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Overweight and obesity status from the prenatal period to adolescence and its association with Non-alcoholic fatty liver disease in young adults: cohort study

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Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body Mass Index
ELEMENT	Early Life Exposure in Mexico to Environmental Toxicants
GSEM	Generalized Structural Equation Model
IQR	Inter Quartile Range
MR	Magnetic Resonance
MRS	Magnetic Resonance Spectroscopy
NAFLD	Non-Alcoholic Fatty Liver Disease
OWOB	Overweight and Obesity
PDFF	Proton Density Fat Fraction
RMSEA	Root Mean Square Error of Approximation
SES	Socioeconomic Status
SEM	Structural Equation Modeling
VAT/SAT	Visceral/Subcutaneous Fat Ratio

WHO	World Health Organization
WLZ	weight-for-length z-score

ABSTRACT

Objective: To examine the associations of maternal and child overweight status across multiple time-points with liver fat content in the offspring during young adulthood.

Design: Cohort study

Setting: ELEMENT Cohort in Mexico City

Population: Pregnant women with singleton births (n = 97)

Methods: We quantified hepatic triglyceride content (liver fat content) by proton magnetic resonance spectroscopy (1H MRS) and conventional T2-weighted MRIs (3T scanner) in 97 young adults from the ELEMENT birth cohort in Mexico City. Historical records of the cohort were used as a source of pregnancy, childhood and adolescence anthropometric information, overweight and obesity (OWOB) were defined. Adjusted structural equation models were run to identify the association between OWOB in different life stages with liver fat content (log-transformed) in young adulthood.

Main Outcome: Maternal OWOB at the time of delivery was directly and indirectly associated with the liver fat content in the offspring at young adulthood.

Results: Seventeen percent of the participants were classified as having NAFLD. We found a strong association of OWOB between all periods assessed. Maternal OWOB at time of delivery (β=1.97 95%CI 1.28, 3.05), and OWOB status in the offspring at young adulthood (β=3.17, 95%CI 2.10, 4.77) were directly associated with the liver fat content in the offspring. Also, maternal OWOB was indirectly associated with liver fat content through offspring OWOB status.

Conclusion: We found that maternal OWOB status is related to fatty liver content in the offspring as young adults, even after taking into account OWOB status and lifestyle factors in the offspring.

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Key Words: liver fat content, maternal overweight, cohort

Tweetable abstract: There was an association between pre-pregnancy overweight and the development of NAFLD in adult offspring.

Introduction

Non-Alcoholic Fatty Liver Disease (NAFLD), defined as hepatic fat infiltration involving more than 5% of the hepatocytes in the absence of high alcohol intake and other causes of liver pathology [1], is the most common cause of chronic liver disease in Western Countries [2] and may be a precursor to other leading chronic diseases like type 2 Diabetes Mellitus [3-6]. Known as the "silent liver disease," most individuals with NAFLD are asymptomatic, until progression to advanced stages of disease involving inflammation (Non-Alcoholic steatohepatitis-NASH), fibrosis, cirrhosis, and ultimately in some cases, hepatocellular carcinoma [7].

The worldwide prevalence of NAFLD is around 20% [1], and in young adults, it has more than doubled since the 1980s [8, 9], particularly among obese individuals [10]. In Mexico, the national prevalence of NAFLD is unknown; however, a 2006 study of asymptomatic individuals from the general population reported a 17% prevalence [11], with an expected prevalence of up to26% in adults based on current obesity rates [12, 13]. Perhaps more concern is the fact that NAFLD is now on the rise at younger ages [14], reflecting, in part, the childhood obesity pandemic and the relatively high intakes of energy-dense processed foods and sugar-sweetened beverages[15].

Some cohort studies in developed nations have identified early risk factors for NAFLD, including *in utero* exposure to maternal obesity [16], and childhood growth patterns [17-19]. Less is known of these associations in developing countries undergoing the nutrition transition [20] where rapid shifts in diet and lifestyle may further compound the long-term consequences of obesogenic early life exposures. Thus, the goals of this study were to: (1) estimate liver fat content and NAFLD prevalence, (2) assess the independent, cumulative and trans-

generational effects of exposure to overweight/obesity (OWOB) across the life course from the *in utero* period through young adulthood on liver fat content in a sample of young adults in Mexico City, MX.

Methods

This study was conducted in a subsample of young adult offspring from the first birth cohort of the *E*arly *L*ife *E*xposure in *M*exico to *En*vironmental *T*oxicants (ELEMENT) project. Details of the cohort are reported elsewhere [21]. In summary, between 1994 and 1995 a total of 631 mothers were recruited at delivery, and their offspring have been followed over time. Information from pregnancy (pre-preganancy self-reported weight and parity), delivery (mother´s weight, birth weight, offspring sex) and up through four years post-partum (breastfeeding practices, weight, length/height) were obtained from the historical records of the cohort. From 2008 to 2010, a subsample of 206 participants (from the original 631) participated in a research visit during adolescence at approximately 14 to 16 years of age [22].

In 2016, a young-adult visit (21 to 22 years of age) was conducted [23]. Of the 206 participants who attended the previous visit, 55 did not respond, and 51 did not choose to participate. Of the remaining 100, the present analysis included 97 participants with complete information key variables. At the young adult visit, participants were asked to participate in the assessment of liver fat content following a 10-hour fast. All subjects provided written informed consent. Participants involvement in this study is described in the supporting information (Appendix S1).

Outcome Variable: Quantification of liver fat in young adulthood

In order to estimate the hepatic triglyceride content, we performed proton magnetic resonance spectroscopy (1H MRS)[24], with the calculation of proton density fat fraction (PDFF). PDFF, a standardized magnetic resonance (MR)-biased biomarker of steatosis, is defined as the fraction of mobile protons (1H) derived from triglycerides relative to those derived from water [25]. A Philips Achieva 3.0 T MR-scanner (Philips Healthcare, Best, The

Netherlands) was used for imaging. Conventional MR imaging was done prior to the spectroscopy acquisition. The methodology to measure the fat fraction using 1H MRS was previously described by our group [26]. The protocol included plane localizers: transversal T2w, Transversal T2w with fat saturation. A board certified radiologist (ERV) and a biomedical engineer who post-processed the information and gave the results, were "blinded" about the participant's BMI status.

Liver images were acquired with an 8-channel torso coil during a breath-hold. This breath-hold was monitored with a respiratory belt. Two 30x30x30 mm voxels were selected within normal liver tissue in the right lobe of the liver as described elsewhere[26], avoiding the edge of the liver and major blood vessels. The resonances used for calculation of the triglycerides were water (peak at 4.7 ppm), methylene (CH2 peak at 1.3 ppm, and methyl (CH3 speak at 0.9 ppm). The fat fraction in each pixel then was calculated using 1H MRS as the ratio of the fat density to the total (fat and water) density. A detailed description of the imaging examination and post-processing analysis has been described elsewhere [26-28].

An example of the acquired images and spectra is depicted in Figure S1. In the analysis, we assessed liver fat content as continuous variable (log transformed), and as a dichotomous NAFLD (yes/no) using a cut-off value of 5% hepatic fat fraction to define presence of NAFLD [29].

Exposures Variables: OWOB in mothers (pre-pregnancy and delivery), and OWOB in offspring (childhood, adolescence and young adulthood)

Maternal OWOB. The Cohort´s historical records were used to obtain maternal information including: self-reported pre-pregnancy weight, weight and height measured at the end of pregnancy (using professional scales PAME, Puebla), which were used to calculate pre-pregnancy body mass index (BMI) and maternal BMI at delivery. Parity information was categorized as first pregnancy; and breastfeeding practices, recorded as total months and categorized as never breastfeeding vs at least one month during the first year postpartum. Maternal BMI was classified as normal weight ($<25 kg/m^2$) and OWOB ($\geq 25 kg/m^2$) for

pre-pregnancy and delivery[30], we did not include underweight (<18.5kg/m2) as none of the participants fell in this category.

Offspring OWOB at different periods. Anthropometric measures of the participants during preschool period were also captured (weight and stature, using a calibrated beam scale, Model TD16 and infantometer, SECA) every six months from birth to four years of age. This information was used to estimate weight for length/height Z score according to the World Health Organization (WHO) growth standard. We defined overweight status between one to two years of age as weight-for-length z-score (WLZ) >2 SD, and from two to four years as weight-for-height z-score (WHZ) >2SD, in at least one time-measure [31].

In adolescence, trained personnel measured weight and height using standard techniques. Weight was measured using a digital scale (BAME 147 Mod 420; Catálogo Médico) and read to the nearest 0.1 kg. Standing height was evaluated using a calibrated stadiometer (BAME Mod 420; Catálogo Médico) and read to the nearest 0.5 cm. Body Mass Index (BMI) was calculated as an age- and sex-specific Z score, and classified as OWOB ≥ 1 SD of the BMI Z-score [32].

In adulthood, weight and height were measured using a Tanita digital scale with a height rod (model WB-3000m). Weight was recorded to the nearest 0.1kg and height to the nearest 0.5 cm. BMI was calculated and classified as OWOB (for BMI ≥25kg/m^2). All the measurements were done by trained personnel.

Covariates: socio-demographic and lifestyle information in young adulthood

Demographic characteristics, socioeconomic status (SES), smoking habits and alcohol intake were derived from validated questionnaires. The AMAI scale (*Asociación Mexicana de Agencias de Investigación de Mercado*) was used as an indicator of SES; and for the analysis, we collapsed the 6-cathegories to 2 (very-low/low & medium/high), as the sample has low variability in SES [33]. We obtained information about alcohol intake from the National Addiction Survey, and classified the individuals according to their habitual intake

(daily-weekly, monthly, annually-never) [34]. We used the same survey to gather information on smoking habits, and classified individuals as non-smokers, past-smokers and active smokers. We also administered a food frequency questionnaire [35] which was used to derive total energy intake.

Statistical Analysis

We compared the participant's background characteristics, as well as their mother´s BMI before pregnancy (self-reported) and at delivery with respect to NAFLD status (yes vs. no), using the appropriate statistical tests based on the distribution of the variables – i.e., two sample T-test or Median (IQR) and Kolmogorov Smirnov test for continuous variables and Fisher's Exact test for categorical variables. These associations informed selection of covariates for multivariable models.

Then, we explored the independent associations of maternal OWOB before and at the end of pregnancy, and of participant´s OWOB at different life stages (childhood, adolescence and young adulthood), with ln-transformed liver fat content in adulthood using linear regression models; and with the diagnose of NAFLD with using logistic regression models. All models were adjusted for mother's age and education, socioeconomic level of the family, and participant´s sex, smoking, alcohol and energy intake.

Generalized Structural Equation Model (GSEM) is an extension of generalized linear models that allowed us to model direct and mediated effects that are expressed in a multiple equation system where outcome variables could be of any type (continuous or categorical variables)[36]. We used a GSEM to assess the cumulative effects of maternal OWOB and offspring OWOB during early life on NAFLD risk. Our hypothesis was that maternal pre-pregnancy OWOB increases the possibility of excess gestational weight gain and thus, maternal OWOB at the end of pregnancy. Maternal obesity, in turn, increases risk of OWOB in her offspring across the life course. Given that obesity is a key risk factor of NAFLD, the inter-generational nature of excess adiposity will likely be related to higher percentage of liver fat and NAFLD. (Figure 1).

The specification of paths, and the selection of the variables that were included based on an *a priori* conceptual framework. The root mean square error of approximation (RMSEA) was used to evaluate the goodness-of-fit, where a value <0.9 was considered acceptable. In this analysis, we assessed ln-transformed liver fat content as a continuous outcome via linear regression. The estimate of interests were exponentiated beta estimates and 95% confidence intervals (CI) from the linear regression models, and odds ratios (OR) and 95% CI from the logistic regression models (OWOB).

Finally, to assess the possibility of selection bias, we compared delivery characteristics (mother, ie: age, schooling; and offspring, ie: birth weight, length) of participants included in analytical sample vs. the original cohort.

All the analyses were performed in STATA 15 statistical software.

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Results

The main characteristics of the participants are described in table 1. About half of the participants were male (55%), at delivery they presented a mean weight of 3,093gr (7.2% presented low birth weight) and a mean gestational age of 39 weeks. Twenty-eight percent of Mother´s participants started the pregnancy with overweight/obesity (BMI>25kg/m2) and at delivery, 59% presented this condition.

Median liver fat content was 1.4% (IQR 2.9), and 17% (n = 17) of participants had NAFLD. Participants with NAFLD had mothers who were more likely to be OWOB at

delivery (83% vs. 55%, p=0.03), and were themselves more likely to have been OWOB during adolescence (59% vs. 19%, p=0.01) and young adulthood (94% vs. 31%, p<0.01) in comparison to their healthy counterparts. When comparing the analytical sample with the original cohort, we found no differences on the variables evaluated except from mother´s education (almost one year more in the analytical sample, Table S1), so we used this variable in the adjusting of the models.

At the young-adult visit, the average age was 21.4 years (±0.5); 51% were classified as being at very-low/low socioeconomic status and 44% were active smokers. Forty-eight percent reported that they consumed alcohol once per year or not at all, and 20% consumed alcohol on a weekly/daily basis, no difference were found on alcohol intake between those with and without NAFLD. None of the participants reported consumption of more than 20 g of alcohol per day (more than 2 and 3 servings per day men and women respectively). Table 2 shows the association of OWOB variables at different stages with ln-transformed liver fat content as well as with odds of NAFLD. Participants whose mothers were OWOB ($\geq$25kg/m^2) at delivery had more posibility (OR=4.16, p=0.05]) of having NAFLD. The relationship strengthened with a later life stages of being OWOB (at the MRS time).

GSEM results are shown in table 3, maternal pre-pregnancy OWOB increases the likelihood of maternal OWOB at delivery almost two times (OR: 1.79; 95% CI: 1.51-2.14). The subsequent possibility of offspring´s OWOB during childhood (before 4 years of age) was six times that of participant´s whose mothers presented OWOB at delivery, as compared with those born to women in the normal weight BMI category at delivery (OR:6.02; 95% CI: 1.12-32.30). Moreover, these same participants who were OWOB before 4 years of age had almost seven times greater odds of being OWOB during adolescence (OR: 6.83; 95% CI: 1.12-24.24), compared to those classified as normal weight by 4 years of age. Finally, being OWOB vs. normal weight during adolescence was a strong determinant of staying OWOB in adulthood (OR: 23.82; 95% CI: 6.06-93.53).

Finally, we found that OWOB in both the mothers as well as the participants themselves was directly associated with higher liver fat content. Participants whose mothers were

OWOB at delivery presented a higher average liver fat content, than those whose mothers were classified as normal BMI (exp(β) 1.97; 95%CI: 1.28, 3.05). OWOB in adulthood was also cross-sectional associated with higher percentage of liver fat content (exp(β) 3.17; 95%CI: 2.10, 4.7700).

Discussion

Main Findings

To our knowledge, this is the first study in a Mexican population of young adults to investigate life course associations of exposure to maternal and offspring OWOB from the *in utero* period onward on offspring liver fat content in young adulthood. Our estimations through the GSEM documented the influence of maternal OWOB on offspring OWOB, as well as the influence of childhood OWOB in adolescence and finally in young adulthood, which is consistent with previous findings from other cohort studies [37-40].

We found that 17% of the participants presented with the more than 5% of liver fat fraction considered to be NAFLD[29], which is consistent with what has been reported for this age range[8, 41]. We identified OWOB as a determinant (directly and indirectly) related to the development of NAFLD among offspring in adulthood. This finding is highly relevant in a country like Mexico where more than 70% of women at reproductive age present overweight or obesity[20]; furthermore, around 30% of women are expected to start pregnancy with a BMI>30kg/m2[42].

Our findings align with previous cross-sectional and cohort studies that had demonstrated the association of maternal obesity and NAFLD with larger samples [16, 43-45]. Previous studies have shown that maternal BMI is directly correlated with neonatal intrahepatocellular lipid content [44, 46], a phenomenon that can be attributed to the fact that obese mothers, as compared to normal weight women, mobilize increased nutrient (glucose and fatty acids) availability to the fetus [47]. This may present a challenge for the fetus in early pregnancy (first trimester) as excess of nutrients are not stored in the form of

subcutaneous fat until the third trimester) [48]. Instead, excess fuels made available to the fetus result in fat accumulation in fetal hepatocytes [49].

We also found a strong a positive and direct association between the participants' current BMI status and liver fat content. These findings align with those of a systematic review [50], and a recent cohort study which detected 3 times greater odds of NAFLD in midlife among those with high BMI during adolescence [51] and with other reports that showed an increase in the severity of hepatic steatosis in adolescents with higher BMI [52]. The mentioned associations were independent of the lifestyle covariates like smoking, energy and alcohol intake.

It is also important to note that we did not find a difference by sex in liver fat content, which is surprising given a study in adolescents [53] and several population-based studies reporting higher NAFLD prevalence among men than women [54-57]. However, our finding is consistent with a previous study that found equal amounts of liver fat in adult men and women [58].

Strengths and Limitations

There are some limitations to the present study. First, there was a possible selection bias as the participants were selected as a convenience sample from the overall ELEMENT cohort, however the only statistically different variable was mother´s education and was not associated to the outcome. Second, the self-report of pre-pregnancy weight could possibly underestimate the role of pre-pregnancy BMI on overweight at delivery. However previous studies that have used the same approach have shown that this self-reported variable can be useful for screening and for discerning associations with health outcomes[59, 60]. Lastly, the small sample size in this analysis did not allow us to run a logistic model using NAFLD as the outcome. The power estimation for a sample of 97 required a minimum prevalence of 30% and the observed prevalence in this sample was 17% (as expected for this age group). Nevertheless, we were able to detect associations with the continuous variable (liver fat content).

One strength of this study is the rich data on historical exposure variables, which allowed us to assess the influence of pregnancy, childhood and adolescent weight status on liver fat content in early adulthood. Our method of liver fat assessment (1H MRS to measure the liver fat fraction) has been previously validated and is currently the best best non-invasive method to quantify fat within the liver [26].

Interpretation

Dietary and lifestyle modifications, like weight control, are currently the main method for treatment of NAFLD, especially in youth [61]. The determinants of liver fat content that we identified in this study point towards potential avenues for early interventions. The strong association of maternal overweight with offspring liver fat fraction during early adulthood points to the possible beneficial effect of achieving a healthy weight and weight gain during pregnancy on offspring metabolic health. The pregnancy period constitutes a window of opportunity for prevention of non-communicable diseases since most pregnant women attend antenatal care and are in contact with the healthcare system (in Mexico 98.4% of pregnant women attend antenatal care) during their pregnancy[62]. It is also a unique opportunity to identify women at high risk and make lifestyle changes as women are often highly motivated, especially when they perceive associated benefits to their offspring[63, 64].

Finally, public health actions that promote weight control throughout life need to be reinforced as a way to prevent complications related to obesity as NAFLD.

Conclusion

We found that maternal OWOB status is related to fatty liver content in the offspring as young adults, even after taking into account OWOB status and lifestyle factors in the offspring. Encouraging overweight women to make a lifestyle changes before pregnancy that result in adequate weight control could subsequently prevent chronic diseases in the offspring.

Disclosure of interests

The authors declare that they have no conflicts of interest. Completed disclosure of interest forms are available to view online as supporting information.

Contribution to authorship

AC, MHA, MMTR, DK, KEP and HH conceived and designed the study; LLV, AC, EARV participated in the data collection; AM, WP conducted the statistical analyses; JAR, WP, HH, and AC interpreted the results; AC, AM, WP, HH wrote the article. All authors have been involved in the production of the article, and have approved the final version.

Details of ethics approval

Written informed consent was obtained from all the participants. The project protocol was reviewed and approved by the Ethics in Research Committee of the National Institute of Public Health, Mexico, and by the Institutional Review Board of the University of Michigan that also supported this research. Approved project by the Research and Ethics committee of the National Institute of Public Health on June 15th 2016 with the ID-project CI: 1377; and by the Biosafety committee of the National Institute of Public Health on June 13th 2016 with the ID-project CB: 1368.

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The data used to support the findings of this study are available from the corresponding author upon request.

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Table 1. Characteristics of the analytical sample comparing pregnancy, childhood, adolescence and young-adulthood related to the presence of offspring NAFLD

	All n= 97	non-NAFLD n=80	NAFLD n=17	p
		n (%)		
Maternal:				
Pre-pregnancy BMI classification				
Normal (%)	58 (67.44)	47 (66.20)	11 (73.33)	
Overweight/Obesity (%)	28 (32.56)	24 (33.8)	4 (26.67)	0.76
BMI classification at delivery				
Normal (%)	39 (39.80)	36 (45.00)	3 (16.67)	
Overweight/Obesity (%)	59 (60.20)	44 (55.00)	15 (83.33)	0.03
Offspring, at birth				
Birth Weight (gr)*	3,093 (398.10)	3,075 (416.08)	3,178 (394.79)	0.3
Low birth weight (<2500gr) (%)	7.2	8.7	0.0	0.2
Gestational age (weeks)*	39.4 (1.3)	39.1 (1.4)	39.4 (1.1)	0.3
Sex (% male)	53 (54.64)	44 (55.00)	9 (52.94)	0.5
Infant				
Breastfeeding				
Total (months)**	8.35 (7.89)	8.53(8.06)	7.47 (7.18 1)	0.9
Never Breastfed (%)	21 (21.65)	18 (22.5)	3 (17.65)	0.5
Breastfed (%)	76 (78.350)	62 (77.50)	14 (82.35)	
Offspring, Childhood				
Being overweight/obese before 4 years of age				
No (%)	82 (84.54)	70 (87.5)	12 (70.59)	0.08
Yes (%)	15 (16.16)	10 (12.50)	5 (29.41)	
Offspring, Adolescence				
Being overweight/obese				
No (%)	72 (74.23)	65 (81.25)	7 (41.18)	0.01
Yes (%)	25 (25.77)	15 (18.75)	10(58.82)	
Offspring, Young adulthood (at the time of MRS)				
Age (years)*	21.4 (0.5)	21.4 (0.5)	21.4 (0.5)	0.9
Being overweight/obese				
No (%)	56 (57.73)	55 (68.75)	1 (5.88)	<0.01
Yes (%)	41 (42.27)	25 (31.25)	16 (94.12)	
Smoking				

Never	14 (14.43)	14 (17.5)	0 (0)	
Past smoker	40 (41.24)	33 (41.25)	7 (41.18)	0.1
Active smoker	43 (44.33)	33 (41.25)	10 (58.82)	
Alcohol intake				
Never/Annually	47 (48.45)	38 (47.5)	9 (52.94)	
Monthly	30 (30.93)	23 (28.75)	7 (41.18)	0.2
Weekly/daily	20 (20.62)	19 (23.75)	1 (5.88)	
Socioeconomic Status				
Very-Low/Low	49 (50.52)	11(64.71)	38(47.50)	0.3
Medium/High	48 (49.48)	6 (35.29)	42(52.50)	
Energy intake (Kcal/d)**	2,811.2 (1,956 - 3670)	2,814.3 (2,029- 3,927)	2,443.9 (1,887 – 3,358)	0.8

Maternal BMI classification: Normal (<25kg/m2), Overweight (≥25 kg/m2); Childhood overweight >2SD of the WHZ-score (WHO 2006); Adolescence and adult overweight/obese (≥25kg/m2)

* Mean (SD), two sample T-test

** Median (IQR), Kolmogorov Simonov test

Exact-Fisher test for categorical variables

Table 2. Association between OWOB at different stages and liver fat (log transformed) or Odds Ratio of having NAFLD

	Liver fat content*		NAFLD**	
	β	p	OR	p
Maternal pre-pregnancy Overweight/Obesity	0.15	0.61	0.49	0.32
Maternal Overweight/Obesity at delivery	0.72	<0.01	4.16	0.05
Childhood Overweight/Obesity	0.23	0.51	2.70	0.19
Adolescence Overweight/Obesity	1.02	<0.01	6.03	<0.01
Young-Adulthood Overweight/Obesity	1.29	<0.01	33.68	<0.01

*Linear regression model

** Logistic regression model

Models adjusted by mother's age & education, sex, socioeconomic level, smoking alcohol and energy intake.

Maternal Overweight (≥25 kg/m2); Childhood overweight >2SD of the WHZ-score (WHO 2006) before 4 years of age; Adolescent and adult overweight/obesity (≥25kg/m2)

Table 3. Association´s coefficients estimated from a Generalized Structural Equation model of OWOB at different time periods and liver fat content

			OR (95%CI)
		Predictors	
Overweight/Obesity at delivery	Pre-pregnancy overweight/obesity		
		Normal	ref.
		Overweight/Obesity	1.79*(1.51-2.14)
	Mother's First pregnancy		1.29*(1.06-1.58)
	Mother's Years of schooling		1.02 (0.99-1.05)

	Mother's Age		1.02(1.01-1.03)
Overweight/Obesity before 4 years of age	Overweight/Obesity at delivery		
		Normal	ref.
		Overweight/Obesity	6.02*(1.12-32.30)
	Breast feeding		
		Never Breastfed	ref.
		Breastfed	0.91(0.82-1.01)
	Sex		
		Female	ref.
		Male	3.98(0.92-17.20)
	Mother's Years of schooling		1.11 (0.90-1.36)
	Mother's Age		0.92 (1.00-1.03)
Overweight/Obesity at Adolescence	Overweight/Obesity before 4 years of age		
		Normal	ref.
		Overweight/Obesity	6.83*(1.12-24.24)
	Sex		
		Female	ref.
		Male	0.98(0.34-2.84)
	Mother's Years of schooling		1.03 (0.88-1.22)
	Mother's Age		1.08(0.98-1.19)
Overweight/Obesity at Young Adulthood	Overweight/Obesity at Adolescence		
		Normal	ref.
		Overweight/Obesity	23.82*(6.06-93.53)
	Sex		
		Female	ref.
		Male	1.05(0.38-2.88)
	Mother's Years of schooling		0.89 (0.75-1.05)
	Mother's Age		1.03(0.92-1.11)
Liver fat content (log)	Overweight/Obesity at delivery		
		Normal	ref.
		Overweight/Obesity	1.97*(1.28-3.05)
	Overweight/Obesity at Young Adulthood		
		Normal	ref.
		Overweight/Obesity	3.17*(2.10-4.77)
	Sex		
		Female	ref.
		Male	1.25(0.81-1.94)
	Alcohol intake		
		Never/Annually	ref.
		Monthly	0.97(0.59-1.60)
		Weekly/daily	0.92(0.52-1.66)
	Smoking		
		Never	ref.
		Past smoker	1.30(0.69-2.46)

		Active smoker	1.89*(1.01-3.69)
	Socioeconomic Status		
		Very-Low / Low	ref.
		Medium/ High	1.26(0.82-1.95)
	Energy intake		1.00(0.99-1.00)
	Mother's Years of schooling		0.94 (0.88-1.01)
	Mother's Age		1.00(0.99-1.05)

*=p<0.05

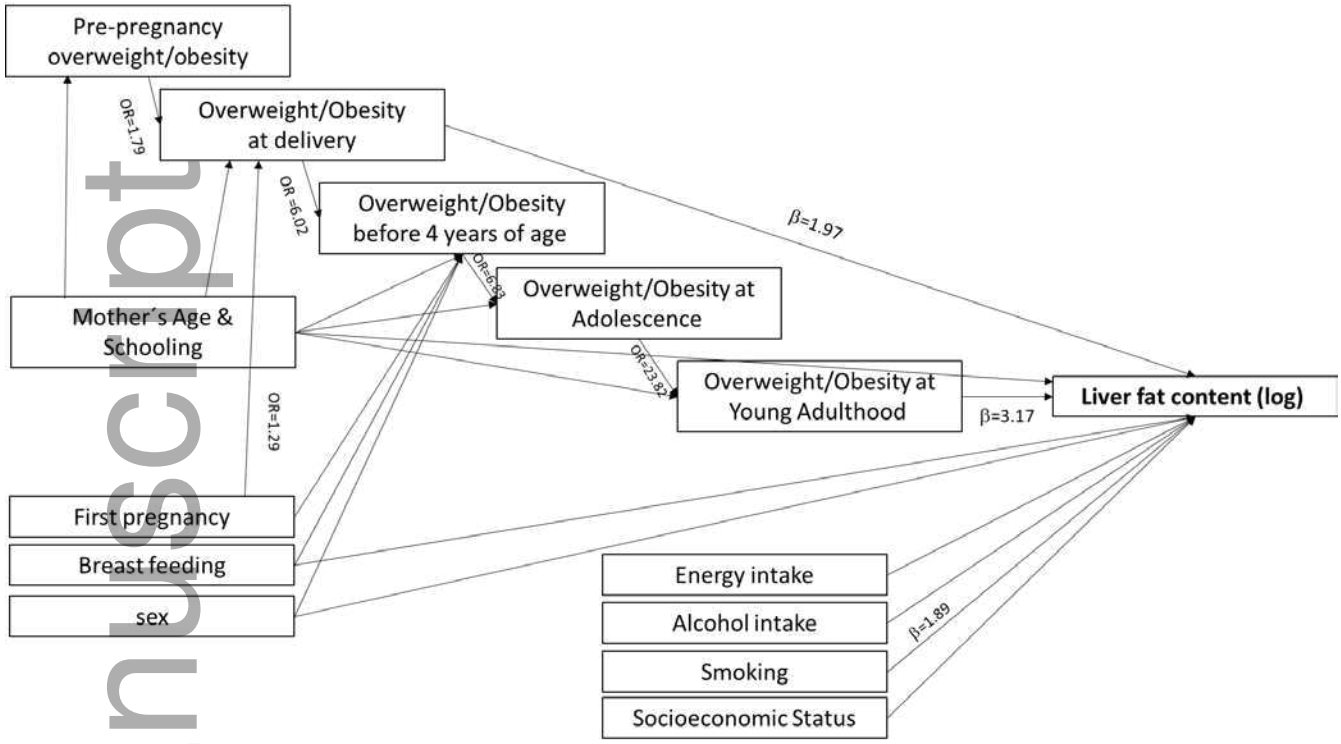

Figure 1. Generalized Structural equation model of maternal and child overweight/obesity and its association with liver fat content (only statistically significant coefficients/odds ratio are presented in the figure, for more detail please see table 3)