Childhood Adiposity Trajectories and Risk of Nonalcoholic Fatty Liver Disease in Adolescents

Short Title: Childhood Adiposity Predictors of NAFLD

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Conflicts of Interest

The authors have no conflict of interest relevant to this study or manuscript

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Abbreviations: NAFLD - nonalcoholic fatty liver disease; BMI - body mass index; NASH - nonalcoholic steatohepatitis; SFT – skinfold thickness, SAT - subcutaneous adipose thickness; VAT - visceral adipose thickness; SBP - systolic blood pressure; DBP - diastolic blood pressure; ALT - alanine aminotransferase; AST - aspartate aminotransferase; GGT - gamma-glutamyl transpeptidase, HDL-C – high density lipoprotein cholesterol; LDL-C - low density lipoprotein cholesterol, hs-CRP - high sensitivity C-reactive protein.

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Author contributions

1. Oyekoya T. Ayonrinde contributed to study concept and design, data analysis, interpretation of data, drafting the manuscript, revision of the manuscript and obtaining funding.
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Abstract

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) and its metabolic risk factors are recognized during childhood and adolescence. Identification of adolescents at risk of NAFLD from childhood anthropometry may expose opportunities to influence the hepatic and metabolic destinies of individuals. We sought associations between NAFLD diagnosed during adolescence and earlier life trajectories of anthropometry, in a population-based cohort of predominantly Caucasian adolescents.

Methods: Assessment for NAFLD, using questionnaires and liver ultrasound was performed on 1170 adolescents, aged 17 years, from the population-based Raine Cohort. We sought associations between NAFLD in adolescents and serial anthropometric measurements recorded from birth, childhood and adolescence.

Results: NAFLD was diagnosed in 15.2% of adolescents. Birth anthropometry, including birth weight, skinfold thickness and ponderal index, was not associated with NAFLD. However, adiposity differences between 17-year-old adolescents with NAFLD and those without NAFLD were apparent from age 3 years. Greater adiposity trajectories for weight, body mass index, skinfold thickness, mid-arm circumference and chest circumference from age 3 years onwards, particularly in males, were associated with the diagnosis of NAFLD and severity of hepatic steatosis at age 17 years ($p<0{\cdot}05$). The strength of the associations increased with age after 3 years for each adiposity measure (all $p<0{\cdot}001$).

Conclusions: Trajectories of childhood adiposity are associated with NAFLD. Adiposity attained by three years of age and older, but not at birth, was associated with the diagnosis and severity of hepatic steatosis in late adolescence. Exploration of clinically relevant risk factors and preventative measures for NAFLD should begin during childhood.

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Introduction

Metabolic disorders associated with obesity are increasingly recognized in adults and children. Nonalcoholic fatty liver disease (NAFLD) is predominantly diagnosed in adults, however adolescent and childhood NAFLD phenotypes share adiposity, dyslipidemia, insulin resistance or the metabolic syndrome with adult NAFLD.[1] Whilst generally considered a disease of modern times, detailed clinico-pathologic descriptions of NAFLD are found in the medical literature dating back to the 1850s.[2] With increasing population trends of overweight and obesity, NAFLD is now very prevalent in many countries[3] and may have implications for liver, cardiovascular and metabolic health. The histology of NAFLD has been refined during the last 40 years.[4-6]. Nonalcoholic steatohepatitis (NASH), the histologically more adverse form of NAFLD, is associated with increased risk of cirrhosis, atherosclerotic cardiovascular disease[7,8] and type 2 diabetes.[9] Several reports describe the spectrum of NAFLD, from plain steatosis through NASH and cirrhosis in children and adolescents.[10,11] Though adults and children with NAFLD may share similar metabolic risk factors, NAFLD in children may have distinct histopathological characteristics compared with adult NAFLD[12] and is frequently not suspected.[13]

The underlying pathogenesis of NAFLD is complex. Although the genetic risk and heritability of NAFLD is increasingly described,[14-18] the influence of intrauterine, postnatal and childhood growth, on the diagnosis of NAFLD later in life remains poorly defined. The developmental origins of health and disease hypothesis proposes that environmental factors during pregnancy and infancy influence the risk of adult disease.[19] Though low birth weight followed by rapid weight gain has been associated with adult insulin resistance and coronary events,[20] elevated hepatic aminotransaminase levels in older women[21] and future NAFLD,[22] the influences of postnatal and childhood growth have also been suggested as dominant drivers in the development of factors associated with NAFLD, namely cardiovascular risk, hypertension, obesity and raised liver enzymes in later life.[23-26] This observation has been extended to body mass index (BMI) at age 17 years conferring risk for coronary artery disease in young adults.[27] Hence adiposity trajectories during childhood and adolescence may offer insights into future NAFLD and highlight the appropriate time period for intervention.

A previously published cross-sectional assessment of 1,170 adolescents aged 17 years in the Western Australian Pregnancy (Raine) Cohort reported gender-specific differences in the prevalence of the metabolic syndrome, visceral and subcutaneous adipose tissue distribution, serum adipocytokine and transaminase levels, insulin resistance and systolic blood pressure between those with NAFLD compared with those without NAFLD.[1] Suprailiac skinfold thickness (a measure of subcutaneous adiposity) in both genders and serum alanine aminotransferase (ALT) level, in males, predicted NAFLD in adolescents in the Raine cohort. Candidate gene and genome-wide association studies of NAFLD in the Raine cohort also detected effects of suprailiac skinfold thickness independent of various polymorphisms,[17,18] with suprailiac skinfold thickness accounting for a greater improvement in the NAFLD prediction model fit compared to BMI.

The Raine cohort was representative of the Western Australian adolescent population at the time of the 17-year assessment[28] and has well-defined longitudinal characterization. Consequently, knowledge of the prospective risk of adolescent NAFLD from anthropometry serially measured from birth through adolescence has potential to contribute to the understanding of initial pathogenic factors for NAFLD and provide rationale for early intervention. Recent commentary has drawn attention to the difficulty of treating adult obesity and related conditions such as NAFLD and highlighted the importance of identifying the onset of risk for these conditions to enable timely preventative strategies.[29] Therefore, our study aimed to examine and identify associations between anthropometry at different time-points, adiposity trajectories from birth, through childhood and adolescence and a subsequent diagnosis of NAFLD at 17 years of age.

Subjects and Methods

Study population

The Raine Study was initiated as a pregnancy and birth cohort comprising 2,868 predominantly Caucasian live-born children recruited from King Edward memorial Hospital for Women between 1989 and 1992 from 2,900 pregnancies, in Perth, Western Australia. Of these, 1170 out of 1754 adolescents participating in the 17-year cross-sectional assessment attended ultrasound examination for fatty liver. The background and assessments in serial follow-up of the cohort has been detailed previously.[30]

Assessments

Anthropometric measurements were recorded at birth and serially through childhood and adolescence. Assessments occurred at ages 1, 2, 3, 5, 8, 10, 14 and 17 years, however

skinfold thickness was not measured at ages 8 and 14 years and waist circumference was only available at ages 14 and 17 years. BMI was derived from weight (kg)/ height (m^2). Ponderal index, a measure of leanness,[25] was calculated from weight/ $height^3$ (kg/m^3) and percentage of expected birth weight defined as the percentage of expected weight adjusted for gestational age. Weight (birth, year one) and BMI (all age assessments) were standardised for sex and age (age at birth was represented by a single time point) using the WHO Growth Standards for ages ≤2 years and using CDC Growth Standards for ages over 2 years.[31,32]. Weight and BMI z-scores were calculated and used in analyses. The 17-year cross-sectional assessment of the Raine cohort, conducted between July 2006 and June 2009, involved detailed questionnaires, anthropometric and cardiovascular examination and liver ultrasound. Serum from venous blood samples taken from an antecubital vein after overnight fasting was tested for glucose, insulin, ALT, aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), triglyceride, total cholesterol, HDL-C, low-density lipoprotein cholesterol (LDL-C), highly sensitive C-reactive protein (CRP), adiponectin, and leptin levels. All laboratory assays were performed at an accredited central laboratory (Pathwest Laboratories, Perth, Western Australia, Australia) using standard methodologies.[1,23] Data from the 17-year assessment, including the ultrasound methodology for diagnosing fatty liver, subcutaneous and visceral adipose thickness have previously been published.[1]

Diagnosis of NAFLD

Assessment for NAFLD in the Raine Study was performed for the first time during the 17-year cross-sectional assessment. The diagnosis of NAFLD was based on ultrasound characteristics and exclusion of significant alcohol intake. Ultrasound was used as it was the most practical method to screen large numbers of adolescents in a community setting. We used the protocol described by Hamaguchi and colleagues that provides 92% sensitivity and

100% specificity for the histological diagnosis of > 10% hepatic steatosis.[33] Information on alcohol intake patterns over the previous year was documented by self-reporting and by the completion of a validated semiquantitative food frequency questionnaire developed by the Commonwealth Scientific and Industrial Research Organisation (Adelaide, Australia).[34] In the current study adolescents with sonographic fatty liver and weekly alcohol intake of less than 210 grams and 140 grams for males and females, respectively, were classified as having NAFLD, consistent with recent NAFLD diagnosis and management guidelines.[35] As part of a subsequent assessment, subjects underwent noninvasive assessment of liver fibrosis using tissue elastography. Participants with a liver stiffness of greater than 8.7 kPa underwent standard clinical evaluation, with exclusion of autoimmune, viral or metabolic diseases. Institutional ethics committee approval was obtained from the Princess Margaret Hospital for Children Human Research Ethics Committee. Signed informed parental consent and adolescent assent at 17 years were obtained.

Statistical Analysis

Sex-specific analyses were performed to characterize gender differences between adolescents diagnosed with or without NAFLD at age 17 years, as previously described in the Raine Study (1). Variables were summarized by the mean and standard deviation for symmetrical distributions and median and interquartile range (IQR) for asymmetric distributions. Birth anthropometry and change in weight z-score between birth and one year were analyzed using Student's t-test. Anthropometry, serum biochemistry and cardiovascular characteristics between adolescents with or without NAFLD were compared using the independent t-test or Mann-Whitney U-test. Skinfold thicknesses, chest, mid-arm and waist circumference in adolescents with or without NAFLD were compared at each available age assessment using the Mann-Whitney U-test. Associations between suprailiac skinfold thickness and the

severity of hepatic steatosis were analysed using the Kruskal-Wallis test. Skinfold thickness was displayed as mean time-response curves for the NAFLD and non-NAFLD groups, with confidence limits calculated using a bootstrap technique (5000 repetitions) designed for repeated measures. BMI z-scores (adjusted for age and sex) were compared, between adolescents with or without NAFLD, using linear mixed effects models for longitudinal data; including fixed effects for age and age-squared, random effects for slope and intercept and a correlation structure of autoregressive order one. From each age assessment, independent predictors of adolescent NAFLD were determined using multivariate logistic regression analysis including terms for skinfold thickness, mid-arm circumference, chest circumference and BMI z-score. Due to consistency of skinfold thickness between various skinfold regions we used only suprailiac skinfold thickness in longitudinal and multivariate analyses, as it demonstrated the earliest differences between NAFLD and non-NAFLD groups and has previously been found to have the strongest association with NAFLD in this cohort. All statistical tests were two-sided and based on a significance level of 5%. No correction was made for multiple testing due to the correlated nature of the anthropometric data. Data were analyzed using IBM SPSS statistics package (version 20·0) and R: A language and environment for statistical computing (version 2·11·1).

Results

In the 17-year cross-sectional study abdominal ultrasound was performed on 1170 adolescents, of whom 1127 had waist circumference measured. After excluding 3 adolescents with fatty liver who consumed excessive amounts of alcohol, the prevalence of NAFLD was 15·2% (177/1167). NAFLD was more prevalent in females than in males (19·6% vs. 10·8%, p<0·001). Central obesity (waist ≥80 cm in females and waist ≥ 94 cm in males) was detected in 236 i.e. 21.1 percent (32·7% female and 9·9% male, p<0.001), of whom 63/180 (35%) of

females and 34/56 (60·7%) of males had NAFLD. Adolescents with NAFLD had a more adverse metabolic phenotype than those without NAFLD (Table 1).

Associations between Birth to Age 1 Year Anthropometry and Adolescent NAFLD

Birth anthropometry (birth weight z-score, percentage of expected birth weight, ponderal index, and all skinfold thickness measurements) was similar in adolescents diagnosed with or without NAFLD (all p>0·05) (Table 2). The change in weight z-score between birth and age 1 was similar in adolescents with or without NAFLD. Similarly, skinfold thickness, weight, crown-heel length and z-BMI at age 1 year were not associated with the diagnosis of NALFD (p>0·05 for all, data not shown).

Associations between Age Three to Ten Years (Childhood) Anthropometry and Adolescent NAFLD

Adolescents diagnosed with NAFLD at age 17 already had greater pre-existing adiposity, particularly BMI z-score, suprailiac skinfold thickness, chest and mid-arm circumference, from age 3 years onwards compared with those without NAFLD (Table 2 and Figures 1 and 2). By age 10 years, median suprailiac skinfold thickness in males who were subsequently diagnosed with NAFLD was nearly double that of males who did not have NAFLD (p<0·001) (Figure 1).

Associations between Ages 14 and 17 Years (Adolescent) Anthropometry and Adolescent NAFLD

By adolescence there were well-established differences in anthropometric features between adolescents with or without NAFLD. Adolescents diagnosed with NAFLD had significantly higher adiposity (p<0·001 for weight, BMI, skinfold thickness, mid-arm and waist

circumference) compared with those without NAFLD. In particular, median skinfold thickness in 17-year old males with NAFLD was twice that of males without NAFLD (Figure 1). Figure 2 illustrates the strong association between increasing BMI and diagnosis of NAFLD from the longitudinal analysis ($p<0{\cdot}001$).

Childhood Adiposity and Severity of Sonographic Hepatic Steatosis

Increasing adiposity from age 3 years onwards was associated with increasing sonographic severity of liver steatosis at age 17 years ($p<0{\cdot}05$ at 3 years, $p<0{\cdot}001$ from 5 years onwards for suprailiac skinfold thickness; $p<0{\cdot}001$ from 5 years onwards for longitudinal BMI z-score in both genders [Figure 3]).

Relationship between childhood and adolescent suprailiac skinfold thickness and serum ALT in adolescents

Suprailiac skinfold thickness from age 3 years onwards in females and from age 10 years onwards in males was associated with raised serum ALT levels (> 30U/L in females, >40U/L in males) at age 17 years (all $p<0{\cdot}05$).

Age-specific Prediction of Adolescent NAFLD

The strength of association between childhood adiposity and NAFLD risk increased with age. Using multivariate logistic regression analysis, adiposity predictors of adolescent NAFLD were determined from skinfold thickness, BMI z-score and mid-arm circumference. Suprailiac skinfold thickness contributed more to the prediction of NAFLD in adolescents at all ages from 3 years onwards compared to the other measures of adiposity, including BMI. (Table 3). No association was detected between gender and risk of NAFLD after adjustment

for suprailiac skinfold thickness, whereas gender differences were still detected after adjustment for BMI z-score.

Discussion

In this study, pre-school age childhood anthropometry was associated with a diagnosis of NAFLD at age 17 years. Adiposity gains from age 3 years onwards were greater in adolescents diagnosed with NAFLD than those without NAFLD. The association of adiposity gains with NAFLD was most apparent in males and increased with age, highlighting a critical period of childhood when environmental influences (nutrition, physical activity), gene-environmental interactions and epi-genetic programming may influence the trajectory towards obesity-related diseases such as NAFLD.

In the Raine Cohort, childhood adiposity trajectories have already been shown to be associated with adolescent insulin resistance.[30] Our study examines the genesis of risk factors for NAFLD from childhood and adolescent anthropometric characteristics. There are presently no longitudinal data regarding the predictive utility of basic childhood anthropometry for future NAFLD in adolescence. In this cohort, suprailiac skinfold thickness in adolescents aged 17 years independently predicted NAFLD compared to metabolic factors and other anthropometry. We have now tracked anthropometric characteristics in the cohort starting from birth and observed suprailiac skinfold thickness, as a marker of adiposity from as early as age 3 years onwards, to be strongly associated with adolescent NAFLD. A role for dietary and physical activity habits is supported by the finding that in the Raine Study the Western dietary pattern, lower rates of physical activity and longer television-watching duration at age 14 years were associated with NAFLD at age 17 years.[36] Other data from the same cohort found childhood growth trajectories for weight and BMI were associated with

cardio-metabolic risk factors at age 17 years.[37] Also, NAFLD combined with co-existing cardio-metabolic risk factors was associated with subclinical cardiovascular disease determined by increased arterial stiffness in adolescents in the Raine Study.[38] These data demonstrate that the pathway to NAFLD and associated adverse cardio-metabolic characteristics is established in the first few years of life. Further studies examining the role of physical activity, infant and early childhood diet, as well as possible emerging risk factors such as gut microbiome diversity, will be important to guide interventions to prevent future metabolic disease.

Though subcutaneous fat is considered less metabolically active, hence less relevant to metabolic health than visceral fat, subcutaneous fat measured by skinfold thickness is easy to measure in children and adolescents and is positively associated with adolescent NAFLD. (1) Visceral adipose mass is much less developed in children, compared with adults, though accumulating rapidly with weight gain, particularly in males.[39,40] The potential importance of subcutaneous fat is also reported in the Amsterdam Growth and Health Longitudinal Study, in which skinfold thickness was a better predictor of high body fatness in adults than the BMI.[41] Thus both fat compartments may be relevant as markers of future NAFLD at varying points in the life spectrum

Strengths of our study include the prospective collection of quality data based on standardized study protocols, the longitudinal nature of the study, duration of follow up and previously well-described outcome measures in a population-based cohort. Limitations of this study are the single cross-sectional assessment for NAFLD, the use of ultrasound rather than histology, magnetic resonance imaging (MRI) or magnetic resonance spectroscopy to diagnose and quantify liver fat. Whilst the absence of histology restricts our ability to distinguish bland steatosis from NASH, hence interpretation of risk of future cirrhosis,

diabetes or cardiovascular disease relative to general population risk, liver biopsy of healthy adolescents in this population-based study is not justifiable. Further, a meta-analysis of the diagnostic accuracy and reliability of ultrasound has concluded that it is the imaging technique of choice for clinical and population settings, as well as correlating with metabolic abnormalities and visceral adiposity.[42,43] Thus, from a practical clinical translational perspective an understanding of the significance of ultrasound-diagnosed NAFLD remains relevant.

In conclusion, the genesis of risk of late adolescent NAFLD begins in the first few years of life, with differences in adiposity evident from three years of age. Examination of genetic-environmental interactions, epi-genetic and metabolic alterations in this critical early period of life may shed light on important risk factors for the development of future NAFLD. Knowledge that childhood obesity and trajectories of increasing adiposity have potential to confer not only increased risk for adverse cardiovascular outcomes but also adverse liver outcomes could provide insights for public health education and targeted research and interventional studies during childhood and adolescence to ameliorate the risk factors for future NASH, cirrhosis, type 2 diabetes mellitus and cardiovascular disease in adulthood.

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	Characteristic	Male			Female		
		NAFLD (n = 63)	**Non-NAFLD (n = 528)**	**p value**	**NAFLD n =113**	**Non-NAFLD (n = 463)**	**p value**
Adiposity	**Weight (kg)**	94.5 (20.2)	69.4 (11.0)	< 0.001	72.9 (17.2)	60.9 (10.0)	< 0.001
	Waist (cm)	97.7 (15.8)	78.3 (7.8)	< 0.001	85,3 (14.6)	75.5 (9.3)	< 0.001
	BMI (kg/m^2)	29.2 (5.9)	21.8 (3.1)	< 0.001	26.4 (5.9)	22.2 (3.4)	< 0.001
	Waist/hip ratio	0.90 (0.08)	0.83 (0.05)	< 0.001	0.82 (0.07)	0.78 (0.06)	<0.001
	Waist/height ratio	0.55 (0.09)	0.44 (0.04)	<0.001	0.51 (0.09)	0.46 (0.6)	<0.001
	SAT (mm)	31.0 (14.3)	12.5 (7.7)	<0.001	30.0 (14.7)	18.6 (8.6)	<0.001
	VAT (mm)	41 (16.6)	34.7 (9.9)	< 0.001	31.4 (9.8)	29.5 (8.7)	0.94
	Abdominal SFT (mm)	29.9 (11.1)	15.5 (8.5)	< 0.001	29.2 (8.5)	23.4 (7.3)	< 0.001
	Triceps SFT (mm)	20.5 (10.5)	10.0 (4.3)	< 0.001	22.9 (7.5)	18.3 (5.4)	< 0.001
	Subscapular SFT(mm)	22.3 (10.5)	11.0 (4.7)	<0.001	20.5 (8.4)	14.7 (5.4)	< 0.001
	Suprailiac SFT (mm)	26.2 (10.9)	11.4 (6.9)	<0.001	24.0 (9.1)	17.0 (6.7)	< 0.001
CVS	**SBP (mm Hg)**	124 (10)	119 (10)	< 0.001	110 (9.0)	109 (10.0)	0.30
	DBP (mm Hg)	60 (7)	59 (7)	0.37	60 (6)	60 (7)	0.85
	Pulse (per minute)	66 (12)	63 (10)	0.005	68 (10)	67 (10)	0.47
Biochemistry	**ALT (U/L)**	39.0 (23.3)	22.0 (9.9)	< 0.001	19.7 (13.3)	18.1 (10.2)	0.20
	AST (U/L)	31.3 (14.4)	27.0 (8.3)	0.001	21.3 (5.4)	22.0 ((5.1)	0.19
	GGT (U/L)	23.6 (14.1)	15.4 (7.3)	< 0.001	13.9 (6.8)	13.0 (6.8)	0.24
	Triglycerides (mmol/L)	1.25 (0.6)	1.0 (0.6)	0.006	1.1 (0.6)	1.0 (0.5)	0.01
	HDL-C (mmol/L)	1.08 (0.18)	1.22 (0.25)	<0.001	1.31 (0.28)	1.42 (0.31)	0.001
	LDL-C (mmol/L)	2.35 (0.79)	2.22 (0.64)	0.18	2.52 (0.74)	2.41(0.62)	0.13
	Glucose (mmol/L)	5.0 (0.5)	4.8 (0.7)	0.07	4.6 (0.4)	4.7 (0.4)	0.70
	Insulin (mU/L)	10.5 (6.7-19.2)	6.8 (4.4-9.9)	< 0.001	9.7 (6.8-15.6)	7.5 (5.1-10.7)	< 0.001
	hsCRP (mg/L)	1.1 (0.5-2.4)	0.4 (0.2-0.8)	<0.001	1.3 (0.4-4.6)	0.7 (0.3-1.8)	0.001
	HOMA-IR	2.34 (1.45-4.09)	1.43 (0.94-2.13)	< 0.001	2.05 (1.32-3.13)	1.53 (1.03-2.18)	< 0.001
	Adiponectin (mg/L)	6.6 (2.2)	8.4 (5.2)	0.009	9.3 (4.6)	11.9 (6.4)	<0.001
	Leptin (µg/L)	12.4 (6.2-28.4)	2.3 (1.4-5.2)	<0.001	43.3 (27.1-66.4)	22.4 (13.9-35.8)	<0.001

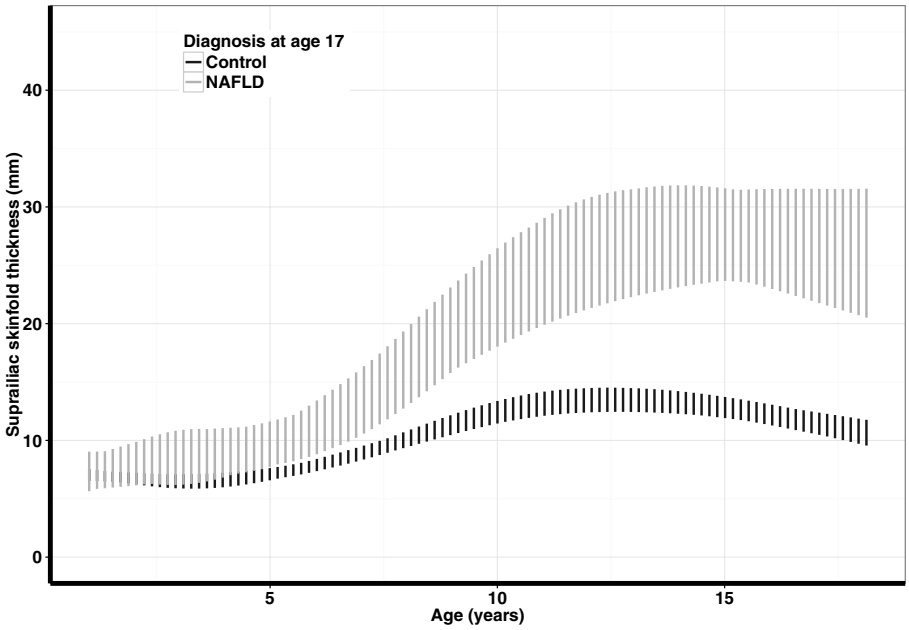
Table 1. Characteristics of the Cohort Comparing Anthropometric, Cardiovascular, and Biochemical Features in Males and Females. Results are presented as means and standard deviations or medians and IQRs. The P values compare adolescents with NAFLD to those without NAFLD. Adolescents with NAFLD had significantly greater adiposity, HOMA-IR, serum leptin and hsCRP, but lower HDL cholesterol and adiponectin values than those without NAFLD. Males with NAFLD also had greater visceral adiposity, systolic blood pressure and liver enzymes compared with males without NAFLD.

AGE	MEASUREMENT	MALE			FEMALE		
		Difference	**95% CI**	**P-value**	**Difference**	**95% CI**	**P-value**
0 (Birth)	Birth Weight z-score (SD)	-0·21	-0·17,0·58	0·27	0·01	-0·28,0·25	0·91
	% Expected Birth Weight	-2%	-2%, 5%	0·39	1%	-3, 2%	0·53
	Ponderal Index (kg/m^3)	0·06	-0·92,0·80	0·88	-0·25	-0·37,0·86	0·43
	Triceps SFT (mm)	0·00	-0·30,0·20	0·85	0·00	-0·20,0·20	0·77
	Parascapular SFT (mm)	0·00	-0·20,0·30	0·88	0·00	-0·20,0·30	0·82
	Infrascapular SFT (mm)	0·00	-0·20,0·30	0·73	0·00	-0·20,0·20	0·99
1	Change in weight z-score birth to 1 year	0·27	-0·73,0·18	0·24	-0·01	-0·25,0·26	0·96
	Chest circumference (cm)	-0·40	-1·00,0·20	0·21	-0·20	-0·60,0·30	0·45
	Arm circumference (cm)	0·00	-0·40,0·30	0·72	0·00	-0·30,0·20	0·92
	Suprailiac SFT (mm)	-0·10	-0·60,0·40	0·68	-0·20	-0·60,0·20	0·28
3	Suprailiac SFT (mm)	-1·10	-1·80,-0·40	0·002	-1·10	-1·60,-0·50	0·0002
	Chest circumference (cm)	-1·00	-1·80,-0·20	0·018	-0·60	-1·20,0·00	0·07
	Arm circumference (cm)	-0·50	-0·90,-0·10	0·019	-0·30	-0·60,0·00	0·06
5	Suprailiac SFT (mm)	-2·20	-3·50,-1·20	$6{\cdot}2\times10^{-6}$	-2·40	-3·20,-1·50	$3{\cdot}4\times10^{-8}$
	Chest circumference (cm)	-2·50	-3·50,-1·60	$9{\cdot}0\times10^{-8}$	-1·40	-2·20,-0·60	0·0003
	Arm circumference (cm)	-1·30	-1·80,-0·80	$1{\cdot}2\times10^{-6}$	-0·60	-1·00,-0·30	0·0008
8	Chest circumference (cm)	-4·50	-6·10,-3·00	$4{\cdot}9\times10^{-9}$	-2·50	-3·70,-1·40	$1{\cdot}4\times10^{-5}$
	Arm circumference (cm)	-1·90	-2·70,-1·20	$8{\cdot}3\times10^{-8}$	-1·10	-1·60,-0·60	$4{\cdot}0\times10^{-5}$
10	Suprailiac SFT (mm)	-10·80	-13·90,-7·90	$5{\cdot}5\times10^{-13}$	-5·10	-7·00,-3·10	$9{\cdot}0\times10^{-8}$
	Arm circumference (cm)	-3·30	-4·20,-2·50	$4{\cdot}5\times10^{-12}$	-1·40	-2·00,-0·80	$1{\cdot}8\times10^{-5}$
14	Waist Circumference (cm)	-16·00	-19·55,-12·50	$4{\cdot}9\times10^{-16}$	-7·50	-9·65,-5·40	$4{\cdot}3\times10^{-12}$
	Arm circumference (cm)	-4·00	-5·00,-3·00	$1{\cdot}2\times10^{-13}$	-2·00	-2·50,-1·10	$2{\cdot}5\times10^{-7}$
17	Suprailiac SFT (mm)	-16·30	-19·20,-12·50	$1{\cdot}7\times10^{-17}$	-6·95	-8·80,-5·10	$3{\cdot}6\times10^{-12}$
	Arm circumference (cm)	-5·00	-6·00,-4·00	$3{\cdot}0\times10^{-16}$	-2·50	-3·20,-2·00	$2{\cdot}2\times10^{-12}$
	Waist Circumference (cm)	-19·80	-23·35,-16·15	$1{\cdot}3\times10^{-19}$	-8·25	-10·70,-5·75	$4{\cdot}4\times10^{-11}$

Table 2. Associations between anthropometry from birth to age 17 years in subjects with or without NAFLD diagnosed at 17 years. P-values compare NAFLD and non-NAFLD groups based on the Mann-Whitney U-test. Suprailiac skinfold thickness (SFT) from age 3 years onwards was associated with NAFLD in adolescents.

	Male				Female			
Age (years)	**Independent Predictive Factors**	**Odds Ratio**	**95% CI for Odds Ratio**	**P value**	**Independent Predictive Factors**	**Odds Ratio**	**95% CI for Odds Ratio**	**P value**
0	None	-	-	-	None	-	-	-
1	↑Suprailiac SFT (mm)	1·34	0·64, 2·77	0·43	↑Suprailiac SF (mm)	1·21	0·67, 2·14	0·53
3	↑Suprailiac SFT (mm)	4·02	1·72, 9·42	0·001	↑Suprailiac SF (mm)	2·17	1·21, 3·91	0·009
5	↑Suprailiac SFT (mm)	1·99	1·51, 2·64	<0·001	↑Suprailiac SF (mm)	2·39	1·78, 3·27	<0·001
10	↑Suprailiac SFT (mm)	1·73	1·51, 2·02	<0·001	↑Suprailiac SF (mm)	1·43	1·25, 1·64	<0·001
17	↑Suprailiac SFT (mm)	2·11	1·80, 2·52	<0·001	↑Suprailiac SF (mm)	1·79	1·54, 2·10	<0·001

Table 3. Sex-specific risk of NAFLD at age 17 presented as adjusted odds ratio per 5mm increase in suprailiac skinfold thickness (SFT). Suprailiac skinfold thickness was consistently the strongest adiposity predictor of NAFLD from age 3 years.



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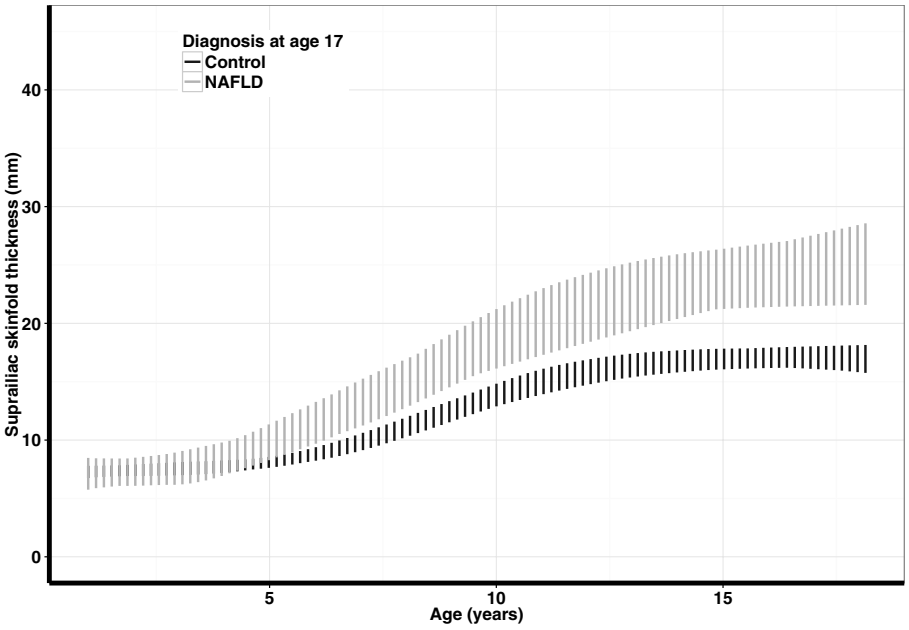

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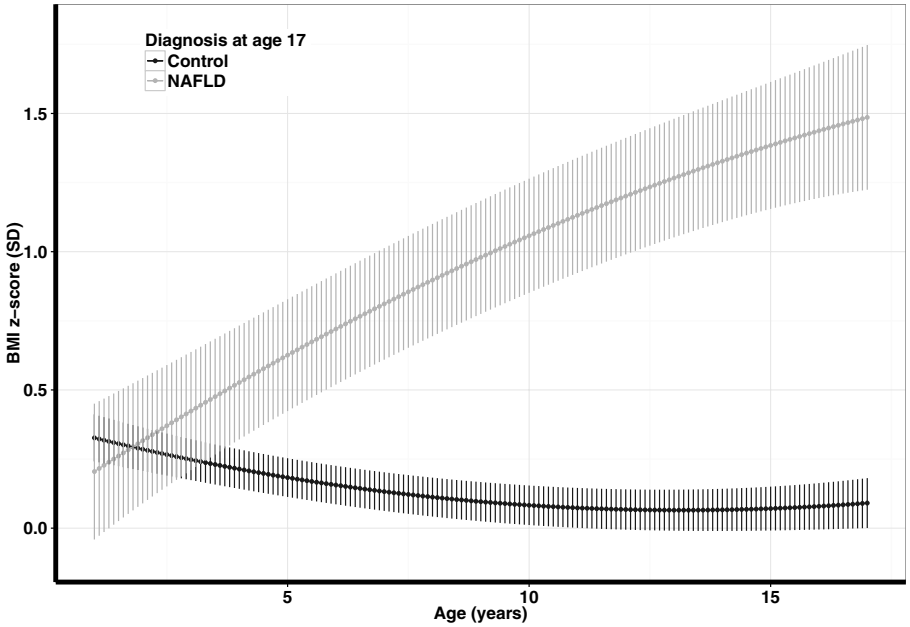

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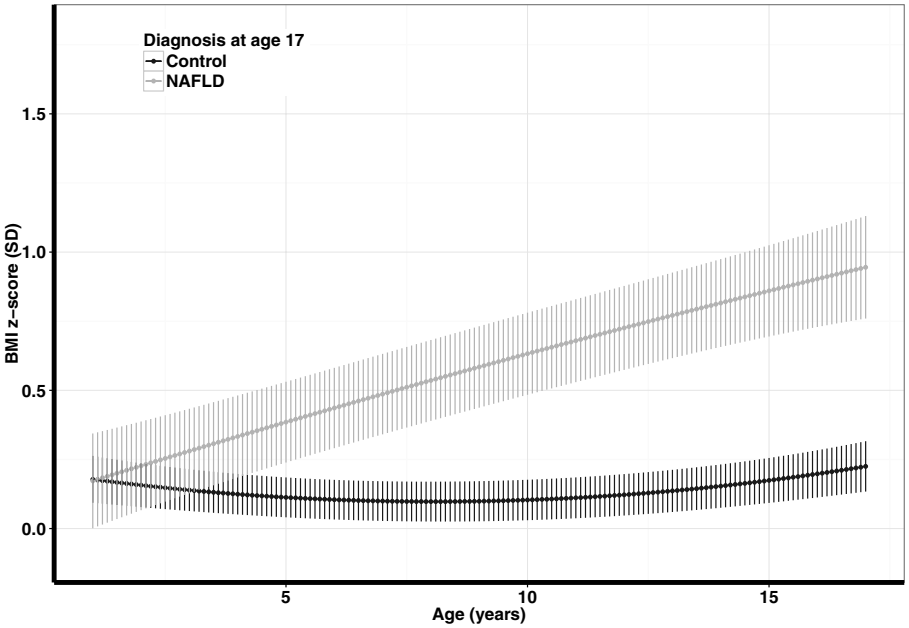

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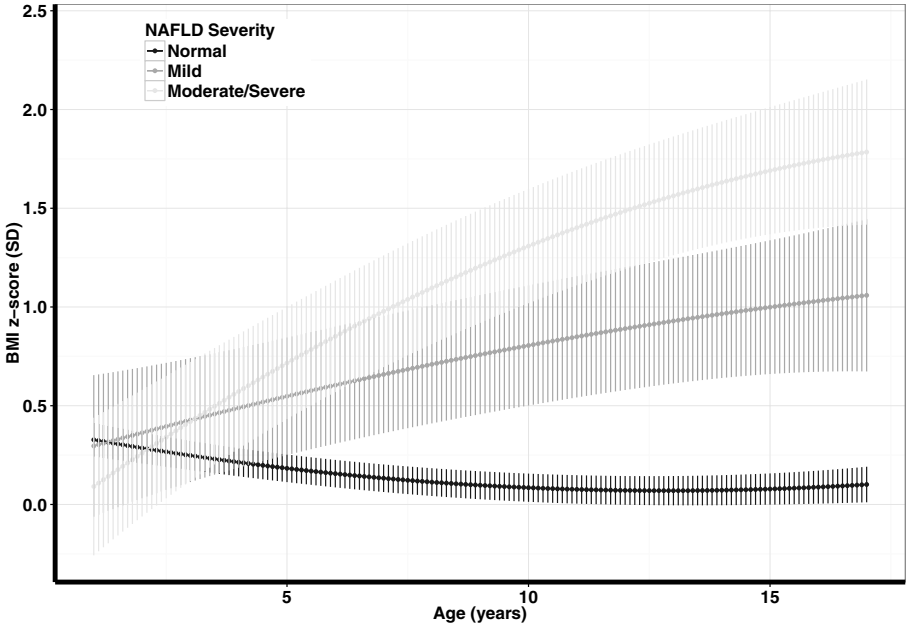

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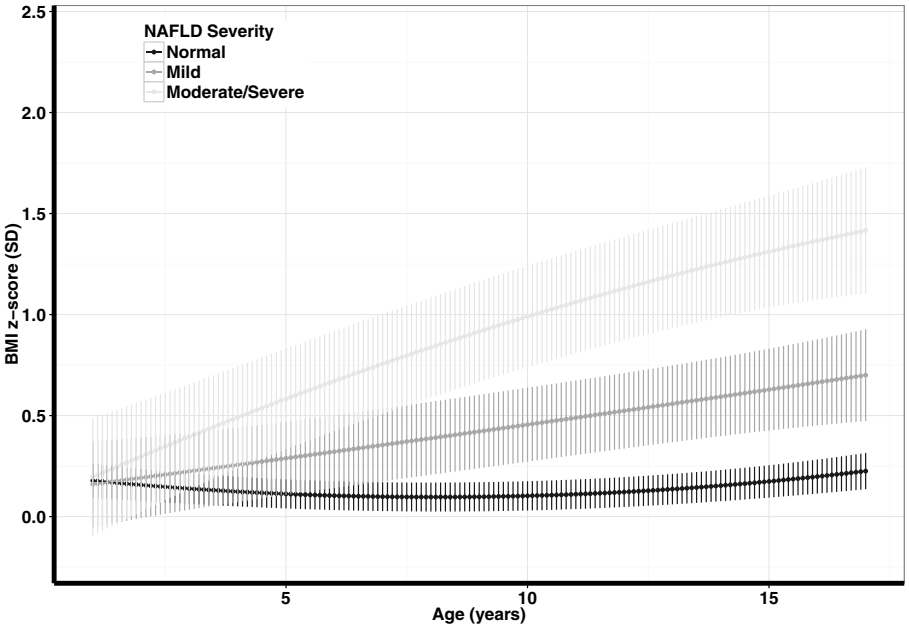

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