

Association of Serum Uric Acid with Lung Function in the National Health and Nutrition Examination Survey (NHANES), 2007-2012: A Cross-Sectional Study.

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Research

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Abstract

Background

Evidence regarding the relationship between serum uric acid and lung function was controversial. Therefore, this study is designed to investigate whether serum uric acid was independently related to lung function in the National Health and Nutrition Examination Survey (NHANES) (2007-2012) after adjusting for other covariates.

Methods

The present study was a cross-sectional study. The total participants from NHANES (2007-2012) were 30442. After exclusion of subjects, 9474 subjects remained for the final analysis. The target independent variable and the dependent variable were serum uric acid measured at baseline and lung function respectively. Covariates involved in this study included age, sex, race, income-poverty ratio, body mass index, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, cholesterol, creatinine, total protein, FeNO, calcium, alcohol drinking, smoke, phosphorus and total bilirubin.

Results

The average age of 9626 selected participants was 37.12 ± 16.03 years old, and about 49.19% of them were male. Result of fully adjusted linear regression showed serum uric acid was negatively associated with FEV1, FEV and PEF after adjusting confounders (Odds ratio (OR)= for FEV1 [-21.28 (-32.26, -10.30)], for FVC [-26.79 (-40.56, -13.01)] and for PEF [-72.19 (-101.93, -42.46)]). FEV1 and PEF were found a non-linear relationship with serum uric acid and the inflection points was 6.5mg/dl and 7.3 mg/dl respectively. The effect sizes and the confidence intervals in FEV1 and PEF of the left and right sides of inflection point were -11.50 (-25.55, 2.54) and -48.07 (-74.49, -21.66), -38.17 (-71.91, -4.43) and -311.11 (-427.28, -194.94) respectively.

Conclusions

We find serum uric acid was negatively associated with FEV1, FVC and PEF in a general population. Besides, there is a threshold effect on the independent association between serum uric acid and FEV1 and PEF. Those results are only found in the general population. Further epidemiologic studies will still be required to confirm this reverse association between serum uric acid and lung function.

Background

Serum uric acid (sUA) is the final breakdown product of purine degradation and present in the epithelial lining fluid of the respiratory tract and in plasma [1, 2]. Previous studies have suggested that elevated sUA were associated with cardiovascular diseases, including hypertension, stroke, coronary heart disease and congestive heart failure [3–6]. Similarly, there are also a variety of research to investigate the relationship between sUA and respiratory disease, including chronic obstructive pulmonary disease (COPD), pulmonary hypertension and obstructive sleep apnea and a significant correlation was found [7–9].

Lung function gradually decreases with the passage of time and varies greatly among individuals [10]. Individuals with an accelerated decline in lung function are more likely to suffer from chronic respiratory diseases and face a higher risk of all-cause death [11]. Therefore, it would be very necessary to identify biomarkers associated with this decline [12].

A few epidemiological studies have investigated the relationship between sUA and lung function in the general population [13–17]. However, the results have been controversial. In this study, we investigated the association between sUA and lung function in US population using data from the National Health and Nutrition Examination Survey (NHANES 2007-2012).

Methods

Study Population

The National Health and Nutrition Examination Survey (NHANES) was a representative survey of the national population of the United States (US), which was designed and conducted by the National Center for Health Statistics (NCHS). The present study was a cross-sectional study. The data analyzed were gained from the NHANES (2007-2012). The NHANES methodological details are available at www.cdc.gov/nchs/nhanes/.

The population was limited to participants with complete data on sUA and lung function (mainly includes forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF)). The total participants from NHANES (2007-2012) were 30442. After exclusion of subjects with missing FEV1 (n=10392), baseline FEV1 Quality Attribute not A or B (n=1841), missing sUA (n=3776), gout (n=152), asthma (n=1190), FEV1/FVC<0.7 (n=1813), pregnant women (n=82), Coronary heart disease (n=185), liver disease (n=286), tumor (n=497), kidney disease (n=119), diabetes (n=635), 9474 subjects remained for the final analysis (see Figure 1 for a flow chart).

For participants aged <18 years, their parents/guardians furnished informed consent, and participants aged ≥ 18 years furnished informed consent on their own. The NCHS Ethics Review Board granted approval for the conduct of NHANES, and written informed consents were obtained from all participants.

Study Variables

The principal variables of this study were lung function (dependent variable, include FEV1, FVC and PEF) and sUA (independent variable). SUA were measured using a Beckman Synchron LX20 (Beckman Coulter, Inc., Brea, CA). Lung function was measured by Ohio 822/827 dry-rolling seal volume spirometers.

The following covariates were included: age, sex, race, income-poverty ratio, body mass index, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, cholesterol, creatinine, total protein, FeNO, calcium, alcohol drinking, smoke, phosphorus and total bilirubin. Details of sUA and total lung function measurement process and other covariate acquisition process were available at www.cdc.gov/nchs/nhanes/.

Statistical Analyses

All estimates were calculated considering for NHANES sample weights. Our presentation of continuous variables was based primarily on whether they are normally distributed. If it was a normal distribution, we present the continuous variable as mean \pm standard, and vice versa as the medium (Q1, Q3). Categorical variables were expressed in frequency or as a percentage. Weighted linear regression models (continuous variables) and weighted chi-square tests (categorical variables) were applied to calculate differences between different groups.

After adjustment for potential confounders, weighted multiple regression analyses were applied to calculate the independent relationship between sUA and lung function. Weighted generalized additive models and smooth curve fittings were applied to estimate the non-linearity of sUA and lung function. After adjusting for the same covariates in the linear regression models, two-piece wise linear regression models were further employed to examine the threshold effect of sUA on lung function. All the analyses were performed with the statistical software packages R (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc, Boston, MA). *P* values less than 0.05 (two-sided) were considered statistically significant.

Results

Baseline characteristics of selected participants

We showed the description of weighted baseline characteristics of these final selected population in table 1 according to quartiles of sUA. In general, the average age of the 9474 selected participants was 37.12 ± 16.03 years old, and about 49.19% of them were male. Among different groups of sUA (quartiles, Q1-Q4), the variables presented in table 1 were all significantly different.

Association between sUA and lung function (FEV1, FVC and PEF)

In this study, we constructed three models to analyze the independent effects of sUA on lung function (weighted multivariate linear regression). Crude Model, not adjusted; model I, age, sex and race were adjusted; model II, the covariates presented in Table 1 were all adjusted. The effect sizes (Odds ratio (OR)), 95% confidence intervals and *P* value were listed in Table 2. In the fully adjusted model, we

found a negative association between sUA and FEV1 [-21.28 (-32.26, -10.30)], FVC [-26.79 (-40.56, -13.01)] and PEF [-72.19 (-101.93, -42.46)]. For the purpose of sensitivity analysis, we converted the sUA from continuous variable to categorical variable (quartiles of sUA). The effect sizes of each quartile of sUA were all negative association with FEV, FVC and PEF in the fully adjusted model, which was consistent with the result when sUA was a continuous variable. The *P* for trend of sUA with categorical variables in fully adjusted model were also consistent with the result when sUA was a continuous variable. Besides, we also found the trend of the effect size in different sUA groups was non-equidistant (see table 2).

The results of nonlinearity of sUA and lung function

In the present study, we analyzed the non-linear relationship between sUA and lung function (Figure.2). Smooth curve and the result of Generalized additive model showed that the relationship between sUA and lung function was non-linear after adjusting for the covariates presented in Table 1. We used both linear regression and two-piecewise linear regression to fit the association and select the best fit model based on *P* for log likelihood ratio test.

The *P* for log likelihood ratio test of FEV1 and PEF was less than 0.05, which indicated a non-linear relationship between sUA and FEV1 and PEF. Therefore, we chose two-piecewise linear regression for fitting the association between sUA and FEV1 and PEF because it can accurately represent the relationship. By two-piecewise linear regression and recursive algorithm, we calculated the inflection point was 6.5mg/dl and 7.3 mg/dl for FEV1 and PEF respectively. FEV1 and PEF had a negative association with sUA and the effect sizes were different on the sides of the inflection point. The effect sizes and the confidence intervals in FEV1 and PEF of the left and right sides of inflection point were -11.50 (-25.55, 2.54) and -48.07 (-74.49, -21.66), -38.17 (-71.91, -4.43) and -311.11 (-427.28, -194.94) respectively (see table 3 and Fig.2). We can see a sharp increase in the absolute value of the effect sizes after the level of sUA was larger than the inflection point.

Discussion

In this study, we used a big and nationwide representative sample of US population. Our findings indicated sUA was negatively associated with lung function (FEV1, FVC and PEF) after adjusting other covariates. Besides, we also found a non-linear relationship between sUA and FEV1 and PEF, and the effect sizes on the sides of the inflection point were not consistent. This result suggested a threshold effect on the independent association between sUA and lung function. When the level of sUA was larger than 6.5mg/dl or 7.3 mg/dl, the FEV1 or PEF sharply decreased than before.

Previous studies have estimated the association between sUA and lung function in the general population, however, the results have been inconsistent. Ahn KM et al. suggested that "increased sUA level was significantly associated with accelerated FEV1 and FVC" by a sample of 19237 participants [17]. Similar findings were also reported in studies of Aida Y et al, Hong JW et al and Kobylecki CJ et al [13, 15, 16]. Their conclusions are consistent with our findings. However, some other studies are inconsistent with our findings. Song JU et al. reported that sUA may have a positive effect on lung function in middle aged healthy population [14]. We speculate that the reasons for the different results may be caused by the following factors: (1) the research population is different. Our study was a general population of US, while the study, which was inconsistent with our findings, was targeted at middle aged healthy population of South Korea; (2) the different conclusion did not clarify the nonlinear relationship; (3) compared with our work, the study did not take into account the effect of FeNO, total bilirubin and income-poverty ratio on the sUA and lung function relationship when adjusting covariates. However, previous studies have confirmed that these variables were related to lung function [18–20].

The exact mechanism of this association between sUA and lung function is still unclear. The effect of uric acid on lung function appears to be a double-edged sword in vivo. Possible explanations for negative association between sUA and lung function are as follows. First, sUA have been shown to be risen in hypoxic states. Previous studies have suggested that sUA increase in hypoxic states, such as chronic heart failure and COPD [21]. It has also been pointed out that pulmonary hypoxia promotes purine catabolism, leading to increased production of sUA [22]. However, it is unclear whether the low-level hypoxia observed in the general population affects sUA levels, as our study excluded subjects with overt clinical disease, such as asthma, airflow limitation, or coronary heart disease. Second, although sUA has antioxidant properties, sUA activates leukocytes through NALP3 inflammatory inflammasome [23]. Subsequently, activated leukocytes cause damage to vascular endothelial cells. Studies have shown that the pathogenesis of COPD included pulmonary vascular endothelial dysfunction [24, 25]. Therefore, the endothelial dysfunction induced by hyperuricemia may be related to the impairment of lung function in the general population. Possible explanations for positive association between sUA and lung function are as follows. Under normal physiological conditions, uric acid acts as an antioxidant in plasma, so it can prevent oxygen

free radical inducing toxicity [26–28]. It is known that uric acid plays a major antioxidant protective role on the airway surface, thus protecting the airway from the effects of reactive species [29, 30]. Uric acid from the human epithelial lining fluid of the respiratory tract is thought to be co-secreted with mucus by submucosal nasal glands after uptake from plasma [1]. Subjects with sufficient uric acid pools to combat oxidative stress may be protected from the decline in lung function caused by continuous exposure to oxidative stress. These explanations still need to be treated with caution because the double-edged characteristics of sUA and the inconsistent results from previous studies make it difficult to conclude about whether sUA has a beneficial or noxious effect on lung function. Further research is still needed to investigate the molecular mechanism toward the relationship between sUA and lung function, given the importance of evidence to determine whether sUA concentration is an eligible diagnostic or prognostic indicator for related diseases.

The clinical value of this study is as follows. (1) the findings of this study should be helpful for future research on the establishment of diagnostic or predictive models of lung function; (2) if uric acid truly had a contributes to lung function decline, Allopurinol maybe protective. Scott JP, et al. reported that the effect of allopurinol in heart-lung transplant patients with deteriorating lung function could stabilize lung function [31].

Our study has some strengths. (1) we addressed the nonlinearity in the present study and further calculated the inflection point, which could more accurately evaluate the relationship between sUA and lung function; (2) we adjusted more confounders, such as FeNO, total bilirubin and income-poverty ratio; (3) we handled target independent variable as both continuous variable and categorical variable and the results of two types of data were consistent. Such an approach can reduce the contingency in the data analysis and enhance the robustness of results. (4) our sample size is relatively large compared with previous similar studies.

Our work has several limitations. First, because this study has a cross-sectional design, it could not determine whether there was a causal relationship between sUA and lung function. Second, sUA level was measured at a single time point. Third, we did not take into account the use of uric acid-lowering drugs, but we exclude the population with gout. Finally, our research subjects are from NHANES (2007-2012), and there are some exclusion criteria. Therefore, there is a certain deficiency in the universality and extrapolation of research.

Conclusions

In conclusion, we find that increased serum uric acid level was negatively associated with FEV1, FVC and PEF in a general population. Besides, there is a threshold effect on the independent association between serum uric acid and lung function. When the level of serum uric acid was large than 6.5mg/dl or 7.3 mg/dl, the FEV1 or PEF sharply decreased than before. Those results are only found in the general population. Further epidemiologic studies will still be required to confirm this reverse association between serum uric acid and lung function.

Abbreviations

sUA: Serum uric acid; COPD: chronic obstructive pulmonary disease; NHANES: the National Health and Nutrition Examination Survey; NCHS: the National Center for Health Statistics; FEV1: forced expiratory volume in one second; FVC: forced vital capacity; PEF: and peak expiratory flow; NALP3: the Neutrophil Alkaline Phosphatase 3; FeNO: Fractional exhaled nitric oxide; OR: Odds ratio.

Declarations

Authors' contributions

LYH designed the study and revised the manuscript. LW conducted data collection and analysis and drafted the manuscript. WWY, SYH, WDH, YXY and LF conducted data collection and analysis. The authors read and approved the final manuscript.

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Availability of data and materials

The datasets analyzed during the current study can be found in <https://www.cdc.gov/nchs/nhanes/>.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

TABLE 1 Description of 9474 participants included in the present study.

Characteristic	serum uric acid (mg/dl)					P value
	All	Q1 (0.40-4.20 mg/dl)	Q2 (4.21-5.10 mg/dl)	Q3 (5.11-6.00 mg/dl)	Q4 (6.01-11.70 mg/dl)	
Age (years)	37.12 ± 16.03	35.95 ± 15.64	36.27 ± 16.46	37.58 ± 16.26	38.47 ± 15.66	<0.0001
Sex (%)						<0.0001
male	49.19	11.68	33.58	61.99	83.63	
female	50.81	88.32	66.42	38.01	16.37	
BMI (kg/m ²)	27.51 ± 6.41	24.86 ± 5.31	26.62 ± 6.13	28.05 ± 6.14	30.07 ± 6.67	<0.0001
Blood urea nitrogen (mg/dL)	12.02 ± 3.93	10.93 ± 3.50	11.54 ± 3.84	12.21 ± 3.83	13.21 ± 4.11	<0.0001
Creatinine (mg/dL)	0.83 ± 0.19	0.71 ± 0.14	0.78 ± 0.16	0.86 ± 0.17	0.95 ± 0.18	<0.0001
Cholesterol, total (mg/dL)	191.17 ± 40.34	187.47 ± 39.37	188.59 ± 40.99	191.11 ± 40.11	196.68 ± 40.20	<0.0001
Total protein (g/dL)	7.16 ± 0.44	7.09 ± 0.45	7.13 ± 0.43	7.19 ± 0.43	7.23 ± 0.43	<0.0001
Total bilirubin (mg/dL)	0.77 ± 0.30	0.68 ± 0.25	0.73 ± 0.27	0.79 ± 0.32	0.86 ± 0.33	<0.0001
Calcium (mg/dL)	9.45 ± 0.35	9.39 ± 0.35	9.44 ± 0.34	9.47 ± 0.34	9.50 ± 0.35	<0.0001
Phosphorus (mg/dL)	3.84 ± 0.61	3.88 ± 0.58	3.88 ± 0.63	3.85 ± 0.61	3.77 ± 0.61	<0.0001
SBP (mmHg)	117.94 ± 14.50	114.25 ± 14.63	116.01 ± 14.31	119.07 ± 13.75	121.81 ± 14.15	<0.0001
DBP (mmHg)	69.59 ± 12.04	67.76 ± 11.44	68.07 ± 11.76	70.08 ± 11.77	72.07 ± 12.54	<0.0001
FeNO (ppb)	13.50(9.00,19.50)	12.00(8.00,17.16)	13.00(8.50,19.00)	14.00(9.00,20.50)	14.00(9.50,21.00)	<0.0001
FEV1 (ml)	3447.27 ± 853.08	3064.73 ± 615.05	3280.99 ± 794.19	3562.62 ± 897.54	3818.40 ± 863.05	<0.0001
FVC (ml)	4215.87 ± 1041.74	3711.99 ± 745.90	3986.82 ± 966.88	4369.95 ± 1082.09	4711.99 ± 1031.79	<0.0001
PEF (ml)	8628.66 ± 2059.55	7544.41 ± 1520.75	8174.15 ± 1883.05	8958.88 ± 2106.47	9662.32 ± 1997.74	<0.0001
Race (%)						<0.0001
Mexican American	10.44	11.15	10.58	10.18	9.95	
Other Hispanic	6.12	6.96	6.83	6.23	4.67	
Non-Hispanic White	65.64	63.42	65.79	64.56	68.31	
Non-Hispanic Black	10.80	11.02	11.76	10.43	10.08	
Other Race	7.00	7.45	5.04	8.61	6.99	
Income-poverty ratio (%)						0.0268
Poor	21.49	22.46	22.45	22.62	18.82	
Nearly poor	8.20	8.44	7.29	8.24	8.78	

Not poor	64.28	62.84	64.25	63.29	66.40
Missing	6.03	6.27	6.01	5.85	6.00
Alcohol drinking (%)					<0.0001
Yes	7.94	10.28	8.00	7.69	6.13
No	7.33	8.82	8.12	6.92	5.74
Missing	84.73	80.90	83.88	85.39	88.13
Smoke (%)					<0.0001
Yes	32.88	28.16	31.47	32.89	38.11
No	50.64	53.27	49.23	50.42	49.94
Missing	16.48	18.57	19.31	16.70	11.95

Mean \pm SD or medium (Q1, Q3) for continuous variables: *P*-value was calculated by weighted linear regression model. % for categorical variables: *P*-value was calculated by weighted chi-square test.

Definitions: body mass index (BMI); Systolic blood pressure (SBP); Diastolic blood pressure (DBP)

TABLE 2 Association of serum uric acid with lung function in different models.

Variable	Crude Model		Model I		Model II	
	β (95% CI)	<i>P</i> -value	β (95% CI)	<i>P</i> -value	β (95% CI)	<i>P</i> -value
For FEV1						
sUA (mg/dl)	211.85 (199.55, 224.15)	<0.0001	13.81 (3.56, 24.06)	0.0083	-21.28 (-32.26, -10.30)	0.0001
sUA in quartiles						
Quartile 1	Reference		Reference		Reference	
Quartile 2	216.26 (169.63, 262.89)	<0.0001	-7.61 (-40.82, 25.60)	0.6534	-24.29 (-55.70, 7.12)	0.1295
Quartile 3	497.88 (450.77, 545.00)	<0.0001	17.35 (-18.48, 53.18)	0.3426	-20.96 (-56.00, 14.07)	0.2409
Quartile 4	753.67 (708.01, 799.32)	<0.0001	57.40 (19.63, 95.17)	0.0029	-43.72 (-82.99, -4.45)	0.0291
<i>P</i> for trend	<0.001		0.001		0.048	
For FVC						
sUA (mg/dl)	282.69 (267.85, 297.53)	<0.0001	16.06 (3.09, 29.02)	0.0152	-26.79 (-40.56, -13.01)	0.0001
sUA in quartiles						
Quartile 1	Reference		Reference		Reference	
Quartile 2	274.84 (218.59, 331.08)	<0.0001	-23.19 (-65.20, 18.82)	0.2793	-43.45 (-82.85, -4.04)	0.0307
Quartile 3	657.96 (601.13, 714.80)	<0.0001	8.68 (-36.65, 54.00)	0.7075	-37.52 (-81.47, 6.43)	0.0943
Quartile 4	1000.01 (944.93, 1055.08)	<0.0001	56.31 (8.53, 104.08)	0.0209	-70.31 (-119.57, -21.05)	0.0052
<i>P</i> for trend	<0.001		0.008		0.012	
For PEF						
sUA (mg/dl)	586.04 (556.91, 615.16)	<0.0001	53.77 (25.78, 81.76)	0.0002	-72.19 (-101.93, -42.46)	<0.0001
sUA in quartiles						
Quartile 1	Reference		Reference		Reference	
Quartile 2	629.74 (519.69, 739.79)	<0.0001	49.52 (-41.15, 140.19)	0.2845	-24.37 (-109.46, 60.72)	0.5746
Quartile 3	1414.47 (1303.27, 1525.66)	<0.0001	116.17 (18.34, 214.00)	0.0200	-46.27 (-141.18, 48.65)	0.3394
Quartile 4	2117.91 (2010.16, 2225.66)	<0.0001	246.25 (143.12, 349.37)	<0.0001	-123.49 (-229.87, -17.12)	0.0229
<i>P</i> for trend	<0.001		<0.001		0.023	

Crude Model, no covariates were adjusted.

Model I, age, sex and race were adjusted.

Model II, age, sex, race, income-poverty ratio, BMI, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, cholesterol, creatinine, total protein, FeNO, calcium, alcohol drinking, smoke, phosphorus and total bilirubin were adjusted.

TABLE 3 The threshold effect analysis for the relationship of between sUA and lung function

Models	FEV1		FVC		PEF	
	Adjusted OR (95%CI)	<i>P</i> -value	Adjusted OR (95%CI)	<i>P</i> -value	Adjusted OR (95%CI)	<i>P</i> -value
Model I						
One line slope	-21.28 (-32.26, -10.30)	0.0001	-26.79 (-40.56, -13.01)	0.0001	-72.19 (-101.93, -42.46)	<0.0001
Model II						
Turning point (K)	6.5		7.1		7.3	
⊠ 5.3 slope 1	-11.50 (-25.55, 2.54)	0.1085	-19.03 (-35.07, -2.98)	0.0201	-38.17 (-71.91, -4.43)	0.0266
⊠ 5.3 slope 2	-48.07 (-74.49, -21.66)	0.0004	-69.56 (-116.95, -22.16)	0.0040	-311.11 (-427.28, -194.94)	<0.0001
Slope 2 – Slope 1	-36.57 (-69.36, -3.78)	0.0288	-50.53 (-104.11, 3.05)	0.0646	-272.94 (-401.24, -144.64)	<0.0001
LRT test	0.029		0.064		<0.001	

Data were presented as OR (95%CI) *P*-value; Model I, linear analysis; Model II, non-linear analysis. LRT test, Logarithmic likelihood ratio test. (*p*-value<0.05 means Model II is significantly different from Model I, which indicates a non-linear relationship); adjust for age, race, income-poverty ratio, BMI, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, cholesterol, creatinine, total protein, FeNO, calcium, alcohol drinking, smoke, phosphorus and total bilirubin.

Figures

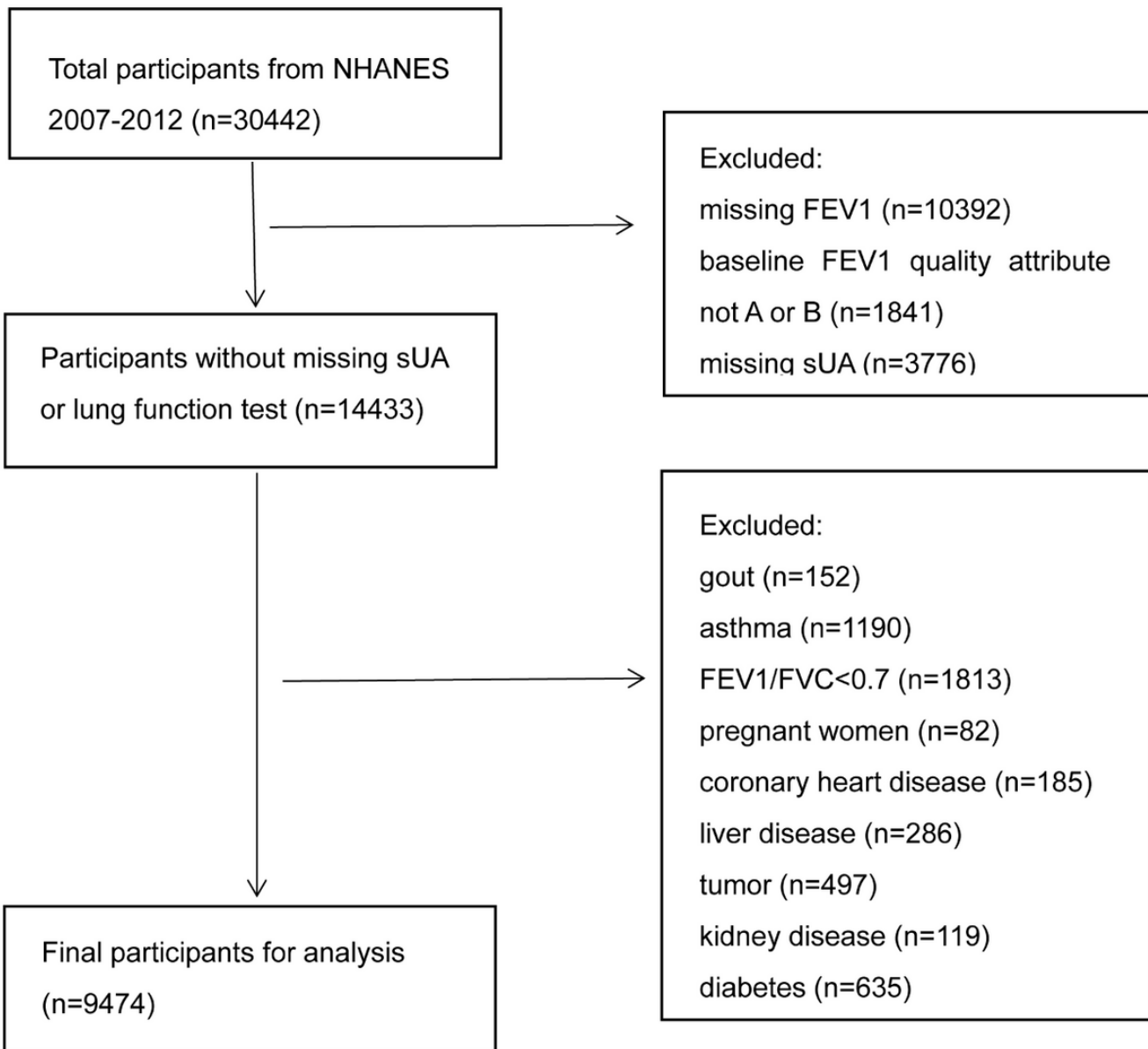


Figure 1

Flowchart of the inclusion of participants.

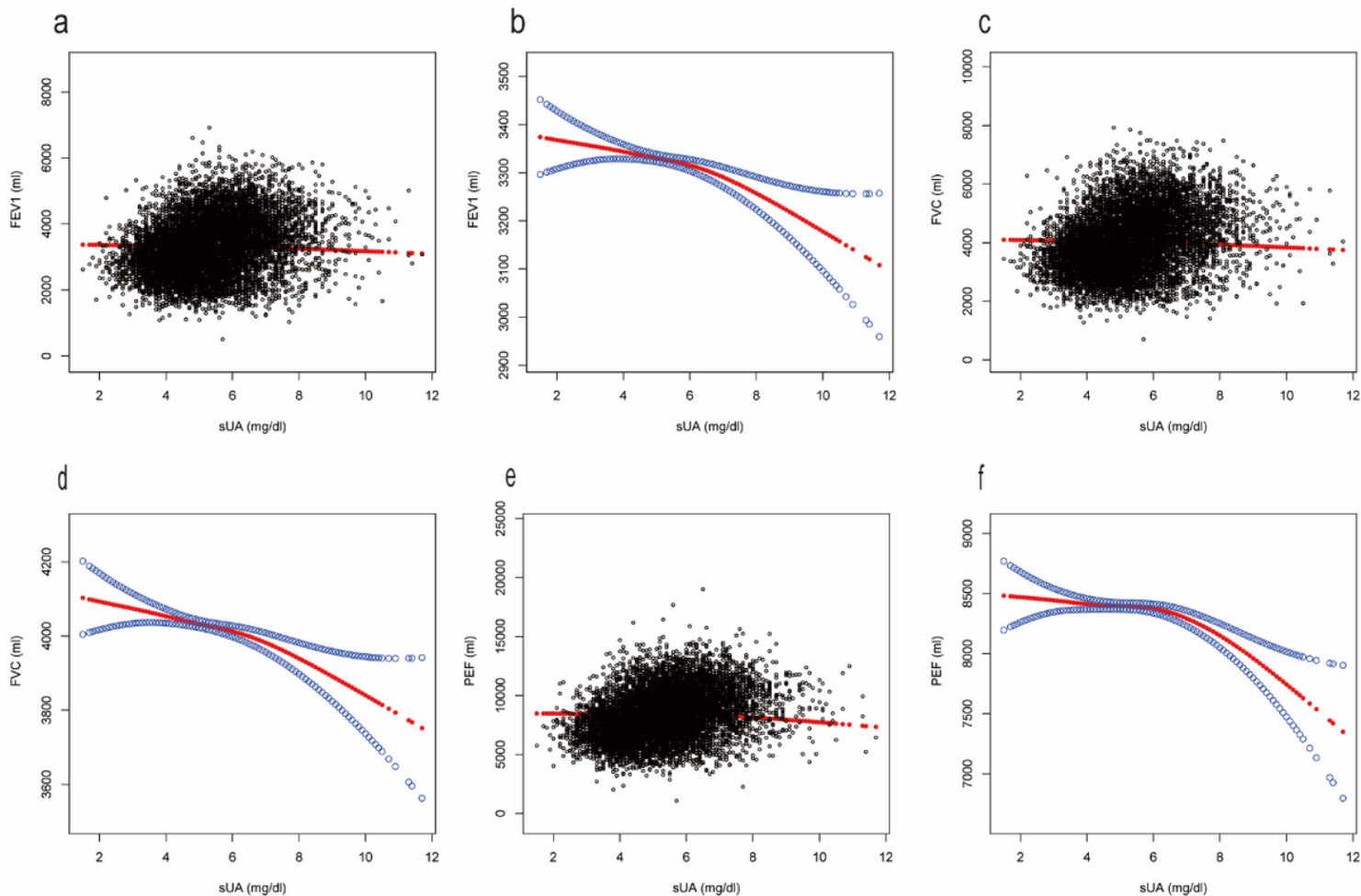


Figure 2

Correlation between serum uric acid and lung function (FEV1, FVC and PEF). (a, c, e) Each black point represents a sample. (b, d, f) The area between two blue dotted lined is expressed as a 95% CI. Each point shows the magnitude of the serum uric acid and is connected to form a continuous red line. Age, sex, race, income-poverty ratio, BMI, systolic blood pressure, diastolic blood pressure, blood urea nitrogen, cholesterol, creatinine, total protein, FeNO, calcium, alcohol drinking, smoke, phosphorus and total bilirubin were adjusted.