DIETARY FRUCTOSE IN RELATION TO BLOOD PRESSURE AND SERUM URIC ACID IN ADOLESCENT BOYS AND GIRLS

Kelly S Bobridge MNutr&Diet[1], Gemma L Haines MNutr&Diet [1], Trevor A Mori PhD[2], Lawrie J Beilin MBBS MD[2], Wendy H Oddy PhD[3], Jill Sherriff PhD[4], Therese A O'Sullivan PhD[1,3]

[1]School of Exercise and Health Science, Edith Cowan University, Joondalup, Western Australia, Australia; [2]School of Medicine and Pharmacology Royal Perth Hospital Unit, University of Western Australia, Perth, Australia; [3]Telethon Institute for Child Health Research, Centre for Child Health Research, The University of Western Australia, Perth, Western Australia, Australia; [4]School of Public Health, Curtin Health Innovation Research Institute, Curtin University, Perth, Australia.

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Correspondence: Dr Therese O'Sullivan, School of Exercise, Biomedical and Health Science, Edith Cowan University, 270 Joondalup Drive, Joondalup, Western Australia 6027, Australia. Phone: +61 8 6304 5055 Fax: +61 8 6304 5384

Email: t.osullivan@ecu.edu.au

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ABSTRACT

Evidence that fructose intake may modify blood pressure is generally limited to adult populations. This study examined cross-sectional associations between dietary intake of fructose, serum uric acid and blood pressure in 814 adolescents aged 13-15 years participating in the Western Australian Pregnancy Cohort (Raine) Study. Energy adjusted fructose intake was derived from 3-day food records, serum uric acid concentration was assessed using fasting blood, and resting blood pressure was determined using repeated oscillometric readings. In multivariate linear regression models, we did not see a significant association between fructose and blood pressure in boys or girls. In boys, fructose intake was independently associated with serum uric acid ($P<0.01$), and serum uric acid was independently associated with systolic blood pressure ($P<0.01$) and mean arterial pressure ($P< 0.001$). Although there are independent associations, there is no direct relationship between fructose intake and blood pressure. Our data suggests that gender may influence these relationships in adolescence, with significant associations observed more frequently in boys than girls.

Key Words: fructose; blood pressure; uric acid; adolescents; Raine Study; Australia

INTRODUCTION

Hypertension is the most common disease of Western populations and is becoming increasingly common in adolescents.[1, 2] Between the 1988-1994 and 1999-2000 National Health and Nutrition Examination Survey (NHANES), systolic blood pressure (SBP) and diastolic blood pressure (DBP) significantly increased by 1.4 mmHg and 3.3 mmHg, respectively, in American children and adolescents (aged 8-17 years).[2] Hypertension in adolescence has been associated with increased risk of early development of coronary artery disease and left ventricular hypertrophy, as well as numerous other conditions.[3] Additionally, adolescent hypertension has been linked with an increased risk of hypertension and chronic disease in adulthood.[4] Although the increasing trend in adolescent blood pressure (BP) has been largely attributed to increasing obesity, there are still unknown contributing factors.[2] Dietary fructose is one of the potential risk factors currently under investigation in this regard.[5-7]

Fructose intake has been following an upward trend.[8] In 2004 it was estimated that 9.1 % of total energy intake for Americans was derived from fructose, an increase from the 8.1 % in 1978.[9] Fructose is a monosaccharide naturally occurring in fruit and also commonly consumed as table sugar (sucrose) or high fructose corn syrup.[10] A study of 1999-2004 NHANES data estimated non-alcoholic beverages to contribute 46 % of total fructose intake, followed by grain products at 17.3 %.[9] Several researchers have examined BP in relation to sugar-sweetened beverage intake in particular, because they are known to contribute a large proportion of fructose to Western diets.[6, 11] Sugar-sweetened beverage intake was weakly but significantly related to greater SBP independent of obesity in a study of 4867 American adolescents by Nguyen et al.[11] The authors suggest elevated serum uric acid is part of a

potential causal mechanism behind these findings. Studies of adult subjects also support the concept of a link between fructose and BP.[5-7, 12]

To our knowledge, the only published fructose data for adolescents to date are from the United States of America and Switzerland, and there are no published national statistics for fructose intake in Australia.[9, 10, 13, 14] However, Woolley et al. recently collated a fructose database for adolescents involved in the 14 year follow-up of the Western Australian Pregnancy Cohort (Raine) Study.[15] We have used this data in conjunction with BP measurements to conduct a cross-sectional analysis between fructose intake and BP in this group of Australian adolescents. We aimed to: 1) investigate the cross-sectional association between fructose intake and BP in adolescents participating in the Raine Study, 2) determine if fructose intake is associated with serum uric acid and if serum uric acid is associated with BP in adolescents, and 3) determine if serum uric acid is significant in the fructose-BP physiological pathway. We hypothesised that BP would be positively associated with fructose intake after adjustment for potential confounding factors, and that uric acid would be a significant factor in the physiological pathway.

METHODS

Research Design

This cross-sectional study uses data from the 14 year follow-up of the Raine study.[16] The study involves a large cohort, with dietary intake information, biochemical analyses, anthropometry and lifestyle data available.

Subjects

The Raine Study began with 2900 women at 16-20 weeks of gestation who were involved in research evaluating the effects of ultrasounds in pregnancy. Women were recruited from King Edward Memorial Hospital (KEMH) in Perth, and private clinics. More detailed recruitment information has been published previously.[16] The children born within the study were followed up at birth and at years 1, 2, 3, 5, 8, 10 and 14. There were 2868 live births, of which 1861 adolescents participated in at least one aspect of the 14 year follow-up. Of those who agreed to participate in the dietary assessment (n = 1286), 962 completed and returned the required 3-day food diary and 822 produced usable diaries which were complete and representative of usual intake. Five were excluded due to use of medications known to affect BP and three did not have their BP measured, which reduced the subject number to 814 (419 boys and 395 girls). Consent for participation in the study was obtained from the subjects and their parents or guardians. Ethics were approved via the ethics committees of Princess Margaret Hospital and KEMH.

Assessment of Dietary Intake

A 3-day food diary in household measures was used to assess dietary intake. This is a validated tool for use in a younger population.[17] Subjects who agreed to participate were provided with a food diary, metric spoons and cups, and both written and verbal instructions.

The food diaries were completed by the adolescents with parental assistance if required. The adolescent was asked to reflect whether each day of the food diary was an accurate representation of their usual diet. Unrepresentative food diaries were excluded from analysis. Additional information required was obtained by a dietitian via telephone in order to improve accuracy of estimated intake.[18]

Records were entered into FoodWorks Professional Version 5 (Xyris Software Pty Ltd, Queensland, Australia), a dietary analysis program used to analyse nutrient intake in the Australian population.[19] As fructose values are not calculated by the software at the time of the study, intake was estimated for all foods containing 0.1 g of carbohydrate per 100 g or more with the aid of various nutrient databases.[15] Fructose data were adjusted for total energy intake using the residuals method.[20] Using energy-adjusted fructose intake takes into account the amount of fructose an adolescent is consuming in relation to their energy intake. This helps to distinguish between adolescents who eat larger volumes of food and therefore have greater fructose intake as a result of overall higher intake, and those who are consuming a fructose-rich diet.

Assessment of Physical and Physiological Characteristics

The adolescents underwent a physical assessment at the Telethon Institute of Child Health Research in Perth, Western Australia. Height was measured to the nearest 0.1 cm using a Holtain Stadiometer, and weight to the nearest 100 g using a Wedderburn Digital Chair Scale. Adolescents were dressed in singlet tops and running shorts for both measurements. Body mass index (BMI) was calculated (weight (kg)/ (height $(m)^2$). BMI categories of underweight, normal weight, overweight, and obese were defined using the Cole criteria for this age group.[21, 22] A research assistant took waist measurements at the level of the umbilicus to the

nearest 0.1 cm until two readings were within a centimetre of each other. The Tanner stages of pubic hair development scale was used to determine reproductive development stage of the adolescents via a privately completed questionnaire.[23] Aerobic fitness, used to represent physical activity, was determined from the heart rate whilst on a bicycle ergometer using the Physical Work Capacity 170 protocol.[24]

A Dinamap ProCare 100 Monitor (General Electric Healthcare Technologies, Rydalmere, New South Wales Australia) with appropriate cuff sizes was used to measure BP. Adolescents were rested for five minutes in a sitting position and BP's were determined from the last five readings taken over a period of 10 minutes. Mean arterial pressure (MAP) was calculated as DBP plus one third of the pulse pressure. Fasting blood samples were analysed by the PathWest Laboratory at Royal Perth Hospital for uric acid using a Technicon Axon analyser and Technicon methods and reagents (Bayer Diagnostics).

Subjects were categorised as having high blood pressure if either their systolic or diastolic blood pressure was above age and gender specific adolescent definitions derived from the International Diabetes Federation (IDF) and the National Cholesterol Education Program Adult Treatment Panel III (ATP).[25]

Sociodemographic and Family Characteristics

The carers of the adolescents were asked to report their education level, maternal age at conception, family income, family history of hypertension and whether the household was single or double parent. Maternal education level was categorised by the highest school year completed (grade 10 or less, grade 11 or grade 12). Maternal age at conception was also stratified (less than 20 years, 20-29 years, or 30 years and older). Family income, reported as

gross annual Australian dollars, was divided into three groups; less than $35 000, $35 000- 70 000, or greater than $70 000. A positive history of family hypertension was recorded if a biological parent had been medically diagnosed.

Potential Confounding Factors

The potential confounding factors considered in this study included age, corrected gestational age, gender, birth weight, BMI, waist to height ratio, waist circumference, pubic hair development stage, family history of hypertension, level of maternal education, maternal age at birth, single parent families, family income, energy intake, dietary sodium, dietary potassium, dietary fibre, dietary vitamin C, caffeine intake, alcohol intake, physical activity, screen time and aerobic fitness. Any supplementary vitamin C recorded in the food diary was included in assessment of dietary vitamin C intake.

Statistical Analysis

Predictive Analytics Software (PASW) for Windows, version 18.0 2009 (SPSS Inc., IBM, Chicago, IL, USA) was used for statistical analysis. Potential confounding factors were assessed for normality and were tested accordingly. Pearson's correlation assessed normally distributed continuous variables. Spearman's Rho correlation was used to assess skewed, continuous data. Independent t-tests assessed normally distributed variables with two categories and one-way ANOVA assessments were conducted for normally distributed variables with three or more categories. Significant confounding factors were then further assessed by multiple linear regression to determine their impact on the dependent variables (SBP, DBP, MAP and serum uric acid). Confounding factors which were not significant and did not contribute to improving the R square value for the multiple linear regression models were removed.

Boys and girls were compared by independent t-tests for dietary, BP, uric acid or physical characteristic differences (mean ± standard deviation (s.d.) reported). Multivariate linear regression analyses which were unadjusted, adjusted for age and BMI, and fully adjusted for confounding factors, were used to analyse relationships between energy adjusted fructose intake with SBP, DBP, MAP and serum uric acid. For comparison, absolute fructose was assessed by multivariate linear regression using the full models, but with additional adjustment for energy intake. Multivariate linear regression also assessed the relationship between serum uric acid and BP variables using unadjusted, adjusted for age and BMI, and fully adjusted models. As boys and girls had significantly different values for energy adjusted fructose intake, serum uric acid, SBP and MAP, the multivariate linear regression analyses were conducted by gender. One way ANOVA and chi-square analyses compared quartiles of energy adjusted fructose intake and serum uric acid with BP variables. Confounders were considered significant at $P < 0.05$.

RESULTS

Subjects

Mean age of the adolescents included in this study was 14.2 ± 0.2 years, ranging between 13.0 and 14.9 years. Descriptive data for anthropometric, BP and dietary intakes for the girls and boys are given in **Table 1**. Boys were significantly heavier and taller than girls, with higher energy intakes. Boys also had larger intakes of carbohydrate than girls; however this difference was insignificant when adjusted for energy. Absolute fructose intake was higher in boys ($P<0.01$). When adjusted for energy, fructose intake was lower in boys than girls ($P<0.01$). The average intake for energy adjusted fructose intake in the 95^{th} percentile (top 5 %) for the genders combined was 84.5 g. Fructose provided 9.2 % of total energy intake in

the group. There were no significant correlations determined between energy adjusted fructose intake with weight (P= 0.481) or BMI (P= 0.991). Serum uric acid was significantly higher in boys, when compared to girls. Systolic BP and MAP were lower in girls than boys (P<0.01). Diastolic BP was not significantly different between genders. The prevalence of high SBP and/or DBP in the group was 10.6% when defined using age and gender-specific blood pressure cut-points.[25]

Fructose, Serum Uric Acid and Blood Pressure

Multivariate linear regression models examined energy adjusted fructose intake with SBP, DBP, MAP and serum uric acid (**Table 2**). There were no significant associations between energy adjusted fructose and the BP variables for either gender. Multivariate linear regression analyses for serum uric acid showed a positive association with energy adjusted fructose for boys in an unadjusted model, a model adjusted for age and BMI only (partially adjusted), and a fully adjusted model. Assessment for girls showed a significant negative association in unadjusted and partially adjusted models, but not the fully adjusted model. Absolute fructose was assessed using the fully adjusted models but with the addition of energy intake as a confounding factor. Similar results were obtained for absolute fructose and uric acid with statistical significance observed in boys only (unstandardised β coefficient 0.001; CI 95% 0.0002 -0.001; standardised β coefficient 0.207; P<0.01).

Uric Acid and Blood Pressure

Multivariate linear regression models examined serum uric acid with SBP, DBP and MAP (**Table 3**). Boys showed significant relationships between serum uric acid and SBP in all three models (P< 0.01) and MAP in unadjusted and fully adjusted models (P< 0.01), with borderline significance when adjusted for age and BMI (P= 0.053). An association was

observed for girls between serum uric acid and SBP in an unadjusted model, but significance disappeared when confounding factors were considered.

Energy Adjusted Fructose Quartiles

Quartiles of energy adjusted fructose intake were determined for girls and boys separately (**Table 4**). Assessment by one way ANOVA showed borderline significance for serum uric acid (P= 0.052) in boys. However, post hoc testing showed no significant differences between energy adjusted fructose quartiles for serum uric acid. Assessment by quartile also demonstrated associations for height, sodium, caffeine and vitamin C in boys which were considered in the multivariate linear regression analyses. In girls significance was observed for dietary sodium, caffeine and vitamin C, also accounted for in multivariate linear regression.

Serum Uric Acid Quartiles

Assessment of energy adjusted fructose intake and BP variables by quartiles of serum uric acid were conducted for both genders (**Table 5**). For boys, one way ANOVA analyses showed that SBP and MAP were significantly different between quartiles of serum uric acid. Systolic BP and MAP increased in a step-wise manner with increasing serum uric acid. Boys in the highest quartile of serum uric acid had significantly higher SBP (P< 0.0001) and MAP (P< 0.05) than those in the lowest quartile of serum uric acid. One way ANOVA demonstrated an association for SBP in girls, but no significance was demonstrated in post hoc testing between quartiles.

DISCUSSION

Relationship between Fructose Intake and Blood Pressure

No direct relationships were shown between absolute or energy adjusted fructose and SBP, DBP and MAP in boys or girls which supports the null hypothesis. Several cross sectional studies differ from our findings, reporting significant positive associations between fructose intake or sugar-sweetened beverage intake with BP.[6, 7, 11] Points of difference include the use of 24-hour food recalls in other studies, which may produce less representative results compared with 3-day food diaries,[17] the measurement of fructose from sugar-sweetened beverages alone rather than from the whole diet, the smaller sample size of this study, differing nationalities, the assessment of genders combined rather than independently, and the younger age of the Raine Study population.

Relationship between Fructose and Uric Acid

A positive association was observed between absolute and energy adjusted fructose with serum uric acid in boys. Assessment for girls showed a significant negative association in unadjusted and partially adjusted models, but not in fully adjusted models, which suggests that the result may be due to confounding. When boys were divided into quartiles of energy adjusted fructose the relationship was less distinct. Weakly but significantly greater uric acid concentrations and BP have been previously observed with greater intakes of sugar-sweetened beverage intake in 4867 American adolescents ($P< 0.05$).[11] However, gender was reported as an insignificant modifier for the relationship between sugar-sweetened beverage intake and serum uric acid.

The link we observed between fructose intake and serum uric acid in boys may be due to the way fructose is metabolised. Unlike glucose and galactose, fructose oxidation in the liver bypasses several regulatory stages. The liver therefore has less control over the flux of fructose through fructolysis, resulting in uric acid as a by-product.[8]

Relationships between Serum Uric Acid and Blood Pressure

Our study results showed positive associations between serum uric acid with SBP and MAP in boys, but not DBP. Analysis for girls showed significance in unadjusted models, but not the partially or fully adjusted models, suggesting that serum uric acid is not a significant independent predictor of BP in girls. In adolescents, serum uric acid has been related to both hypertension and metabolic syndrome.[11, 26] A positive uric acid-BP association (SBP and DBP $P< 0.001$) has been previously shown in adolescents with and without hypertension,[27] and uric acid concentrations in childhood and adolescence have been shown to predict adult SBP and DBP $P<0.001$).[26] Elevated serum uric acid is also considered to be a potential risk factor for cardiovascular disease in the adult population.[28]

Results of rodent models and human studies suggest that the link between uric acid and BP is due to endothelial dysfunction resulting from a reduction in nitric oxide formation and pro-oxidant effects on endothelial cells.[29, 30] Along with a response to this by the renin-angiotensin system[30], hyperuricaemia would result in vasoconstriction, thus leading to an elevation in blood pressure. Adding strength to the association are studies which have shown that fructose-induced hypertension can be changed by manipulating uric acid concentrations.[12, 31] In an uncontrolled study of healthy men, a high fructose diet for two weeks increased uric acid and BP but subjects who were given allopurinol (a xanthine oxidase inhibitor preventing the formation of uric acid) did not experience a significant increase in uric acid or BP.[12] Similarly in hypertensive adolescents, allopurinol significantly reduced uric acid and BP over a two week period.[31] These studies support the association observed in our study between uric acid and BP in boys.

Approximately 11% of our cohort were defined as having high blood pressure according to adolescent age-specific criteria. Based on a similar criteria, our figure is slightly higher than the 7% of US adolescents aged 12 to 19 years reported in the National Health and Nutrition Examination Survey (NHANES) as having high blood pressure,[32] which may be due to differences in age.

Gender Differences

There is literature which may explain why our study found associations in boys only. One common theory is that sex hormones contribute to the differences in serum uric acid concentrations between males and females.[33, 34] Serum uric acid concentrations increase in boys at the time of puberty, and also in postmenopausal women, further adding weight to the link between sex hormones and serum uric acid.[33, 34] Several studies support this theory, and have found oestrogen is protective against excessive serum uric acid concentrations in women.[33, 35] It is hypothesised that oestrogen increases uric acid excretion, resulting in reduced serum uric acid concentrations.[36] Additionally, oestrogen may promote vasodilation.[37] The adolescents from the current study were nearing the end of puberty, with a mean Tanner stage of four, the maximum stage being five.[23] This suggests that hormone concentrations in the adolescents would be nearing adult levels. This could explain the lower serum uric acid and BP in the girls who may have been benefitting from protective oestrogen effects. A study of 6768 American adolescents aged 12-17 years reported a similar effect with a significant positive association between uric acid and BP in males but not females.[38] Although a negative association was seen in girls in the partially adjusted model, the association was no longer significant in the fully adjusted model which accounted for additional confounding factors. This suggests that a true negative association is unlikely to be present.

Implications

Our results suggest that moderating fructose intake in adolescence, particularly for boys, may be beneficial in maintaining normal serum uric acid concentrations, which were independently associated with BP. In our population, beverages (excluding 100% fruit juice, milk and flavoured milks) were found to be the greatest contributors to fructose in the adolescents' diets.[15] Per capita, Australia ranks amongst the top 10 countries for soft drink consumption in the world.[39] Sugar sweetened carbonated beverages were the largest contributor at 62%, suggesting that reducing consumption of soft drinks and other sugar sweetened beverages could be a potential strategy for decreasing fructose intake in adolescents. Whole fruit was the second largest contributor to fructose intake, however, fruit is nutrient dense and therefore fruit restriction is not recommended to reduce fructose consumption due to health effects of fibre, potassium, vitamins and phytochemicals contained in fruit. It has been previously been reported that socioeconomic characteristics were associated with food sources of fructose in our cohort.[15] Adolescents who had older and more educated mothers consumed higher quantites of fructose from fruit, while consumption of fructose from from beverages was higher in adolescents from families with lower incomes.[15]

Strengths and Limitations

A strength of our study is the use of 3-day food diaries for the assessment of nutritional intake. Three-day food diaries assess nutrient intake more accurately than 24 hour recalls and have been validated in a younger population.[17] However, 3-day food diaries can also be considered as limited as only three days are covered, and therefore some foods eaten on

occasion may go unreported. Another strength of the study is the extensive assessment of fructose values by Woolley et al. which included 99.7% of foods consumed containing a minimum of 0.1 g of carbohydrate per 100 g.[15] A limitation stems from the cross-sectional study design, as no cause-effect relationships can be determined, and we also acknowledge that some of the observed significant associations may be due to chance, owing to the large number of statistical tests performed in analysis. A further limitation is the lack of a robust measure of dietary sodium as 24-hour urine collections were not conducted for this study. The adolescents who completed the 3-day food diaries did have similarities which may distinguish them from the general population of West Australian adolescents. They were more likely to have older mothers, higher family income or a lower BMI than the non-respondents.[40] This could limit generalisation of study findings, although the pregnant women involved in the Raine study were recruited from a public hospital (KEMH), and families who were involved in the study were more likely to be of middle to lower socioeconomic status initially.[41]

CONCLUSION

To our knowledge, the current study provides the first investigation of relationships between fructose intake, uric acid and BP in Australian adolescents. No independent significant relationships were observed between absolute or energy adjusted fructose and SBP, DBP and MAP in boys or girls which supports the null hypothesis. However, our results showed that increased fructose intakes in boys aged 13-15 years are associated with increased serum uric acid concentrations, which could act independently to increase SBP and MAP. This association was not observed in adolescent girls, possibly due to protective hormonal effects and smaller body size contributing to lower average serum uric acid, SBP and MAP. Maintenance of a healthy adolescent BP is essential in reducing the risk of diseases such as

early coronary heart disease.[3] Adolescent hypertension has also been associated with hypertension in adulthood and the associated increased risks of chronic disease, such as the cardiovascular diseases.[4] Our study adds to the limited body of evidence that investigates the relationship between increased fructose intake, serum uric acid and BP in adolescent populations. Longer term research is required to determine the underlying mechanisms between fructose metabolism, uric acid and BP to enable a better understanding of the effects of altering fructose intake on the health status of adolescents.

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SUMMARY TABLE

What is known about this topic

- Higher fructose intakes have been associated with higher serum uric acid and blood pressure in American adolescents and several studies of adults.
- The relationship is usually more prominent in males than females, which may be due to protective hormonal effects in females.
- Sugar-sweetened beverages contribute the largest proportion of fructose to Western diets.

What this study adds

- This research provides further evidence of a significant positive relationship between fructose and serum uric acid, and serum uric acid with systolic blood pressure and mean arterial pressure in male adolescents.
- To our knowledge, this research provides the first assessment between fructose intake, serum uric acid and blood pressure in Australian adolescents.

Table 1 Age, anthropometry, blood pressure and daily dietary intakes (mean ± s.d.) by gender of Raine study adolescents included in analysis.

	Girls (n=395)	Boys (n=419)	P[a]
Age (years)	14.0 ± 0.18	14.0 ± 0.18	0.83
Weight (kg)	55.9 ± 11.1	57.7 ± 12.6	0.03
Height (m)	1.62 ± 0.10	1.66 ± 0.09	<0.01
BMI (kg/m^2)	21.2 ± 3.8	20.7 ± 3.7	0.06
Underweight[b]	8.4%	5.3%	<0.01
Normal[b]	69.2%	71.4%	<0.01
Overweight[b]	18.6%	17.4%	<0.01
Obese[b]	3.8%	6.0%	0.04
Systolic Blood Pressure (mmHg)	108.8 ± 9.1	114.3 ± 10.2	<0.01
Diastolic Blood Pressure (mmHg)	59.3 ± 6.8	58.8 ± 6.8	0.27
Mean Arterial Pressure (mmHg)	75.8 ± 6.7	77.3 ± 6.8	<0.01
Serum Uric Acid (mmol/L)	0.27 ± 0.05	0.32 ± 0.07	<0.01

	Girls (n=395)	Boys (n=419)	P[a]
Total Energy Intake (kJ)	8271 ± 1769	10495 ± 2463	<0.01
Carbohydrate (g)	248 ± 62	315 ± 85	<0.01
Carbohydrate (%)	49.4 ± 6.4	49.4 ± 5.9	0.87
Dietary Fibre (g)	20.2 ± 6.2	24.3 ± 8.5	<0.01
Protein (g)	76.3 ± 19.7	100.5 ± 26.0	<0.01
Protein (%)	15.8 ± 2.9	16.4 ± 2.9	<0.01
Fat (g)	72.3 ± 19.7	90.1 ± 25.3	<0.01
Fat (%)	32.3 ± 5.0	31.7 ± 4.7	0.106
Fructose Intake (g)	48.3 ± 20.2	58.8 ± 26.6	<0.01
Energy Adjusted Fructose (g)	55.8 ± 16.2	51.9 ± 20.3	<0.01
Sodium (g)	2.48 ± 0.71	3.16 ± 0.91	<0.01
Potassium (g)	2.64 ± 0.73	3.35 ± 1.02	<0.01
Vitamin C (mg)	124.5 ± 84.1	134.3 ± 95.6	0.37

Abbreviation: BMI, body mass index.

[a] P values represent independent t-tests.

[b] Cole criteria categories for adolescent BMI.[21, 22]

Table 2 Multivariate linear regression analysis with energy adjusted fructose intake as the independent variable and systolic blood pressure, diastolic blood pressure, mean arterial pressure and serum uric acid as the dependent variables, in Raine study adolescents.

	Girls			Boys		
	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value
SBP						
Unadjusted	0.009 (-0.047, 0.065)	0.016	0.746	0.006 (-0.042, 0.055)	0.013	0.795
Age & BMI model	0.013 (-0.043, 0.068)	0.023	0.650	0.013 (-0.033, 0.058)	0.025	0.581
Full model[a]	-0.010 (-0.072, 0.052)	-0.018	0.754	0.008 (-0.044, 0.060)	0.016	0.759
DBP						
Unadjusted	-0.003 (-0.044, 0.038)	-0.007	0.886	0.007 (-0.026, 0.039)	0.020	0.688
Age & BMI model	-0.001 (-0.042, 0.041)	-0.002	0.970	0.009 (-0.024, 0.041)	0.025	0.605
Full model[b]	-0.005 (-0.049, 0.040)	-0.011	0.837	0.015 (-0.017, 0.048)	0.046	0.356
MAP						
Unadjusted	0.001 (-0.040, 0.042)	0.003	0.960	0.007 (-0.026, 0.039)	0.019	0.692
Age & BMI model	0.004 (-0.037, 0.045)	0.009	0.858	0.010 (-0.022, 0.042)	0.030	0.537

	Girls			Boys		
	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value
Full model[c]	0.001 (-0.043, 0.045)	0.003	0.957	0.015 (-0.016, 0.047)	0.047	0.342
SerumUA						
Unadjusted	**0.0004 (-0.001, 0.00004)**	**-0.119**	**0.029**	**0.0004 (0.00008, 0.001)**	**0.125**	**0.015**
Age & BMI model	**0.0003 (-0.001, 0.00001)**	**-0.101**	**0.043**	**0.0004 (0.00009, 0.001)**	**0.121**	**0.010**
Full model[d]	0.0003 (-0.001, 0.00003)	-0.109	0.073	**0.0005 (0.0001, 0.001)**	**0.154**	**0.006**

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; UA, uric acid; BMI, body mass index.

[a] Age, BMI, sodium, puberty, maternal education, fibre.

[b] Age, BMI, sodium, aerobic fitness, family history of hypertension.

[c] Age, BMI, sodium, aerobic fitness, family history of hypertension, fibre

[d] Age, BMI, sodium, vitamin C, puberty, aerobic fitness.

Bolded values are significant (P< 0.05).

Table 3 Multivariate linear regression analysis with serum uric acid as the independent variable and systolic blood pressure, diastolic blood pressure and mean arterial pressure as the dependent variables, in Raine study adolescents.

	Girls			Boys		
	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value
SBP						
Unadjusted	**24.43 (6.09, 42.76)**	**0.142**	**0.009**	**48.97 (34.55, 63.40)**	**0.325**	**<0.001**
Age & BMI model	12.20 (-7.90, 32.30)	0.071	0.233	**33.44 (18.39, 48.48)**	**0.222**	**<0.001**
Full model[a]	7.19 (-17.73, 32.11)	0.040	0.570	**28.44 (10.66, 46.23)**	**0.182**	**0.002**
DBP						
Unadjusted	4.63 (-9.13, 18.39)	0.036	0.508	2.12 (-8.14, 12.37)	0.021	0.685
Age & BMI model	5.22 (-9.91, 20.36)	0.041	0.498	-0.691 (-11.88, 10.49)	-0.007	0.903
Full model[b]	8.83 (-10.58, 28.24)	0.066	0.371	9.08 (-4.20, 22.35)	0.086	0.179
MAP						
Unadjusted	11.230 (-2.23, 24.69)	0.089	0.102	**17.74 (7.62, 27.85)**	**0.175**	**0.001**
Age & BMI model	7.55 (-7.29, 22.39)	0.060	0.318	10.68 (-0.158, 21.53)	0.105	0.053

	Girls			Boys		
	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value	Unstandardised β coefficient (95%CI)	Standardised β coefficient	P-value
Full model[c]	7.28 (-8.28, 22.84)	0.058	0.358	**15.00 (3.78, 26.23)**	**0.150**	**0.009**

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; UA, uric acid; BMI, body mass index; ad, adjusted.

[a] Age, BMI, sodium, puberty, maternal education, fibre.

[b] Age, BMI, sodium, puberty, family history of hypertension, single parent family, fibre.

[c] Age, BMI, sodium, aerobic fitness, family history of hypertension, single parent family, fibre.

Bolded values are significant (P< 0.05).

Table 4 One way ANOVA analyses of Raine study adolescent characteristics by quartile (Q) of energy adjusted fructose (mean ± s.d.).

	Quartile of energy adjusted fructose (g)				
	Q1	Q2	Q3	Q4	P[a]
	Boys (n= 418)				
Quartile	28.4 ± 7.8	44.2 ± 3.4	56.4 ± 4.4	78.7 ± 14.1	**<0.001**
Weight (kg)	57.4 ± 13.4	56.0 ± 11.5	58.9 ± 14.1	58.4 ± 12.6	0.345
Height (m)	1.66 ± 0.08	1.65 ± 0.10	1.67 ± 0.09	1.68 ± 0.08	**<0.05**
BMI (kg/m^2)	20.7 ± 4.1	20.5 ± 3.3	21.1 ± 4.3	20.5 ± 3.7	0.636
SBP (mmHg)	114.2 ± 10.8	112.6 ± 9.4	115.2 ± 10.3	115.3 ± 10.2	0.198
DBP (mmHg)	58.6 ± 6.7	58.7 ± 6.7	59.2 ± 7.0	58.7 ± 7.1	0.936
MAP (mmHg)	77.1 ± 6.7	76.7 ± 6.6	77.8 ± 7.0	77.6 ± 7.0	0.636
Serum UA (mmol/L)	0.31 ± 0.07	0.32 ± 0.07	0.33 ± 0.06	0.34 ± 0.07	0.052
Sodium (mg)	3433 ± 896	3204± 892	3017 ± 924	2987 ± 884	**0.001**
Potassium (mg)	3374 ± 957	3303 ± 1110	3360 ± 1031	3383 ± 983	0.943
Fibre (g)	25.0 ± 8.2	23.6 ± 8.6	24.0 ± 7.6	24.4 ± 8.5	0.668

	Quartile of energy adjusted fructose (g)				
	Q1	Q2	Q3	Q4	P[a]
Caffeine (mg)	14.9 ± 22.1	21.3 ± 26.2	27.3 ± 41.3	34.4 ± 36.1	**<0.05**
Vitamin C (mg)	100.9 ± 78.0	130.5 ± 98.6	143.2 ± 91.3	163.7 ± 103.2	**<0.001**
			n (%)		
Family history of HT	4 (3.8)	9 (8.6)	8 (7.7)	7 (6.7)	0.541
Annual family income ($AUD)					
< $35 000	19 (15.5)	19 (18.4)	18 (18)	19 (20.6)	0.648
$ 35000- $ 70 000	37 (41.7)	37 (33.0)	36 (31)	37 (38.2)	
> $70 000	47 (42.7)	47 (48.5)	46 (51)	47 (41.2)	
Maternal education					
Year 10 or less	35 (33.3)	33 (31.4)	30 (28.8)	37 (35.5)	0.755
Year 11	18 (17.1)	23 (21.9)	21 (20.2)	14 (13.5)	
Year 12	52 (49.5)	49 (46.7)	53 (51.0)	53 (51.0)	

	Quartile of energy adjusted fructose (g)				
	Q1	Q2	Q3	Q4	P[a]
	Girls (n= 394)				
Quartile	37.4 ± 6.2	49.4 ± 2.7	59.5 ± 3.0	76.9 ± 12.5	<**0.001**
Weight (kg)	56.6 ± 12.1	56.4 ± 11.4	54.9 ± 9.5	55.3 ± 11.4	0.628
Height (m)	1.62 ± 0.62	1.62 ± 0.60	1.61 ± 0.17	1.62 ± 0.06	0.870
BMI (kg/m^2)	21.5 ± 4.3	21.5 ± 3.7	20.7 ± 3.2	20.9 ± 3.7	0.313
SBP (mmHg)	109.4 ± 9.3	108.4 ± 9.5	109.1 ± 9.2	108.5 ± 8.3	0.815
DBP (mmHg)	60.2 ± 6.4	59.1 ± 6.5	58.7 ± 7.4	59.4 ± 6.7	0.468
MAP (mmHg)	76.6 ± 6.7	75.5 ± 6.7	75.5 ± 7.3	75.8 ± 6.0	0.628
Serum UA (mmol/L)	0.27 ± 0.06	0.27 ± 0.05	0.27 ± 0.05	0.26 ± 0.04	0.226
Sodium (mg)	2735 ± 750	2395 ± 554	2480 ± 796	2282 ± 628	<**0.001**
Potassium (mg)	2756 ± 714	2540 ± 712	2604 ± 650	2665 ± 832	0.197
Fibre (g)	21.2 ± 6.3	19.4 ± 6.3	19.8 ± 6.0	20.3 ± 6.6	0.217
Caffeine (mg)	15.3 ± 24.2	19.2 ± 24.8	18.1 ± 26.6	21.3 ± 23.3	<**0.05**

	Quartile of energy adjusted fructose (g)				
	Q1	Q2	Q3	Q4	P[a]
Vitamin C (mg)	96.9 ± 63.9	121.8 ± 88.8	126.4 ± 81.3	153.0 ± 91.7	**<0.001**
			n (%)		
Family history of HT	4 (4.0)	12 (12.2)	3 (3.0)	6 (6.1)	**0.037**
Annual family income ($AUD)					
< $35 000	17 (17.5)	28 (28.9)	25 (23.2)	23 (26.0)	0.114
$ 35000- $ 70 000	42 (43.3)	23 (23.7)	35 (39.4)	34 (35.4)	
> $70 000	38 (39.2)	46 (47.4)	40 (37.4)	39 (38.5)	
Maternal education					
Year 10 or less	43(43.4)	28 (28.6)	41 (41.4)	32 (33.0)	0.219
Year 11	12 (12.1)	21 (21.4)	13 (13.1)	14 (14.4)	
Year 12	44 (44.4)	49 (50.0)	45 (45.5)	51 (52.6)	

Abbreviations: ANOVA, analysis of variance; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; HT, hypertension; UA, uric acid.

[a] P values for one way ANOVA equality of means or Chi-square test for equality of proportions.

Bolded values are significant (P< 0.05).

Table 5 One way ANOVA analyses of energy adjusted fructose, systolic BP, diastolic BP and mean arterial pressure by quartile (Q) of serum uric acid (mean ± s.d.).

	Quartile of serum uric acid (mmol/L)				
	Q1	Q2	Q3	Q4	P[a]
	Boys (n= 380)				
Quartile	0.24 ± 0.03	0.30 ± 0.01	0.34 ± 0.1	0.41 ± 0.04	<0.001
Fructose[b] (g)	57.8 ± 18.9	56.8 ± 14	53.8 ± 16.3	54.1 ± 14.1	0.082
SBP (mmHg)	110.3 ± 9.0	114.1 ± 10.1	115.5 ± 0.5	118.0 ± 10.8	**<0.001**
DBP (mmHg)	58.7 ± 6.1	59.2 ± 7.4	58.5 ± 6.5	58.9 ± 7.5	0.917
MAP (mmHg)	75.9 ± 6.0	77.5 ± 7.4	77.5 ± 6.2	78.6 ± 7.6	**0.049**
	Girls (n= 338)				
Quartile	0.21 ± 0.02	0.25±0.01	0.28±0.01	0.34±0.03	<0.001
Fructose[b](g)	57.8 ± 18.9	56.8 ± 14. 9	53.8 ± 16.29	54.1 ± 14.1	0.284
SBP (mmHg)	107.3 ± 8.7	107.5± 9.9	110.1± 8.4	110.5 ± 8.6	**0.034**
DBP (mmHg)	59.1 ± 6.3	59.0 ± 6.1	59.7 ± 7.3	58.7 ± 7.0	0.794
MAP (mmHg)	75.1 ± 6.1	75.2 ± 6.5	76.5 ± 6.8	76.0 ± 6.8	0.426

Abbreviations: ANOVA, analysis of variance; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure.

[a] P values for one way ANOVA.

[b] Energy adjusted fructose.

Bolded values are significant (P< 0.05).