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Roles of gender and smoking in the associations between urinary phytoestrogens and asthma/wheeze and lung function: evidence from a cross-sectional study

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ABSTRACT

Background The role of phytoestrogens in asthma/wheeze and lung function remains controversial. Thus, we aimed to examine whether phytoestrogens have beneficial effects on asthma/wheeze, lung function for subgroups and mortality.

Methods Participants in this study were individuals aged 20 years or older from the National Health and Nutrition Examination Survey. Multivariate logistic regression models were fitted to examine the associations of urinary phytoestrogens with the risk of asthma/wheeze and lung function in individuals with and without asthma/wheeze. Cox proportional hazards regression was used to examine the relationship between urinary phytoestrogens and all-cause mortality. Stratified analyses were conducted based on gender and smoking status.

Results We included 2465 individuals in this study. Enterolactone levels in the highest quartile were associated with a lower risk of asthma than those in the lowest quartile. As compared with the lowest quartile, the highest quartile of enterodiol and enterolactone was associated with a lower risk of wheeze. Significant associations were observed between subtypes of phytoestrogens (equol and enterolactone) and lung function (forced vital capacity (FVC) and forced expiratory volume in 1 s). Besides, FVC was higher in individuals with higher levels of enterodiol. The results were consistent in subpopulations without asthma/wheeze, while the significant difference was not observed in individuals with asthma/wheeze. The stratified analyses revealed that the associations between phytoestrogens and lung function differed by gender and smoking status among subgroups. No significant association was found between urinary phytoestrogens and all-cause mortality.

Conclusion In summary, subtypes of phytoestrogens were associated with lower risk of asthma/wheeze and beneficial for lung function improvement in individuals without asthma/wheeze. Furthermore, gender and smoking may interact in the relationship between phytoestrogens and asthma/wheeze, and lung function. Further researches are needed to confirm these associations and explain the results of stratified analyses.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Human health has been closely associated with the consumption of phytoestrogen-rich foods.

WHAT THIS STUDY ADDS

⇒ Subtypes of phytoestrogens were associated with lower risk of asthma/wheeze and beneficial for lung function improvement in individuals without asthma/wheeze. Gender and smoking may interact in the relationship between phytoestrogens and asthma/wheeze, and lung function.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The findings of this study provide useful recommendations for the application of phytoestrogens in human health management. Further researches are needed to confirm these associations and explain the results of stratified analyses.

INTRODUCTION

Asthma is a heterogeneous disease characterised by persistent airway inflammation and variable airflow limitation, with lung function impairment.[1 2] Diet and nutrition have been suggested to be associated with asthma development and lung function improvement through their effects on systemic inflammation, oxidation, microbial composition, etc.[3 4] Natural phytoestrogens, mainly found in beans, grains and seeds, are non-steroidal plant phenolics.[5] They can be divided into two main groups: flavonoids and non-flavonoids, of which flavonoids are comprised of isoflavones, coumestans and prenylflavonoids, while non-flavonoids mainly include lignans and stilbenes.[6 7] Isoflavones, mainly derived from soy products, include genistein, daidzein, glycitein, biochanin A and formononetin.[7] Bacteria in the gastrointestinal tract can further metabolise daidzein into two endogenous products, o-desmethylangolensin and equol.[8] Enterolactone and enterodiol are two types of lignans commonly

consumed by humans.[9] Researchers have shown that phytoestrogen-rich foods can protect against a wide range of diseases, such as hormone-sensitive cancers, cardiovascular diseases, menopausal symptoms, osteoporosis, etc.[10–13] However, the evidence regarding the role of phytoestrogens in asthma and lung function is still limited. Animal models have shown that certain subtypes of phytoestrogens inhibit inflammation, hyperresponsiveness and remodelling of the airways.[14–17] Cardet *et al* reported that enterolactone was independently associated with a reduced risk of asthma and wheezing.[18] There was, however, no protective effect of three major types of dietary flavonoids (flavones, flavonols and total catechins) on asthma in a case–control study.[19] The results of a multicentre, randomised, double-blind, placebo-controlled trial indicated that soy isoflavone supplements (genistein, daidzein and glycitein) did not improve asthma symptoms or lung function in patients with poorly controlled asthma.[20] The effects of phytoestrogen exposure on lung function were not well assessed, especially in subgroups of individuals with asthma and those without asthma. Using a large sample of representative US civilians, we explored the association between phytoestrogens and asthma, wheezing, lung function and mortality, and examined the factors that may interact with the associations.

METHODS

Study design and participants

Using a complex, multistage probability cluster design, the National Health and Nutrition Examination Survey (NHANES) collects data from representative US civilians. This study included individuals aged 20 years or older from NHANES (2007–2010). All individuals included in the study completed the questionnaire, lung function test and urinary phytoestrogen test at the same time.

Urinary phytoestrogen measurement

The majority of phytoestrogens in the body are derived from food and diets in daily life, and they exist in the serum and urine after they have been metabolised. A specific detection process was followed: briefly, human urine samples were processed by enzymatic deconjugation of the glucuronidated, then they were filtered by size exclusion, separated by reverse phase high-performance liquid chromatography (HPLC), detected by atmospheric pressure photoionisation-tandem mass spectrometry (APPI-MS/MS) and quantified by isotope dilution. Subsequently, HPLC-APPI-MS/MS was used to quantitatively analyse phytoestrogen compounds, including genistein, daidzein, equol, o-desmethylangolensin, enterodiol and enterolactone. For each analyte, carbon-13-labelled internal standards were incorporated, as well as 4-methylumbelliferyl glucuronide and 4-methylumbelliferyl sulfate standards for monitoring deconjugation efficiency. This selective method allowed for rapidly detecting phytoestrogens in human urine with detection limits as low as parts per billion range (ng/mL).

Outcome measures

Asthma and wheeze

Current asthma was defined by affirmative answers to both of the following questions: (1) 'Has a doctor or other health professionals ever told you that you have asthma?' and (2) 'Do you still have asthma?'. Current wheeze was defined by an affirmative answer to the question 'In the past 12 months, have you had wheeze or whistling in your chest?'.

Lung function

A pre-bronchodilator spirometry measurement was performed in this study between 2007 and 2010. Lung function parameters in the present study included forced expiratory volume in 1 s (FEV_1) (L), forced vital capacity (FVC) (L) and FEV_1/FVC ratio. The procedures were developed based on the American Thoracic Society's (ATS) standards for lung function, equipment, testing and interpretation. The spirometry equipment met all of the ATS guidelines regarding accuracy and precision. The spirometers used in the study were Ohio 822/827 dry-rolling seal volume spirometers. A computerised algorithm was used to evaluate the spirometry results. Spirometry training was required for all health technologists at the National Institute for Occupational Safety and Health. There is a detailed description of spirometry methodology on the official website of the NHANES (wwwn.cdc.gov/Nchs/Nhanes/2009–2010/SPXRAW_F.htm).

All-cause mortality

All-cause mortality status and follow-up time for all individuals were retrieved from the National Death Index by 31 December 2019.

Covariates

In this study, baseline information was collected including age, gender, body mass index (BMI), race/ethnicity, educational level, poverty-to-income ratio (PIR), smoking status, serum cotinine, daily energy intake and urinary creatinine. BMI was calculated using the height and weight that were measured during the medical examination. In terms of race/ethnicity, Mexican Americans, other Hispanics, non-Hispanic white, non-Hispanic black and other races were categorised. The educational level was categorised as below high school, high school and above high school. Income status was classified into two levels of PIR: ≤1 or >1. Smoking status was characterised as never (smoked ≤100 cigarettes in lifetime), former (smoked >100 cigarettes in lifetime, but currently non-smoking) or current (smoked >100 cigarettes in lifetime and currently smoking). The extent of exposure to environmental tobacco smoke was determined by measuring serum cotinine levels. Daily energy intake was calculated

as the average energy intake of the first and second day of interview, otherwise it was the same value of the daily energy intake as one single day.

Statistical analyses

Continuous variables were presented as mean (SD), and categorical variables were presented as numbers (percentage). The Mann-Whitney U test and X^2 test were used to compare continuous and categorical variables between the groups of participants, respectively. ORs and 95% CIs were calculated in multivariate logistic regressions for the associations between quartiles of urinary phytoestrogens and the incidence of asthma/wheeze, with the lowest quartile as the reference group. Multivariate linear regressions were also performed to assess the associations between quartiles of urinary phytoestrogens and the FVC, FEV_1 and FEV_1/FVC in all included population, and in individuals with and without asthma/wheeze. HRs and 95% CIs were calculated in Cox proportional hazards regression for the associations of quartiles of urinary phytoestrogens and all-cause mortality in all included participants. According to previous research, factors associated with asthma/wheeze, lung function or urinary phytoestrogens were adjusted for in three adjustment models.[21–24] Model 1 was adjusted for age, gender and BMI. Model 2 was adjusted for age, gender, BMI and daily energy intake. A number of factors were taken into consideration when developing model 3, including age, gender, weight, BMI, race/ethnicity, educational level, PIR, serum cotinine, daily energy intake and urinary creatinine. Further stratified analyses were performed based on gender and smoking status in model 3. A two-tailed p value less than 0.05 was considered significant. The statistical analyses were conducted using SPSS V.25.0 and R V.3.6.1 software.

Patient and public involvement

Patients did not take part in the development, conduct, reporting or dissemination of this study.

RESULTS

Characteristics of study participants

A total of 2465 individuals were included in this study (online supplemental figure 1). There were 2288 participants in the non-asthma group (n=2288) and 177 participants in the asthma group (n=177). The asthma group was older (p=0.048) and had a higher BMI (p=0.001). Urinary creatinine was significantly lower in the asthma group (p=0.004). FVC, FEV_1 and FEV_1/FVC values were lower in the asthma group than the non-asthma group (all p<0.001). There were also significant differences in gender, race/ethnicity and smoking status between the two groups (all p<0.05). The characteristics of the included individuals are reported in detail in table 1.

Association between urinary phytoestrogens and asthma/wheeze

Figure 1 shows the associations between urinary phytoestrogens and asthma/wheeze. For asthma, compared with the lowest quartile of enterolactone, the highest quartile was associated with a lower risk of asthma (OR_{Q4vsQ1}: 0.53; 95% CI: 0.34, 0.84; p-trend=0.016 (model 1); OR_{Q4vsQ1}: 0.54; 95% CI: 0.34, 0.85; p-trend=0.021 (model 2); OR_{Q4vsQ1}: 0.58; 95% CI: 0.36, 0.93; p-trend=0.064 (model 3)). For wheeze, the highest quartile of enterodiol (OR_{Q4vsQ1}: 0.64; 95% CI: 0.46, 0.88; p-trend=0.014 (model 1); OR_{Q4vsQ1}: 0.64; 95% CI: 0.46, 0.88; p-trend=0.014 (model 2); OR_{Q4vsQ1}: 0.70; 95% CI: 0.49, 0.99; p-trend=0.073 (model 3)) or enterolactone (OR_{Q4vsQ1}: 0.49; 95% CI: 0.35, 0.68; p-trend<0.001 (model 1); OR_{Q4vsQ1}: 0.50; 95% CI: 0.36, 0.69; p-trend<0.001 (model 2); (OR_{Q4vsQ1}: 0.56; 95% CI: 0.39, 0.79; p-trend=0.001 (model 3) was associated with lower risk of wheeze, compared with the lowest quartile, respectively.

Association between urinary phytoestrogens and lung function

Figure 2 reports the results of the multivariate linear regression for the association between urinary phytoestrogens and lung function (FVC, FEV_1 and FEV_1/FVC ratio). Significant associations were observed between equol and enterolactone and both FVC and FEV_1, in all adjustment models. Additionally, in all adjustment models, individuals in higher enterodiol quartiles had higher FVC than those in the lowest quartile. There was a similar trend between enterodiol and FEV_1 in model 1 and model 2, but the association became insignificant in model 3. Furthermore, higher quartiles of enterolactone were significantly associated with higher FEV_1/FVC in model 1 and model 2, but not model 3.

Additionally, we examined the association between subtypes of phytoestrogens and lung function in individuals with and without asthma/wheezing. In individuals with current asthma or wheeze, no significant associations were observed between phytoestrogens and FVC and FEV_1 in all adjustment models. In all adjustment models, higher quartiles of enterodiol were associated with lower FEV_1/FVC in individuals with asthma. A significant association was observed between higher intake of phytoestrogens (equol, enterodiol and enterolactone) and higher FVC in individuals without asthma/wheezing. There was a significant association between higher intake of phytoestrogens (equol and enterolactone) and FEV_1. The results were consistent with those observed in all of the participants (online supplemental figures 2–4).

Urinary phytoestrogens and all-cause mortality

Online supplemental table 1 shows the results of the Cox proportion regression for the association between urinary phytoestrogens and all-cause mortality. The calculated HRs showed no association between urinary

Table 1 Baseline characteristics of included individuals in the National Health and Nutrition Examination Survey, 2007–2010

	Overall	Non-asthma	Asthma	P value
Sample size, n	2465	2288	177	–
Age, years	46.76 (16.2)	46.58 (16.17)	49.11 (16.44)	0.048
Body mass index, kg/m^2	29.29 (6.84)	29.06 (6.64)	32.2 (8.55)	<0.001
Gender, n (%)				<0.001
Female	1254 (50.87)	1136 (49.65)	118 (66.67)	
Male	1211 (49.13)	1152 (50.35)	59 (33.33)	
Race/ethnicity, n (%)				0.003
Mexican American	496 (20.12)	478 (20.89)	18 (10.17)	
Other Hispanics	238 (9.66)	218 (9.53)	20 (11.3)	
Non-Hispanic white	1176 (47.71)	1074 (46.94)	102 (57.63)	
Non-Hispanic black	446 (18.09)	413 (18.05)	33 (18.64)	
Other races	109 (4.42)	105 (4.59)	4 (2.26)	
Poverty-to-income ratio, n (%)				0.159
≤1	498 (20.2)	455 (19.89)	43 (24.29)	
>1	1967 (79.8)	1833 (80.11)	134 (75.71)	
Educational level, n (%)				0.886
Below high school	638 (25.88)	592 (25.87)	46 (25.99)	
High school	579 (23.49)	540 (23.6)	39 (22.03)	
Above high school	1248 (50.63)	1156 (50.52)	92 (51.98)	
Smoking status, n (%)				0.018
No	1293 (52.45)	1218 (53.23)	75 (42.37)	
Yes	1172 (47.55)	1070 (46.77)	102 (57.63)	
Serum cotinine, ng/mL	64.77 (138.08)	64.11 (137.82)	73.38 (141.46)	0.285
Urinary creatinine, mg/dL	123.06 (77.3)	123.9 (76.6)	112.28 (85.37)	0.004
Total energy intake, kcal/day	2082.03 (873.49)	2085.95 (876.2)	2031.4 (838.41)	0.275
FVC, L	3.83 (1.51)	3.85 (1.51)	3.49 (1.33)	<0.001
FEV_1, L	3.02 (1.19)	3.06 (1.2)	2.56 (1.14)	<0.001
FEV_1/FVC	0.79 (0.09)	0.8 (0.09)	0.75 (0.11)	<0.001

FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

phytoestrogens and all-cause mortality in all adjustment models.

Stratified analyses

Based on gender and smoking status, we conducted stratified analyses. A higher level of enterolactone was associated with a lower incidence of wheeze in males, but not in females. However, genistein, daidzein, equol and o-desmethylangolensin were positively associated with incidence of asthma in non-smokers, and o-desmethylangolensin was positively associated with the incidence of asthma in women, who were less likely to smoke (table 2). Besides, higher urinary equol was associated with higher FVC and FEV_1 in smokers as well as non-smokers, and the results were also consistent between genders. O-desmethylangolensin and enterolactone were positively associated with FVC and FEV_1 in females, while enterodiol was associated with increased FVC in males. Higher enterolactone was associated with increased values of FVC, FEV_1 and FEV_1/FVC in smokers, but not in non-smokers (table 3).

Online supplemental table 2 shows the association between urinary phytoestrogens and all-cause mortality. Based on the stratified analysis, no significant associations were found in different genders or smoking statuses, in accordance with the results of the primary analysis.

DISCUSSION

The findings of this population-based study provide new evidence regarding the relationship between subtypes of phytoestrogens and asthma/wheeze, lung function and all-cause mortality in US adults. There was a significant association between enterolactone and a decreased risk of asthma, while enterodiol and enterolactone were both associated with a decreased risk of wheezing. In addition, our results suggested that urinary equol, enterodiol and enterolactone were associated with improved FVC and

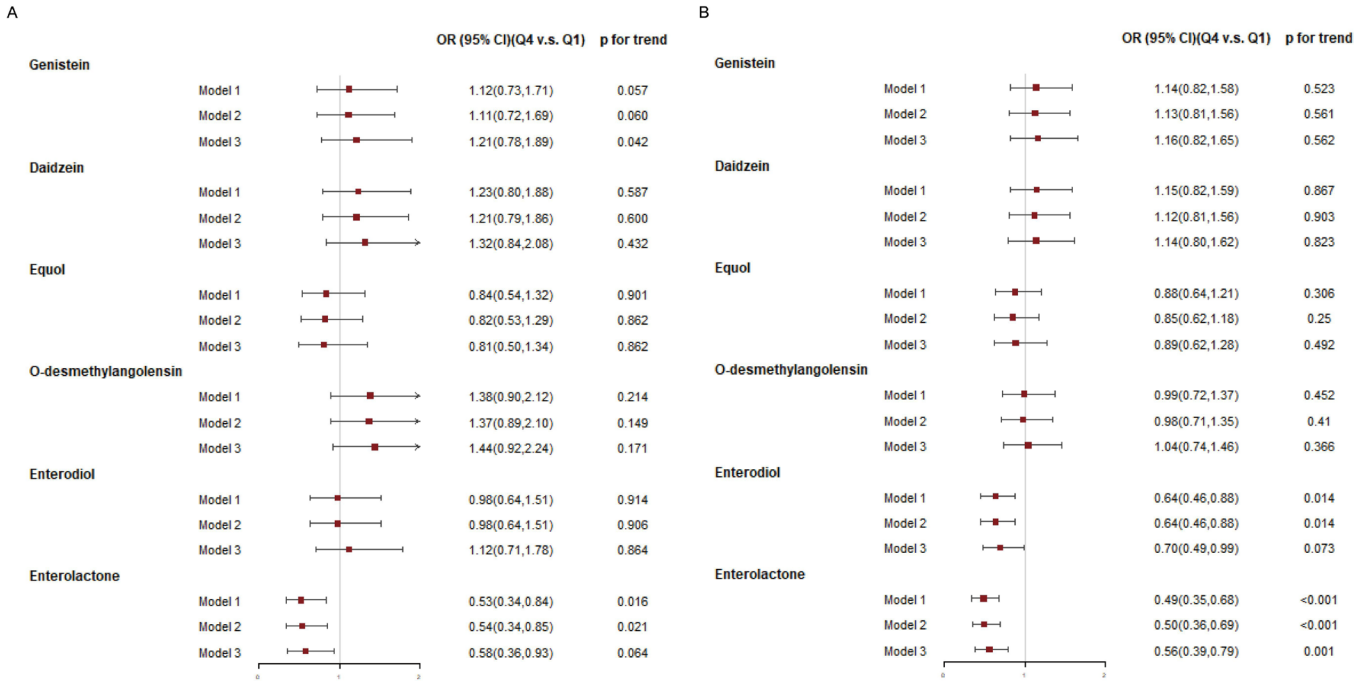

Figure 1 ORs of the association between urinary phytoestrogens and (A) asthma and (B) wheeze.

FEV_1 values in all included individuals and those without asthma/wheeze. However, phytoestrogens were not associated with FVC, FEV_1 or FEV_1/FVC in individuals with asthma/wheeze. This study did not find an association between urinary phytoestrogens and all-cause mortality.

There were some phytoestrogen subtypes associated with asthma/wheeze in this study, which was consistent with the results of the previous abstract published.[18] In addition, the present study added new evidence that urinary equol, enterodiol and enterolactone were associated with improved FVC and FEV_1 values in the US population. Of note, this study found that enterligans (eg, enterodiol and enterolactone) exerted a greater protective effect on asthma/wheeze and lung function than isoflavones, although the reason remained unclear.

Since lung function (FVC, FEV_1 and FEV_1/FVC) was significantly lower in patients with asthma than in individuals without asthma, we explored the relationship between phytoestrogens and lung function in individuals with and without asthma. Consequently, several subtypes of phytoestrogens (equol, enterodiol and enterolactone) were observed to play a role in lung function improvement in individuals without asthma/wheeze, but not in individuals with current asthma/wheeze. A study conducted in Japan suggested the significant positive association between dietary intake of total isoflavone, genistein and daidzein and lung function in individuals with and without chronic obstructive pulmonary disease.[25] However, another randomised controlled trial suggested the soy isoflavone supplement did not result in improved

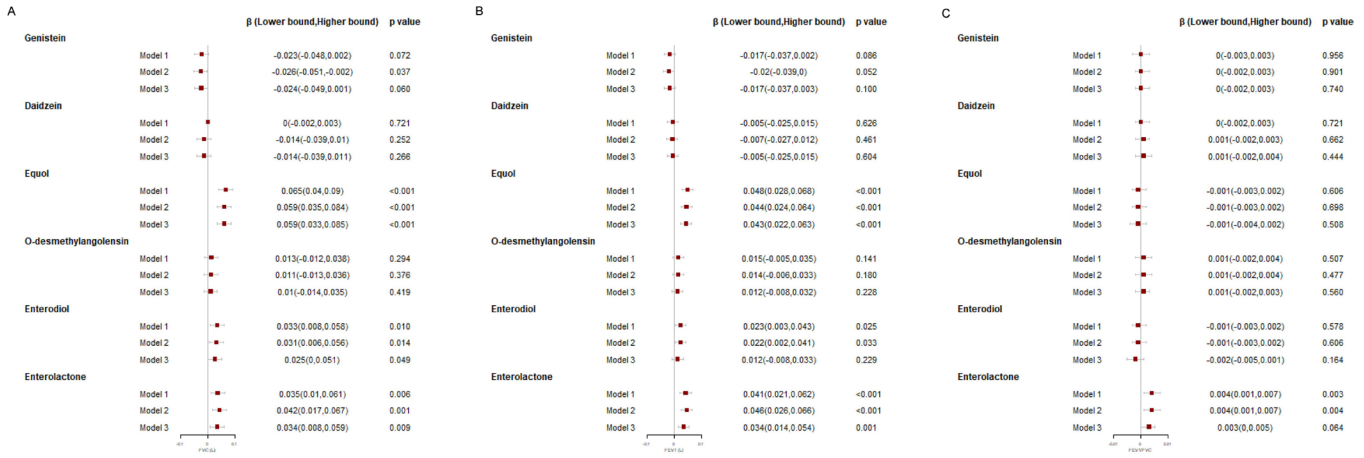

Figure 2 Linear regression for associations between urinary phytoestrogens and (A) FVC, (B) FEV_1 and (C) FEV_1/FVC. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

Table 2 Association between urinary phytoestrogens and asthma/wheeze in a subgroup population

	Female		Male		Non-smokers		Smokers	
	Asthma	Wheeze	Asthma	Wheeze	Asthma	Wheeze	Asthma	Wheeze
OR Q4 vs Q1 (95% CI)								
Genistein	1.56 (0.88, 2.74)	1.11 (0.69, 1.79)	0.76 (0.35, 1.63)	1.1 (0.66, 1.85)	2.22 (1.11, 4.42)	1.62 (0.91, 2.86)	0.75 (0.40, 1.39)	0.89 (0.57, 1.40)
Daidzein	1.34 (0.74, 2.42)	1.10 (0.67, 1.80)	1.19 (0.59, 2.40)	1.1 (0.66, 1.82)	2.6 (1.24, 5.42)	1.54 (0.87, 2.74)	0.80 (0.43, 1.48)	0.94 (0.60, 1.47)
Equol	0.67 (0.35, 1.29)	0.75 (0.44, 1.25)	1.04 (0.48, 2.27)	1.01 (0.59, 1.71)	2.6 (1.24, 5.42)	0.55 (0.30, 1.02)	0.71 (0.36, 1.40)	1.09 (0.68, 1.72)
O-desmethylangolensin	1.93 (1.08, 3.46)	1.21 (0.74, 1.98)	1.01 (0.49, 2.07)	0.85 (0.52, 1.4)	2.87 (1.37, 6.01)	1.00 (0.58, 1.73)	0.88 (0.49, 1.58)	1.13 (0.74, 1.74)
Enterodiol	1.21 (0.66, 2.20)	0.85 (0.52, 1.38)	0.91 (0.43, 1.95)	0.65 (0.39, 1.09)	0.75 (0.38, 1.51)	0.58 (0.32, 1.03)	1.36 (0.72, 2.58)	0.92 (0.59, 1.43)
Enterolactone	0.66 (0.36, 1.21)	0.88 (0.54, 1.41)	0.50 (0.23, 1.10)	0.33 (0.19, 0.58)	0.43 (0.21, 0.90)	0.67 (0.38, 1.18)	0.71 (0.37, 1.36)	0.51 (0.32, 0.80)

Adjusted for age, gender, body mass index, race/ethnicity, educational level, poverty-to-income ratio, serum cotinine, daily energy intake and urinary creatinine.

lung function in patients with asthma when compared with placebo.[20] Although there are numerous cofactors that cannot be ignored such as sample size, ethnic difference, dosage of phytoestrogens and subclasses of phytoestrogens, the results in this study, combined with the above evidence, might indicate that some subtypes of phytoestrogens would be protective factors for lung function decline in individuals without asthma/wheeze, but not able to be a suitable treatment for lung function improvement in current asthma or wheeze.

According to stratified analyses in this study, associations between phytoestrogens and lung function differed by gender. To be specific, positive associations were observed between o-desmethylangolensin, enterolactone and FVC and FEV_1 values in women, but not in men. Interestingly, the effects of phytoestrogens on lung carcinoma showed the same gender trend.[26 27] It has already been established that soybean consumption increases plasma oestradiol only in women.[28] However, it remains to be clarified why there is a significant association between some subtypes of phytoestrogens and lower risk of wheeze or improved lung function only in men, but not in women. Generally, the sex-specific analyses performed in this study were in agreement with the theory suggesting that phytoestrogens may be influenced by sex hormones. The study further demonstrated that sex may play an interactive role in phytoestrogen intake and human health. More research should be conducted to explore the dose-dependent effect of phytoestrogens on different genders.

The stratified analyses according to smoking showed enterolactone was also associated with higher FVC, FEV_1 and FEV_1/FVC values only in smokers. To our knowledge, smoking stimulates lung resident immune cells and proinflammatory mediator release, leading to enhanced neutrophil recruitment in the airways,[29] which relates to lung function decline.[30] Therefore, enterolactone was more effective at reducing inflammation in smokers. Interestingly, we found that the subtypes of isoflavones (eg, genistein, daidzein, equol, o-desmethylangolensin) were associated with higher risk of asthma in non-smokers. Phytoestrogen exposure in the first 6 months of life is discouraged in children with atopy or cow's milk allergy to prevent sensitisation.[31] In agreement with some evidence, soy protein products, which contain abundant phytoestrogens, may induce allergy as one of the allergens.[32] It is possible that the sensitising effect may prevail over the anti-inflammatory effect in non-smokers. In order to fully understand this issue, further research is required.

We have identified the following strengths in our study. First, this study adds new evidence regarding the relationship between subtypes of phytoestrogens and lung function in individuals with and without asthma/wheeze. Second, stratified analyses evaluated the role of gender and smoking in the relationship between phytoestrogens and the outcomes. Third, the urinary phytoestrogens were standardised and precise, and the urinary content

Table 3 Association between urinary phytoestrogens and lung function in a subgroup population

	Female			Male			Non-smokers			Smokers		
	FVC	FEV_1	FEV_1/FVC	FVC	FEV_1	FEV_1/FVC	FVC	FEV_1	FEV_1/FVC	FVC	FEV_1	FEV_1/FVC
	β coefficients (95% CI)			β coefficients (95% CI)			β coefficients (95% CI)			β coefficients (95% CI)		
Genistein	−0.02 (−0.049, 0.009)	−0.013 (−0.037, 0.01)	0.001 (−0.002, 0.005)	−0.028 (−0.069, 0.012)	−0.015 (−0.047, 0.017)	0.001 (−0.003, 0.005)	−0.028 (−0.062, 0.006)	−0.019 (−0.045, 0.008)	0.001 (−0.002, 0.004)	−0.024 (−0.061, 0.013)	−0.019 (−0.048, 0.011)	0 (−0.005, 0.004)
Daidzein	0.007 (−0.022, 0.036)	0.004 (−0.02, 0.027)	0 (−0.003, 0.003)	−0.033 (−0.074, 0.007)	−0.010 (−0.042, 0.022)	0.003 (−0.002, 0.007)	−0.014 (−0.048, 0.02)	−0.01 (−0.037, 0.016)	0 (−0.003, 0.003)	−0.017 (−0.053, 0.02)	−0.003 (−0.033, 0.027)	0.002 (−0.002, 0.006)
Equol	0.05 (0.019, 0.08)	0.038 (0.014, 0.063)	−0.001 (−0.004, 0.003)	0.074 (0.031, 0.116)	0.052 (0.019, 0.086)	−0.001 (−0.006, 0.003)	0.063 (0.028, 0.099)	0.047 (0.019, 0.075)	0 (−0.004, 0.003)	0.049 (0.011, 0.087)	0.035 (0.004, 0.065)	−0.001 (−0.006, 0.003)
O-desmethylangolensin	0.04 (0.011, 0.068)	0.027 (0.004, 0.05)	−0.001 (−0.005, 0.002)	−0.011 (−0.051, 0.030)	0.007 (−0.025, 0.039)	0.003 (−0.001, 0.007)	0.005 (−0.029, 0.038)	0.004 (−0.022, 0.03)	−0.001 (−0.004, 0.003)	0.016 (−0.02, 0.051)	0.021 (−0.008, 0.05)	0.002 (−0.002, 0.007)
Enterodiol	0.009 (−0.02, 0.039)	0.002 (−0.022, 0.026)	−0.003 (−0.007, 0)	0.045 (0.004, 0.087)	0.025 (−0.007, 0.058)	−0.001 (−0.005, 0.003)	0.007 (−0.027, 0.042)	−0.002 (−0.029, 0.025)	−0.002 (−0.006, 0.001)	0.034 (−0.003, 0.071)	0.013 (−0.017, 0.044)	−0.003 (−0.007, 0.002)
Enterolactone	0.055 (0.026, 0.084)	0.048 (0.024, 0.071)	0.001 (−0.002, 0.005)	0.020 (−0.021, 0.062)	0.032 (−0.001, 0.064)	0.004 (0, 0.009)	0.011 (−0.024, 0.045)	0.011 −0.016, 0.038)	0 (−0.003, 0.004)	0.061 (0.024, 0.098)	0.061 (0.031, 0.091)	0.005 (0.001, 0.01)

Adjusted for age, gender, body mass index, race/ethnicity, educational level, poverty-to-income ratio, serum cotinine, daily energy intake and urinary creatinine.

of conjugated metabolites may reflect the actual absorption of phytoestrogens.[9] Fourth, the analyses had been adjusted for potential confounding factors in different models, in order to ensure that the results were reliable.

This study also has several limitations. First, the causal relationship could not be accessed due to the cross-sectional design of this study. Second, NHANES database did not contain all types of urinary phytoestrogen content, so the dietary intake of total phytoestrogens for included participants could not be calculated. Third, the diagnosis of asthma and wheeze was self-reported; therefore, the possibility of reporting bias cannot be ruled out. Fourth, there is no detailed information in NHANES database on the association between phytoestrogens and respiratory-related or asthma-related mortality.

Conclusions

In this population-based study, we add new findings regarding the correlation between phytoestrogens and asthma/wheeze, lung function and all-cause mortality among US adults. It was found that enterolactone was associated with a significant reduction in asthma risk, while enterodiol and enterolactone were both associated with a decrease in wheezing risk. We further observed that urinary equol, enterodiol and enterolactone were associated with improved FVC and FEV_1 in individuals without asthma/wheeze. Furthermore, the associations between phytoestrogens and the outcome measures were inconsistent when stratified by gender and smoking. There was no association between urinary phytoestrogens and all-cause mortality in this study. Further research is required in order to confirm these results and explain the results of the subgroup analyses.

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REFERENCES

1 King-Biggs MB. Asthma. *Ann Intern Med* 2019;171:ITC49–64.
2 Centers for Disease Control and Prevention. n.d. Most recent asthma data. Available: www.cdc.gov/asthma/most_recent_data.htm
3 Alwarith J, Kahleova H, Crosby L, *et al*. The role of nutrition in asthma prevention and treatment. *Nutr Rev* 2020;78:928–38.
4 Hanson C, Lyden E, Furtado J, *et al*. Serum tocopherol levels and vitamin E intake are associated with lung function in the normative aging study. *Clin Nutr* 2016;35:169–74.
5 Cornwell T, Cohick W, Raskin I. Dietary Phytoestrogens and health. *Phytochemistry* 2004;65:995–1016.
6 Ionescu VS, Popa A, Alexandru A, *et al*. Dietary Phytoestrogens and their metabolites as epigenetic Modulators with impact on human health. *Antioxidants (Basel)* 2021;10:1893.
7 Křížová L, Dadáková K, Kašparovská J, *et al*. Isoflavones. *Molecules* 2019;24:1076.
8 Atkinson C, Frankenfeld CL, Lampe JW. Gut bacterial metabolism of the soy isoflavone daidzein: exploring the relevance to human health. *Exp Biol Med (Maywood)* 2005;230:155–70.
9 Lampe JW. Isoflavonoid and Lignan Phytoestrogens as dietary biomarkers. *J Nutr* 2003;133 Suppl 3:956S–964S.
10 Bennetau-Pelissero C. Risks and benefits of Phytoestrogens: where are we now *Curr Opin Clin Nutr Metab Care* 2016;19:477–83.
11 Patisaul HB, Jefferson W. The pros and cons of Phytoestrogens. *Front Neuroendocrinol* 2010;31:400–19.
12 Zaheer K, Humayoun Akhtar M. An updated review of dietary Isoflavones: nutrition, processing, Bioavailability and impacts on human health. *Crit Rev Food Sci Nutr* 2017;57:1280–93.
13 Reger MK, Zollinger TW, Liu Z, *et al*. Urinary Phytoestrogens and cancer, cardiovascular, and all-cause mortality in the continuous national health and nutrition examination survey. *Eur J Nutr* 2016;55:1029–40.
14 Regal JF, Fraser DG, Weeks CE, *et al*. Dietary Phytoestrogens have anti-inflammatory activity in a guinea pig model of asthma. *Proc Soc Exp Biol Med* 2000;223:372–8.
15 Duan W, Kuo IC, Selvarajan S, *et al*. Antiinflammatory effects of Genistein, a tyrosine kinase inhibitor, on a guinea pig model of asthma. *Am J Respir Crit Care Med* 2003;167:185–92.
16 Bao Z-S, Hong L, Guan Y, *et al*. Inhibition of airway inflammation, Hyperresponsiveness and remodeling by soy isoflavone in a murine model of allergic asthma. *Int Immunopharmacol* 2011;11:899–906.
17 Solopov P, Colunga Biancatelli RML, Dimitropoulou C, *et al*. Dietary Phytoestrogens ameliorate Hydrochloric acid-induced chronic lung injury and pulmonary fibrosis in mice. *Nutrients* 2021;13:3599.
18 Cardet JC, Johns CB, Savage JH. Bacterial metabolites of diet-derived Lignans and Isoflavones inversely associate with asthma and wheezing. *J Allergy Clin Immunol* 2015;135:267–9.
19 Garcia V, Arts ICW, Sterne JAC, *et al*. Dietary intake of flavonoids and asthma in adults. *Eur Respir J* 2005;26:449–52.
20 Smith LJ, Kalhan R, Wise RA, *et al*. Effect of a soy isoflavone supplement on lung function and clinical outcomes in patients

with poorly controlled asthma: a randomized clinical trial. *JAMA* 2015;313:2033–43.
21 Chu LM, Pahwa P. Prevalence and associated factors for self-reported asthma in a Canadian population: the Canadian community health survey, 2014. *J Asthma* 2018;55:26–34.
22 Reyes Noriega N, Del-Río-Navarro BE, Berber A, *et al*. Effect of obesity on lung function in the pediatric and adult populations with asthma. *J Clin Med* 2023;12:5385.
23 Barr DB, Wilder LC, Caudill SP, *et al*. Urinary creatinine concentrations in the U.S. population: implications for urinary biologic monitoring measurements. *Environ Health Perspect* 2005;113:192–200.
24 Butland BK, Fehily AM, Elwood PC. Diet, lung function, and lung function decline in a cohort of 2512 middle aged men. *Thorax* 2000;55:102–8.
25 Hirayama F, Lee AH, Binns CW, *et al*. Dietary intake of Isoflavones and polyunsaturated fatty acids associated with lung function, Breathlessness and the prevalence of chronic obstructive pulmonary disease: possible protective effect of traditional Japanese diet. *Mol Nutr Food Res* 2010;54:909–17.
26 Grosso G, Godos J, Lamuela-Raventos R, *et al*. A comprehensive meta-analysis on dietary Flavonoid and Lignan intake and cancer risk: level of evidence and limitations. *Mol Nutr Food Res* 2017;61.
27 Wang Q, Ru M, Zhang Y, *et al*. Dietary Phytoestrogen intake and lung cancer risk: an analysis of the prostate, lung, colorectal and ovarian (PLCO) cancer screening trial. *Carcinogenesis* 2021;42:1250–9.
28 Ostatníková D, Celec P, Hodosy J, *et al*. Short-term soybean intake and its effect on steroid sex hormones and cognitive abilities. *Fertil Steril* 2007;88:1632–6.
29 Blidberg K, Palmberg L, Dahlén B, *et al*. Increased neutrophil migration in Smokers with or without chronic obstructive pulmonary disease. *Respirology* 2012;17:854–60.
30 Pouwels SD, van Geffen WH, Jonker MR, *et al*. Increased neutrophil expression of pattern recognition receptors during COPD exacerbations. *Respirology* 2017;22:401–4.
31 British Dietetic Association. Paediatric group position statement on the use of soya protein for infants. *J Fam Health Care* 2003;13:93.
32 Savage JH, Kaeding AJ, Matsui EC, *et al*. The natural history of soy allergy. *J Allergy Clin Immunol* 2010;125:683–6.