0.06 (−0.16, 0.05) | −0.01 (−0.11, 0.09) | 1.09 (0.67, 1.77) |
| High-high (n = 468) | 0.06 (−0.06, 0.18) | 0.05 (−0.07, 0.16) | 0.03 (−0.09, 0.15) | 0.05 (−0.07, 0.16) | 1.07 (0.61, 1.88) |
| Total cholesterol | | | | | |
| Normal-normal (n = 1591) | Reference | Reference | Reference | Reference | Reference |
| Normal-high (n = 287) | 0.10 (−0.04, 0.25) | 0.04 (−0.10, 0.18) | 0.12 (−0.03, 0.26) | 0.13 (−0.01, 0.27) | 1.00 (0.49, 2.02) |
| High-normal (n = 275) | −0.12 (−0.28, 0.04) | −0.05 (−0.20, 0.10) | −0.11 (−0.27, 0.04) | −0.13 (−0.28, 0.02) | 1.05 (0.50, 2.21) |
| High-high (n = 442) | 0.07 (−0.05, 0.19) | 0.06 (−0.05, 0.18) | 0.02 (−0.10, 0.14) | 0.03 (−0.09, 0.15) | 0.80 (0.43, 1.51) |
| HDL cholesterol | | | | | |
| Normal-normal (n = 1631) | Reference | Reference | Reference | Reference | Reference |
| Normal-low (n = 326) | −0.07 (−0.22, 0.08) | −0.03 (−0.17, 0.11) | −0.07 (−0.22, 0.07) | −0.12 (−0.25, 0.02) | 1.82 (1.00, 3.30)* |
| Low-normal (n = 274) | 0.03 (−0.12, 0.19) | 0.02 (−0.12, 0.16) | 0.01 (−0.14, 0.16) | 0.06 (−0.08, 0.21) | 0.81 (0.36, 1.85) |
| Low-low (n = 362) | −0.05 (−0.19, 0.08) | −0.10 (−0.22, 0.03) | 0.05 (−0.08, 0.19) | −0.03 (−0.15, 0.10) | 1.03 (0.53, 1.98) |
| Triglycerides | | | | | |
| Normal-normal (n = 1546) | Reference | Reference | Reference | Reference | Reference |
| Normal-high (n = 404) | −0.10 (−0.23, 0.03) | −0.08 (−0.21, 0.04) | −0.05 (−0.18, 0.08) | −0.06 (−0.18, 0.07) | 0.61 (0.30, 1.23) |
| High-normal (n = 386) | −0.03 (−0.16, 0.10) | −0.03 (−0.15, 0.09) | −0.02 (−0.15, 0.11) | −0.00 (−0.12, 0.12) | 0.73 (0.38, 1.40) |
| High-high (n = 245) | −0.08 (−0.24, 0.08) | −0.06 (−0.21, 0.09) | −0.04 (−0.20, 0.12) | −0.11 (−0.26, 0.05) | 0.71 (0.31, 1.62) |
| Insulin | | | | | |
| Normal-normal (n = 1500) | Reference | Reference | Reference | Reference | Reference |
| Normal-high (n = 427) | 0.01 (−0.11, 0.14) | −0.05 (−0.17, 0.07) | 0.10 (−0.03, 0.22) | 0.07 (−0.05, 0.20) | 1.09 (0.61, 1.95) |
| High-normal (n = 421) | −0.00 (−0.13, 0.12) | −0.08 (−0.20, 0.04) | 0.10 (−0.02, 0.23) | 0.09 (−0.03, 0.21) | 0.83 (0.44, 1.55) |
| High-high (n = 218) | −0.12 (−0.29, 0.05) | −0.16 (−0.32, −0.00)* | 0.08 (−0.09, 0.25) | 0.01 (−0.15, 0.17) | 0.66 (0.25, 1.71) |
| CRP | | | | | |
| Normal-normal (n = 1564) | Reference | Reference | Reference | Reference | Reference |
| Normal-high (n = 374) | −0.12 (−0.26, 0.02) | −0.08 (−0.21, 0.05) | −0.07 (−0.21, 0.06) | −0.11 (−0.24, 0.02) | 1.48 (0.80, 2.75) |
| High-normal (n = 378) | 0.06 (−0.08, 0.19) | 0.06 (−0.06, 0.19) | 0.01 (−0.12, 0.14) | 0.05 (−0.07, 0.18) | 1.14 (0.61, 2.12) |
| High-high (n = 283) | −0.19 (−0.35, −0.03)* | −0.21 (−0.36, −0.06)** | 0.05 (−0.11, 0.03) | 0.01 (−0.15, 0.16) | 0.92 (0.39, 2.16) |

*Note:* Values are derived from linear or logistic regression models and reflect changes in Z-scores or odds ratios (OR) (respectively) with 95% confidence interval (95% CI) for longitudinal groups of cardio-metabolic risk factors, as compared to the reference group. High-density lipoprotein (HDL) cholesterol, C-reactive protein (CRP), forced expiratory flow in 1 second ($FEV_1$), forced vital capacity (FVC), forced expiratory flow after exhaling 75% of FVC ($FEF_{75}$), body mass index (BMI). "N" represents the number of the total group. Models are adjusted for maternal pre-pregnancy BMI, educational level, smoking during pregnancy, history of asthma or atopy and parity and child's sex, gestational age at birth, birthweight, ethnic background, ever breastfeeding, physical activity, age, and BMI.

*$P < .05$ and; **$P < .009$ (after multiple testing correction).

## 4 | DISCUSSION

In this population-based study, we observed that a higher diastolic blood pressure at the age of 6 years was associated with a higher FVC at the age of 10 years. Furthermore, children with high CRP concentrations at both 6 and 10 years had a lower FVC. Higher insulin concentrations tended to be associated with a lower FVC, but this association did not remain after correction for multiple testing. We observed no consistent associations of cardio-metabolic risk factors with asthma in childhood.

### 4.1 | Comparison with previous studies

Previous studies in adults or adolescents showed that, despite different defined populations and study designs, hypertension, dyslipidemia, insulin resistance, or low-grade systemic inflammation as measured by higher CRP levels were related to a lower $FEV_1$ or FVC, but not with the $FEV_1$/FVC ratio.[6,7,15-19] In addition, a cross-sectional study showed a significant association of a higher systolic blood pressure, and borderline association of a higher diastolic blood pressure, with a higher $FEV_1$ in children and young adults, but this association was reversed in adults above 40 years of age.[20] We observed that in children aged 6 years, a higher diastolic blood pressure was associated with a higher FVC at age 10 years, and tended to be associated with a higher $FEV_1$ but a lower $FEV_1$/FVC ratio. We could speculate that the underlying mechanisms of the association of blood pressure with lung function outcomes differ between children and adults. Our findings on the borderline associations of higher insulin concentrations with a lower FVC were in line with the results of previous studies, although we observed less strong effects in children as compared to studies in adolescents or adults.[6,7] One study in adolescents showed that a higher CRP concentration at age 14 years was only after adjustment for BMI associated with a lower FVC at age 20 years.[21] Interestingly, child's BMI was also in our study of importance as the association of high CRP concentrations at age 6 and 10 years with a lower FVC became significant after adjustment for BMI, probably because BMI is strongly related to both CRP and FVC.[9,22]

In adults, hyperglycemia or diabetes mellitus were independently associated with a higher risk of asthma.[8] Also, children with asthma were more likely to have higher triglyceride concentrations and insulin resistance.[10] The absence of associations of cardio-metabolic risk factors with asthma in our study might be due to a low variation in the cardio-metabolic risk factors in our population, with most children within the healthy range. However, the presence of similar subclinical cardio-metabolic risk factors in childhood has been shown to increase the risk of cardiovascular disease later in life,[2] and the risk of respiratory diseases may become obvious at later ages as well. Hence, more studies on the longitudinal effects of cardio-metabolic risk factors on respiratory health at later ages, and on the potential bidirectional associations, are needed.

### 4.2 | Interpretation of the results

A higher diastolic blood pressure at age 6 years was associated with a higher FVC at age 10 years, and tended to be associated with a higher $FEV_1$ but a lower $FEV_1$/FVC ratio. Similar directions were observed for the associations of systolic blood pressure with respiratory outcomes. These observations may be explained by dysanapsis, a disproportional growth of the lungs and airways, which has previously been related to obesity and especially visceral fat accumulation.[9] We speculate that a higher blood pressure could lead to left ventricular hypertrophy, which might affect the pulmonary blood flow and subsequently result in dysanaptic growth of the lungs and airways.[23] However, we should interpret the observed associations with substantial caution, as the associations of a high blood pressure at both age 6 and 10 years with lung function were less obvious, and therefore, we cannot exclude a temporal effect or chance finding. When we restricted our population to children with a Dutch ethnic background, the association of diastolic blood pressure with FVC was not statistically significant, which is most likely due to reduced power or potentially genetic predisposition. Animal studies suggest that allergic airway inflammation might play a role in the association of hypertension with lung function outcomes, but we did not observe effect modification by inhalant allergic sensitization in our human cohort.[24]

Dyslipidemia could lead to oxidative stress and inflammation, and therefore affect respiratory health.[5] We did not find an association of lipids with respiratory outcomes, which may be explained by relatively normal lipid levels in our cohort, in case any adverse effects occur above a certain threshold.[10]

In vitro and in vivo studies showed that high insulin concentrations might delay lung development and lead to airway smooth muscle hypertrophy and lung remodeling.[25] In adults, treatment with inhaled insulin for diabetes was associated with a lung function decline.[26] Although the association in our study of longitudinal high insulin with a lower FVC attenuated after correction for multiple testing, it suggests that especially prolonged exposure to high insulin concentrations could lead to alterations in lung growth, as reflected by a lower FVC.

CRP is a marker of low-grade systemic inflammation and is produced in the liver under stimulation of the pro-inflammatory cytokine interleukin-6 (IL-6). High IL-6 concentrations could affect the pulmonary endothelium and increase the vascular permeability, which might result in inflammation and airway obstruction.[27] Airway remodeling after IL-6 stimulation seems to occur mainly in the central airways, and this might explain the absence of an association of CRP with the $FEV_1$/FVC ratio, as this ratio also depends on patency of more peripheral airways.[27]

To our best knowledge, this is the first study that examines the associations of cardio-metabolic risk factors throughout childhood with respiratory outcomes. The observed effect estimates were small and might not be clinically meaningful on an individual level in childhood. Although replication is needed, our results are of importance from an etiologic perspective and might have a small

impact on a population level, since cardio-metabolic risk factors can be prevalent despite a normal BMI, and were independently associated with lung function outcomes. It has been suggested that especially the preschool period is of importance for later life lung function, and future studies might therefore focus on the association of cardio-metabolic risk factors with respiratory health during this age period, and with respiratory outcomes throughout the life course.[28]

### 4.3 | Strengths and limitations

Strengths of our study are the prospective population-based design, with detailed longitudinal information on a wide range of confounders including growth factors that are known to affect respiratory outcomes. We measured cardio-metabolic risk factors at different time points in childhood, thereby limiting the chance of exposure misclassification. We also need to mention limitations of our study. First, non-response might have given a selection toward a more healthy and affluent population, which could lead to biased effect estimates. Second, blood samples were drawn after a 30-minute fasting state, which may have resulted in non-differential misclassification especially of the lipid and insulin concentrations. Nevertheless, studies in adults showed that non-fasting lipid measures or semi-fasting insulin resistance correlated well with fasting measures.[29,30] Third, current asthma was defined based on questionnaires, which might have introduced information bias, although we used validated questions that are widely used in epidemiologic studies.[13] Finally, despite adjustment for multiple confounders, as in all observational studies residual confounding may occur.

## 5 | CONCLUSION

Blood pressure and CRP, but not serum lipids and insulin, were independently associated with lung function. We found no associations of cardio-metabolic risk factors with current asthma at 10 years. The underlying mechanisms and long-term effects of these associations require further investigation.

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### CONFLICT OF INTEREST

The authors declare that they have no relevant conflicts of interest.

### AUTHOR CONTRIBUTIONS

Sara M. Mensink-Bout: conceptualization (equal); formal analysis (lead); investigation (supporting); methodology (equal); writing—original draft (lead); writing—review and editing (lead). Susana Santos: conceptualization (supporting); formal analysis (supporting); methodology (equal); writing—review and editing (supporting). Johan C. de Jongste: conceptualization (supporting); supervision (supporting); writing—review and editing (supporting). Vincent W. V. Jaddoe: conceptualization (equal); funding acquisition (lead); supervision (supporting); writing—review and editing (supporting). Liesbeth Duijts: conceptualization (equal); formal analysis (supporting); investigation (lead); funding acquisition (lead); methodology (equal); supervision (lead); writing—original draft (lead); writing—review and editing (lead).

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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