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Cardiovascular disease risk factors and their associations with inflammation among US adolescents: NHANES, 2015 to March 2020

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ABSTRACT

Introduction The prevalence of obesity and glycemic dysfunction in adolescents has increased over the past several decades but less is known on how these conditions are associated with systemic inflammation in this population. This study determined the associations between cardiovascular disease (CVD) risk factors and inflammation among a nationally representative sample of US. adolescents.

Research design and methods Cross-sectional analyses were conducted among 2693 adolescents aged 12–19 years who participated in the 2015 to March 2020 National Health and Nutrition Examination Surveys. Chronic inflammation was determined using laboratory measures for high-sensitivity C reactive protein (hs-CRP). Adjusted ORs (aOR, 95% CI) were calculated from logistic regression models to determine the association between CVD risk factors (obesity, overweight, dysglycemia, hypertension, hyperlipidemia) and elevated hs-CRP (>3.0 mg/L) while controlling for sociodemographic characteristics and other CVD risk factors.

Results Overall, 15.3% of adolescents had elevated hs-CRP. Adolescents who were older (16–19 years vs 12–15 years), obese, had A1c ≥5.7% (≥39 mmol/mol), high total cholesterol, or low high-density lipoprotein had hs-CRP distributions that were more high risk (χ^2 p value <0.001). Adolescents with obesity or A1c ≥5.7% had a sixfold and a nearly twofold higher odds of elevated hs-CRP compared those without obesity and A1c <5.7% after full adjustment (aOR=6.39, 4.64 to 8.79 and aOR=1.70, 1.05 to 3.06, respectively). Adolescents with hypertension or hyperlipidemia were significantly more likely to have elevated hs-CRP compared with those without these conditions after adjustment for sociodemographic characteristics (aOR=2.46, 1.08 to 5.60 and aOR=2.19, 1.36 to 3.54, respectively), but the association was not significant after further adjustment for obesity.

Conclusions Among US adolescents, obesity was strongly associated with elevated hs-CRP, a marker for future CVD risk. Given the obesity epidemic and the marked proportion with elevated CRP, concern should be given to future CVD risk in younger adults.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Obesity, elevated glucose, hypertension and hyperlipidemia are risk factors for cardiovascular disease (CVD) and, among adults, have been shown to be strongly associated with inflammation. However, the prevalence of inflammation and its association with CVD risk factors among US adolescents is largely unknown.

WHAT THIS STUDY ADDS

⇒ Fifteen per cent of adolescents had systemic inflammation. Obesity and elevated A1c were the strongest CVD risk factors associated with inflammation even after adjustment for sociodemographic characteristics and other CVD risk factors.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Given the obesity epidemic, the increase in diabetes, and the marked proportion with inflammation among US adolescents, concern should be given to future CVD risk in younger adults.

INTRODUCTION

Inflammation is a risk factor for future cardiovascular events.[1] Obesity, elevated glucose, hypertension and hyperlipidemia are also risk factors for cardiovascular disease (CVD) and have been shown to be strongly associated with inflammation.[2–6]

The prevalence of obesity and glycemic dysfunction in adolescents has increased over the past several decades, but less is known on how these conditions are associated with inflammation in this population. The SEARCH for Diabetes in Youth study demonstrated increases in incidence of type 2 diabetes in US youth 10–19 years of 5.31% (4.46 to 6.17)) per year from 2002 to 2003 to 2017–2018.[7] Data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative US survey, showed that among adolescents aged 12–19 years, the prevalence of obesity has increased from 20.4% in 2011–2012 to 22.1% in 2017–2020,[8] and the prevalence of pre-diabetes has increased from 11.6% in

Table 1 Characteristics of adolescents aged 12–19 years, overall and by sex, NHANES 2015–2020

	Prevalence (SE)			
	Total (N=2693)	Male (N=1401)	Female (N=1292)	P value, χ^2 (t-test for means)
Age (years)				
Mean	15.4 (0.1)	15.4 (0.1)	15.4 (0.1)	0.596
12–15	50.7 (1.1)	52.9 (2.0)	48.4 (1.7)	0.132
16–19	49.3 (1.1)	47.1 (2.0)	51.6 (1.7)	
Sex				<0.001
Male	51.8 (1.6)	100.0	NA	
Female	48.2 (1.6)	NA	100.0	
Race and ethnicity				0.459
Non-Hispanic white	51.6 (3.3)	52.9 (3.7)	50.2 (3.4)	
Non-Hispanic black	12.8 (1.8)	12.1 (1.7)	13.6 (2.0)	
Hispanic	25.1 (2.5)	24.9 (2.8)	25.3 (2.5)	
Non-Hispanic Asian	4.7 (0.9)	4.9 (1.0)	4.4 (0.9)	
Poverty income ratio*				0.782
<1.0 (below poverty threshold)	20.2 (1.3)	19.7 (1.8)	20.8 (1.2)	
1.0–2.0	23.9 (1.3)	23.8 (1.8)	24.0 (1.8)	
≥2.0	55.9 (2.0)	56.5 (2.4)	55.2 (2.4)	
Food security				0.197
Secure	64.0 (1.7)	62.3 (2.4)	65.9 (2.0)	
Marginal/low	36.0 (1.7)	37.7 (2.4)	34.1 (2.0)	
Adiposity†				0.035
Underweight	3.1 (0.6)	4.0 (1.0)	2.1 (0.7)	
Normal	53.6 (1.5)	54.4 (2.0)	52.6 (2.5)	
Overweight	20.3 (1.0)	18.5 (1.4)	22.3 (1.4)	
Obese	23.0 (1.2)	23.0 (1.7)	22.9 (1.5)	
A1c (%)				0.588
<5.7 (<39 mmol/mol)	92.9 (0.8)	93.2 (1.1)	92.6 (1.0)	
5.7%-<6.5 (39–48 mmol/mol)	6.6 (0.7)	6.1 (0.9)	7.0 (1.0)	
≥6.5 (≥48 mmol/mol)	0.5 (0.2)	0.6 (0.4)	0.4 (0.2)	
Fasting plasma glucose (mg/dL)				<0.001
<100	67.1 (3.0)	58.0 (3.8)	76.7 (2.7)	
100-<126	32.3 (3.0)	41.0 (3.8)	23.1 (2.6)	
≥126	0.6 (0.3)	1.0 (0.5)	0.2 (0.1)	
Hypertension‡	2.1 (0.3)	2.7 (0.4)	1.6 (0.5)	0.091
Hyperlipidemia§				
High total cholesterol	27.6 (1.3)	23.2 (1.3)	32.3 (1.8)	<0.001
Low HDL	32.2 (1.5)	40.4 (2.2)	23.4 (1.4)	<0.001
High LDL	16.5 (1.7)	16.1 (2.3)	17.0 (2.3)	0.777
High triglyceride	7.7 (0.9)	8.7 (1.5)	6.6 (1.1)	0.271
C reactive protein (mg/L)				
Mean	1.9 (0.1)	1.8 (0.2)	2.1 (0.1)	0.186
Low risk, <1.0	62.1 (1.5)	65.3 (2.3)	58.6 (1.9)	0.024
Average risk, 1.0–3.0	22.6 (1.1)	22.2 (1.8)	23.0 (1.4)	
High risk, >3.0	15.3 (1.0)	12.5 (1.2)	18.4 (1.6)	

*Poverty income ratio: ratio of family income to poverty; value of <1.0 indicates below the Federal poverty threshold, 1.0–2.0 indicates 1–2 times above the poverty threshold; ≥2.0 indicates two or more times above the poverty threshold.
†Adiposity: Underweight, BMI <5th percentile of age-specific and sex-specific NCHS growth charts. Normal, BMI 5th–<85th percentile of age-specific and sex-specific NCHS growth charts. Overweight, BMI 85th–<95th percentile of age- and sex-specific NCHS growth charts. Obesity, BMI greater ≥95th percentile of age- and sex-specific NCHS growth charts
‡Hypertension, current use of antihypertensive medication or average SBP or DBP ≥95th percentile of age-specific, sex-specific and height-specific blood pressure for age 12–17; BP ≥140/90 mm Hg for male and female age 18–19 years.
§Hyperlipidemia: High total cholesterol, ≥170 mg/dL. High LDL, ≥110 mg/dL. Low HDL, ≤45 mg/dL. High triglyceride, ≥130 mg/dL
DBP, diastolic blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NA, not applicable; NCHS, National Center for Health Statistics; NHANES, National Health and Nutrition Examination Survey; SBP, systolic blood pressure.

Table 2 Distribution of CRP by sociodemographic characteristics and CVD risk factors among adolescents aged 12–19 years, NHANES 2015–2020

	hs-CRP			
	Low risk (<1.0 mg/L) (N=1670)	Average risk (1.0–3.0 mg/L) (N=594)	High risk (>3.0 mg/L) (N=429)	χ^2, p value
Total	62.1 (1.5)	22.6 (1.1)	15.3 (1.0)	
Age (years)				<0.001
12–15	68.1 (1.8)	20.3 (1.5)	11.7 (1.2)	
16–19	55.8 (2.1)	25.1 (1.7)	19.1 (1.5)	
Sex				0.023
Male	65.3 (2.3)	22.2 (1.8)	12.5 (1.2)	
Female	58.6 (1.9)	23.0 (1.4)	18.4 (1.6)	
Race and ethnicity				0.004
Non-Hispanic white	63.7 (2.4)	21.9 (1.6)	14.4 (1.8)	
Non-Hispanic black	64.8 (2.2)	18.2 (1.5)	17.0 (1.7)	
Hispanic	57.5 (1.9)	26.9 (1.6)	15.6 (1.5)	
Non-Hispanic Asian	67.7 (3.0)	21.3 (2.9)	11.0 (1.7)	
Poverty income ratio				0.003
<1.0	53.4 (2.5)	26.5 (2.1)	20.2 (1.7)	
1.0–2.0	60.9 (2.8)	24.4 (2.2)	14.7 (1.6)	
≥2.0	66.5 (2.1)	19.5 (1.7)	14.0 (1.4)	
Food security				0.009
Marginal/low	57.6 (2.0)	26.0 (1.6)	16.4 (1.0)	
Secure	64.9 (1.7)	20.6 (1.4)	14.5 (1.4)	
Adiposity				<0.001
Underweight	93.0 (3.6)	1.3 (1.1)	5.7 (3.1)	
Normal weight	77.7 (1.6)	14.8 (1.2)	7.5 (1.0)	
Overweight	57.2 (3.2)	30.1 (3.0)	12.7 (2.0)	
Obese	25.6 (2.5)	37.3 (2.4)	37.1 (2.1)	
A1c*				
<5.7 (<39 mmol/mol)	63.4 (1.5)	22.4 (1.2)	14.2 (1.0)	<0.001
≥5.7 (≥39 mmol/mol)	45.5 (3.4)	25.5 (3.2)	29.0 (3.9)	
Fasting plasma glucose (mg/dL)†				
<100	61.8 (2.6)	22.7 (1.9)	15.5 (2.1)	0.946
≥100	61.1 (3.7)	22.5 (3.8)	16.4 (2.3)	
Hypertension				0.121
Yes	53.0 (9.9)	17.7 (6.1)[1]	29.3 (8.3)	
No	62.1 (1.6)	22.7 (1.2)	15.3 (1.0)	
Hyperlipidemia				
High total cholesterol				<0.001
Yes	53.8 (2.6)	26.0 (2.1)	20.2 (2.1)	
No	65.1 (1.4)	21.4 (1.0)	13.5 (1.0)	
Low HDL				<0.001
Yes	49.7 (2.5)	26.5 (1.7)	23.8 (1.8)	
No	67.8 (1.5)	20.9 (1.3)	11.3 (1.1)	
High LDL				<0.001
Yes	44.7 (4.8)	32.8 (4.8)	22.5 (4.5)	

Continued

Table 2 Continued

	hs-CRP			
	Low risk (<1.0 mg/L) (N=1670)	Average risk (1.0–3.0 mg/L) (N=594)	High risk (>3.0 mg/L) (N=429)	χ^2, p value
No	64.9 (2.6)	20.7 (1.8)	14.5 (1.8)	
High triglyceride				0.003
Yes	37.6 (5.7)	45.9 (6.9)	16.4 (3.7)	
No	63.5 (2.8)	20.7 (2.1)	15.7 (1.7)	

*Due to the small sample size for A1c≥6.5% (≥48 mmol/mol) (0.5% total sample, see Table 1), the distribution of CRP among those with A1c≥6.5% (≥48 mmol/mol) could not be determined.
†Due to the small sample size for FPG≥126mg/dL (0.6% total sample, see Table 1), the distribution of CRP among those with FPG≥126mg/dL could not be determined.
CRP, C reactive protein; CVD, cardiovascular disease; FPG, fasting plasma glucose; HDL, high-density lipoprotein; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey.

1999–2002 to 28.2% in 2015–2018[9]. Additionally, analyses from the 2005–2014 NHANES showed that the prevalence of CVD risk factors among adolescents with pre-diabetes is concerning.[10] These analyses demonstrated that 28.6% of adolescents aged 12–19 years with pre-diabetes were obese, 4.3% had hypertension, 9.4% had high low-density lipoprotein (LDL)-cholesterol, 19.4% had low high-density lipoprotein (HDL)-cholesterol and 18.4% had high triglycerides, which were significantly higher prevalences compared with their counterparts with normal glucose levels. A systematic review and meta-analysis of data from children and adolescents found that metabolic syndrome, which is a cluster of conditions including high blood pressure, high blood sugar, high waist circumference and abnormal cholesterol levels, was associated with higher levels of CRP compared with those without metabolic syndrome.[11]

The objectives of this study were to determine the prevalence of CVD risk factors by levels of high-sensitivity C reactive protein (hs-CRP), a marker of inflammation and the unadjusted and adjusted association between CVD risk factors and inflammation in a national sample of US. adolescents.

RESEARCH DESIGN AND METHODS

Study participants

The NHANES is a stratified multistage probability cluster survey conducted in the non-institutionalized civilian US population and includes an in-home interview and a physical examination and laboratory measures at a mobile examination center (MEC).[12] Our analyses included 2693 adolescents age 12–19 years who had a hs-CRP measure in the 2015–2020 survey cycles (2020 survey year included data from January to March only due to the COVID-19 pandemic). There were 624 adolescents who did not have a hs-CRP value and were not included in this analysis; adolescents without a hs-CRP value tended to be younger than those with a hs-CRP value (61.2% vs 50.7% age 12–15, respectively) but were otherwise similar with respect to other characteristics. Participants self-reported age at interview, sex and race/ethnicity during the household interview. Household income and household food security were self-reported by an adult during the household interview, which was used to determine the ratio of family income to poverty (poverty income ratio, PIR) and food security status (categorized as secure or marginal/low).

Dependent variable

A phlebotomist obtained a blood sample during the MEC visit using a standardized protocol and hs-CRP was measured using a two-reagent immunoturbidimetric system to measure for hs-CRP.[12 13] A hs-CRP value of >3.0 mg/L was considered a marker for inflammation and elevated risk for CVD.[14 15]

Independent variables

Height and weight were measured by trained technicians to determine body mass index (BMI, kg/m^2). Adiposity was categorized as underweight, normal, overweight and obesity defined as BMI <5th, 5th–<85th, 85th–<95th and ≥95th percentile of age-specific and sex-specific NCHS (National Center for Health Statistics) growth charts, respectively.[16] Blood pressure was taken by a trained technician after resting quietly for 5 min; participants self-reported any antihypertension medication use. Hypertension was defined as current use of antihypertensive medication or average SBP (systolic blood pressure) or DBP (diastolic blood pressure) ≥95th percentile of age-specific, sex-specific and height-specific blood pressure for age 12–17; BP ≥140/90 mm Hg for male and female age 18–19 years.[17]

A phlebotomist obtained a blood sample during the MEC visit using a standard protocol to obtain a measure of hemoglobin A1c ((A1c, elevated cut-point ≥5.7% (≥39 mmol/mol)), fasting plasma glucose (FPG, ≥100 mg/dL), total cholesterol (≥170 mg/dL), HDL ≤45 mg/dL, LDL ≥110 mg/dL) and triglycerides (≥130 mg/dL).[18] Only participants who were properly fasting 8–<24 hours were included in measures for FPG, LDL and triglycerides (N=1111). LDL was determined

using the Friedewald calculation: LDL-C=(total cholesterol)−(HDL cholesterol)−(triglycerides/5).[19]

Statistical analysis

Descriptive statistics were used to determine characteristics of the study sample overall and stratified by sex (per cent, SE). The distribution (percent, SE) of hs-CRP levels (low risk <1.0 mg/L, average risk 1.0–3.0 mg/L, high risk >3.0 mg/L) were described by participant characteristics; a χ^2 test was used to determine significant differences (p<0.05) by characteristics.

The unadjusted and adjusted percentage (95% CI) of each CVD risk factor (obesity, overweight, elevated A1c, elevated FPG, hypertension, hyperlipidemia, elevated total cholesterol) was determined by hs-CRP level (low/average ≤3.0 mg/L, high risk >3.0 mg/L) using conditional marginal regression modeling. Unadjusted and adjusted ORs for elevated hs-CRP (>3.0 mg/L) associated with each CVD risk factor were calculated using logistic regression. For both prevalence and logistic regression analyses, models were (1) unadjusted, (2) adjusted for age, race/ethnicity and sex (demographics), (3) additionally adjusted for PIR and food security (other social determinants of health) and (4) additionally adjusted for other CVD risk factors that were not the outcome for that specific model.

All statistical analyses used sample weights provided by the NHANES and accounted for the cluster design using SUDAAN (SUDAAN User's Manual, Release V.11, 2012; Research Triangle Institute).

Data and resource availability

The dataset generated in the current study is available at: https://wwwn.cdc.gov/nchs/nhanes/[20].

RESULTS

In NHANES 2015–2020, the mean age of adolescents aged 12–19 years was 15.4 years, overall and by sex (table 1). About half of participants were aged 12–15 years with the other half aged 16–19 years. The majority were non-Hispanic white adolescents (51.6%) followed by Hispanic (25.1%), non-Hispanic black (12.8%) and non-Hispanic Asian (4.7%) adolescents. One-fifth (20.2%) had a household PIR <1.0 (ratio of family income to poverty) and over a third (36.0%) had marginal or low food security. Adiposity was similar by sex; 43.3% of adolescents were overweight (20.3%) or obese (23.0%). The prevalence of elevated A1c (≥5.7%, ≥39 mmol/mol) was 7.1%; 32.9% had elevated FPG (≥100 mg/dL). The prevalence of hypertension was low (2.1%). Hyperlipidemia levels ranged from 7.7% for elevated triglycerides to 32.2% for low HDL.

Mean hs-CRP was 1.9 mg/L and 15.3% of adolescents had a high-risk hs-CRP level (>3.0 mg/L) (table 1). Overall, 62.1% of adolescents had a low-risk hs-CRP level, 22.6% had an average-risk hs-CRP level, and 15.3% had a high-risk hs-CRP level (table 2). Adolescents aged 16–19 years more often had a high-risk hs-CRP level (19.1%) compared with those aged 12–15 years (11.7%, χ^2 p value <0.001). The distribution of hs-CRP trended higher (high risk) for women versus men, non-Hispanic black adolescents, those with low PIR (<1.0) and those with marginal or low food security. Adolescents who were obese had A1c≥5.7% (≥39 mmol/mol), high total cholesterol, or low HDL had hs-CRP distributions that trended more high risk.

The prevalence of CVD risk factors by hs-CRP level is presented in table 3. The prevalence of obesity was significantly higher for adolescents with a high-risk hs-CRP level compared with those with a low-risk or average-risk hs-CRP level (55.7% vs 17.1%, p<0.001) and this association remained after adjustment for demographic characteristics, other social determinants of health (herein, sociodemographic characteristics) and other CVD risk factors (53.1% vs 15.3%, respectively, p<0.001). There was a positive linear association between BMI and hs-CRP (beta coefficient=0.19, p<0.001; data not shown). Similarly, the prevalence of A1c≥5.7% (≥39 mmol/mol), hypertension, hyperlipidemia and total cholesterol ≥170 mg/dL was significantly higher for adolescents with high-risk hs-CRP (vs low-risk or average-risk hs-CRP) in unadjusted models and models adjusted for sociodemographic characteristics. However, the association became non-significant after additionally adjusting for other CVD risk factors.

Adolescents with obesity had a sixfold higher odds of having a high-risk hs-CRP level compared those without obesity (OR=6.10, 4.62–8.06) and this association remained after full adjustment for sociodemographic characteristics and other CVD risk factors (adjusted OR (aOR)=6.39, 4.64 to 8.79) (table 4). A similar association, although lower in magnitude, was found for adolescents with overweight (aOR=1.87, 1.12 to 3.14) and A1c≥5.7% (≥mmol/mol) (aOR=1.79, 1.05 to 3.06).

Adolescents with hypertension or hyperlipidemia had over a twofold higher odds of having a high-risk hs-CRP level compared with those without these conditions after adjustment for sociodemographic characteristics (aOR=2.46, 1.08 to 5.60 and aOR=2.19, 1.36 to 3.54, respectively) (table 4). However, the association became non-significant after further adjustment for other CVD risk factors. Further analysis showed that adjusting for sociodemographic characteristics and only obesity resulted in non-significant models for hypertension and hyperlipidemia, whereas the models remained significant when adjusting for overweight, A1c, total cholesterol/hypertension in independent models. Thus, obesity was strongly associated with elevated hs-CRP when assessing the association between hypertension and hyperlipidemia and elevated hs-CRP.

DISCUSSION

In this nationally representative US sample of adolescents, 15% had high-risk hs-CRP levels. Obesity, overweight and A1c≥5.7% (≥39 mmol/mol) were independently

Table 3 Adjusted percentage (95% CIs) of CVD risk factors by hs-CRP level among adolescents, 2015–2020 NHANES

	hs-CRP level		
	Low/average risk (≤3.0 mg/L)	High risk (>3.0 mg/L)	P value
Obesity			
Unadjusted	17.1 (15.0, 19.4)	55.7 (49.2, 61.9)	<0.001
Multivariable model 1*	16.5 (14.5, 18.7)	56.4 (49.5, 63.0)	<0.001
Multivariable model 2†	15.7 (13.5, 18.0)	54.8 (47.7, 61.8)	<0.001
Multivariable model 3‡	15.3 (13.3, 17.7)	53.1 (45.6, 60.5)	<0.001
Overweight			
Unadjusted	20.9 (18.8, 23.2)	16.9 (12.1, 22.9)	0.177
Multivariable model 1*	20.9 (18.8, 23.2)	16.2 (11.7, 22.1)	0.113
Multivariable model 2†	20.6 (18.5, 22.8)	16.3 (11.5, 22.6)	0.173
Multivariable model 3‡	20.6 (18.4, 23.0)	16.7 (11.8, 23.2)	0.230
A1c≥5.7% (≥39 mmol/mol)			
Unadjusted	5.9 (4.5, 7.7)	13.4 (9.9, 17.9)	<0.001
Multivariable model 1*	5.1 (3.6, 7.0)	11.9 (8.7, 16.0)	<0.001
Multivariable model 2†	5.2 (3.6, 7.4)	10.6 (7.4, 15.0)	0.006
Multivariable model 3‡	5.3 (3.6, 7.7)	8.9 (5.3, 14.3)	0.086
FPG≥100 mg/dL			
Unadjusted	32.7 (26.9, 39.0)	34.2 (24.0, 46.0)	0.777
Multivariable model 1*	31.0 (25.3, 37.4)	36.4 (25.8, 48.5)	0.338
Multivariable model 2†	30.6 (24.5, 37.5)	34.8 (24.2, 47.0)	0.452
Multivariable model 3‡	31.2 (24.9, 38.4)	27.8 (17.4, 41.3)	0.577
Hypertension			
Unadjusted	1.8 (1.1, 2.9)	4.0 (2.6, 6.1)	0.048
Multivariable model 1*	1.5 (0.8, 2.6)	3.7 (2.4, 5.6)	0.019
Multivariable model 2†	1.6 (0.9, 2.8)	3.7 (2.3, 6.0)	0.040
Multivariable model 3‡	1.5 (0.8,2.9)	2.4 (1.1, 4.9)	0.410
Hyperlipidemia§			
Unadjusted	49.2 (44.6, 53.7)	71.6 (62.4, 79.4)	<0.001
Multivariable model 1*	49.3 (44.6, 54.0)	71.1 (62.1, 78.7)	<0.001
Multivariable model 2†	51.2 (46.1, 56.3)	69.8 (60.0, 78.1)	<0.001
Multivariable model 3‡	53.5 (47.7, 59.3)	63.6 (50.7, 74.7)	0.143
Total cholesterol≥170 mg/dL			
Unadjusted	26.0 (23.5, 28.7)	36.3 (30.2, 42.8)	0.003
Multivariable model 1*	25.8 (23.3, 28.5)	33.7 (27.9, 40.2)	0.016
Multivariable model 2†	25.9 (23.2, 28.9)	32.9 (26.7, 39.7)	0.046
Multivariable model 3‡	26.5 (23.6, 29.5)	29.7 (23.0, 37.4)	0.409

*Multivariable model 1 adjusted for age, race/ethnicity and sex (demographics).
†Multivariable model 2 additionally adjusted for poverty income ratio, food security (other social determinants of health).
‡Multivariable model 3 additionally adjusted for: Obesity: additionally adjusted for A1c≥5.7% (≥39 mmol/mol), hypertension, total cholesterol. Overweight: additionally adjusted for A1c≥5.7% (≥39 mmol/mol), hypertension, total cholesterol. A1c ≥5.7% (≥39 mmol/mol): additionally adjusted for obesity, overweight, hypertension, total cholesterol. FPG ≥100 mg/dL: additionally adjusted for obesity, overweight, hypertension, total cholesterol. Hypertension: additionally adjusted for obesity, overweight, A1c≥5.7% (≥39 mmol/mol), total cholesterol. Hyperlipidemia: additionally adjusted for obesity, overweight, A1c≥5.7% (≥39 mmol/mol), hypertension. Total cholesterol: additionally adjusted for obesity, overweight, A1c≥5.7% (≥39 mmol/mol), hypertension.
§Hyperlipidemia is defined as any elevated cholesterol marker (total, LDL, HDL or triglyceride); fasting sample.
CRP, C reactive protein; CVD, cardiovascular disease; FPG, fasting plasma glucose; HDL, high-density lipoprotein; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey.

Table 4 Adjusted odds ratio (95% CIs) of elevated hs-CRP associated with CVD risk factors among adolescents, 2015–2020 NHANES

	OR (95% CI) for elevated hs-CRP	
	Low/average risk (≤3.0 mg/L)	High risk (>3.0 mg/L)
Obesity		
Unadjusted	1.00	6.10 (4.62, 8.06)
Multivariable model 1*	1.00	6.58 (4.90, 8.83)
Multivariable model 2†	1.00	6.64 (4.90, 9.01)
Multivariable model 3‡	1.00	6.39 (4.64, 8.79)
Overweight		
Unadjusted	1.00	1.82 (1.12, 2.95)
Multivariable model 1*	1.00	1.82 (1.14, 2.90)
Multivariable model 2†	1.00	1.85 (1.13, 3.02)
Multivariable model 3‡	1.00	1.87 (1.12, 3.14)
A1c≥5.7% (≥39 mmol/mol)		
Unadjusted	1.00	2.46 (1.67, 3.63)
Multivariable model 1*	1.00	2.52 (1.63, 3.90)
Multivariable model 2†	1.00	2.17 (1.35, 3.49)
Multivariable model 3‡	1.00	1.79 (1.05, 3.06)
FPG≥100 mg/dL		
Unadjusted	1.00	1.07 (0.67, 1.71)
Multivariable model 1*	1.00	1.28 (0.79, 2.06)
Multivariable model 2†	1.00	1.22 (0.75, 1.98)
Multivariable model 3‡	1.00	0.89 (0.49, 1.62)
Hypertension		
Unadjusted	1.00	2.30 (1.05, 5.03)
Multivariable model 1*	1.00	2.62 (1.22, 5.64)
Multivariable model 2†	1.00	2.46 (1.08, 5.60)
Multivariable model 3‡	1.00	1.56 (0.59, 4.14)
Hyperlipidemia§		
Unadjusted	1.00	2.61 (1.65, 4.13)
Multivariable model 1*	1.00	2.52 (1.62, 3.94)
Multivariable model 2†	1.00	2.19 (1.36, 3.54)
Multivariable model 3‡	1.00	1.55 (0.85, 2.80)
Total cholesterol≥170 mg/dL		
Unadjusted	1.00	1.62 (1.22, 2.15)
Multivariable model 1*	1.00	1.46 (1.09, 1.95)
Multivariable model 2†	1.00	1.40 (1.03, 1.92)
Multivariable model 3‡	1.00	1.20 (0.83, 1.73)

*Multivariable model 1 adjusted for age, race/ethnicity and sex (demographics).
†Multivariable model 2 additionally adjusted for poverty income ratio, food security (other social determinants of health).
‡Multivariable model 3 additionally adjusted for: Obesity: additionally adjusted for A1c≥5.7% (≥39 mmol/mol), hypertension, total cholesterol. Hyperlipidemia is defined as any elevated cholesterol marker (total, LDL, HDL or triglyceride); fasting sample. Overweight: additionally adjusted for A1c≥5.7% (≥39 mmol/mol), hypertension, total cholesterol. A1c ≥5.7% (≥39 mmol/mol): additionally adjusted for obesity, overweight, hypertension, total cholesterol. FPG ≥100 mg/dL: additionally adjusted for obesity, overweight, hypertension, total cholesterol. Hypertension: additionally adjusted for obesity, overweight, A1c≥5.7% (≥39 mmol/mol), total cholesterol. Hyperlipidemia: additionally adjusted for obesity, overweight, A1c≥5.7% (≥39 mmol/mol), hypertension. Total cholesterol: additionally adjusted for obesity, overweight, A1c≥5.7% (≥39 mmol/mol), hypertension.
§Hyperlipidemia is defined as any elevated cholesterol marker (total, LDL, HDL or triglyceride); fasting sample.
CRP, C reactive protein; CVD, cardiovascular disease; FPG, fasting plasma glucose; HDL, high-density lipoprotein; hs-CRP, high-sensitivity CRP; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey.

associated with elevated hs-CRP even after adjustment for demographic characteristics and other CVD risk factors. Of particular note, adolescents who were obese had over a sixfold higher odds of having a high-risk hs-CRP level after full adjustment.While hypertension, hyperlipidemia and high total cholesterol were associated with elevated hs-CRP after adjustment for demographic characteristics, the associations were no longer significant after adjustment for obesity.

While the overall prevalence of high-risk CRP was 15%, we found that the prevalence was higher in females (18%) compared with males (13%). Previous research among black and white adults in the population-based Dallas Heart study showed that women had higher CRP levels than men (median 3.3 mg/L in women vs 1.8 mg/L in men).[21] The difference in CRP level by sex may be attributed to sex hormones. A cross-sectional study among male adolescents aged 12–16 years found a significant negative correlation between hs-CRP and testosterone after adjusting for BMI (correlation=−0.145, p<0.001), but the correlation disappeared after further adjustment for leptin, a hormone found in adipose tissue that helps the body maintain weight; there was no association between testosterone or estradiol levels and hs-CRP among women.[22] CRP levels in premenopausal women have shown to be quite variable across the menstrual cycle with estrogen exhibiting anti-inflammatory effects.[23] In a prospective study, more women were classified as having elevated CRP (>3.0 mg/L) during the menses phase, when estrogen is low, compared with other phases of the cycle.[24] Thus, CRP measurement in women may have more variability due to fluctuating estrogen levels.

Our findings are consistent with previous research that has shown that obesity, a proinflammatory state,[4] is strongly associated with elevated CRP. An older study in NHANES (1988–1994) among children and adolescents age 6–18 years found that overweight and obesity were associated with a twofold and fivefold higher adjusted odds, respectively, for elevated CRP (>2.1 mg/L).[25] Among adults, weight loss resulted in reduced CRP levels in healthy middle-aged adults[26] as well as obese women[27] and obese men.[28] In a cross-sectional retrospective cohort study that utilized medical records, adults with type 2 diabetes and elevated CRP (>3.0 mg/L) had higher BMI and A1c compared with those with diabetes and lower CRP levels.[29] Furthermore, previous research among adults has shown that higher CRP levels predict the development of diabetes in both obese men and women.[30 31] Thus, CRP plays an important role in the relationship between obesity and diabetes. Given these findings on the positive cross-sectional association between obesity and CRP in adolescents, combined with the prospective findings in adults, it would be expected that adolescents with obesity and elevated CRP are at an increased risk for the development of diabetes.

Hypertension and hyperlipidemia, while well-known risk factors for CVD, are also considered to be the

result of inflammation at the cellular level.[5 6] Thus, our result that adolescents with hypertension or hyperlipidemia were more likely to have elevated hs-CRP level was not unexpected and we found that this association remained after adjustment for demographic characteristics. However, after adjustment for each CVD risk factor alone, adjustment for obesity was the only variable that resulted in a non-significant association between hypertension and hyperlipidemia and elevated hs-CRP. Thus, obesity appears to be an independent risk factor associated with elevated hs-CRP regardless of the presence of hypertension or hyperlipidemia in adolescents.

Clinical studies among adults have demonstrated that elevated CRP predicts increased risk for CVD. In the Women's Health Study, a large prospective study of healthy women aged 45 years or older, CRP was a stronger predictor of CVD events than LDL-cholesterol (relative risk 2.3 for CRP and 1.5 for LDL for the highest vs lowest quintile).[32] Among men in the prospective Physicians' Health Study, baseline CRP level predicted future risk of myocardial infarction and stroke (relative risk of 2.9 and 1.9, respectively).[33]

NHANES is a cross-sectional survey, thus causal associations between CVD risk factors and CRP cannot be determined. In addition, for some subgroups of adolescents, the sample size was small, which limited power to detect significant differences. There was no information on pubertal status for men and only age of menarche for women, thus, these factors and the association with obesity, abnormal glucose and CRP could not be determined and deserve additional study. However, the main independent variables and main outcome (hs-CRP) were determined either during a medical exam by a trained interviewer or by laboratory analysis using standardized measures. Furthermore, this study used a nationally representative sample allowing generalization to the US adolescent population. While out of the scope of this paper, dietary intake and quality may have a proinflammatory effect on the CVD risk factors measured in this study.[34] In addition, there was no information on family history of diabetes or other CVD risk factors to assess how family history may affect the association with CRP. Only CRP was available in NHANES to determine levels of inflammation; other inflammatory markers may have different prevalence estimates in adolescents and may have different associations with CVD risk factors.

Given the rise in obesity among adolescents and the marked proportion with elevated CRP, there should be increasing concerns about excess CVD at younger ages, which should be a priority among researchers, healthcare providers and public health officials.

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