Childhood Adiposity and Nonalcoholic Fatty Liver Disease in Adulthood

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abstract

OBJECTIVE: To investigate the association of childhood adiposity and change in adiposity status from childhood to adulthood with nonalcoholic fatty liver disease (NAFLD) and abnormal liver enzyme levels in adulthood.

METHODS: Data were obtained from a population-based cohort of children aged 6 to 18 years started in 1987. From 2010 to 2014, 1350 subjects (aged 28–45 years) from the original cohort were followed. Childhood overweight and obesity were defined using BMI and subscapular skinfold thickness, respectively. In adulthood, ultrasound-based NAFLD, abnormal liver enzymes, and related risk factors were assessed.

RESULTS: Overweight or obese children were more likely to have adult NAFLD (males: odds ratio [OR] = 2.49 for BMI and 2.78 for subscapular skinfold thickness; females: OR = 3.34 and 3.61; all *P*s < .001) and alanine aminotransferase (ALT) elevation (males: OR = 1.64 and 1.66; females: OR = 2.12 and 3.01; all *P*s < .05) than children with normal weight for both sexes. Compared with subjects who had normal weight in childhood and were nonobese in adulthood, subjects who were obese in adulthood, irrespective of their childhood adiposity status, were more likely to have NAFLD and ALT elevation in adulthood for both sexes. However, subjects who were overweight or obese in childhood but became nonobese in adulthood had similar likelihood of having NAFLD and ALT elevation in adulthood for both sexes.

CONCLUSIONS: Overweight or obese children are more likely to have NAFLD and ALT elevation in adulthood. However, the risk associated with increased weight during childhood can be mitigated by becoming nonobese in adulthood.

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WHAT'S KNOWN ON THIS SUBJECT: Obesity is a well-established risk factor for nonalcoholic fatty liver disease and alanine aminotransferase elevation in both children and adults. However, whether the adverse consequence of childhood adiposity can be reduced by acquiring normal weight in adulthood remains unknown.

WHAT THIS STUDY ADDS: Overweight/obese children are more likely to have nonalcoholic fatty liver disease and alanine aminotransferase elevation in adulthood. In addition, the influence of childhood overweight/obesity on adult liver outcomes could be reduced by becoming nonobese in adulthood.

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Nonalcoholic fatty liver disease (NAFLD) is one of the most common causes of chronic liver disease and is present in >25% of adults worldwide.[1] NAFLD is defined as excessive fat accumulation in the liver without significant alcohol consumption and encompasses a wide spectrum of conditions, ranging from steatosis to steatohepatitis and fibrosis. NAFLD may progress into end-stage liver diseases such as liver cirrhosis, liver failure, and hepatocellular carcinoma.[2,3] NAFLD is a strong predictor of type 2 diabetes,[4,5] liver cancer,[6] and cardiovascular morbidity and mortality.[7,8] Fat in the liver can cause asymptomatic elevation of liver enzyme levels. Alanine aminotransferase (ALT) is considered to be the most specific marker of liver damage and has been shown to predict risks of type 2 diabetes,[9] cardiovascular diseases,[10] cancer,[11] and mortality.[12]

Obesity is a well-established risk factor for NAFLD and ALT elevation in both children and adults.[13,14] A recent meta-analysis showed that obese adults had a 3.5-fold increased risk for developing NAFLD.[15] Several longitudinal studies of children have reported the association between childhood adiposity and NAFLD in later adolescence and adulthood, but the results are inconsistent.[16–19] In addition, whether there is a sex difference in the association between childhood adiposity and adult NAFLD remains unclear. From a public health perspective, it is important to determine whether the adverse impact of childhood adiposity on adult NAFLD can be reduced by achieving normal weight in adulthood. On the basis of the longitudinal data from Beijing Blood Pressure Cohort Study, we aimed to investigate the association of childhood adiposity and change in adiposity status from childhood to adulthood with NAFLD and ALT elevation in adulthood.

METHODS

Study Population

The Beijing Blood Pressure Cohort Study was a population-based prospective cohort study investigating childhood determinants of adult cardiovascular diseases, and more detailed information has been previously described.[20] In brief, at baseline (April 1987–October 1988), 2462 school children aged 6 to 18 years were recruited from 6 elementary schools and 6 high schools located in urban areas of Beijing using a random cluster sampling design. From March 2010 to June 2014, all subjects were invited by mail and phone calls to undergo a health examination, and 1373 subjects aged 28 to 45 years accepted the invitation and had physical and clinical examinations including questionnaires, anthropometry, blood collection, and abdominal ultrasonography. The analysis sample for the current study consisted of 1350 participants after excluding participants who had a history of cancer and hepatitis, were receiving treatments for hepatic disease, or were taking medicines that influence liver function. The average length of follow-up was 23.3 years.

This study was approved by the Institutional Review Board and Ethics Committee of Capital Institute of Pediatrics, Beijing, China. Written informed consents were obtained from children and their parents/guardians at baseline and from themselves at follow-up visit.

Childhood Measurements

Weight was measured using a beam scale (RGT-140, Wuxi Weighing Apparatus Factory, Jiangsu, China), and height was measured using wall-mounted stadiometers (TG-2, Wuxi Weighing Apparatus Factory, Jiangsu, China) for children with lightweight clothing and without shoes according to a standard protocol.[21] Height and weight were measured twice to the nearest 0.1 cm and 0.1 kg, respectively, and the average values of the 2 measurements were used for data analysis. BMI was calculated as weight in kilograms divided by the square of height in meters. Childhood overweight and obesity by BMI were defined on the basis of the international sex- and age-specific BMI cut points.[22] Skinfold thickness (SFT) was measured just below the tip of inferior angle of the left scapula and at an angle of about 45° to the vertical with an Eiken-type skinfold caliper (Shanghai Medical Instrument Development, Shanghai, China) according to a standard protocol.[23] The subscapular SFT was measured twice to the nearest millimeter, and the average value was used in the analysis. Overweight/obesity by subscapular SFT was defined as subscapular SFT greater than or equal to age- and sex-specific 85th percentile.[24] Questionnaires including information on demographics and family history of chronic diseases were completed by parents of the participants.

Adulthood Measurements

All adulthood measurements were performed in Beijing Children Center for Chronic Prevention and Management. Height and weight were measured twice using an automatic instrument (BSM330, Biospace, Seoul, Korea), and the average of 2 measurements was used for analysis. For adults, overweight was defined as BMI ≥25 and <30, and obesity was defined as BMI ≥30. After fasting for at least 12 hours, venous blood samples were taken from the forearm of each participant. Serum samples were then separated within 30 min of collection and then stored at –80°C. Blood samples were tested in the clinical biochemical laboratory of Beijing Children Center for Chronic Prevention and Management, which was certified and licensed by local

quality and technical authority. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), ALT, and aspartate aminotransferase were measured with enzymatic methods in an automated analyzer. ALT elevation was defined by ALT >35 U/L for men or 23 U/L for women.[25] All inter- and intracoefficients of variation for these blood-based assays were <5%.

A questionnaire was used to collect demographic data, lifestyle factors (smoking and physical activity), medical history, and family history of chronic diseases. Cigarette smoking was defined as smoking at least 1 cigarette per day during the past 12 months.[26] Physical inactivity was defined as having moderate or vigorous physical activity <1.5 h per week during the past 12 months.[27] Alcohol consumption was obtained by a validated semiquantitative alcohol intake frequency questionnaire, including separate items for beer, wine, and liquor.[28] The participants were asked if they drank regularly (ie, drank at least once a week on a regular basis) during the past year. If so, participants reported the frequency and average amount (grams) each time for each type of alcohol on a typical drinking week during the past year. We then calculated the total alcohol intake per day (grams/day) assuming the following alcohol content by vol (v/v): beer 4%, wine 15%, and liquor 53%.[28] Alcohol drinking was defined as drinking more than once a week and heavy alcohol drinking was defined as consumption of alcohol ≥40 g/day in males and ≥20 g/day in females during the previous 12 months.[29]

Diagnosis of NAFLD

Abdominal ultrasonography was performed by a trained ultrasound physician with SonoSite M-Turbo Portable ultrasound equipped with a P21 1- to 5-MHz probe (SonoSite, Bothell, WA). Fatty liver disease (including alcoholic fatty liver disease and NAFLD) was diagnosed according to the criteria (2006) developed by the Fatty Liver Disease and Alcoholic Liver Disease Group, Chinese Society of Hepatology, Chinese Medical Association[29]: diffuse enhancement of near field echo in the liver (higher than that of kidney and spleen) and gradual attenuation of far-field echo. NAFLD was diagnosed as the presence of fatty liver on ultrasonography but without heavy alcohol drinking (as defined earlier).

Statistical Analysis

Values for TG were log-transformed before analyses because of skewed distribution. Comparison of variables for childhood weight categories was performed using *t* tests for continuous variables and χ^2 tests for categorical variables. To examine the influence of change in adiposity status from childhood on adult liver outcome, participants were categorized into 4 groups based on adiposity status in childhood and adulthood: participants who had normal weight in childhood and were nonobese in adulthood, participants who were overweight/obese in childhood but nonobese in adulthood, participants who had normal weight in childhood but were obese in adulthood, and participants who were overweight/obese in childhood and obese in adulthood. Multivariate logistic regression models were used to examine the association of childhood adiposity and change in adiposity status with NAFLD and ALT elevation in adulthood, adjusted for childhood age, length of follow-up, and adult factors. Before multivariate analyses, we used multivariate multiple imputation to replace missing values for potential confounders. We repeated all the analyses with similar results after excluding subjects with missing values for any covariates (n = 79) or subjects who had heavy alcohol drinking (n = 75). Statistical analyses were performed using SAS version 9.3 (SAS Institute, Cary, NC). Statistics significance was inferred at a 2-tailed P value <.05.

RESULTS

During 23.3 years of follow-up, among 1234 subjects who had normal weight in childhood, 95 (7.7%) became obese adults; among 88 subjects who had been overweight in childhood, 34 (38.6%) were obese in adulthood, and among 28 subjects who had been obese, 20 (71.4%) were obese in adulthood. Compared with subjects who had normal weight in childhood (defined by BMI), those who were overweight/obese in childhood had higher adult levels of BMI and ALT for males, and higher BMI, TC, TG, HDL-C, LDL-C, and ALT for females (all *P*s < .05) (Table 1).

Prevalence of NAFLD and ALT elevation

In adulthood, the prevalence of NAFLD and ALT elevation was 30.5% and 20.9%, respectively. Men had higher prevalence of NAFLD (41.7% versus 17.7%, P < .001) and ALT elevation (29.6% versus 10.9%, P < .001) than women. The prevalence of NAFLD and ALT elevation was higher among subjects who were overweight/obese in childhood compared with subjects who had normal weight for both sexes (all *P*s associations < .05) (Table 1).

Childhood adiposity and adult liver outcome

As shown in Table 2, after adjusting for sex, childhood age, and length of

TABLE 1 Characteristics of the Study Subjects Based on Assessment at Baseline in 1987 and During Follow-up in 2010–2014 According to Wt Status in Childhood ($N = 1350$)

Variables	Male		P^a	Female		P^a
	Childhood Normal Wt	Childhood Overweight/ Obesity		Childhood Normal Wt	Childhood Overweight/ Obesity	
N	659	72	—	575	44	—
Follow-up length, y	23.2±1.2	23.1±1.2	.79	23.4±1.3	23.4±1.7	.67
Childhood						
Age, y	11.8±3.8	11.3±2.7	.23	11.3±3.7	11.7±3.3	.45
BMI	16.7±2.4	23.1±2.6	<.001	16.3±2.6	23.5±3.4	<.001
Subscapular SFT, mm	7.5±2.9	16.4±6.2	<.001	9.3±4.7	18.6±7.7	<.001
Adulthood						
Age, y	35.0±3.9	34.5±2.7	.31	34.7±3.9	35.0±3.7	.68
BMI	25.6±3.5	31.1±4.4	<.001	22.6±3.6	27.8±3.9	<.001
Wt status, *n* (%)			<.001			<.001
Overweight	306 (46.4)	28 (38.9)		103 (17.9)	25 (52.3)	
Obesity	66 (10.0)	40 (55.6)		29 (5.0)	14 (31.8)	
TC, mg/dL	189.87±37.12	196.06±45.24	.21	173.24±29.78	185.62±34.03	.014
TG (mg/dL)[b]	139.02 (87.66–208.97)	165.58 (114.22–251.47)	.44	73.49 (53.13–107.14)	108.02 (69.07–123.08)	.05
HDL-C, mg/dL	45.63±10.83	44.08±8.89	.29	56.07±12.37	51.43±10.83	.03
LDL-C, mg/dL	116.01±29.78	116.78±28.23	.82	100.16±24.36	111.76±30.16	.007
ALT, U/L	32.7±27.9	37.4±24.3	.03	13.8±12.8	15.8±11.7	.05
AST, U/L	22.7±12.2	24.9±13.5	.14	16.6±7.2	16.3±6.7	.55
Drinking, *n* (%)	323 (53.0)	30 (45.5)	.24	131 (25.6)	9 (23.7)	.80
Smoking, *n* (%)	380 (62.4)	42 (63.6)	.84	150 (29.3)	10 (26.3)	.70
Physical inactivity, *n* (%)	251 (41.2)	26 (39.4)	.78	129 (25.2)	16 (42.1)	.02
NAFLD, *n* (%)	257 (39.1)	44 (62.0)	<.001	89 (15.5)	17 (38.6)	<.001
ALT elevation, *n* (%)	200 (30.3)	29 (40.3)	.05	68 (11.8)	10 (22.7)	.04

Values are mean ± SD for continuous variables or *n* (%) for dichotomous variables unless stated otherwise. Childhood overweight and obesity were defined using BMI. AST, aspartate aminotransferase.

[a] Comparison between groups was performed using *t* tests for continuous variables and χ^2 tests for categorical variables.

[b] Median interquartile range.

TABLE 2 Association Between Childhood Overweight/Obesity (in 1987–1988) and NAFLD and ALT Elevation in Adulthood (in 2010–2014) With 23 Years of Follow-up ($N = 1350$)

Adiposity Status in Childhood	Outcome: NAFLD				Outcome: ALT elevation			
	Model 1[a]		Model 2[b]		Model 1[a]		Model 2[b]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	P	OR (95% CI)	*P*
Male subjects								
Overweight/obesity by BMI[c]	2.49 (1.51–4.11)	<.001	2.32 (1.35–3.99)	.002	1.64 (1.03–2.63)	.04	1.48 (0.86–2.55)	.16
Overweight/obesity by subscapular SFT[c]	2.78 (1.71–4.50)	<.001	2.59 (1.56–4.30)	<.001	1.66 (1.03–2.67)	.04	1.43 (0.87–2.35)	.16
Female subjects								
Overweight/obesity by BMI[c]	3.34 (1.77–6.29)	<.001	2.63 (1.17–5.89)	.02	2.12 (1.00–4.46)	.05	1.59 (0.60–4.19)	.35
Overweight/obesity by subscapular SFT[c]	3.61 (2.13–6.12)	<.001	2.43 (1.32–4.47)	.004	3.01 (1.66–5.46)	<.001	2.32 (1.21–4.45)	.01

CI, confidence interval.

[a] Adjusted for childhood age and length of follow-up.

[b] Adjusted for childhood age, length of follow-up and adult factors (TC, TG, HDL-C, LDL-C, smoking, alcohol consumption, and physical activity).

[c] The reference group was children with normal wt by BMI or by subscapular SFT.

follow-up (model 1), children who had overweight/obesity defined by BMI or subscapular SFT were more likely to have adult NAFLD and ALT elevation than those with normal weight for both sexes, with females showing a stronger association than males. After additional adjustment for adulthood factors (TC, TG, HDL-C, LDL-C, smoking, alcohol consumption, and physical activity), the association of childhood overweight/obesity with NAFLD was reduced but still significant for both sexes, whereas the association with ALT elevation became nonsignificant except for the association for childhood overweight/obesity defined by subscapular SFT in females.

Change in Adiposity Status and Adult Liver Outcome

The prevalence of NAFLD and ALT elevation among subjects with different patterns of adiposity changes

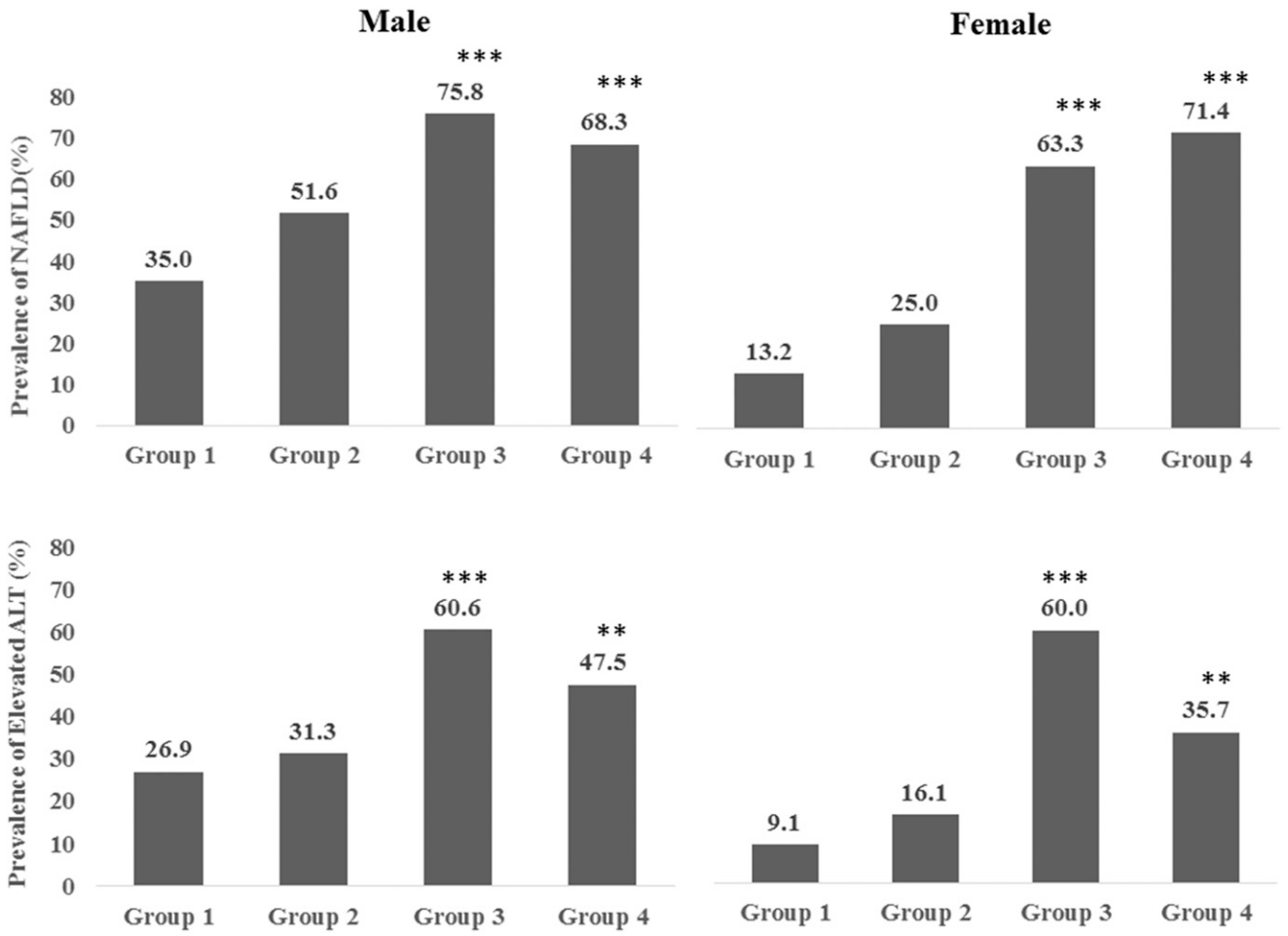

FIGURE 1

Prevalence of NAFLD and ALT elevation among individuals with 4 patterns of adiposity status changes between childhood and adulthood. Group 1 included participants who had normal weight in childhood and were nonobese in adulthood; group 2 included participants who were overweight/obese in childhood and nonobese in adulthood; group 3 included participants who had normal weight in childhood and were obese in adulthood; group 4 included participants who were overweight/obese in childhood and obese in adulthood. Compared with group 1: $^{**}P < .01$, $^{***}P < .001$.

between childhood and adulthood by sex is shown in Fig 1. As shown in Table 3, compared with subjects who had normal weight (defined by BMI) in childhood and were nonobese in adulthood, subjects who were obese in adulthood, irrespective of their childhood adiposity status, were more likely to have NAFLD and ALT elevation for both sexes, with females exhibiting a stronger association. However, subjects who were overweight/obese in childhood but nonobese in adulthood had similar likelihood of having adult NAFLD and ALT elevation for both sexes. After additional adjustment for adulthood factors (TC, TG, HDL-C, LDL-C, smoking, alcohol consumption, and physical activity), the odds ratios (ORs) for NAFLD and ALT elevation were largely attenuated but still significant among subjects who had normal weight in childhood but were obese in adulthood and subjects who were overweight/obese in childhood and obese in adulthood. In addition, we observed similar ORs of NAFLD but greater ORs of ALT elevation among subjects who had normal weight in childhood and were obese in adulthood compared with those who were overweight/obese in childhood and obese in adulthood for both sexes. We found similar results when childhood overweight/obesity was defined by subscapular SFT (Table 4).

DISCUSSION

This study demonstrated that children identified as overweight/obese by either BMI or subscapular SFT at ages 6 to 18 years were more likely to have NAFLD and ALT elevation in adulthood for both sexes after 23 years of follow-up. However, this association could be reduced by acquiring normal weight in adulthood. Among the 4 groups with different adiposity status changes between childhood and adulthood, those who kept high adiposity status and those who become heavier from childhood to adulthood had higher likelihoods of having NAFLD and ALT elevation. These findings indicate

TABLE 3 Association of Change in Adiposity Status From Childhood With NAFLD and ALT Elevation in Adulthood With 23 Years of Follow-up ($N = 1350$)

Change in Adiposity Status[a]	Outcome: NAFLD				Outcome: ALT elevation			
	Model 1[b]		Model 2[c]		Model 1[b]		Model 2[c]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Male								
Child normal wt and adult nonobese ($n = 593$)	Reference	—	Reference	—	Reference	—	Reference	—
Child overweight/obese and adult nonobese ($n = 32$)	2.00 (0.97–3.13)	.07	2.13 (0.98–4.65)	.08	1.24 (0.57–2.67)	.59	1.47 (0.66–3.31)	.35
Child normal wt and adult obese ($n = 66$)	6.06 (3.35–10.95)	<.001	3.90 (2.08–7.28)	<.001	4.12 (2.44–6.98)	<.001	2.73 (1.54–4.86)	.001
Child overweight/obese and adult obese ($n = 40$)	4.22 (2.13–8.35)	<.001	3.48 (1.64–7.38)	.001	2.41 (1.26–4.60)	.008	2.00 (1.03–3.96)	.05
Female								
Child normal wt and adult nonobese ($n = 546$)	Reference	—	Reference	—	Reference	—	Reference	—
Child overweight/obese and adult nonobese ($n = 30$)	2.22 (0.96–5.13)	.06	1.90 (0.67–5.40)	.23	1.93 (0.71–5.23)	.20	1.26 (0.34–4.74)	.73
Child normal wt and adult obese ($n = 29$)	12.05 (5.47–26.54)	<.001	3.08 (1.11–8.58)	.03	14.97 (6.82–32.87)	<.001	6.15 (2.18–17.35)	.001
Child overweight/obese and adult obese ($n = 14$)	15.47 (4.71–50.81)	<.001	7.88 (2.03–30.55)	.003	5.61 (1.80–17.47)	.003	3.88 (1.07–15.55)	.05

CI, confidence interval.
[a] Childhood adiposity status was defined using BMI.
[b] Adjusted for childhood age and length of follow-up.
[c] Adjusted for childhood age, length of follow-up, and adult factors (TC, TG, HDL-C, LDL-C, smoking, alcohol consumption, and physical activity).

TABLE 4 Association of Change in Adiposity Status From Childhood With NAFLD and ALT Elevation in Adulthood With 23 Years of Follow-up ($N = 1350$)

Change in Adiposity Status[a]	Outcome: NAFLD				Outcome: ALT elevation			
	Model 1[b]		Model 2[c]		Model 1[b]		Model 2[c]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Male								
Child normal wt and adult nonobese ($n = 602$)	Reference	—	Reference	—	Reference	—	Reference	—
Child overweight/obese and adult nonobese ($n = 23$)	2.27 (0.96–5.36)	.06	2.00 (0.82–4.88)	.13	0.94 (0.36–2.43)	.90	0.70 (0.26–1.91)	.49
Child normal wt and adult obese ($n = 73$)	5.09 (2.95–8.76)	<.001	3.75 (2.13–6.62)	<.001	3.80 (2.30–6.26)	<.001	2.71 (1.61–4.58)	<.001
Child overweight/obese and adult obese ($n = 33$)	5.50 (2.51–12.04)	<.001	4.80 (2.08–11.07)	<.001	2.45 (1.21–4.98)	.01	1.89 (0.91–3.94)	.09
Female								
Child normal wt and adult nonobese ($n = 495$)	Reference	—	Reference	—	Reference	—	Reference	—
Child overweight/obese and adult nonobese ($n = 81$)	1.82 (0.99–3.35)	.05	1.35 (0.69–2.62)	.38	2.01 (0.94–4.18)	.06	1.66 (0.79–3.49)	.18
Child normal wt and adult obese ($n = 25$)	11.13 (4.76–26.06)	<.001	3.11 (1.18–8.16)	.02	18.79 (7.80–45.26)	<.001	8.19 (3.09–21.74)	<.001
Child overweight/obese and adult obese ($n = 18$)	18.17 (6.26–52.74)	<.001	8.54 (2.69–27.06)	<.001	6.67 (2.44–18.26)	<.001	4.28 (1.45–12.64)	.008

CI, confidence interval.
[a] Childhood adiposity status was defined using subscapular SFT.
[b] Adjusted for childhood age and length of follow-up.
[c] Adjusted for childhood age, length of follow-up, and adult factors (TC, TG, HDL-C, LDL-C, smoking, alcohol consumption, and physical activity).

that childhood adiposity and change in adiposity status from childhood to adulthood play an important role in the development of adult NAFLD and ALT elevation.

Liver biopsy is the gold standard to discriminate all the stages of fatty liver but is unsuitable for large-scale population studies because of its invasive nature. In the current study, NAFLD was diagnosed with ultrasonography, which restricted our ability to distinguish bland steatosis from steatohepatitis. However, a large meta-analysis demonstrated that liver ultrasonography is an accurate and reliable tool to detect moderate-severe fatty liver compared with histology, with sensitivity and specificity of 84.8% and 93.6%, respectively.[30] Because of its low cost, safety, and accessibility,

ultrasonography is a good imaging technique for screening fatty liver in clinical and population settings. Fatty liver disease can cause asymptomatic abnormality of liver enzymes, among which ALT is most closely related to liver fat accumulation and used as a surrogate marker of liver damage. However, previous studies suggest that ALT elevation values have higher specificity (88.9%) but lower sensitivity (28.6%) for both nonalcoholic steatohepatitis and advanced fibrosis.[31]

Cross-sectional studies have suggested that overweight/obese children had an increased risk of NAFLD assessed by ultrasound,[32] blood-based indicators,[33] biopsy,[34] and at post mortem.[35] A recent meta-analysis of 21 cohort studies including 381 655 adults reported that obese individuals had a 3.5-fold increased risk of developing NAFLD, and there was a clear dose-dependent relationship between BMI and NAFLD risk.[15] Several cohort studies have demonstrated that childhood BMI is positively associated with adolescent or adult NAFLD risk with different follow-up time and methods to assess NAFLD.[16–18] However, a study from Denmark did not find a clear association between childhood BMI and ultrasound-determined NAFLD routinely diagnosed at 18 years of age or older.[19] In the current study, we found that childhood overweight/obesity was positively related to NAFLD and ALT elevation over 2 decades. These results were partly supported by the previous report from the same cohort showing that obese children had increased risks of adult metabolic syndrome and type 2 diabetes.[36] It is known that NAFLD and ALT elevation predict future liver cancer risk.[6,11] Therefore, our findings of the positive association between childhood adiposity and adult NAFLD may support the previously observed relationship between childhood obesity and adult liver cancer risk.[37]

BMI is the most widely accepted method to evaluate overweight and obesity because of its ease of measurement, but it cannot discriminate between fat mass and lean mass and thus is limited as a diagnostic measure of true adiposity. SFT may be a more reliable measurement to represent body composition.[38] BMI has been shown to be at least as strongly related to lipids and insulin among children as the sum of the triceps and subscapular SFT.[39] Data from a cohort study demonstrated that suprailiac SFT measured from 3 years onward contributed more to the prediction of NAFLD in adolescence compared with BMI.[18] Our study demonstrated that for both sexes, childhood overweight/obesity by BMI was as strongly related to adult liver outcome as overweight/obesity by subscapular SFT. Given substantial variability in the measurement of skinfold thickness, the advantages of BMI should be considered in the design and interpretation of clinical and epidemiologic studies.[39]

In the current study, we observed a stronger association of childhood overweight/obesity with adult NAFLD and ALT elevation in female than male subjects, consistent with a previous study showing that the influence of birth weight and childhood adiposity on subsequent cardiovascular risk is greater in females than in males.[40] The sex difference in the association between childhood adiposity and NAFLD could be partly explained by the fact that the association between BMI and percent body fat is stronger in girls than boys.[41] Another reason may be that the association of sex hormones with adiposity is different between males and females.[42] Further investigations are needed to understand the mechanism in detail.

Interestingly, we found that the impact of childhood overweight/obesity on the NAFLD could be substantially reduced and even eliminated once childhood overweight/obesity disappeared in adulthood, consistent with previous studies reporting that the association became nonsignificant and even negative after adjustment for adult BMI.[16,17] In addition, a previous study showed that overweight/obese children who became nonobese adults had a similar adult cardiovascular risk profile as those who had consistently low adiposity status.[43] Childhood obesity often persists into adulthood and is difficult to reverse once established. In the current study, >86% of overweight/obese children were persistently overweight/obese in adulthood. When overweight/obesity is detected in childhood, effective weight-loss interventions should be implemented to reduce further adverse liver outcome and cardiovascular risk.

The key strengths of the current study include a larger sample size, longitudinal nature of the study, long follow-up durations, and sufficient data. Nevertheless, this study has several limitations. First, approximately half of the original cohort participants were lost to follow-up. However, there was no significant difference in baseline characteristics between subjects who were followed up and those who were not. Second, the number of participants with ALT elevation was small, which might result in insufficient statistical power in the analyses of childhood adiposity in relation to adult ALT elevation. Third, information on pubertal status, blood glucose, lipid levels, smoking, drinking, and physical activity were not collected in childhood; therefore, we could not rule out the influence of these factors on

our observed associations. Fourth, lack of indicators of nonalcoholic steatohepatitis or fibrosis limits us to evaluate the association of these outcomes with childhood adiposity and change in adiposity status. Finally, data on liver outcome were not collected in childhood, thus we could not evaluate the influence of childhood adiposity in relation to incidence of NAFLD and ALT elevation from childhood to adulthood.

CONCLUSIONS

In conclusion, this 23-year cohort study shows that overweight/obese children are more likely to have NAFLD and ALT elevation in adulthood. However, this association could be largely reduced by becoming nonobese during adulthood. These findings underscore the importance of both early prevention and lifelong treatment of overweight and obesity to reduce the risk of adverse liver outcome in adulthood.

ABBREVIATIONS

ALT: alanine aminotransferase
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
NAFLD: nonalcoholic fatty liver disease
OR: odds ratio
SFT: skinfold thickness
TC: total cholesterol
TG: triglyceride

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