The Western dietary pattern is prospectively associated with non-alcoholic fatty liver disease in adolescents

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Short running head: The Western dietary pattern and fatty liver disease

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Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; FFQ, food frequency questionnaire

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Abstract

OBJECTIVES: Poor dietary habits have been implicated in the development of non-alcoholic fatty liver disease (NAFLD); however, little is known about the role of specific dietary patterns in the development of NAFLD. Our aim was to examine prospective associations between healthy and Western dietary patterns and NAFLD in a population-based cohort of adolescents.

METHODS: Participants in the Western Australian Pregnancy Cohort (Raine) Study completed a dietary assessment using a food frequency questionnaire at 14 years and liver ultrasound at 17 years (n = 995). Healthy and Western dietary patterns were identified using factor analysis and all participants received a z-score for these patterns. The Western dietary pattern was characterised by high intakes of soft drink, refined grains, red meat, full-fat dairy products, takeaway food, processed meats, sauces and dressings. Prospective associations between the dietary pattern scores and risk of NAFLD were examined using logistic regression models.

RESULTS: NAFLD was present in 151/995 adolescents (15.2%). A higher Western dietary pattern score at 14 years was associated with a greater risk of NAFLD at 17 years (Odds ratio 1.59; 95% confidence interval 1.17,2.14; $p < 0.005$) after adjustment for healthy dietary pattern, sex, dietary misreporting, family income, physical activity and sedentary behaviour. These associations were no longer significant after adjustment for body mass index at 14 years of age. In adolescents with a high waist circumference at 17 years, a healthy dietary pattern at age 14 was protective against NAFLD (OR 0.63, 95% 0.41, 0.96; $p = 0.033$), whilst a Western dietary pattern was associated with increased risk of NAFLD. **CONCLUSIONS:** A Western dietary pattern at 14 years was associated with an increased risk of NAFLD at 17 years and this relationship may act through an obesity pathway. In adolescents with a high waist

circumference, a healthy dietary pattern may protect against NAFLD, while a Western dietary pattern may increase the risk of NAFLD.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is pathogenically associated with obesity and insulin resistance and has been identified as a predictor of cardiovascular disease and type 2 *diabetes mellitus* in adults and children (1). As the prevalence of obesity and diabetes has increased world-wide over the past two decades, NAFLD is now the leading cause of liver injury (1). NAFLD may progress to cirrhosis, risking complications of hepatocellular carcinoma and liver failure, and is becoming an increasingly common indication for liver transplant (2). The paediatric and adolescent age group has not been immune to the global overweight and obesity epidemic, with the prevalence of NAFLD ranging between 3-13% in these populations (1, 3) and NAFLD affects up to 52% of overweight and obese children (4). These children are potentially at life-long risk of developing NAFLD related complications.

The pathogenesis of NAFLD and obesity is traditionally thought to be due to excess caloric intake in association with reduced energy expenditure (5); however, there is a paucity of evidence examining specific dietary habits and the development of NAFLD. Although excess adiposity is a major risk factor for NAFLD, it is not known whether specific dietary patterns predispose to NAFLD independently of excessive adiposity. Conversely, as not all overweight individuals will develop NAFLD, it is unknown whether specific dietary patterns may protect against the development of NAFLD in normal or overweight groups. Diet consists of complex combinations of foods and nutrients ingested together, which may act independently or interact in a complimentary, synergistic or antagonistic manner. Dietary pattern analysis examines the overall effect of diet (6), allowing quantification of the cumulative effect of multiple foods and nutrients and avoids issues of confounding and colinearity.

There are a number of studies reporting a prospective association between dietary patterns, adiposity and the metabolic syndrome in children (7-10); however, the evidence relating dietary patterns to NAFLD is limited. To our knowledge an association between dietary patterns and NAFLD has not been reported, although a higher intake of soft drinks and meat - the main components of a Western dietary pattern - has previously been associated with NAFLD in adults (11). We investigated the prospective relationship between dietary patterns at age 14 years with NAFLD at 17 years in adolescents participating in the Western Australian Pregnancy Cohort (Raine) Study.

Methods

Study Population

The Western Australian Pregnancy Cohort (Raine) Study is a prospective longitudinal study on which details have been published previously (12). In brief, 2,900 pregnant women were recruited through the public antenatal clinic and local private clinics in Perth, Western Australia between 1989 and 1991. A total of 2,804 women (97%) had 2,868 live births, and these children have undergone serial assessment at birth and at ages 1, 2, 3, 5, 8, 10, 14 and 17 years. All data collection for the Raine Study occurred in accordance with Australian National Health and Medical Research Council Guidelines for Ethical Conduct in Human Research and was approved by the ethics committees of King Edward Memorial Hospital for Women and Princess Margaret Hospital for Children, Perth Western Australia. Informed consent was obtained in writing from the adolescent and their primary caregiver.

Dietary patterns assessment at age 14 years

Identification of the Western and healthy dietary patterns in this cohort at age 14 years has previously been described (13) and evaluated (14). An evaluated semi-quantitative food frequency questionnaire (FFQ) (15) was mailed to the study adolescents' primary caregiver to complete with the adolescent. The FFQ provided usual frequency of consumption and serving size information on 212 foods or dishes, which were collapsed into 38 food groups that were defined *a priori* (13). Foods with a factor loading greater than an absolute value of 0.30 were considered important components of each pattern.

The healthy and Western dietary patterns differed predominantly in fat and sugar intakes and explained 84% of the total variance in food intakes (13). The healthy pattern was positively correlated with whole grains, fruit, vegetables, legumes, fish, fibre, folic acid and most micronutrients, and was inversely correlated with energy from total fat, saturated fat and refined sugar (13). The Western pattern was characterised by high intakes of take-away foods, red meats, processed meats, full-fat dairy products, fried potatoes ('hot chips' or 'French fries'), refined cereals, cakes and biscuits, confectionery, soft drinks, crisps, sauces and dressings. This pattern was positively correlated with most micronutrients except vitamin C and folic acid. Each subject received a z-score for each pattern, indicating how closely their reported dietary intake corresponded with the two patterns.

Dietary misreporting is a common source of measurement error that can obscure diet-disease relationships (16). Dietary misreporting was estimated using the Goldberg method (17), which estimates the cut-off levels for plausible reporting based on energy intake relative to basal metabolic rate and is an established method to identify the level of misreporting from dietary surveys (18, 19). These cut-offs were used to classify respondents as likely under-reporters, plausible reporters or over-reporters. Since dietary under-reporting is strongly associated with risk of overweight (20), excluding under-reporters would have removed those participants at greatest risk. Therefore, a categorical variable for misreporting was included as a covariate in the logistic regression models.

Liver ultrasonography at age 17 years

Liver ultrasonography was conducted at the 17 year follow-up. Trained ultrasonographers performed liver ultrasound using a Siemens Antares ultrasound machine, with a CH 6-2 curved array probe (Sequoia, Siemens Medical Solutions, Mountain View, U.S.A.) according to the protocol described by Hamaguchi and colleagues that provides 92% sensitivity and 100% specificity for the histological diagnosis of fatty liver (21). A single specialist radiologist, blinded to the clinical and laboratory characteristics of the subjects, interpreted the ultrasound images. Scores of 0-3, 0-2 and 0-1 were determined from captured images for liver echotexture (bright liver and hepatorenal echo contrast), deep attenuation (diaphragm visibility) and vessel blurring (intrahepatic vessel visibility), respectively. The diagnosis of FLD required a total score of at least 2, including echotexture score of at least 1.

Information on alcohol intake over the past 12 months was obtained from the FFQ. Adolescents with sonographic fatty liver and a self-reported weekly alcohol intake of less than 210 g and 140 g for males and females, respectively, were classified as having NAFLD (22). Medications and a comprehensive medical history were documented to exclude secondary causes of NAFLD and concomitant liver disease.

Biochemistry at age 17 years

Venous blood samples were taken after an overnight fast. Results from non-fasting samples were excluded from this analysis. Serum insulin, glucose, triglycerides, high density lipoprotein cholesterol (HDL-cholesterol), alanine transaminase (ALT), gamma glutamyltransferase (GGT) and high sensitivity C-reactive protein (hsCRP) were measured as previously described (23). HOMA-IR, as a measure of insulin resistance, was calculated by insulin [mU/L] x glucose [mmol/L] / 22.5) (24).

Anthropometry

Height, weight and waist circumference were measured by trained assessors using standardised methods at 14 and 17 years. Body mass index (BMI: weight (kg)/height $(m)^2$) was calculated and subjects were grouped into underweight, normal weight, overweight, and obese categories using International Obesity Task Force (IOTF) criteria at 14 years (25,26). Waist circumference was measured as the mid-point between the iliac crest and the lower costal margin by horizontally positioning a tape measure across the belly button and at the smallest girth at the back, taking the average of two measurements.

Family income

Primary caregivers were asked to report their gross family income per year at the 14 year follow-up (2003-2006). Eleven categories of income (in Australian dollars) were collapsed into four categories (≤ $30 000 pa, $30 001 - $50 000 pa, $50 001 - $78 000, > $78 000).

Physical activity and sedentary behaviour

At the 14 year follow-up, hours of physical activity per week and time spent watching television were assessed using a self-reported written questionnaire. Participants detailed the time spent exercising vigorously during physical education at school, and how often and for how long they got out of breath or perspired while exercising outside school hours.

Statistical methods

Chi square tests were used to compare characteristics of study participants at 14 years including sex, family income, BMI status, dietary misreporting, physical activity per week and sedentary behaviour (television viewing) according to NAFLD status at 17 years. Independent samples t-tests were used to compare mean values for biochemistry and central adiposity according to NAFLD status at 17 years. The odds of NAFLD were analysed in relation to z-scores for both dietary patterns using logistic regression. Further, dietary pattern scores were analysed in quartiles based on the total sample distribution. Associations between the dietary pattern as a continuous score and in quartiles are presented for three different models. The first model included scores for both healthy and Western dietary patterns, sex and dietary misreporting. A second model additionally adjusted for family income, frequency and intensity of physical activity and sedentary behaviour at 14 years. The third model adjusted for adolescent BMI at 14 years. A subgroup of adolescents with a waist circumference above 80 cm for females and 94 cm for males at age 17 (27) was examined in logistical regression models, adjusting for dietary patterns, sex, dietary misreporting, physical activity and television viewing.

To further explore any associations between the dietary patterns and NAFLD, intakes of key food groups in each pattern i.e. those having a factor loading ≥ 0.30 (13) were examined in relation to NAFLD risk. These were converted into quartiles and entered into separate logistic models adjusting for covariates, as per the models described above. In addition, the healthy and Western dietary pattern scores were retained in the models to test if food group associations were independent of the overall dietary patterns.

Initial exploratory analyses in the continuous models also tested the importance of aerobic fitness (watts) and alcohol intake at 14 years of age as confounders. However these did not improve the model or alter the associations between dietary patterns and NAFLD risk, and were, therefore, not retained in final models. All data analyses were conducted using IBM SPSS Statistics Release Version 19.0.0.1 (IBM SPSS Inc., 2010, Chicago, IL).

Results

Study participant characteristics

At the 14 year follow-up there were 2337 adolescents eligible (alive and not withdrawn from the study) and at 17 years 2168 adolescents were eligible to participate. A total of 1857 (79.5 % of traced) adolescents responded to the 14 year follow-up, of whom 1613 had complete plausible data from the FFQ (due to highly implausible energy intakes [<3000kJ/day or > 20,000kJ/day] 18 respondents were excluded from analysis). At age 17 years 1,170 adolescents underwent hepatic ultrasound. Complete data were available for 995 adolescents who provided dietary information and had ultrasound assessment for NAFLD. Of the 995 study participants with complete data, NAFLD was present in 151 (15.2%) at age 17 years (Table 1). Of those with NAFLD at age 17 years, 54.1% were overweight or obese at age 14 years.

Biochemistry and anthropometry profile at 17 years

The serum biochemistry and anthropometry profiles of study participants at 17 years are shown in order to characterise NAFLD in the cohort (Table 2). Subjects with NAFLD had higher insulin resistance (HOMA-IR), raised triglycerides and reduced HDL-C, elevated ALT, GGT and hsCRP, as well as greater adiposity (BMI, waist circumference and waist-to-hip ratio).

Dietary patterns and NAFLD

Associations between the dietary patterns scores at 14 years and NAFLD at 17 years are shown in Table 3. In the total population, the healthy dietary pattern did not show any associations with the odds of NAFLD, either as a continuous outcome (Model 2: OR 1.15; 95% CI 0.92, 1.44; $p = 0.212$) or as quartiles. However, a higher score for the Western dietary pattern was positively associated with the odds of NAFLD at 17 years (Model 2: OR 1.59; 95% CI 1.17, 2.14; $p = 0.003$). There was a significant association between increasing quartiles of Western dietary pattern scores and the odds of NAFLD (p for trend = 0.030). Those in the highest quartile for the Western dietary pattern had a 2.6 times greater odds of NAFLD (OR 2.64, 95% CI 1.34, 5.18; $p = 0.005$) compared to those in the lowest quartile (Model 2). However, after adjustment for BMI at age 14 years (Model 3), these associations were attenuated and no longer statistically significant, indicating that the association between the Western dietary pattern and NAFLD is likely acting through an obesity pathway. These associations did not change if waist circumference or abdominal skinfold was applied instead of BMI. The same result was found when BMI at 17 years was included in the model (data not shown). Figure 1 shows the association between Western dietary pattern and risk of NAFLD stratified by sex. There was a significant interaction between sex and the Western dietary pattern scores (p = 0.008) but not for the healthy dietary pattern, nor when BMI was included in the model (p = 0.079).

In a subgroup of adolescents with a high waist circumference at age 17, a healthy dietary pattern was significantly associated with reduced risk of NAFLD (OR 0.63, 95% 0.41, 0.96; p = 0.033). There was a strong trend towards the Western dietary pattern increasing the risk of NAFLD in this subgroup (OR 1.53, 95% 0.94, 2.50; p = 0.090).

Components of the Western dietary pattern

Since the Western dietary pattern was significantly associated with risk of NAFLD following adjustment for covariates, Table 4 illustrates the Western dietary pattern and main food components that make up the pattern, including the mean and median intakes in grams per day as well as the inter-quartile range of intake of these components. Adolescents in the top quartile for soft drink and sauces/dressings consumption had twice the odds of NAFLD. The sex specific results of Table 4 are provided in supplementary tables.

In multi-linear models the Western dietary pattern was a significant risk for BMI at 14 years (β 1.41; 95%CI 0.12-1.82; $p<0.0005$), abdominal skinfold at 17 years (β 2.14;

95%CI 1.26, 3.03; p<0.0005) and being in the top 25% of BMI categories at 17 years (OR: 2.17; 95%CI 1.65, 2.85; p<0.0005).

Discussion

A Western dietary pattern characterised by a high intake of takeaway foods, confectionary, red meat, refined grains, processed meats, chips, sauces, full fat dairy products and soft drinks was prospectively associated with NAFLD independent of sex, dietary misreporting, family income, frequency of physical activity and sedentary behaviour. In particular, high intakes of soft drinks, sauces and dressings were associated with an increased risk of NAFLD. The association between the Western dietary pattern and NAFLD was not independent of BMI, suggesting that this dietary pattern acts predominantly on NAFLD via obesity. Indeed, other studies have linked similar dietary patterns with obesity in adolescents (28,29). Whilst we did not observe any protective relationship between the healthy dietary pattern and NAFLD in the total cohort, in those females and males who had waist circumferences greater than 80 cm and 94 cm, respectively, the healthy dietary pattern reduced the risk of subsequent NAFLD, whilst the Western dietary pattern was associated with risk of NAFLD at age 17 years. Since dietary habits are formed during childhood and retained into adulthood, the Western dietary pattern has a potential influence on the perpetuation of NAFLD risk. These results support our previous finding in the Raine Study linking the Western dietary pattern with greater cardiometabolic risk (30). Although relationships with the dietary patterns were different for males and females, both were positively related to NAFLD.

Few studies have looked at the association of dietary patterns and NAFLD. One previous cross-sectional study of Israeli adults aged 24 to 70 years (*n* = 375) found an increased risk of NAFLD in those with a higher intake of soft drinks, while a higher intake of omega-3 rich foods reduced the risk (11).

A Western diet high in processed sugars and fat has been shown to cause deleterious effects in non-obese rats, with such a diet leading to the development of hepatic steatosis (31). We showed that a higher consumption of soft drink was associated with greater risk of NAFLD and the mechanism behind this may be through provision of excess kilojoules and large amounts of sugars such as fructose (29, 32). The consumption of fructose has been linked to NAFLD, as well as various aspects of the metabolic syndrome, including dyslipidemia, visceral adiposity, insulin resistance and high blood pressure (33). Soft drinks may contain large amounts of high fructose corn syrup (HFCS) (55% fructose; 45% glucose), consumption of which has increased substantially in the past 30 years (34).

Foods common in the Western dietary pattern - including refined grains, white bread, and confectionary - cause a rapid increase in postprandial plasma glucose and insulin levels and are associated with obesity, insulin resistance and diabetes (36). Such high glycemic index (GI)-foods cause increased hepatic fat storage in animal studies (37), with a similar association seen in humans, where high dietary GI was associated with increased hepatic steatosis, particularly in insulin resistant subjects (38). It is possible that some of the foods of the Western dietary pattern - if consumed in large serving sizes – may cause rapidly increased plasma glucose levels, which may translate into hepatic fat via the *de novo* lipogenesis pathway (39). Indeed, in one study, obese subjects with raised insulin levels had a higher rate of *de novo* lipogenesis compared to lean individuals when fed the same Western style diet (40).

We found that the Western dietary pattern was significantly associated with greater measures of anthropometry. The Western dietary pattern contains high concentrations of saturated, trans and monounsaturated fats (13) and animal models indicate that these fats may play a role in hepatic steatosis (41, 42). Fat accumulation occurs in the liver via chylomicron uptake after dietary fat intake, as well as via *de novo* synthesis of free fatty acids following dietary carbohydrate intake (43). There are few other studies considering dietary patterns and NAFLD in adolescents.

Our study benefits from being a population-based study in which a range of information on socio-demographic factors, physical activity and sedentary behaviour has been collected, thus allowing a thorough investigation of possible covariates. Our dietary patterns were similar to those described by others (16). We have previously shown that, when compared to a 3 day food record our FFQ classified 80 to 90% of subjects' nutrient intakes into the same or adjacent tertile as their food record and the FFQ was able to correctly rank a reasonable proportion of adolescents (28). In addition, we controlled for dietary misreporting using a standard method.

In conclusion, a higher score for a Western dietary pattern at 14 years of age was prospectively associated with NAFLD at 17 years following adjustment for sex, dietary misreporting, family income, physical activity and sedentary behaviour. This relationship appears to be acting through obesity, suggesting that efforts to reduce obesity in childhood and adolescence may be important for preventing the early development of NAFLD. In those adolescents with a high waist circumference, a healthy dietary pattern may protect against NAFLD, while a Western dietary pattern may increase the risk of NAFLD.

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Highlights

1. WHAT IS CURRENT KNOWLEDGE

NAFLD is linked to obesity but many patients have a normal BMI

Particular dietary components increasing risk are poorly documented

2. WHAT IS NEW HERE

A Western style diet increased the risk of NAFLD in adolescents

In adolescents with a high waist circumference, a healthy dietary pattern reduced the risk of NAFLD, while a Western dietary pattern increased the risk of NAFLD.