Risk for Nonalcoholic Fatty Liver Disease in Young Adults Born Preterm

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Key Words

Nonalcoholic fatty liver disease · Weight gain · Infant growth · Catch-up

Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is considered the hepatic manifestation of metabolic syndrome. Accelerated catch-up in weight during infancy in subjects born at full term has been associated with increased risk for NAFLD in adulthood, but this association has not been studied in subjects born preterm. **Methods:** In 162 young adults born at a gestational age <36 weeks, we assessed the associations between fatty liver index (FLI, 0–100) and birth weight standard deviation score and first-year weight gain. We performed comparisons between subjects with and without accelerated catch-up in weight in the first year after term age. An FLI score was assigned to each participant to determine the clinical relevance, and regression analyses were performed. **Results:** Accelerated weight gain in the first 3 months after term age was associated with FLI as a continuous variable, whereas gestational age and low birth weight were not. Of the subjects with accelerated catch-up in weight-for-length after term age, 7.3% had a high FLI at the age of 21 years, whereas none of the subjects without accelerated catch-up in weight had a high FLI. **Conclusion:** Our study

shows that accelerated weight gain after term age is associated with an increased risk of developing NAFLD in young adults born preterm.

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Introduction

Nowadays, 8–10% of all newborns in developed countries are born preterm, and due to advances in neonatal intensive care, most of them reach adulthood [1]. Preterm infants are frequently exposed to fetal growth restriction, glucocorticoid treatment, and stressful events, which may contribute to the development of organ dysfunction and adverse vascular outcome later in life. In recent years, long-term outcomes for young adults born preterm were found to be less favorable than for those born at full term. Adults born preterm are at an increased risk of developing cardiovascular diseases [2–4] and have increased cardiovascular mortality [5, 6].

Nonalcoholic fatty liver disease (NAFLD) is considered to be the hepatic manifestation of metabolic syndrome and has been associated with several risk factors for cardiovascular diseases [7]. As NAFLD is strongly associated with obesity, its prevalence is rapidly increasing [8].

Recently, our group showed that young adults who were born at full term and underwent accelerated weight gain during infancy had an increased fatty liver index (FLI), a measure of NAFLD in early adulthood [9]. While the gold standard for determining NAFLD is liver biopsy, the FLI is widely used and has recently been validated for identifying NAFLD in a large population-based study [10–14]. The FLI is a measure to predict hepatic steatosis in the general population, using an algorithm based on body mass index (BMI), waist circumference, triglycerides, and gamma-glutamyltransferase (γ -GT), with, in case of a high FLI score (>60), a positive predictive value of 72.2% in detecting fatty liver.

Because many preterm infants are prone for accelerated weight gain after an initial period of weight loss [15], we hypothesized that adults born preterm with accelerated weight gain after term age are at an increased risk for NAFLD compared with those without accelerated weight gain during infancy. We also hypothesized that adults born preterm have a higher FLI than adults born at full term [9, 16, 17]. We therefore investigated associations of birth weight, gain in weight-for-length, and accelerated catch-up in weight in the first year after term age with the FLI in general and with individual biochemical markers of FLI as well as with other markers indicating liver damage in a cohort of young adults born preterm [7, 18–21].

Materials and Methods

Subjects

The study population consisted of 162 healthy young adults (PREMS study) who were registered because of being born preterm (gestational age <36 weeks). The data of the participants were compared with the data of 268 young adults born at full term (PROGRAM study) [9]. Both cohorts had similar inclusion criteria and measurements and were from the same research center, but they had a different gestational age. All included subjects were aged 18–24 years, Caucasian, born singleton, and had an uncomplicated neonatal period without severe asphyxia (defined as an Apgar score <3 after 5 minutes), sepsis, or long-term complications of respiratory ventilation and/or oxygen supply. Birth data were obtained from medical records, primary health care records, and general practitioner records. Data on educational level, socioeconomic status, use of medication, and alcohol use were obtained using questionnaires [22]. None of the participants had alcohol abuse, defined as a maladaptive pattern of alcohol use leading to clinically significant impairment or distress. Weight and length at 3, 6, 9, and 12 months after birth had been measured prospectively at primary health care centers or hospitals. The Medical Ethics Committee of Erasmus Medical Centre, Rotterdam, The Netherlands, approved the study. Written informed consent was obtained from all participants.

Measurements

All participants visited the Erasmus Medical Centre in Rotterdam and were reimbursed for travel expenses. Prior to the visit, the participants had fasted for at least 12 h. All anthropometric measurements were performed twice; the mean value was used for the analyses. Height was measured to the nearest 0.1 cm by a Harpenden stadiometer and weight to the nearest 0.1 kg by a Servo Balance KA-20-150S scale. Waist circumference was measured to the nearest 0.1 cm using a plastic flexible measuring tape. It was measured at the midway between the lower margin of the lowest rib and the upper margin of the iliac crest, at the end of a normal expiration.

All fasting blood samples were drawn between 08.00–13.00 h, centrifuged after clotting, and kept frozen until assayed (-80°C). All serum parameters were determined in the same laboratory. Triglycerides were measured using the GPO-PAP reagent kit (Roche Diagnostics). γ -GT, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels were determined using standard laboratory routines.

Statistical Analysis

Standard deviation (SD) scores (SDS) for birth length, birth weight, and first year weight and length were calculated to correct for gestational age and sex [23]. SDS for adult height and weight were calculated to correct for sex and age [24]. The FLI was used to determine the risk for fatty liver disease [18]. The FLI is calculated as: $\text{FLI} = (e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\gamma\text{-GT}) + 0.053 \times \text{waist circumference} - 15.745}) / (1/e^{0.953 \times \ln(\text{triglycerides}) + 0.139 \times \text{BMI} + 0.718 \times \ln(\gamma\text{-GT}) + 0.053 \times \text{waist circumference} - 15.745}) \times 100$, and varies between 0 and 100. An FLI score was assigned to the participants as follows: an FLI <30 corresponds to a low risk (FLI score 1, specificity = 87%), 30–60 to an intermediate risk (FLI-score 2), and >60 to a high risk (FLI score 3, specificity = 86% for fatty liver) [18].

Multiple linear regression analyses were performed to investigate the association between weight gain per each 3 months during 1 year after term age, and several markers of NAFLD and liver damage in young adults born preterm. The 4 periods were analyzed separately from each other. In addition, we investigated the effect of weight gain from birth to term age on the FLI at 21 years. We performed a multiple regression analysis with the FLI at 21 years as dependent variable, as independent variables gestational age, gender, socioeconomic status, and adult age, and as dummy a decrease of weight SDS ≥ 1 between birth and term age and no decrease in weight SDS.

Ordinal regression analyses were performed to determine the associations of FLI scores with birth weight SDS, birth length SDS, and weight gain during the 5 periods in the first year of life.

All regression analyses were adjusted for age, gender, gestational age, and socioeconomic status. To investigate the association between weight and outcome variables independently of length, as a measure for adiposity, adjustments were made for length growth during the same period.

Catch-up in weight in the first year after term age was defined as an increase in weight SDS of >0.67 , because this represents the width of each percentile band on standard growth curves (2nd–9th percentile, 9th–25th percentile, etc.) [25].

Of the group with a catch-up in weight, one subgroup was formed based on accelerated ($\text{SD} \geq 0.5$) weight gain during the first 3 months after term age. Additionally, young adults born preterm with accelerated catch-up and without accelerated catch-

Table 1. Clinical characteristics of the total preterm group and subjects with accelerated versus nonaccelerated catch-up growth in weight in the first year after term age

	Preterm				Term				Preterm vs. term	
	total study group (n = 162)	accelerated catch-up (n = 55)	non-accelerated catch-up (n = 36)	p value*	total study group (n = 268)	accelerated catch-up (n = 54)	non-accelerated catch-up (n = 19)	p value*	accelerated p value	non-accelerated p value
Male, %	50	41.8	50	0.443	107	31.5	57.9	0.042	0.267	0.585
Age, years	20.8 (1.68)	20.5 (1.81)	20.8 (1.76)	0.595	20.9 (1.66)	20.7 (1.68)	21.0 (1.94)	0.557	0.683	0.688
Gestational age, weeks	32.0 (2.22)	32.7 (2.07)	32.1 (2.07)	0.146	39.2 (1.59)	38.6 (1.46)	39.2 (2.00)	0.145	<0.001	<0.001
<i>Weight SDS</i>										
Birth	-0.51 (1.80)	-0.88 (1.75)	-1.16 (1.56)	0.439	-1.12 (1.36)	-2.19 (0.69)	-2.09 (0.90)	0.620	<0.001	0.007
Term age	-1.42 (1.17)	-1.58 (1.18)	-1.99 (0.98)	0.088	-	-	-	-	-	-
3 months post-term	-1.01 (1.38)	-0.34 (1.38)	-1.99 (1.07)	<0.001	-0.91 (1.10)	-0.70 (0.87)	-2.13 (0.95)	<0.001	0.114	0.625
6 months post-term	-0.77 (1.23)	-0.06 (1.16)	-1.28 (0.94)	<0.001	-0.83 (1.02)	-0.40 (0.80)	-1.51 (0.81)	<0.001	0.072	0.388
9 months post-term	-0.68 (1.14)	0.01 (1.10)	-0.91 (0.93)	<0.001	-0.80 (1.07)	-0.36 (0.73)	-1.00 (0.82)	0.002	0.045	0.740
12 months post-term	-0.66 (1.17)	0.06 (1.12)	-0.69 (0.91)	0.001	-0.72 (1.01)	-0.28 (0.74)	-0.77 (0.78)	0.017	0.065	0.767
<i>Length SDS</i>										
Length	-1.27 (1.88)	-1.37 (1.96)	-1.95 (1.72)	0.178	-1.39 (1.41)	-2.13 (1.15)	-2.07 (1.55)	0.859	0.016	0.800
Term age	-1.82 (1.51)	-1.74 (1.51)	-2.56 (1.34)	0.013	-	-	-	-	-	-
3 months post-term	-1.30 (1.22)	-0.98 (1.18)	-1.95 (1.11)	<0.001	-1.02 (1.21)	-1.04 (1.01)	-1.71 (1.14)	0.018	0.787	0.464
6 months post-term	-0.98 (1.09)	-0.56 (0.97)	-1.45 (0.88)	<0.001	-0.94 (1.19)	-0.61 (0.99)	-1.60 (1.08)	<0.001	0.789	0.568
9 months post-term	-0.68 (1.14)	-0.18 (0.88)	-0.94 (0.80)	<0.001	-0.91 (1.26)	-0.45 (0.93)	-1.27 (1.03)	0.002	0.122	0.190
12 months post-term	-0.66 (1.17)	0.02 (0.91)	-0.72 (0.81)	<0.001	-0.92 (1.20)	-0.42 (0.94)	-1.16 (1.02)	0.005	0.015	0.084
Adult height SDS	-0.42 (0.95)	-0.18 (0.97)	-0.30 (0.91)	0.553	-1.00 (1.36)	-0.63 (0.91)	-1.01 (0.91)	0.118	0.015	0.008
Adult weight SDS	-0.28 (1.22)	0.19 (1.09)	-0.57 (1.02)	0.001	-0.63 (1.43)	0.04 (1.12)	-0.72 (1.03)	0.011	0.469	0.618

Data are given as mean (SD). Accelerated catch-up = increase in weight SDS >0.67 in the first year of life and >0.5 in the first 3 months; nonaccelerated catch-up = increase in weight SDS >0.67 in the first year of life and <0.5 in the first 3 months. * Accelerated versus nonaccelerated. Significant p values are indicated in bold.

up in weight were compared to those born at full term. Differences in clinical characteristics were determined by an independent t test.

Statistical package SPSS version 20.0 (SPSS, Inc., Chicago, Ill., USA) was used for analyses. Results were regarded statistically significant if p was <0.05 (two-sided).

Results

Clinical characteristics, the FLI and its components, and other liver markers are shown in tables 1 and 2. The mean (SD) FLI was 12.7 (16.4). A high FLI score was present in 5% of the total preterm study group.

Fatty Liver Index

Total Study Population of Adults Born Preterm

In table 3, the results from the linear regression analyses are shown, with the FLI (0–100) and individual components of the FLI (triglycerides, BMI, waist circumfer-

ence, and serum levels of γ -GT) as dependent variables. The increase in weight SDS adjusted for length SDS in the first 3 months after term age was significantly associated with FLI at the age of 21 years (FLI increased with 29.1% per 1 SDS increase in weight gain, $p = 0.034$, model 2). In addition, the increase in weight SDS adjusted for length SDS in the first 3 months after term age showed a significant association with waist circumference ($p = 0.004$). Birth weight SDS and gestational age were not significantly associated with the FLI or with the individual components of the FLI (model 1).

In addition, subjects with a decrease in weight SDS ≥ 1 between birth and term age had a higher FLI at the age of 21 years than those without any decrease in weight SDS ($p = 0.01$).

Adults Born Preterm with Catch-Up in Weight after Term Age

To determine if the speed of weight gain after term age was associated with determinants of NAFLD in young

Table 2. Determinants of NAFLD of the preterm and term groups, divided into subjects with accelerated and nonaccelerated catch-up growth in weight in the first year after term age

	Preterm				Term				Preterm vs. term	
	total study group (n = 162)	accelerated catch-up (n = 55)	nonaccelerated catch-up (n = 36)	p value*	total study group (n = 268)	accelerated catch-up (n = 54)	nonaccelerated catch-up (n = 19)	p value*	accelerated p value	non-accelerated p value
TG, mmol/l	1.12 (0.52)	1.04 (0.57)	0.85 (0.35)	0.071	1.03 (0.50)	1.17 (0.52)	0.96 (0.33)	0.102	0.216	0.256
BMI	22.3 (3.57)	23.2 (3.84)	21.1 (2.30)	0.004	22.4 (3.51)	23.5 (3.59)	21.8 (2.45)	0.060	0.665	0.305
Waist, cm	77.2 (9.21)	79.8 (11.0)	74.4 (6.51)	0.010	76.9 (9.98)	91.4 (11.2)	75.7 (8.65)	0.047	0.457	0.545
γ-GT, U/l	16.7 (8.13)	16.7 (7.85)	14.5 (5.55)	0.164	17.3 (13.5)	22.4 (24.6)	16.9 (8.40)	0.342	0.101	0.216
FLI	12.7 (17.4)	16.0 (20.8)	6.64 (5.95)	0.012	13.0 (17.1)	21.6 (23.4)	10.2 (12.1)	0.046	0.187	0.157
<i>FLI score, %</i>										
Low	89.9	89.1	97.1	0.255	88.3	72.2	94.7	0.121	0.026	0.662
Intermediate	5.0	3.6	2.9	0.255	8.7	20.4	5.3	0.121	0.007	0.662
High	5.0	7.3	0	0.255	3.0	7.4	0	0.121	0.979	–
ALT, U/l	15.1 (9.80)	16.3 (14.5)	14.5 (5.25)	0.479	20.3 (15.3)	23.1 (24.2)	19.4 (11.2)	0.527	0.076	0.031
AST, U/l	21.5 (6.54)	21.6 (8.68)	21.8 (3.64)	0.884	25.8 (30.2)	25.7 (13.2)	25.1 (10.0)	0.928	0.054	0.058
ALP, U/l	72.0 (24.1)	71.1 (25.7)	73.8 (25.4)	0.626	69.0 (22.1)	70.5 (19.6)	70.9 (24.1)	0.931	0.889	0.692

Data are given as mean (SD). Waist = waist circumference; TG = triglycerides; ALT= alanine aminotransferase; AST: aspartate aminotransferase; ALP = alkaline phosphatase. An FLI score <30 corresponds to a low risk (FLI score 1), 30–60 to an intermediate risk (FLI score 2), and >60 to a high risk (FLI score 3) for fatty liver. Accelerated catch-up = increase in weight SDS >0.67 in the first year of life and >0.5 in the first 3 months; nonaccelerated catch-up = increase in weight SDS >0.67 in the first year of life and <0.5 in the first 3 months. * Accelerated versus nonaccelerated. Significant p values are indicated in bold.

Table 3. Associations of birth size and early weight gain with the FLI and the components of the FLI at 21 years of age in young adults born preterm

	FLI			FLI components											
				triglycerides ^a			BMI ^a			waist ^a			γ-GT ^a		
	β	p	adj. R ²	β	p	adj. R ²	β	p	adj. R ²	β	p	adj. R ²	β	p	adj. R ²
Model 1 ^b Birth weight SDS	–6.32	0.446	0.042	0.10	0.989	–0.044	–2.12	0.107	0.040	–1.55	0.090	0.140	5.87	0.103	0.054
Model 2 ^c Increase in weight SDS during 3 months after term age	29.1	0.034	0.054	4.92	0.388	–0.026	3.54	0.055	0.046	3.63	0.004	0.165	3.73	0.447	0.044

^alog transformed (natural logarithm) for regression analyses. β = Regression coefficient in %. ^bAdjusted for gender, age, socioeconomic status, gestational age and birth length SDS. ^cAdjusted for gender, age, socioeconomic status, gestational age and increase in length during 3 months after term age. Significant p values are indicated in bold.

adults born preterm, those with a catch-up in weight in the first year after term age were divided into 2 subgroups, either with or without accelerated catch-up in weight. Of all young adults with a clinically relevant catch-up in weight of at least 0.67 SDS in the first year after term age (n = 91), 55 had an increase in weight SDS >0.5 in the first 3 months after term age (accelerated catch-up), while 36 had no accelerated catch-up, defined as an increase in weight SDS <0.5 in the first 3 months after term age. The clinical characteristics of these 2 subgroups are shown in table 1.

Gestational age, sex, age, birth length SDS, and birth weight SDS were not different between the accelerated and nonaccelerated catch-up group. The accelerated catch-up group had a higher FLI (p = 0.012), adult weight SDS (p = 0.001), BMI (p = 0.004), and waist circumference (p = 0.010) at the age of 21 years than the nonaccelerated catch-up group, even after adjustment for gender, socioeconomic status, gestational age, and increase in length during the first year of life (p = 0.003; fig. 1).

To investigate whether the effect of accelerated catch-up in weight in subjects born preterm was similar to that

Fig. 1. Adjusted FLI of subjects with accelerated compared to those with nonaccelerated catch-up after term age. Estimated marginal means (95% confidence intervals) are shown. Accelerated catch-up = increase in weight SDS >0.67 in the first year after term age and >0.5 in the first 3 months after term age. Nonaccelerated catch-up = increase in weight SDS >0.67 in the first year after term age and <0.5 in the first 3 months after term age. Adjusted for gender, socioeconomic status, gestational age, and increase in length in the first year of life after term age.

in subjects born at full term, we compared the tempo of catch-up in young adults born preterm to those born at full term (table 2). Our data showed no difference between subjects born at full term and those born preterm.

Fatty Liver Index Score

An FLI score was assigned to each participant in order to obtain an NAFLD risk score (1: low, 2: intermediate, or 3: high). Of all adults born preterm, 5% ($n = 8$) had a high FLI score, and 5% ($n = 8$) had an intermediate FLI score (table 2). In the accelerated catch-up group, 7.3% had a high FLI score, and 3.6% had an intermediate FLI score, while in the nonaccelerated catch-up group, 0% had a high FLI score, and 2.9% had an intermediate score. Lower birth weight and gestational age were not associated with a higher FLI score at 21 years of age.

Discussion

Our study in 162 young adults born preterm shows that accelerated infant weight gain after term age is associated with an increased risk of developing NAFLD in early adulthood. We also demonstrate that subjects born

preterm with accelerated weight gain after term age have a significantly higher FLI in early adulthood than subjects without accelerated catch-up in weight, independent of size at birth and gestational age. Those findings are similar to those found in young adults born at full term.

We found an association between accelerated weight gain during infancy in preterm subjects and a higher NAFLD risk in early adulthood. Previous studies reported associations between small body size at birth and risk factors for NAFLD in adulthood [26, 27], but associations with preterm birth were not investigated. Some studies showed an association between preterm birth and waist circumference, a component of the FLI, but none of these studies investigated any associations with the FLI [28, 29].

Since our study population consisted of young adults, hard endpoints such as NAFLD and steatohepatitis could not be studied. The FLI was used as a proxy for a clustering of risk factors, a condition which precedes hepatic steatosis. A high FLI score (>60) has a predictive value of 72.2% for a fatty liver [18], and although our study population was relatively young and healthy, with a relatively low BMI, a high FLI score was found in 5% of the subjects born preterm.

In addition, it was striking that 10.9% of the subjects born preterm with accelerated catch-up in weight-for-length after term age had a high or intermediate FLI at the age of 21 years, compared with only 2.9% of the subjects without accelerated catch-up in weight-for-length. We previously showed a similar association between accelerated infant weight gain and increased risk for NAFLD in young adults born at full term [9]. Our present study shows that this association is also apparent in young adults born preterm. Besides this, our study shows that preterm subjects with a decrease in weight SDS ≥ 1 between birth and term age had a higher FLI at 21 years than those without any decrease in weight SDS. Both these findings indicate that a balance in neonatal increase in weight compared to length is also important for preterm infants to reduce the risk of developing NAFLD. This may be achieved by modifying nutritional intervention according to weight-for-length trajectories, particularly in the first months after term age. These data should not be interpreted to the effect that we recommend slow weight gain in preterm babies, but we discourage accelerated catch-up in weight-for-length after term age. They also point out that not only weight but also length should be routinely measured during infancy. Earlier studies showed that accelerated weight gain, mediated by nutrition-enriched diets, has adverse effects on cardiovascular risk factors in later life [6, 30]. Our findings warrant that

parents should be informed about the long-term effects of accelerated weight gain, as the first months after the delivery of preterm infants, usually up to around term age, seem to be a critical window for the programming of later body composition.

We acknowledge that when investigating differences between subjects born preterm and those born at full term, differences in early nutritional intake should be taken into account. The prevalence and duration of breastfeeding is lower in infants born preterm [31]. Formula-fed infants have a higher risk of being overweight in childhood and later in life [32, 33]. Infant feeding might thus influence a later risk for NAFLD. Studies in rats showed that the liver might act as a systemic buffer, largely increasing its lipid content in the early stage of high-fat feeding [34]. It has been suggested that breastfeeding protects against the development of nonalcoholic steatohepatitis (NASH) in children [35]. We did not have sufficient nutritional data to investigate differences in nutritional intake in early life between adults born preterm and those

born at full term and its relation with growth in infancy and the risk for NAFLD, but our results warrant further investigations.

In conclusion, our study shows that accelerated increase in weight compared to length in the first 3 months after term age in subjects born preterm is associated with a higher risk of developing NAFLD in adulthood. Long-term prospective studies are warranted to study the effects of various infant feeding practices on the risk for NAFLD.

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Disclosure Statement

The authors have nothing to disclose.

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