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# Urinary enterolignan concentrations and cardiometabolic risk biomarkers in pregnant US women

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## Abstract

**Objective** Prior evidence suggests that dietary lignans may mitigate inflammation, attenuate insulin resistance, and improve blood lipids. Little is known about the effects of lignans in pregnant women who are at elevated risk of glucose and lipid abnormalities, partially due to increase in estrogen levels during pregnancy. This study was designed to investigate the association between dietary lignan intake, measured as urinary enterolignans (enterodiol and enterolactone), with blood biomarkers of cardiometabolic risks in pregnant women.

**Research design and methods** We analyzed data from 480 pregnant women who participated in the National Health and Nutrition Examination Survey (NHANES) 1999–2010 and had data for urinary enterolignan concentrations. Multivariable linear regression analyses were used to examine the association between urinary enterolignan concentrations and cardiometabolic risk biomarkers. Cardiometabolic risk markers were log-transformed and geometric means were calculated by quartiles of urinary enterolignan concentrations.

**Results** Higher urinary enterolignan concentrations were associated with a more beneficial cardiometabolic profile: comparing women in the highest versus lowest quartiles of total enterolignan concentrations, high-density lipoprotein cholesterol (HDL-C) was 62 versus 54 mg/dL (P for trend = 0.01); triacylglycerol (TG) was 141 versus 171 mg/dL (P for trend = 0.004); TG/HDL-C ratio was 2.3 versus 3.2 (P for trend = 0.001); Total cholesterol (TC)/HDL-C ratio was 3.4 versus 3.9 (P for trend = 0.03); C-reactive protein (CRP) was 0.4 versus 0.7 mg/dL (P for trend = 0.01); and fasting insulin was 7.7 versus 13.9 μU/mL (P for trend < 0.0001).

**Conclusions** Lignan intake may have favorable effects on cardiometabolic risk markers in pregnant women.

***Key Messages*** The results of our study showed that urinary excretion of enterolignans were inversely associated with cardiometabolic risk markers in pregnant women. These findings support further investigation on the role of lignans in modifying lipid and glucose metabolism. Given the high prevalence of maternal insulin resistance and hyperlipidemia and its serious health consequences for both women and their offspring, the use of lignans, if demonstrated to be efficacious, could provide a cost-effective option for curbing this epidemic by prevention and early treatment.

**Keywords** Lignan, Pregnancy, Cardiovascular disease, Metabolic risk, Biomarkers

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## Introduction

Carbohydrate and lipid metabolism progressively deteriorates during pregnancy. While the exact mechanisms are not fully understood, evidence suggests that the elevated estrogen levels during pregnancy are partially responsible for maternal insulin resistance and hypertriglyceridemia [1]. Abnormal glucose and lipid levels during pregnancy are associated with adverse maternal and neonatal outcomes, as well as increased risk of subsequent obesity and glucose intolerance [2]. Therefore, it is important to develop effective strategies for prevention and early treatment of these disorders.

Phytoestrogens, primarily isoflavones and lignans, have received considerable attention for their potential hypocholesterolemic and hypoglycemic effects [3–5]. Lignans are abundant in flax seeds, sesame seeds, whole grains, and cruciferous vegetables [6]. When ingested, plant lignan secoisolariciresinol diglucoside (SDG) first undergoes hydrolysis by microbial enzymes to produce the aglycone secoisolariciresinol (SECO) and then is demethylated and dehydroxylated by intestinal microbiota to form enterolignans (also known as mammalian lignans), primarily enterolactone and enterodiol. These metabolites can mimic or modulate the action of endogenous estrogens. Evidence from human observational studies and a limited number of randomized trials suggests that lignans may mitigate inflammation, attenuate insulin resistance, and improve blood lipids [7–12]. However, most of the available data focus on postmenopausal women or individuals with existing cardiometabolic disorders. There is a lack of research on pregnant women, who have elevated estrogen levels- and may thus particularly benefit from lignan intake [13].

The aim of this study was to investigate the association between urinary enterolignans (enterodiol and enterolactone) with blood biomarkers of cardiometabolic risks in pregnant women. It was hypothesized that urinary enterolignan concentrations are inversely associated with fasting glucose, insulin, and lipid levels during pregnancy.

## Participants and methods

### *Study population*

The National Health and Nutrition Examination Survey (NHANES) is a cross-sectional study using questionnaires, physical and laboratory examinations to examine the health and nutritional status of the civilian, non-institutionalized U.S. population. A complex, multi-staged, stratified, clustered sampling method is employed, with oversampling of adolescents, elderly, African- Americans and Mexican- Americans [14].

In the current study, we used data from six NHANES surveys; 1999–2000, 2001–2002, 2003–2004, 2005–2006, 2007–2008, and 2009–2010 in which urinary concentrations of lignans were measured. We restricted our analysis to pregnant women with valid urinary lignan concentrations, excluding those with diabetes, hypertension, or who were taking insulin or diabetic medications at the time of the survey ($n = 480$). The sample sizes differed across cardiometabolic risk biomarkers: $n = 449$ for total cholesterol (TC), $n = 186$ for low-density lipoprotein cholesterol (LDL-C), $n = 458$ for high-density lipoprotein cholesterol (HDL-C), $n = 205$ for triacylglycerol (TG) and TG/HDL-C ratio, $n = 449$ for TC/HDL-C ratio, $n = 450$ for C-reactive protein (CRP), $n = 207$ for fasting glucose, and $n = 205$ for fasting insulin.

### Measurements

Interviewer-administered survey was used to collect demographic data. Age, race/ethnicity, education, pregnancy trimester, alcohol use, cigarette smoking, and physical activity were self-reported during in-person interviews. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Mexican–American, other Hispanic ethnicity, and other races/ethnicities. Education was categorized as less than high school graduate, high school graduate, and college or above. Smoking status was categorized as current smokers or not. Alcohol use was assessed based on the average number of alcoholic drinks consumed per day in the past 12 months, and categorized as non-user, 1–2 drinks per day, and 3 or more drinks per day. Moderate-to-vigorous physical activity (MVPA) was defined as having moderate or vigorous physical activities for at least 10 min over past 30 days.

Dietary intake of variety foods was assessed by using a self-administered food frequency questionnaire (FFQ), which inquires about frequency of food consumption during the past year. Daily food frequency estimates were calculated using the Diet*Calc software [15].

Physical examination including weight, height, waist circumference, and blood pressure measurements was performed following standard protocol (CDC, 2024). Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters ($kg/m^2$).

Blood samples and spot urine samples were collected in the NHANES mobile examination centers (MEC). Urinary excretion of enterolignans were measured by high performance liquid chromatography—atmospheric pressure chemical ionization- tandem mass spectrometry (HPLC-APCI-MS) for NHANES 1999–2002, HPLC- Electrospray Ionization MS (ESI) for NHANES 2003–2004 and HPLC- atmospheric pressure photoionization (APPI)-MS/MS for NHANES 2005–2010. The three methods showed comparable accuracy and strong correlation in quantification of urinary lignans [16]. Total enterolignans included enterodiol and enterolactone.

The concentrations of enterolignans were adjusted for urinary creatinine to account for variability in urine dilution and were expressed in μg/g creatinine (CDC, 2024). Pregnancy tests were conducted using the Icon 25 human chorionic gonadotropin (hCG) test kit (Beckman Coulter) to detect change in hCG in urine or serum. Female participants aged 12–59 years and menstruating females aged 8–11 years received pregnancy testing. Homeostatic model assessment (HOMA) of β-cell function and insulin resistance (IR) was estimated using the original HOMA1 model which is equal to (fasting plasma insulin concentration in mU/L x fasting plasma glucose in mmol/L)/22.5 [17].

### Statistical analysis

The sampling weight and complex sampling design of NHANES were taken into account in statistical analyses. For descriptive analyses, arithmetic mean and weighted standard error (SE) were reported for continuous variables, while counts and weighted percentages were presented for categorical variables. As concentrations of urinary enterolignans and cardiometabolic risk biomarkers were skewed distributed, weighted medians and 95% confidence intervals (CIs) were used to describe their distributions. Sample-weighted partial Pearson correlation coefficients were calculated to assess the correlation between food group consumption and urinary enterolignan excretion.

Multivariable linear regression models were used to examine the associations between cardiometabolic risk biomarkers and urinary excretion of enterolignans, adjusted for age, education, race/ethnicity, pregnancy trimester, alcohol drinking, cigarette smoking, and engaging in MVPA. Sensitivity analyses were conducted with further adjustment for BMI during pregnancy. Cardiometabolic risk biomarkers were log- transformed to normalize the distribution of the biomarkers. Geometric means and 95% CI for cardiometabolic risk biomarkers were estimated based on the least square means by quartiles of urinary enterolignan excretion. The P for trend was tested by modeling the median values of the quartiles of urinary lignan concentrations as a continuous variable. All analyses were performed using SAS software (version 9.4; SAS Institute Inc., Cary, NC).

## Results

The mean age of the participants was 28 ± 0.5 (range: 15, 56) y (Table 1). The majority were non-Hispanic white (51.7%). Nearly one-third of the participants were in the second trimester (30.3%) or the third trimester of pregnancy (29.9%).

The weighted median of urinary enterolignans was 424 (95% CI: 368, 479) μg/g creatinine. The weighted median concentrations of enterodiol and enterolactone were 48 μg/g creatinine (95% CI: 33, 63) and 354 μg/g creatinine (95% CI: 277, 432), respectively. The weighted median values of cardiometabolic risk biomarkers were 207 mg/dL (95% CI: 197, 216) for TC; 97 mg/dL (95% CI: 92, 102) for LDL-C; 55 mg/dL (95% CI: 53, 56) for HDL-C; 154 mg/dL (95% CI: 140, 167) for TG; 2.8 (95% CI: 2.5, 3.1) for TG/HDL-C ratio; 3.5 (95% CI: 3.3, 3.7) for TC/HDL-C ratio; 0.49 mg/dL (95% CI: 0.41, 0.57) for CRP; 86 mg/dL (95% CI: 84, 88) for fasting glucose; 9.9 μU/mL (95% CI: 8.1, 11.8) for fasting insulin; and 2.1 (95% CI: 1.8, 2.5) for HOMA-IR.

Urinary excretion of enterolignans varied by participants' sociodemographic characteristics (Table 2). Non-Hispanic White participants and regular alcohol drinkers had higher concentrations of total lignans. Additionally, participants with college and above education and those engaged in MVPA exhibited higher concentrations of enterodiol.

**Table 1** Characteristics of participants ($n = 480^a$)

| Characteristics | Mean ± SE[b](n, %) |
|---|---|
| Age (y) | 28 ± 0.5 |
| BMI (kg/m$^2$) | 28.5 ± 0.5 |
| Race/ethnicity | |
| Non-Hispanic white | 203 (51.7) |
| Non-Hispanic black | 69 (13.7) |
| Mexican American | 153 (18.6) |
| Other Hispanic ethnicity | 23 (7.3) |
| Other race/ethnicity | 32 (8.7) |
| Education | |
| Less than high school graduate | 108 (17.0) |
| High school graduate | 91 (17.4) |
| College and above | 218 (59.4) |
| Unknown | 63 (7.2) |
| Pregnancy trimester | |
| 1$^{st}$ | 79 (17.0) |
| 2$^{nd}$ | 167 (30.3) |
| 3$^{rd}$ | 154 (29.9) |
| Unknown | 80 (22.8) |
| Current smoker | 36 (6.3) |
| Alcohol use in the past year | |
| Non-drinkers | 267 (49.9) |
| 1–2 drinks/day | 143 (36.6) |
| 3 + drinks/day | 70 (13.5) |
| MVPA [c] | 242 (59.6) |

[a] Unweighted number of participants

[b] Values are mean ± weighted standard error for continuous variables and n (%) for categorical variables; n is the actual number of subjects and % is weighted percentage

[c] MVPA: Moderate to vigorous physical activity

**Table 2** Urinary lignan concentrations (μg/g creatinine): geometric mean and 95% CI

| Characteristics | Lignans | | Enterodiol | | Enterolactone | |
|---|---|---|---|---|---|---|
| | Geometric mean (95% CI) | *P* value | Geometric mean (95% CI) | *P* value | Geometric mean (95% CI) | *P* value |
| Age (y) | | 0.06 | | 0.23 | | 0.07 |
| < 20 | 214.7 (200.0, 230.5) | | 20.9 (19.3, 22.5) | | 179.4 (162.6,198.0) | |
| 20–34 | 381.1 (317.4, 457.5) | | 43.2 (34.2, 54.5) | | 256.8 (206.5, 319.4) | |
| 35–59 | 584.7 (473.4, 722.1) | | 81.4 (72.4, 91.4) | | 464.4 (362.3, 595.2) | |
| Race/ethnicity | | 0.0001 | | 0.001 | | 0.001 |
| Non-Hispanic white | 467.8 (382.2, 572.6) | | 50.0 (38.0, 65.8) | | 363.7 (289.2, 457.3) | |
| Non-Hispanic black | 240.8 (193.7, 299.3) | | 32.0 (20.3, 50.5) | | 114.0 (84.4, 153.9) | |
| Mexican American | 464.0 (376.3, 572.1) | | 54.5 (42.2, 70.5) | | 318.0 (250.3, 403.8) | |
| Other Hispanic ethnicity | 214.8 (201.8, 228.6) | | 25.5 (17.0, 38.4) | | 160.8 (148.1, 174.6) | |
| Other race/ethnicity | 367.5 (350.3, 385.6) | | 54.7 (50.8, 58.9) | | 272.1 (257.1, 287.9) | |
| Education | | 0.17 | | 0.02 | | 0.71 |
| Less than high school graduate | 407.8 (347.0, 479.3) | | 34.8 (28.2, 42.9) | | 334.0 (279.2, 399.6) | |
| High school graduate | 365.6 (276.8, 482.9) | | 40.5 (28.3, 57.9) | | 224.3 (127.0, 396.3) | |
| College and above | 429.9 (326.7, 565.6) | | 57.0 (42.3, 76.7) | | 295.0 (218.2, 398.9) | |
| Pregnancy trimester | | 0.15 | | 0.69 | | 0.18 |
| 1st | 324.4 (237.9, 442.5) | | 35.0 (24.1, 50.7) | | 216.0 (162.2, 287.7) | |
| 2nd | 558.0 (404.4, 769.8) | | 49.0 (32.4, 74.3) | | 442.3 (312.3, 626.4) | |
| 3rd | 280.4 (240.4, 327.1) | | 44.8 (34.1, 58.9) | | 165.4 (118.9, 230.0) | |
| Current smoker | | 0.25 | | 0.73 | | 0.49 |
| Yes | 248.2 (175.9, 350.3) | | 43.4 (27.0, 69.8) | | 182.5 (130.7, 254.8) | |
| No | 407.0 (327.6, 505.7) | | 46.0 (35.6, 59.5) | | 285.9 (221.7, 368.6) | |
| Alcohol use in the past year | | 0.05 | | 0.01 | | 0.14 |
| Non-drinkers | 337.6 (265.0, 430.1) | | 33.9 (26.1, 44.2) | | 263.6 (202.2, 343.6) | |
| 1–2 drinks/day | 470.3 (347.0, 637.3) | | 61.9 (44.1, 87.0) | | 298.3 (195.5, 455.3) | |
| 3 + drinks/day | 436.4 (358.2, 531.7) | | 61.7 (39.4, 96.8) | | 279.1(224.4, 347.2) | |
| MVPA[a] | | 0.10 | | 0.02 | | 0.09 |
| Yes | 408.2 (324.2, 514.0) | | 53.6 (41.7, 68.7) | | 298.2 (230.7, 385.5) | |
| No | 375.3 (305.7, 460.7) | | 36.5 (26.7, 49.9) | | 250.5 (180.5, 347.7) | |

[a] MVPA: Moderate to vigorous physical activity

Urinary enterolignan concentrations were positively associated with the frequency of vegetable consumption ($r = 0.16$, $p = 0.05$), dairy products ($r = 0.20$, $p = 0.02$), and soy foods ($r = 0.21$, $p = 0.01$), and negatively associated with the consumption of sugar-sweetened beverages ($r = -0.25$, $p = 0.002$).

Table 3 presents the multivariable-adjusted geometric means for cardiometabolic risk markers by quartiles of urinary excretion of enterolignans. There was a significant, inverse relationship between concentrations of urinary enterolignans and cardiometabolic risk markers, after adjusting for potential confounders. Comparing women in the highest versus lowest quartiles of total enterolignan excretion, HDL-C was 62 versus 54 mg/dL; TG was 141 versus 171 mg/dL; TG/HDL-C ratio was 2.3 versus 3.2; TC/HDL-C ratio was 3.4 versus 3.9; CRP was 0.4 versus 0.7 mg/dL; fasting insulin was 7.7 versus 13.9 μU/mL; and HOMA-IR was 1.6 versus 2.9.

The concentrations of individual lignan metabolites were also significantly associated with some cardiometabolic risk markers. Higher enterodiol concentrations were associated with lower LDL-C, TC/HDL-C ratio, fasting insulin and HOMA-IR. Higher enterolactone concentrations were associated with higher HDL-C, and lower TG, TG/HDL-C ratio, CRP, fasting insulin and HOMA-IR.

## Discussion

In this cross-sectional study using data from the NHANES 1999–2010, we found a significant, inverse association between urinary excretion of enterolignans and cardiometabolic risk biomarkers in pregnant women, suggesting favorable effects of lignan intake, absorption,

**Table 3** Multivariable-adjusted [a] geometric means of cardiometabolic risk biomarkers by urinary concentrations of enterolignans (μg/g creatinine)

| | Quartiles of urinary enterolignans | | | | P for trend |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| **Total lignans** | | | | | |
| TC (mg/dL) | 207 (200, 216) | 213 (205, 222) | 203 (193, 215) | 210 (200, 220) | 0.99 |
| LDL-C (mg/dL) | 120 (109,133) | 113 (99,128) | 97 (86,109) | 104 (94,115) | 0.09 |
| HDL-C(mg/dL) | 54 (51, 57) | 56 (52, 60) | 60 (56, 63) | 62 (58, 65) | 0.01 |
| TG (mg/dL) | 171 (151, 195) | 179 (163, 196) | 174 (153,197) | 141 (126,157) | 0.004 |
| TG/HDL-C ratio | 3.2 (2.7, 3.8) | 3.2 (2.8, 3.7) | 3.1 (2.7, 3.5) | 2.3 (2.0, 2.7) | 0.001 |
| TC/HDL-C ratio | 3.9 (3.6, 4.1) | 3.8 (3.5, 4.2) | 3.4 (3.2, 3.6) | 3.4 (3.1, 3.7) | 0.03 |
| CRP (mg/dL) | 0.7 (0.5, 0.9) | 0.5 (0.4, 0.6) | 0.4 (0.3, 0.6) | 0.4 (0.3, 0.5) | 0.01 |
| Fasting glucose (mg/dL) | 85.6 (81.0, 90.4) | 84.8 (81.2, 88.5) | 86.1 (83.0, 89.4) | 82.8 (80.6, 85.0) | 0.19 |
| Fasting insulin (μU/mL) | 13.9 (10.7, 18.0) | 12.7 (10.0, 16.2) | 14.9 (10.1, 22.1) | 7.7 (6.2, 9.5) | < 0.0001 |
| HOMA-IR | 2.9 (2.2, 4.0) | 2.7 (2.1, 3.5) | 3.2 (2.1, 4.8) | 1.6 (1.2, 2.0) | 0.0001 |
| **Enterodiol** | | | | | |
| TC (mg/dL) | 211 (202, 219) | 210 (201, 221) | 210 (201, 218) | 203 (193, 213) | 0.22 |
| LDL-C (mg/dL) | 117 (103, 133) | 111 (100, 124) | 112 (102, 124) | 97 (86, 109) | 0.04 |
| HDL-C(mg/dL) | 57 (52, 62) | 54 (50, 57) | 60 (57, 64) | 60 (56, 64) | 0.09 |
| TG (mg/dL) | 159 (133, 190) | 167 (150, 186) | 165 (146, 187) | 160 (145,177) | 0.73 |
| TG/HDL-C ratio | 3.1 (2.4, 4.0) | 3.0 (2.6, 3.4) | 2.9 (2.5, 3.3) | 2.7 (2.4, 3.1) | 0.22 |
| TC/HDL-C ratio | 3.7 (3.4, 4.1) | 3.9 (3.6, 4.3) | 3.5 (3.2, 3.8) | 3.4 (3.1, 3.6) | 0.02 |
| CRP (mg/dL) | 0.4 (0.3, 0.7) | 0.6 (0.5, 0.8) | 0.5 (0.3, 0.6) | 0.4 (0.3, 0.5) | 0.09 |
| Fasting glucose (mg/dL) | 84.4 (81.4, 87.6) | 86.0 (83.4, 88.8) | 86.8 (83.6, 90.1) | 82.6 (79.3, 86.0) | 0.17 |
| Fasting insulin (μU/mL) | 11.8 (9.0,15.5) | 16.1 (11.7, 22.3) | 12.0 (9.2, 15.7) | 8.7 (7.0, 10.9) | 0.01 |
| HOMA-IR | 2.5 (1.8, 3.3) | 3.4 (2.4, 4.8) | 2.6 (1.9, 3.5) | 1.8 (1.4, 2.3) | 0.01 |
| **Enterolactone** | | | | | |
| TC (mg/dL) | 206 (199, 213) | 210 (199, 221) | 207 (197, 218) | 210 (200, 221) | 0.63 |
| LDL-C (mg/dL) | 117 (104, 131) | 98 (84, 114) | 108 (97, 119) | 104 (93, 115) | 0.34 |
| HDL-C(mg/dL) | 55 (52, 59) | 55 (51, 59) | 59 (54.6, 62.6) | 62 (58, 66) | 0.01 |
| TG (mg/dL) | 177 (156, 202) | 180 (163,198) | 161 (141, 183) | 143 (129, 160) | 0.004 |
| TG/HDL-C ratio | 3.3 (2.8, 3.9) | 3.2 (2.8, 3.7) | 2.9 (2.5, 3.4) | 2.3 (2.0, 2.6) | 0.0002 |

**Table 3** (continued)

| | Quartiles of urinary enterolignans | | | | P for trend |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | |
| TC/HDL-C ratio | 3.7 (3.4, 4.0) | 3.8 (3.4, 4.2) | 3.5 (3.3, 3.8) | 3.4 (3.1, 3.7) | 0.08 |
| CRP (mg/dL) | 0.6 (0.5, 0.8) | 0.5 (0.4, 0.7) | 0.4 (0.3, 0.6) | 0.3 (0.3, 0.5) | 0.01 |
| Fasting glucose (mg/dL) | 84.3 (80.1, 88.7) | 87.4 (84.1, 90.8) | 85.1 (82.1, 88.3) | 83.0 (80.7, 85.4) | 0.25 |
| Fasting insulin (μU/mL) | 13.2 (10.2, 17.0) | 13.5 (10.9, 16.7) | 15.4 (10.2, 23.3) | 7.4 (6.0, 9.2) | 0.0001 |
| HOMA-IR | 2.8 (2.1, 3.7) | 2.9 (2.3, 3.7) | 3.2 (2.1, 5.0) | 1.5 (1.2, 1.9) | 0.0002 |

[a] Adjusted for age (year), race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, other Hispanic ethnicity, and other race/ethnicity), education (less than high school, high school graduate, college and above, unknown), pregnancy trimester (1–3 trimester or unknown), current smoker (yes, no), alcohol use (non-user, 1–2 drinks/day, 3 + drinks/day), engaging in moderate to vigorous physical activity (yes, no)

and microbial metabolic capacity on lipid and glucose metabolism during pregnancy. The associations remained significant after adjustment for potential confounders. Sensitivity analyses were performed by adding concurrent BMI into the model. The results remained largely the same: HDL-C, TG, TG/HDL-C ratio, TC/HDL-C ratio, fasting insulin and HOMA-IR remained significantly associated with total enterolignans and enterolactone, although the statistical significance decreased. Higher insulin concentrations and similar glucose concentrations, as reflected in higher HOMA-IR values, in the low enterolignan group suggest moderate insulin resistance. The lower HDL-C and higher TG concentrations are consistent with the clinical manifestation of insulin resistance and elevated cardiometabolic risk seen in non-pregnant individuals.

The associations between LDL-C and HOMA-IR with enterodiol were not statistically significant after adjustment for BMI (p for trend = 0.11 and 0.07, respectively); however, the decreasing trend remained similar. The loss of statistical significance may be attributed to the reduced statistical power when including more covariates in the model. Another plausible rationale for this finding is that, as revealed in previous studies, enterolignan concentrations are associated with less weight gain in women [18, 19], and BMI may serve as a mediator between lignans and cardiometabolic risk biomarkers; therefore, inclusion of concurrent BMI during pregnancy as a covariate in the model might be an over-adjustment.

To date, the beneficial effects of lignans on lipid and glucose metabolism have been observed in animal experiments, human observational studies, and randomized controlled trials [8, 11, 18–24]. However, the vast majority of existing epidemiologic data was collected among post-menopausal women or patients with existing cardiometabolic disorders at baseline. Only a limited number of studies have been conducted in the general population. A 10-year follow-up data from the Nurses' Health Study showed enterolignans were associated with lower BMI at baseline and slower weight gain in US women [18]. In a male Finnish population, who traditionally consume a high lignan diet, serum concentrations of enterolactone were significantly associated with a lower risk of developing myocardial infarction, chest pain and cardiovascular disease-related death: the odds ratios (ORs; 95% CIs) comparing extreme quartiles were 0.35 (0.14, 0.88) and 0.44 (0.20, 0.96), respectively [22, 25]. Using NHANES data, Eichholzer and colleagues found that higher excretion of lignans was associated with lower inflammatory markers including CRP concentrations and white blood cell counts [26]. In a cohort study of US men and women in the Nurses' Health Study and Health Professionals Follow-Up Study, higher lignan intake was found to be inversely associated with incidence of type 2 diabetes [11]. Overall, these studies provided promising evidence on the effects of lignans on reducing cardiometabolic risks.

Several potential mechanisms have been proposed by which lignans may improve lipid and glucose metabolism. Enterolignans have antioxidant effects. Lignans are converted to enterolignans in the colon through a series of reactions by the gut microbiota, including hydrolysis of glucoside, demethylation, dehydroxylation, and oxidation. Several human and animal feeding studies have shown that a portion of ingested plant lignans is absorbed [27, 28]. The peak serum and urinary concentrations of enterodiol and enterolactone occur after the peak serum concentration of SDG, reflecting a time-dependent sequence consistent with the precursor–product relationship [29]. Multiple in vivo

and in vitro studies have demonstrated the antioxidant effects of enterolignans, including inhibition of lipid peroxidation [30, 31], inhibition of oxygen species production [32, 33], induction of gene expression of antioxidant enzymes [34], and reduction of vitamin E catabolism [35]. It has been reported that plant lignans (SDG and its aglycone SECO) have a stronger antioxidant efficacy against DNA damage than enterolignans (enterodiol and enterolactone) [36]. Enterolignans can exert their estrogenic effects through binding preferentially to estrogen receptor-α (ERα) than ERβ and leading to subsequent ER-mediated gene transcription [37–39]. ERα plays an important role in the maintenance of normal body weight and insulin sensitivity, whereas ERβ exhibits the opposite effects [40, 41]. Lignans may also improve insulin resistance through inhibiting pancreatic α-amylase [42], decreasing inflammation [43], and inducing adiponectin expression [44].

During pregnancy, physiologic, hormonal and metabolic changes occur in pregnant women to support the growing fetal needs. As a result, there are progressive changes in carbohydrate and lipid metabolism, leading to the elevated risk for maternal insulin resistance and hyperlipidemia [2]. As lignans possess estrogenic and antiestrogenic properties, it merits investigation of the associations between lignan intake and cardiometabolic risk factors during pregnancy. Furthermore, phytoestrogens are found in amniotic fluid and umbilical cord blood; they can diffuse across the placenta to reach the fetus [45, 46]. Therefore, it is reasonable to assume that maternal intake of lignans will exert beneficial effects on fetal programming and have potential to improve long-term developmental and health outcomes. Currently, there is lack of data available on the association between lignan concentrations and cardiometabolic risk markers among pregnant women. To our knowledge, this study was the first to explore such associations. The results from this study largely supported the findings from previous studies on the beneficial effects of lignans on lipid and glucose metabolism, whereas this study was conducted in pregnant women, a subgroup of population at increased risk for insulin resistance and hyperlipidemia.

The urinary excretion of enterolignans among pregnant women was comparable to population-based reference data. According to the NHANES 1999–2000, the weighted median of urinary enterodiol among all females aged 6 years and older was 35.4 (95% CI: 29.6, 41.6) μg/g creatinine, and the weighted median of enterolactone was 302 (95% CI: 256, 380) μg/g creatinine [22, 47]. Another study using NHANES data 2003–2006 reported the median urinary enterodiol among all females as 48.4 (45.0- 54.6) μg/g creatinine, and the median urinary enterolactone 418 (360- 481) μg/g creatinine (CDC, 2013). In the present study, the lignan concentrations among pregnant women were similar. It was also found that non-Hispanic whites had higher enterolignan concentrations than other races. Consistent patterns were observed in the general population [48].

The major limitations of this study included the cross-sectional design precluding establishment of the temporality as well as causal relationship between lignan intake and cardiometabolic risks. Further evidence from cohort studies and randomized controlled trials is needed to determine the effects of lignan intake on cardiometabolic risks during pregnancy. Secondly, the weak correlation (correlation coefficients around 0.2) between lignan-rich food sources and urinary enterolignans warrants further investigation. As enterolignans are metabolites of gut microbiota, varying levels of urinary enterolignans may reflect individual differences in gut microbial metabolism capacity. It is likely that the gut microbial environment plays a more influential role than dietary lignan intake in determining urinary enterolignan concentrations. Lastly, although we adjusted for potential confounders such as age, race, education, smoking, alcohol drinking, and physical activities, there is likely to be some residual or unmeasured confounding such as consumption of animal foods and other fiber-rich foods. Nevertheless, our findings are consistent with existing evidence from observational studies and randomized controlled trials regarding the beneficial effects of dietary lignan intake on cardiometabolic health.

#### Authors' contributions

LS and QS designed the research and analyzed the data; LS wrote the manuscript and edited the manuscript; YZ conducted literature search and reviewed/edited the manuscript; TAMS, QS, YZ, AHL, and LLH reviewed and edited the manuscript. LS has primary responsibility for the final content. All authors have reviewed and approved the final manuscript.

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#### Data availability

The datasets used in this study are publicly available at https://wwwn.cdc.gov/nchs/nhanes/Default.aspx.

### Declarations

#### Ethics approval and consent to participate

This is a secondary data analysis of publicly available and was deemed exempt from review by the Institutional Review Board at the University of Massachusetts Boston. The NHANES study protocols were reviewed and approved by the National Center for Health Statistics (NCHS) Research Ethics Review Board. The NHANES study has been guided by the ethical principles of the Declaration of Helsinki. All study participants signed an informed consent.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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